

Evaluation of Routine Use of Neoadjuvant Chemo-Radiotherapy for Management of Borderline Resectable Pancreatic Cancer versus Surgery-First Approach

Original
Article

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ABSTRACT

Background: Borderline resectable pancreatic cancer (BRPC) presents a significant treatment challenge, with an elevated likelihood of incomplete resection and early recurrence. While upfront surgery offers immediate tumor removal, neoadjuvant chemoradiotherapy (NACRT) has been proposed to improve resection outcomes by reducing tumor burden and eliminating micrometastases. The optimal treatment strategy remains a topic of ongoing discussion and disagreement.

Objective: To compare the outcomes of NACRT versus upfront surgery in BRPC patients, evaluating tumor resectability intraoperatively, postoperative complications, adjuvant therapy feasibility, and one-year survival rate.

Methods: A retrospective comparative study was conducted at Ain Shams University Hospitals, including 30 patients diagnosed with BRPC based on NCCN classification. Patients were subdivided into two groups: NACRT ($n=15$) and upfront surgery ($n=15$). Data on tumor resectability, R0 and pN0 resection rates, postoperative complications, and survival were analyzed. Statistical significance was set at $p<0.05$.

Results: Tumor resectability was significantly elevated in the upfront surgery group (80.0% vs. 33.3%, $p=0.010$). R0 resection and pN0 rates were 100% in the NACRT group compared to 83.3% R0 resection and 33.3% pN0 rates in the upfront surgery group ($p=0.999$ for R0 resection, 0.029 for pN0). Postoperative complications were similar, with one case of fistula (8.3%) occurring in the upfront surgery group. All resected patients in both groups received postoperative adjuvant therapy and survived at least one year.

Conclusions: Upfront surgery results in a higher initial resectability rate, while NACRT improves margin-negative resection and nodal clearance. Both strategies have distinct advantages, and patient selection should be guided by tumor characteristics and multidisciplinary evaluation. Further prospective research involving bigger participant groups and extended follow-up periods is necessitated to determine the long-term effects of NACRT on survival.

Key Words: Borderline resectable pancreatic cancer, neoadjuvant chemoradiotherapy, R0 resection, tumor resectability, upfront surgery.

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INTRODUCTION

Ranking as the third most prevalent cancer-linked fatality cause in the United States and the fourth in Europe^[1], pancreatic cancer has a dismal five-year survival rate of just 10%, making it the deadliest among all solid tumors^[1]. Depending on the vascular involvement degree, non-metastatic cases are grouped into resectable, borderline resectable, or locally advanced stages^[2].

In cases of pancreatic cancer that is eligible for surgical removal, the established protocol involves surgical resection followed by adjuvant chemotherapy^[3]. For borderline resectable tumors, the National Comprehensive Cancer Network (NCCN) advocates for neoadjuvant

therapy, while NICE guidelines restrict its recommendation to clinical trial settings^[3]. It is important to note that neither guideline's recommendations are supported by evidence from randomized controlled trials (RCTs).

Initial surgery followed by adjuvant therapy could offer certain advantages compared to neoadjuvant therapy. For instance, it eliminates the need for biliary stenting in cases of obstructive jaundice. Additionally, patients avoid the risk of clinical decline during preoperative chemotherapy. Neoadjuvant therapy, while delaying surgery, may lead to tumor progression in cases where chemotherapy is ineffective, potentially rendering the tumor inoperable.

Nevertheless, neoadjuvant treatment provides early systemic chemotherapy and may elevate the possibility of achieving a microscopically complete (R0) resection^[4]. It also helps avoid unnecessary surgery in patients with aggressively advancing disease.

There is a challenge in the evaluation of overall survival in studies that compare neoadjuvant therapy and upfront surgery^[5]. According to early meta-analyses and large cohort studies, neoadjuvant merits a better outcome. Nevertheless, these findings were skewed because they examined only patients who underwent resection^[6].

Our objective is to perform a retrospective comparative study evaluating neoadjuvant therapy versus upfront surgery in individuals with borderline resectable pancreatic cancer (BRPC) as regards resectability status intraoperatively, possibility of postoperative adjuvant therapy, one-year survival rate, and postoperative complications. The present study seeks to compare between neoadjuvant therapy and the surgery-first technique in BRPC patients, as defined by the NCCN criteria as regards resectability status intraoperatively, the possibility of postoperative adjuvant therapy, the one-year survival rate, and postoperative complications.

PATIENTS AND METHODS

This research was designed as a retrospective comparative analysis conducted at Ain Shams University Hospitals following approval by the ethics committee and after obtaining written consent from the participants to study the effectiveness of neoadjuvant chemoradiotherapy (NACRT) versus upfront surgery in BRPC patients. The goal of this study was to compare the two approaches with regard to intraoperative resectability of tumor, postoperative complications, feasibility of adjuvant therapy, and one-year survival rates.

The research spanned a duration from January 2024 to January 2025. The study population included patients who were operated on for open pancreaticoduodenectomy from June 2022 to December 2023 after being diagnosed with BRPC, defined following the NCCN criteria, which consider tumors with venous involvement $>180^\circ$ or any arterial contact as BRPC. In total, 30 patients were included and allocated into two groups (Figure 1):

Group A (NACRT group): 15 patients received neoadjuvant chemoradiotherapy followed by surgical evaluation.

Group B (Upfront surgery group): 15 patients underwent immediate surgical resection without prior therapy.

Inclusion Criteria:

1. Age group: 35 to 65 years old.

2. Borderline resectable pancreatic cancer (i.e. venous contact $>180^\circ$, any arterial contact).
3. Jaundiced patients treated by endobiliary stent.
4. Patients with histopathology of pancreatic ductal adenocarcinoma.
5. Accepting participation in the study.

Exclusion Criteria:

1. Age group: under 35 or over 65 years old.
2. Patients with severe comorbid conditions (renal and liver impairment, etc.).
3. Resectable pancreatic cancer (i.e., venous contact $\leq 180^\circ$, no arterial contact).
4. Locally advanced or metastatic cancer.
5. Recurrent pancreatic cancer.
6. Histopathology of endocrine pancreatic tumors.
7. History of major abdominal operations.
8. Patients were found to be metastatic during diagnostic laparoscopy.

Ethical approval was obtained from the Research Ethical Committee of the General Surgery Department, Faculty of Medicine, Ain Shams University, and all patients provided informed consent before participation.

Study Procedures:

All participants underwent a comprehensive set of procedures. Each patient received an in-depth clinical evaluation, including a full medical history and physical examination. Imaging and staging were performed using contrast-enhanced CT scans with a pancreatic protocol to assess tumor location and resectability. Additionally, PET-CT was used to detect distant metastases, and diagnostic laparoscopy was performed for both groups as an initial step in every case to further evaluate liver metastases and peritoneal nodules.

For group A (NACRT group), patients received neoadjuvant chemotherapy and radiation therapy before surgical reassessment. Preoperative evaluation for both groups included complete blood count, coagulation profile, liver and kidney function tests, blood glucose levels, viral markers, ECG, and anesthesia consultation to ensure patient suitability for surgery.

All cases considered resectable after imaging and diagnostic laparoscopy were operated on for open pancreaticoduodenectomy by the artery-first technique

to exclude arterial invasion, then tumor relation to PV/SMV was assessed, intraoperative resectable cases were forwarded for pancreaticoduodenectomy and lymphadenectomy of Celiac and Portal LNs, and the resected pancreatic and common bile duct margins were sent for frozen section intraoperatively. Then, 3 anastomoses—pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy—were done.

Sample Size:

Patients were divided in a ratio of 1:1 into 2 groups, Group A and Group B. Group A included 15 patients who were subjected to neoadjuvant therapy, and group B included 15 patients who underwent immediate surgery.

Postoperative Follow-Up:

Patients were closely monitored for postoperative complications, including delayed gastric emptying, pancreatic fistula, and post-pancreatectomy hemorrhage. The feasibility of adjuvant therapy was assessed, and the one-year survival rate was recorded.

Ethical Considerations:

Patient information was anonymized, with data organized by diagnosis rather than names to ensure confidentiality. All participants provided informed consent in Arabic, documented with specific dates and times. Privacy was maintained by assigning unique codes to patients' initials, accessible only to the investigator.

Statistical analysis:

The collected data were coded, tabulated, and analyzed statistically utilizing IBM SPSS statistics software (version 28.0, IBM Corp., Chicago, USA, 2021). Normality for

quantitative data was assessed using the Shapiro-Wilk test, with results expressed as mean±standard deviation (SD) and compared via an independent *t*-test. Qualitative data were described as frequencies and percentages, with comparisons made utilizing the Chi-square test and Fisher's Exact test. A *p*-value of <0.05 was considered statistically significant; otherwise, results were deemed non-significant.

RESULTS

Table (1) showed that the mean ± SD of age (years) among the NACRT group and the upfront surgery group was 52.3±6.4 and 53.9±7.3 respectively, with no significant difference between both groups (*p* = 0.512); males were 46.7% and 53.3% respectively, with no significant difference (*p* = 0.715). All cases were of encasement BR-V.

Table (2) showed that Tumor resectability among the NACRT group and the upfront surgery group was 33.3% and 80.0% respectively, the difference was significant (*p* = 0.010). Margin negative resection (R0) was 100.0% and 83.3% in cases that underwent tumor resection among the NACRT group and the upfront surgery group respectively, the difference was non-significant (*p* = 0.999). Pathological negative lymph node (pN0) was 100.0% and 33.3% in cases that underwent tumor resection among the NACRT group and the upfront surgery group respectively, the difference was significant (*p* = 0.029). Postoperative Fistula occurred non-significantly only in the upfront surgery group (8.3%). All cases that underwent tumor resection in either group received postoperative adjuvant therapy and survived for at least one year.

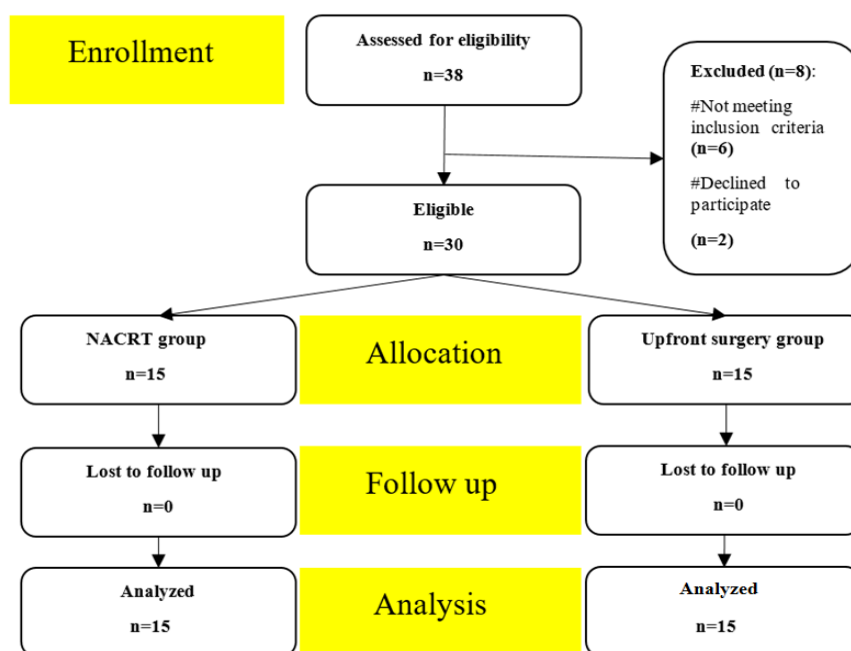


Fig. 1: Study flow diagram (CONSORT).

Table 1: Demographic and clinical characteristics between the study groups:

Variables	NACRT group (Total= 15)	Upfront surgery group (Total= 15)	p-value	Significance
Age (years)	52.3±6.4	53.9±7.3	^0.512	Non-significant
Gender (n, %)	Male 7(46.7%)	8(53.3%)	#0.715	Non-significant
	Female 8(53.3%)	7(46.7%)		
Encasement	BR-V 15(100.0%)	15(100.0%)		Not applicable

^: Independent *t*-test; #: Chi-square test.

Table 2: Operative and postoperative outcomes between the study groups:

Operative	NACRT group (Total= 15)	Upfront surgery group (Total= 15)	p-value	Significance
Tumor resectability	5(33.3%) Total= 5	12(80.0%) Total= 12	#0.010	Significant
Margin negative resection (R0)	5(100.0%)	10(83.3%)	\$0.999	Non-significant
pathological negative lymph node (pN0)	5(100.0%)	4(33.3%)	\$0.029	Significant
Postoperative				
Postoperative adjuvant therapy	5(100.0%)	12(100.0%)		Not applicable
Postoperative fistula	0(0.0%)	1(8.3%)	\$0.999	Non-significant
One-year survival	5(100.0%)	12(100.0%)		Not applicable

#: Chi-square test; \$: Fisher's Exact test.

DISCUSSION

Borderline resectable pancreatic cancer (BRPC) poses a complex anatomical problem with a high risk of a definite incomplete resection. Despite the optimal treatment strategy still being debated, long-term outcomes are improved by achieving a resection with negative margins (R0)^[7]. Some studies advocate for upfront surgery, arguing that immediate tumor removal maximizes resectability. However, neoadjuvant chemoradiotherapy (NACRT) has been alleged to improve surgical outcomes via reducing tumor burden and micrometastases and increasing the probability of obtaining R0 resection^[8].

Given the controversy surrounding the best treatment approach, we sought to compare the efficacy of NACRT to upfront surgery in BRPC patients, based on the diagnosis of that disease by the NCCN criteria. We sought to assess the effects of each approach on tumor resectability intraoperatively, postoperative complications, the feasibility of adjuvant therapy, and one-year survival rates.

In this research, 38 individuals were evaluated for participation. Out of these, 30 participants were enrolled, with 15 in each group. Two others did not wish to participate, and six did not meet the needed inclusion criteria and thus were excluded.

In this work, we have performed a retrospective comparative study at Ain Shams University Hospitals to evaluate neoadjuvant chemoradiotherapy (NACRT) versus upfront surgery in BRPC. Two groups of patients with BRPC were studied: Neoadjuvant Chemoradiotherapy (NACRT) and the upfront Surgery Approach.

The two groups revealed a nearly similar mean age (52.3±6.4 years for NACRT and 53.9±7.3 years for upfront surgery; $p=0.512$). The genders were also distributed similarly in the NACRT group (46.7% males, 53.3% females) and in the upfront surgery group (53.3% males, 46.7% females) ($p=0.715$). All cases in both groups had encasement of the BR-V (100%).

Contextually, Khalil *et al.*,^[9] carried out a prospective cohort analysis that included 40 patients (20 in each group) comparing upfront surgery versus neoadjuvant chemotherapy in BRPC cases with venous encasement exceeding 180 degrees. Also, Javed *et al.*,^[10] used a prospectively maintained database of a single institution to assess resection rates, survivals, and treatment courses in patients treated with neoadjuvant chemotherapy for BRPC. Both studies also found no statistically significant difference in demographic characteristics.

Additionally, Kurahara *et al.*,^[11] conducted a multicenter retrospective study in ten institutions to clarify the prognostic effect of neoadjuvant therapy in BRPC patients with venous or arterial invasion. They found that individuals who were undergoing NAT tended to be marginally younger (median age) but that this was not a significant factor in treatment outcomes. Kim *et al.*,^[12] used a retrospective approach to evaluate neoadjuvant treatment outcomes and prognostic factors in BRPC patients. McClaine *et al.*,^[13] performed a retrospective database analysis of BRPC cases treated with neoadjuvant therapy at the University of Cincinnati, aiming to determine resection feasibility and survival improvements. Han *et al.*,^[14] performed a comparative study at Samsung Medical

Center, focusing on survival differences between upfront surgery and neoadjuvant therapy in BRPC patients. Kim *et al.*,^[12] reported a higher proportion of males undergoing neoadjuvant therapy, which aligns with McClaine *et al.*,^[13] and Han *et al.*,^[14] both of whom observed a similar gender distribution. Chaudhari *et al.*,^[15] conducted a large retrospective cohort study analyzing changing treatment practices in BRPC, assessing long-term survival and perioperative outcomes, and found a near-equal gender distribution but noted that a higher proportion of patients in the NAT group presented with advanced-stage disease in comparison with upfront surgery.

Regarding tumor resectability and surgical outcomes, a significant difference in tumor resectability was noticed between both groups ($p=0.010$). The NACRT group exhibited a resectability rate of 33.3%, whereas the upfront surgery group exhibited a much greater rate of 80.0%. This suggests that the upfront surgery approach was more successful in achieving immediate tumor removal.

For individuals undergoing tumor resection, all cases (100%) in the NACRT group achieved R0 resection (negative margins), compared to 83.3% in the upfront surgery group ($p=0.999$). 100% of the NACRT group had pathological negative lymph nodes (pN0), whereas only 33.3% of the upfront surgery group had pN0 ($p=0.029$). These findings suggest that NACRT was superior in eliminating cancerous involvement at the lymph nodes with non-significant improvement in margin-negative resection.

This finding aligns with Khalil *et al.*,^[9] where upfront surgery resulted in a 75% resection rate, significantly higher than the 20% resection rate in the neoadjuvant group. However, Kurahara *et al.*,^[11] and Kim *et al.*,^[12] reported improved resectability in the neoadjuvant group, emphasizing that NAT helped convert initially unresectable tumors into resectable ones. Javed *et al.*,^[10] showed a resectability rate of 63.6% after neoadjuvant therapy, indicating a better outcome compared to our findings. McClaine *et al.*,^[13] documented a 46% resectability rate in the neoadjuvant group, which is higher than our study but still suggests a lower probability of immediate resectability compared to upfront surgery. Chaudhari *et al.*,^[15] found that while resection rates were lower in NAT (42.56% vs. 75.47%), R0 resections were significantly more frequent in NAT (74.6% vs. 42.5%), reinforcing the benefit of preoperative treatment.

Regarding postoperative outcomes, our study reported that all resected patients in both groups received postoperative adjuvant therapy and survived for at least one year. Postoperative fistula occurred only in the upfront surgery group (8.3%), with no significant differences ($p=0.999$).

This agrees with Khalil *et al.*,^[9] who found no statistically significant variation in postoperative complications, including pancreatic fistula rates, between groups. Javed *et al.*,^[10] also reported that postoperative complications were similar between resected BRPC patients, regardless of treatment approach. McClaine *et al.*,^[13] noted that 67% of resected patients experienced postoperative complications, though these were mostly minor. Han *et al.*,^[14] found higher rates of T4 disease and arterial involvement in the NAT group, making surgery more complex and potentially increasing complications. Kim *et al.*,^[12] observed a 50% rate of postoperative complications, with postoperative pancreatic fistula being the most frequent complication. Chaudhari *et al.*,^[15] similarly reported no significant difference in overall complications but highlighted that NAT reduced lymph node positivity (60% to 31.7%) and perineural invasion (70% to 41.6%), indicating better disease control.

In concordance with our study, Han *et al.*,^[14] found no significant variation within two-year survival rates between upfront surgery (51.1%) and NAT (36.7%) ($p=0.001$), suggesting that the benefit of NAT may not always translate into improved overall survival. Chaudhari *et al.*,^[15] found that while overall survival between the NAT and upfront surgery groups revealed no significant variation (15 vs. 18 months, $p=0.431$), survival improved significantly in patients who completed the full NAT course (34 vs. 22 months, $p=0.010$).

In contrast, Javed *et al.*,^[10] showed significantly enhanced survival among patients undergoing resection after receiving neoadjuvant chemotherapy, reporting a median overall survival of 28.8 months vs. 14.5 months in non-resected cases ($p<0.001$). Kurahara *et al.*,^[11] similarly found that NAT improved median overall survival (53.7 months) in comparison with upfront surgery (17.8 months). Kim *et al.*,^[12] found that patients who achieved partial response to neoadjuvant therapy had a significantly better two-year survival rate (60.6% vs. 24.3%). McClaine *et al.*,^[13] also found that resected patients exhibited a median survival of 23.3 months, in contrast to 15.5 months for non-resected cases, reinforcing the neoadjuvant therapy benefit.

Strengths of Our Study:

Our study offers multiple notable strengths that enhance its significance in the ongoing discussion on BRPC management. Our study provides a direct comparison between neoadjuvant chemoradiotherapy (NACRT) and upfront surgery in BRPC, offering valuable insights into their respective benefits. By assessing tumor resectability, R0 resection rates, and postoperative outcomes, we highlight the potential role of NACRT in improving surgical success. Additionally, our emphasis on one-year survival rate and adjuvant therapy feasibility contributes to the ongoing debate on the best treatment approach.

A key strength of our study is the use of standardized NCCN criteria for BRPC classification, ensuring that our results align with international research. This allows for better comparability with other studies and enhances the reliability of our findings. Furthermore, our study's focus on surgical margins and nodal clearance provides clinically relevant data that can help refine treatment decision-making.

LIMITATIONS OF OUR STUDY

While our research offers valuable insights, it is not without its constraints, primarily its small sample size (30 patients, 15 per group), which affects the broader applicability of the results. A larger, multicenter study would provide more statistically robust conclusions. Additionally, the retrospective design of our study may lead to inherent biases in data collection and patient selection, reducing the capacity to account for variables that could influence outcomes.

Another limitation is the short follow-up period, which only allowed for an assessment of one-year survival. While this provides useful short-term data, long-term survival and recurrence patterns remain unclear. Moreover, we did not analyze tumor biology or molecular markers, which could help identify patient subgroups who may benefit more from NACRT.

CONCLUSION

Our study demonstrates that both NACRT and upfront surgery have distinct advantages in the management of BRPC. Upfront surgery resulted in a significantly higher resectability rate (80% vs. 33.3%), suggesting that immediate surgical intervention is more effective in achieving tumor removal. However, NACRT led to a superior R0 resection rate (100% vs. 83.3%) and improved pathological nodal clearance (100% vs. 33.3%), indicating its critical importance in optimizing surgical outcomes by reducing residual disease.

Despite concerns about tumor progression during NACRT, our study showed that all resected patients in both groups successfully received postoperative adjuvant therapy and survived for at least one year. This suggests that while NACRT may delay surgical intervention, it does not compromise postoperative treatment continuation in successfully resected cases.

AUTHOR CONTRIBUTIONS

All authors have significantly contributed to this work, whether in conception, study design, execution, data acquisition, analysis and interpretation, or across multiple phases. They took part in writing, editing, or providing critical feedback on the manuscript, approved the final draft for publication, consented to the journal where the work

was submitted, and committed to taking responsibility for every aspect of the research.

CONFIDENTIALITY OF DATA

The authors affirm that they have adhered to their institution's guidelines regarding the publication of patient-related information.

PROTECTION OF HUMAN AND ANIMAL SUBJECTS

The authors state that all procedures conducted align with the ethical standards set by the appropriate clinical research ethics board and comply with the World Medical Association's Code of Ethics (Declaration of Helsinki).

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All authors have declared that no financial assistance was provided by any entity for the research presented in this work.

FINANCIAL RELATIONSHIPS

The authors confirm that they currently have no financial ties, nor have they had any in the past three years, with entities that could potentially have an interest in the work presented.

OTHER RELATIONSHIPS

All authors stated that no additional relationships or activities exist that might be perceived as having influenced the outcomes of this research.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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