Upfront surgery versus neoadjuvant chemotherapy for borderline resectable pancreatic carcinoma with venous encasement more than 180 degree, comparative study

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Background
Pancreatic cancer is considered the seventh cause of cancer-related death worldwide, and has low resection rate and a poor prognosis. Surgical resection to achieve R0 followed by adjuvant chemotherapy is the treatment of choice. Borderline resectable pancreatic cancer (BRPC) is technically difficult tumor with high risk of non-radical resection R1 and early postoperative recurrence.
A neoadjuvant chemotherapy in BRPC instead of upfront surgical resection has advantages of increase R0 resection rate, treatment of undetected micro metastases and decrease postoperative pancreatic fistula.
Objective
Comparing the short-term outcome between upfront surgery and neoadjuvant chemotherapy for borderline resectable pancreatic carcinoma for venous encasement only as regards the ability to do R0 resection, early surgical complications and the progression rate of the disease
Design
Prospective cohort.
Patients and methods
Patients age between 20–70, with only venous encasement (no arterial encasement) with encasement>180 degrees and a segment of venous encasement not more than 2 cm were included.
Patients with an arterial encasement, distant metastasis, and not fit for chemotherapy were excluded.
Results
The upfront surgery group has higher resection rate (75%) with portal/SMV reconstruction needed in one-third of the cases (33.3%) while the neoadjuvant chemotherapy group has higher progression rate (55%) and low resection rate (only 20%). No significant difference between the groups as regards the complication rate (morbidity and mortality), R1 resection(margin invasion), blood loss or time of surgery.
Conclusion
Upfront surgery can be done in selected patients with BR-PDAC to avoid the progression of the disease with no statistically significant difference as regards the short-term complications in comparison to the neoadjuvant group.

Keywords:
borderline tumor, neoadjuvant chemotherapy, upfront surgery

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Introduction

Pancreatic cancer is considered the seventh cause of cancer-related death worldwide, and has low resection rate and a poor prognosis [1,2]. Surgical resection to achieve R0 followed by adjuvant chemotherapy is the treatment of choice [3]. Nowadays pancreatic cancer is considered as a systemic disease, and surgery to achieve R0 to enhance quality of life but recurrence may occur due to non-detected micro metastases [4–8].

Borderline resectable pancreatic cancer introduced in 2006 by Varadhachary *et al.* [9] is technically difficult tumor with high risk of non-radical resection R1 and early postoperative recurrence. Borderline resectable pancreatic cancer (BRPC) has many definitions by different international guidelines, but this heterogenicity make it difficult to compare results of different studies.

Borderline resectable pancreatic cancer can be divided into:

(1) Relationship between peripancreatic vessels (venous and arterial) and tumor.
(2) Patient general condition and comorbidities.

Multiple terms developed in BRPC as 'abutment', 'encasement', 'reconstructable', 'occlusion' and 'impingement', this terms according to tumor contact with veins (portal vein or superior mesenteric vein 180° or greater or invasion less than 3C.M.) or arteries (celiac axis or the superior mesenteric artery less than 180° without invasion) [10].

A neoadjuvant chemotherapy in BRPC instead of upfront surgical resection has advantages of increase R0 resection rate, treatment of undetected micro metastases and decrease postoperative pancreatic fistula [11,12]. A neoadjuvant chemotherapy in BRPC may has disadvantages of decrease chance of surgery due to disease progression or limited downstaging, or deterioration of the patients general condition after chemotherapy [13,14].

Choice of treatment is still debatable in management of BRPC as most of studies of neoadjuvant chemotherapy are non randomized trials [15,16]. There is a debate about use of chemotherapy alone and types of neoadjuvant chemotherapy or chemoradiation [17–19].

Patients and Methods

This is a prospective cohort study conducted at Ain-Shams University Hospitals, in the period from November 2021 to December 2022. Forty patients with malignant masses in pancreatic head were recruited for this study. Twenty patients underwent upfront surgery and the other twenty patients received neoadjuvant chemotherapy before surgery Ethical approval was obtained from Al Demerdash ethical committee.

Inclusion criteria

(1) Age from 20 to 70 years.
(2) Has no distant metastases at first presentation.
(3) Patients with ECOG PS 0–2
(4) Cooperative patient.
(5) Psychologically stable patients.
(6) Patient with portal vein or superior mesenteric vein contact 180° or greater or invasion less than 2 C.M.

Exclusion criteria

(1) Patient presented with distant metastases at first presentation.
(2) Patients refusing participation in the study.
(3) Patient presented with arterial encasement or invasion.
(4) Patient presented with duodenal mass.
(5) Presence of contraindications to chemotherapy.
(6) Patients with double malignancy.

All patients included in our study were subjected to:

Clinical assessment including: History (past medical, surgical, family history and history of comorbidities). Clinical examination of abdomen and pelvis.

Investigations

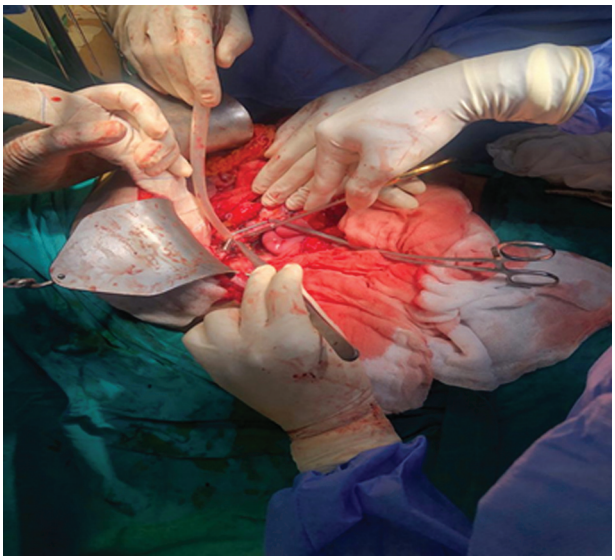
(1) Routine laboratory investigations: CBC, INR, urea and creatinine, liver function, CA 19.9.
(2) Imaging include: pelvi-abdominal US, pelvi-abdominal C.T with contrast, dynamic magnetic resonance imaging (MRI) with MRCP, PET C.T.
(3) Biopsy: ultrasound-guided core biopsy, C.T. guided biopsy in the neoadjuvant group or EUS guided biopsy.
(4) ERCP if bilirubin more than 12 mg/dl with stent insertion in patient who will undergo upfront surgery.
(5) ERCP if bilirubin more than 2 mg/dl with stent insertion in patient who will receive neoadjuvant chemotherapy.
(6) Metastatic work-up: CT chest, Bone scan, and/or PET CT scan.

Operative details

After pancreaticoduodenectomy,the resected pancreatic margin was always evaluated intraoperatively by frozen section to be sure it is free. In cases where portal/SMV reconstruction needed, assessment was done to know if complete resection of the circumference is needed or just side wall reconstruction is needed. In case of side wall reconstruction, vascular clamps were applied and side wall was removed with the specimen and primary closure as done, but in case of complete resection of the circumference of the vein was needed, mobilization of the SMV usually done by ligation of the small jejunal branches to give more length followed by resection and reconstruction by 6/0 prolene in end to end fashion. (Figs. 1 and 2).

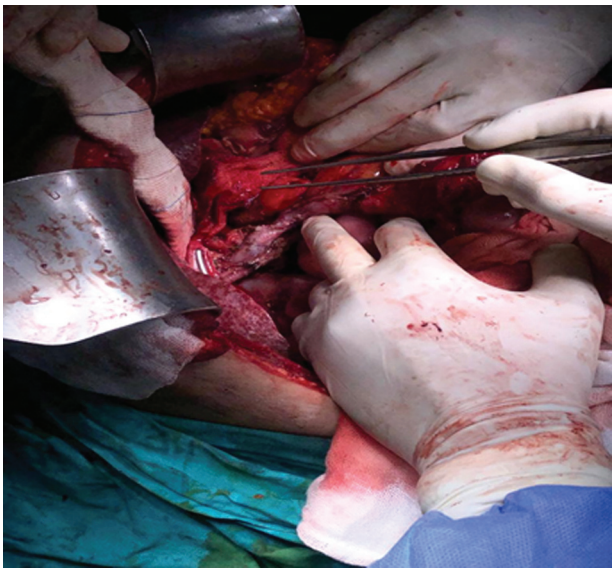
Then the anastomosis started by the pancreaticojeujonostomy. The proximal end of the jejunum was passed retro-colic in a window of the transverse mesocolon and connected to the remnant of the pancreases in a double layer end to side

Figure 1



Side wall excision.

Figure 2



After reconstruction of the portal vein.

pancreatojejunostomy by PDS 4/0 with the inner layers holding the pancreatic duct to the jejunal edge (double layered duct to mucosa) without stent. Followed by the gastrojejunostomy in a side to side anastomosis then hepaticojejunostomy was done interrupted PDS 4/0 followed in a Rou en Y reconstruction (isolated biliary limb technique) followed by the entero-enteric anastomosis

Neoadjuvant chemotherapy

Twenty patients received 3 months neoadjuvant chemotherapy before surgery.

12 patients with ECOG performance status 0–1 received 3 months of modified FOLFORINOX protocol (oxaliplatin 85 mg/m2 IV over 2 hours, irinotecan 150 mg/m2 IV over 90 min, leucovorin 400 mg/m2 IV over 90 min and fluorouracil 2400 mg/m2 continuous intravenous infusion over 46 hours) every 2 weeks for 6 cycles (12 weeks).

8 patients with ECOG performance 2 received neoadjuvant chemotherapy with Gemcitabine plus fractionated Cisplatin protocol (Gemcitabine 1000 mg/m2 IV over 30 min day 1 and day 8 plus Cisplatin 30 mg/m2 IV over 60 min infusion day 1 and day 8) every 21 days for 4 cycles

These patients were evaluated preoperatively by dynamic MRI pancreatic protocol before any surgical intervention and disease progression is assess by either progression of the mass size with more encasement on the vessels or appearance of liver metatsasis or peritoneal nodules.

Postoperative chemotherapy

Patients with ECOG performance status 0–1 received adjuvant modified FOLFORINOX protocol (oxaliplatin 85 mg/m2 IV over 2 h, irinotecan 150 mg/m2 IV over 90 min, leucovorin 400 mg/m2 IV over 90 min and fluorouracil 2400 mg/m2 continuous intravenous infusion over 46 h) every 2 weeks for 12 cycles (24 weeks). The remaining patients who underwent surgical resection with ECOG performance status 2 will receive adjuvant Capecitabine and Gemcitabine (Gemcitabine 1000 mg/m2 on days 1,8,15 IV over 30 min plus Capecitabine 830 mg/m2 PO BID on days 1 to 21 (total daily dose = 1660mg/m2) repeat cycle every 28 days for 6 cycles.

Results

As regards the age, there was no statistically significant difference between the 2 groups. The mean age for the neoadjuvant group was 54 years and ranging between 42 and 63 years, while for the upfront surgery group, the mean age was 55 years and ranging between 39 and 66 years (*P* value 0.96).

As regard the gender distribution, also no significant difference between the 2 groups, for the neoadjuvant group 12 patients were males (60%) and 8 patients were females while the upfront surgery group 11 patients were males (55%) and 9 patients were females (45%) (*P* value 1).

As regards the segment of venous encasement, the mean length of the venous segment for the neoadjuvant group was 12.85 mm with SD 12.95

and ranging between 9–19 mm while for the upfront group the mean length of the venous segment encased was 13 mm with SD 3.48 and range between 8–19 mm. with no statistically significant difference (P 0.88)

For the Upfront group, all the 20 patients were operated upon with successful resection in 15 cases only (75% successful resection rate) and portal/SMV resection and reconstruction was needing in only 5 cases (33.3% of cases with successful resection) mean operative time as 6.14 Hrs, mean blood loss was 527 ml, hospital stay was 12.7 days.

While the neoadjuvant group, progression had happened in 11 cases (55%) while only 5 cases were stationary (25%) and 4 cases showed regressive course (20%). These 9 cases were operated upon with successful resection achieved only in 4 cases (20% of the neoadjuvant group) only 2 of them required portal –SMV reconstruction (50% of cases of successful resection) and 5 cases were showed to be locally advanced or metastatic in spite of being stable or regressed in radiologic evaluation preoperatively. The operation time as longer in cases after the neoadjuvant with mean time 6.40 hours but not statistically significant between the 2 groups (*P* value 0.594)

The mean blood loss for the upfront surgery group was 527.3 ml and ranging between 300 to 800 ml while for the neoadjuvant group the mean blood loss was slightly higher 573.33 ml and ranging between 450 to 770 ml but not statistically significant (*P* value 0.645).

As regards the hospital stay, the mean hospital stay for the upfront group was 12.73 with SD 3.011 and range between 9–21 days while for the neoadjuvant group the mean hospital stay was 13 days with SD 2 days and the range was between 11–15 days with not statistically significant difference between the 2 groups (*P* value 0.886).

The post operative pancreatic fistula had occurred in 3 cases (20%) of the upfront surgery group while occurred in only one case of the cases had successful resection of the neoadjuvant group (33.3%) with not statistically significant difference between the 2 groups, (*P* value 0.61).

2 patients from the upfront group required reoperation either for bleeding or drainage of collection after pancreatic fistula (13.3%) while no cases from the neoadjuvant group required any additional surgery with no statistically significant difference.

The resection margins was involved in only 2 cases of the upfront group (13.3% from the total cases of successful resection) while there was no positive margins in the three cases with successful resection after the neoadjuvant therapy with no statistically significant difference between the 2 groups, *P* value was 0.5.

The mortality rate for the upfront group as 5% only one case had preoperative mortality while the there as no mortality for the neoadjuvant group with no statistically significant difference (*P* value 0.645).

Postoperative chemotherapy

Of the fifteen patients who succeeded surgical resection 9 patients with ECOG performance status 0–1 received adjuvant modified FOLFORINOX protocol (oxaliplatin 85 mg/m^2 IV over 2 hours, irinotecan 150 mg/m^2 IV over 90 min, leucovorin 400 mg/ m^2 IV over 90 min and fluorouracil 2400 mg/m^2 continuous intravenous infusion over 46 hours) every 2 weeks for 12 cycles (24 weeks). The remaining 6 patients who underwent surgical resection with ECOG performance status 2 received adjuvant Capecitabine and Gemcitabine (Gemcitabine 1000 mg/m^2 on days 1,8,15 IV over 30 min plus Capecitabine 830 mg/m^2 PO BID on days 1 to 21 (total daily dose = 1660mg/m^2) repeat cycle every 28 days for 6 cycles.

5 patients who failed surgical resection received induction chemotherapy with modified FOLFORINOX protocol (oxaliplatin 85 mg/m^2 IV over 2 hours, irinotecan 150 mg/m^2 IV over 90 min, leucovorin 400 mg/m^2 IV over 90 min and fluorouracil 2400 mg/m^2 continuous intravenous infusion over 46 h) every 2 weeks for 6 cycles (12 weeks). Followed by concurrent chemoradiation consisted of 50 Gy 3D conformal radiotherapy /2 Gy/Fr/25 fractions concurrent with Capecitabine 830 mg/m^2 PO BID on days 1 to 5 every week for 5 weeks

Discussion

Pancreatic duct adenocarcinoma (PDAC) is an highly aggressive solid tumor and is the fourth leading cause for cancer-related deaths in western countries [20]. Surgical resection remains the main line of treatment and early surgical intervention is preferred for surgically resectable PDAC.

The term borderline resectable pancreatic tumor constitute a wide range of patients with different criteria which makes comparison is very difficult,

also the ability to perform R0 resection in borderline respectable pancreatic duct adenocarcinoma (BR-PDAC) differ between surgeons according to the experience and the ability to do vascular resection with less morbidity and mortality.

Many studies showed that Neoadjuvant chemotherapy for DR-PDAC gives superior results than upfront surgery as regards the overall survival and the ability to perform R0 resection but these studies were criticized for being non randomized, heterogenous as regards the type of vascular encasement either arterial or venous and also the degree of vascular affection either just abutment or occlusion of the vessels also some studies included patients with no any vascular encasement(patients who are not BR-PDAC who are candidate for upfront surgery).

Another criticism which we consider is the most important is the selection bias is that the patients got surgery after neoadjuvant therapy are the patients with better tumor biological behavior who got responded to chemotherapy and these patients will have better survival than patients with aggressive tumor and on the other hand patients with aggressive tumor progressed and excluded that's why many authors now try to compare the results by calculating the intention to treat to minimize this selection bias. Also many patients who progressed on chemotherapy lost their chance to get R0 resection and no one can predict the survival for these patients if they offered upfront surgery.

Also surgery for arterial resection and reconstruction is much more complex and carries higher morbidity and mortality than venous reconstruction that's why till now the treatment of BR-PAC is debatable.

In a study done by Wittel and his colleagues, He got the opinion of 5 different pancreatic surgeons on the same scans of the same patients with BR-PDAC and the results showed difference in the decision between the surgeons as regards the ability to perform R0 resection which prove that surgeon experience is an important factor in management and these complex cases should be treated in a multidisciplinary team with highly specialized pancreatic surgery team [21].

In order to decrease the heterogenicity between different types of BR-PDAC, we compared the short-term results of BR-PDAC for venous encasement only and we found that disease progression happened in about 75% of cases with the neoadjuvant group which is higher than different studies compared both neoadjuvant to upfront surgery. On the other hand the success rate of resection was about 75% in the upfront surgery. The margin was microscopically involved in 13% of cases in the upfront surgery group but was statistically non-significant.

The cause of this high rate of progression is not clear but may be attributed to many factors like aggressive tumor, delay in the start of the chemotherapy or difference in tolerance of the patients to the chemotherapy regimen.

Also one of the debates about going to upfront surgery in BR-PDAC is the high complication rate which decrease the percentage of patients receiving adjuvant chemotherapy and this gave support to the opinion of starting neoadjuvant but in our study although slightly higher complication rate in the upfront group, it was not statistically significant and did not delay the adjuvant therapy except in only 2 patients it patients with pancreatic fistula treated conservatively for weeks which was not marked delay.

We believe that upfront surgery can be better option for a selected group of BR-PDAC with higher resection rate and non-significant rate of complications if done by specialized pancreatic surgeon in high volume center.

Conclusion

Upfront surgery can be done for selected cases of BR-PDAC (venous encasement) with no significant increase morbidity to avoid disease progression in Neoadjuvant treatment.

One of the limitations of this study is the low number of the cases in the Neoadjuvant group which we were able to do resection, more studied is recommended with recruitment of more patients to get better conclusion about the debate of either going for upfront surgery or adopting the neoadjuvant protocol of BR-PDAC for venous encasement.

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Conflicts of interest

There are no conflicts of interest.

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