# Impact of Neoadjuvant Therapy for Pancreatic Cancer: Transatlantic Trend and Postoperative Outcomes Analysis

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**BACKGROUND:** The introduction of modern chemotherapy a decade ago has led to increased use of neoadjuvant therapy (NAT) in patients with pancreatic ductal adenocarcinoma (PDAC). A recent North American study demonstrated increased use of NAT and improved operative outcomes in patients with PDAC. The aims of this study were to compare the use of NAT and short-term outcomes in patients with PDAC undergoing pancreatoduodenectomy (PD) among registries from the US and Canada, Germany, the Netherlands, and Sweden.

**STUDY DESIGN:** Databases from 2 multicenter (voluntary) and 2 nationwide (mandatory) registries were queried from 2018 to 2020. Patients undergoing PD for PDAC were compared based on the use of upfront surgery vs NAT. Adoption of NAT was measured in each country over time. Thirty-day outcomes, including the composite measure (ideal outcomes), were compared by multivariable analyses. Sensitivity analyses of patients undergoing vascular resection were performed.

**RESULTS:** Overall, 11,402 patients underwent PD for PDAC with 33.7% of patients receiving NAT. The use of NAT increased steadily from 28.3% in 2018 to 38.5% in 2020 ($p < 0.0001$). However, use of NAT varied widely by country: the US (46.8%), the Netherlands (44.9%), Sweden (11.0%), and Germany (7.8%). On multivariable analysis, NAT was significantly ($p < 0.01$) associated with reduced rates of serious morbidity, clinically relevant pancreatic fistulae, reoperations, and increased ideal outcomes. These associations remained on sensitivity analysis of patients undergoing vascular resection.

**CONCLUSIONS:** NAT before PD for pancreatic cancer varied widely among 4 Western audits yet increased by 26% during 3 years. NAT was associated with improved short-term outcomes. (J Am Coll Surg 2024;238:613–621. © 2024 by the American College of Surgeons. Published by Wolters Kluwer Health, Inc. All rights reserved.)

Drs Koerkamp and Pitt contributed equally to this work.

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**Abbreviations and Acronyms**

| | | |
|---|---|---|
| ACS | = | American College of Surgeons |
| CR-POPF | = | clinically relevant-postoperative pancreatic fistula |
| CRT | = | chemoradiotherapy |
| IO | = | ideal outcome |
| LOS | = | length of stay |
| NAC | = | neoadjuvant chemotherapy |
| NACRT | = | combined neoadjuvant chemotherapy and radiation therapy |
| NART | = | neoadjuvant radiation therapy |
| NAT | = | neoadjuvant therapy |
| OPS | = | optimal pancreatic surgery |
| PD | = | pancreatoduodenectomy |
| PDAC | = | pancreatic ductal adenocarcinoma |



The introduction of modern chemotherapy a decade ago has led to increased use of neoadjuvant therapy (NAT) in patients with pancreatic ductal adenocarcinoma (PDAC).[1,2] Increasingly, patients receive NAT, consisting of chemotherapy and radiation therapy, before curative intent resection for PDAC. A recent study from the American College of Surgeons (ACS) NSQIP demonstrated that NAT before pancreatoduodenectomy (PD) increased more than 3-fold during the past decade and was associated with improved optimal operative outcomes.[3] On multivariate analysis, patients receiving NAT had less serious morbidity, fewer organ space infections, and the need for percutaneous drainage or reoperation. As a result, the composite outcomes, optimal pancreas surgery (OPS), increased over time in patients receiving NAT with no change seen in patients undergoing upfront surgery. Clinically relevant postoperative pancreatic fistula (CR-POPF) improved in all patients. Saadat and colleagues[4] also compared treatment modalities and outcomes of pancreatic cancer patients treated in the US vs Canada between 2005 and 2016. They found that the use of neoadjuvant chemotherapy (NAC) was almost 4 times higher in the US as compared with in Canada (12.0% vs 3.2%) but that the groups had similar overall survival.

Several high-quality clinical trials have been initiated in Europe to assess the use of NAT in PDAC. The PREOPANC trial from the Netherlands randomized patients with borderline-resectable pancreatic cancer to combined neoadjuvant chemotherapy and radiation therapy (NACRT) with adjuvant gemcitabine vs upfront surgery, and reported a 5-year overall survival of 20.5% vs 6.5%, respectively.[5] More recently, NAC was compared with NACRT in the PREOPANC-2 trial from the Netherlands.[6] Recently presented results demonstrated no difference between NAC and NACRT arms (total neoadjuvant FOLFIRINOX vs neoadjuvant gemcitabine-based chemoradiotherapy [CRT] with adjuvant gemcitabine). The ongoing PREOPANC-3 clinical trial (NCT04927780) is currently randomizing patients with resectable pancreatic cancer to perioperative vs adjuvant mFOLFIRINOX, with an estimated primary completion date of 2026. In addition, the NorPACT-1 trial comparing short-course neoadjuvant FOLFIRINOX vs upfront surgery for resectable pancreatic head cancer has recently been reported. However, whether the same NAT use trend with improved short-term outcomes demonstrated in North America has evolved in other northern European countries is unclear. This study aimed to compare the use and short-term outcomes of NAT in patients with PDAC undergoing PD without and with NAT among registries from the US or Canada, Germany, the Netherlands, and Sweden.

## METHODS

### Patient population and trends

A retrospective cohort study was performed based on the Global Audits on Pancreatic Surgery Group (GAPASURG) collaboration of 4 pancreatic registries: (1) the multicenter ACS NSQIP in the US and Canada, involving 170 centers in 2020; (2) the multicenter Deutsche Gesellschaft fur Allgemein- und Viszeralchirurgie- Studien-, Dokumentations- und Qualitatszentrum (DGAV StudoQ Pancreas) in Germany, involving 67 centers in 2020; (3) the nationwide Dutch Pancreatic Cancer Audit in the Netherlands, with a 100% coverage compared with the national cancer registry; and (4) the nationwide Swedish National Pancreatic and Periampullary Cancer Registry in Sweden, with a 94% coverage rate since 2014 compared with the national cancer registry. Extensive efforts previously have been undertaken to harmonize patient characteristics among the 4 registries.[7]

Patients undergoing PD between 2018 and 2020 were selected for retrospective cohort analysis; patients undergoing distal pancreatectomy, total pancreatectomy, enucleation, and ampullectomy were excluded. Next, patients with a primary histologic diagnosis of PDAC were selected, and all other histologic processes were excluded. Patients were categorized as undergoing upfront surgery or receiving NAT. Patients receiving NAT were further characterized by receipt of NAC alone, neoadjuvant radiation therapy (NART) alone, or NACRT. The use of NAT was characterized over time during the 3-year period.

### Outcomes

Baseline patient characteristics, surgical parameters, pathological stages, and postoperative outcomes were

derived from the 4 registries. All of these factors among the 4 registries have been harmonized.[7,8] Thirty-day in-hospital serious morbidity, mortality, and multiple other postoperative outcomes were described by NAT status. Serious morbidity was defined as a Clavien–Dindo ≥grade 3 complication.[9] CR-POPF, as updated in 2016 by the International Study Group for Pancreatic Surgery, also was tracked by NAT status.[10] Delayed gastric emptying was defined in accordance with the International Study Group for Pancreatic Surgery.[11] Surgical site infection was a combination of superficial infections, deep incisional infections, and wound disruption. The composite variable, "ideal outcome (IO)," was defined as a dichotomous outcomes measured by the absence of postoperative mortality, serious morbidity, CR-POPF, and reoperations while maintaining an acceptable postoperative length of stay (LOS; <75th percentile) with no readmission.[12]

### Statistical analysis

Patient demographic data were described by NAT status. Statistical analyses for trends over time were performed using Wilcoxon rank sum and Mann–Kendall trend tests. Direct comparisons of continuous variables were compared using 2-sample *t*-tests, and binary variables were compared using chi-square tests. Multivariate analyses for NAT and serious morbidity were performed using logistic regression with covariates that were clinically relevant and statistically significant on univariate analyses. A p value of <0.01 was considered significant because of the large sample size. All statistical analyses were performed using STATA SE, version 14 (College Park, TX).

## RESULTS

### Patient population

Overall, 11,402 patients were included in the study, of whom 3,837 (33.7%) underwent NAT. Included patients by registry were as follows: 8,097 from the US or Canada, 884 from the Netherlands, 2,010 from Germany, and 411 from Sweden. Among all patients, 23.1% received NAC alone, 9.6% received NACRT, and 1.1% received NART. Preoperative patient characteristics, operative details, and pathology are described in Table 1. Patients undergoing

**Table 1.** Patient Characteristics

| Factor | Upfront surgery (n = 7,565) | Neoadjuvant therapy (n = 3,837) | p Value |
|---|---|---|---|
| Mean age, y | 68.6 | 65.5 | <0.001 |
| Male sex, n (%) | 4,016 (53.1) | 1,995 (52.0) | 0.281 |
| Mean BMI, kg/m$^2$ | 26.7 | 27.1 | 0.426 |
| Diabetes, n (%) | 2,138 (28.3) | 1,260 (32.8) | <0.001 |
| American Society of Anesthesiologists classification, n (%) | | | <0.001 |
| 1 | 137 (1.8) | 23 (0.6) | |
| 2 | 2,150 (28.4) | 702 (18.3) | |
| 3 | 4,731 (62.5) | 2,887 (72.5) | |
| 4 | 539 (5.8) | 221 (7.1) | |
| 5 | 2 (0.03) | 1 (0.03) | |
| Biliary stent, n (%) | 4,382 (57.9) | 2,617 (68.2) | <0.001 |
| Soft gland texture, n (%) | 2,293 (41.2) | 718 (23.5) | <0.001 |
| Pancreas duct ≤3 mm, n (%) | 1,881 (33.2) | 786 (25.0) | <0.001 |
| Vascular reconstruction, n (%) | 1,606 (21.2) | 1,324 (34.5) | <0.001 |
| T stage, n (%) | | | <0.001 |
| 0 | 42 (0.6) | 91 (2.4) | |
| 1 | 994 (13.3) | 1,147 (30.5) | |
| 2 | 4,103 (54.2) | 1,915 (51.0) | |
| 3 | 2,162 (28.6) | 546 (14.5) | |
| 4 | 150 (2.0) | 57 (1.5) | |
| N stage, n (%) | | | <0.001 |
| 0 | 2,086 (28.1) | 1,704 (45.1) | |
| 1 | 3,362 (45.4) | 1,528 (40.4) | |
| 2 | 1,927 (26.0) | 528 (14.0) | |
| 3 | 27 (0.4) | 21 (0.4) | |

NAT were more likely to be younger (65.5 vs 68.6 years, p < 0.001), have diabetes (32.8% vs 28.3%, p < 0.001), have an American Society of Anesthesiologists class ≥3 (81.8% vs 69.7%), have biliary stents (68.2% vs 57.9%, p < 0.001), and require vascular reconstruction (34.5% vs 21.2%, p < 0.001). Patients receiving NAT were less likely to have a soft gland (23.5% vs 41.2%, p < 0.001) or a small pancreatic duct (25.0% vs 33.2%, p < 0.001). Finally, patients receiving NAT had lower pathologic T and N stages (p < 0.001).

## Trends

The use of NAT increased significantly during the 3-year study period, from 28.3% in 2018 to 38.5% in 2020 (p < 0.0001, Fig. 1). However, use of NAT varied widely by country with the US (46.8%) and the Netherlands (44.9%) using NAT most frequently in 2020. In comparison, Sweden and Germany used NAT less frequently in 2020 (11.0% and 7.8%, respectively). The use of NAC, with or without NART, increased from 27.1% in 2018 to 37.2% in 2020 (p < 0.0001). The use of NART, with or without the use of NAC, increased from 10.1% in 2018 to 11.2% in 2020 (p < 0.0001). Vascular reconstruction rates, including arterial or venous reconstruction, remained stagnant during the 3-year period at 24.7% (trend p = 0.672).

## Outcomes

On univariable analysis, patients receiving NAT had lower postoperative serious morbidity than patients not receiving NAT (17.7% vs 24.7%, p < 0.001) and lower mortality (1.7% vs 2.7%, p < 0.001; Table 2 and Fig. 2). Specifically, patients receiving NAT were less likely to experience procedure-specific delayed gastric emptying (12.7% vs 14.4%, p < 0.001) and CR-POPF (5.4% vs 9.6%, p < 0.001). Similarly, patients receiving NAT had fewer cases of pneumonia (2.9% vs 4.4%, p < 0.001), organ failure (2.8% vs 4.1%, p < 0.001), reoperation (4.8% vs 7.5%, p < 0.001), and were more likely to have acceptable LOS (85.1% vs 68.6%, p < 0.001). An IO also was more likely (69.0% vs 58.9%, p < 0.001) in patients receiving NAT.

On multivariable analyses, patients receiving NAT had 29% lower odds of serious morbidity (odds ratio [OR] 0.71, p < 0.001), 42% lower odds of CR-POPF (OR 0.58, p < 0.001), 25% lower odds of reoperation (OR, 0.75, p = 0.015), 62% higher odds of acceptable LOS (OR 1.62, p < 0.001), and 47% higher odds of having an IO (OR 1.47, p < 0.001; Table 2). No significant differences were observed between groups in odds of mortality, delayed gastric emptying, surgical site infection, pneumonia, organ failure, or readmission.

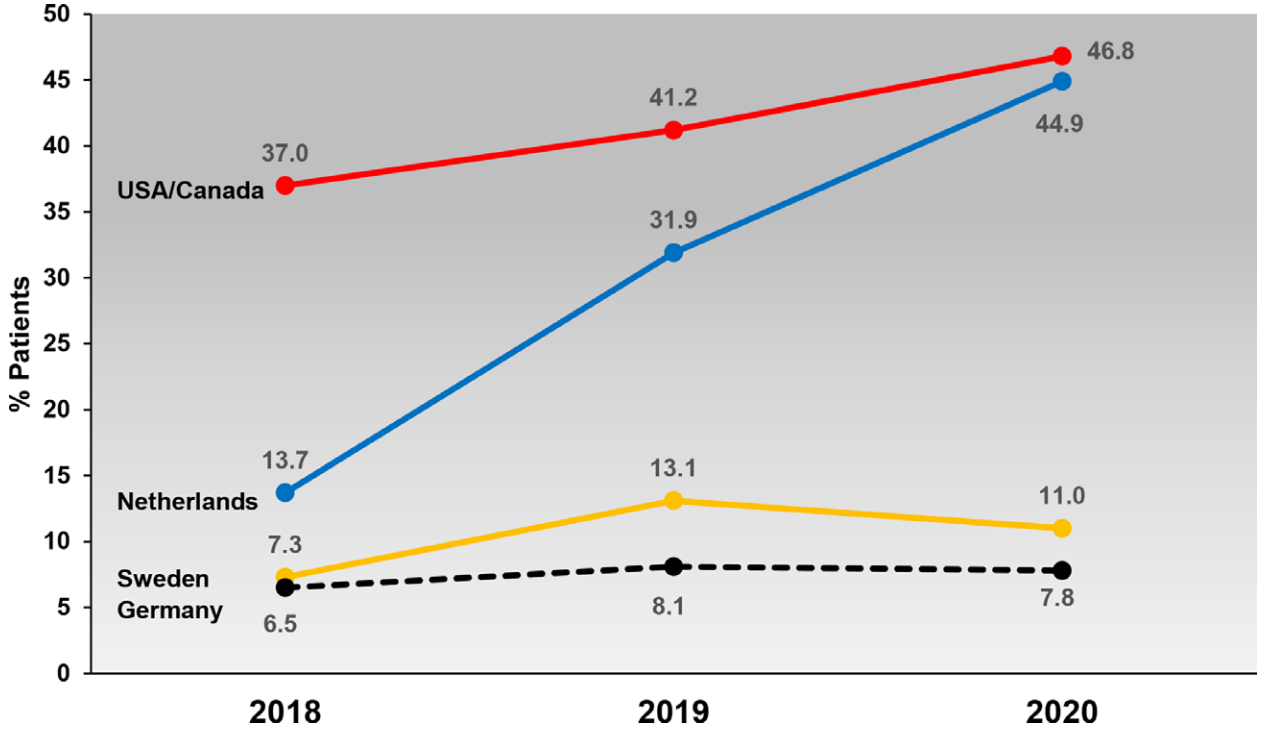


**Figure 1.** Percent of patients receiving neoadjuvant therapy by country (2018 to 2020).

**Table 2.** Univariable Analysis Comparing Upfront Surgery with Neoadjuvant Therapy and Multivariable Analysis

| Outcomes | Upfront surgery (n = 7,565) | Neoadjuvant therapy (n = 3,837) | p Value | Odds ratio* | p Value |
|---|---|---|---|---|---|
| Serious morbidity | 1,867 (24.7) | 678 (17.7) | <0.001 | 0.71 | <0.001 |
| Mortality | 201 (2.7) | 65 (1.7) | <0.001 | 0.94 | 0.775 |
| Delayed gastric emptying | 1,086 (14.4) | 487 (12.7) | 0.001 | 0.87 | 0.069 |
| Clinically relevant postoperative pancreatic fistula | 724 (9.6) | 206 (5.4) | <0.001 | 0.58 | <0.001 |
| Surgical site infection | 689 (9.1) | 338 (8.8) | 0.412 | 0.98 | 0.809 |
| Pneumonia | 332 (4.4) | 110 (2.9) | <0.001 | 0.83 | 0.202 |
| Organ failure | 307 (4.1) | 107 (2.8) | <0.001 | 0.84 | 0.268 |
| Reoperation | 565 (7.5) | 185 (4.8) | <0.001 | 0.75 | 0.015 |
| Length of stay <75th percentile | 5,186 (68.6) | 3,266 (85.1) | <0.001 | 1.62 | <0.001 |
| Readmission | 1,084 (14.3) | 560 (14.6) | 0.829 | 1.13 | 0.048 |
| Ideal outcomes | 4,417 (58.4) | 2,648 (69.0) | <0.001 | 1.47 | <0.001 |

Data presented as n (%).
*Odds ratio reference = upfront surgery.

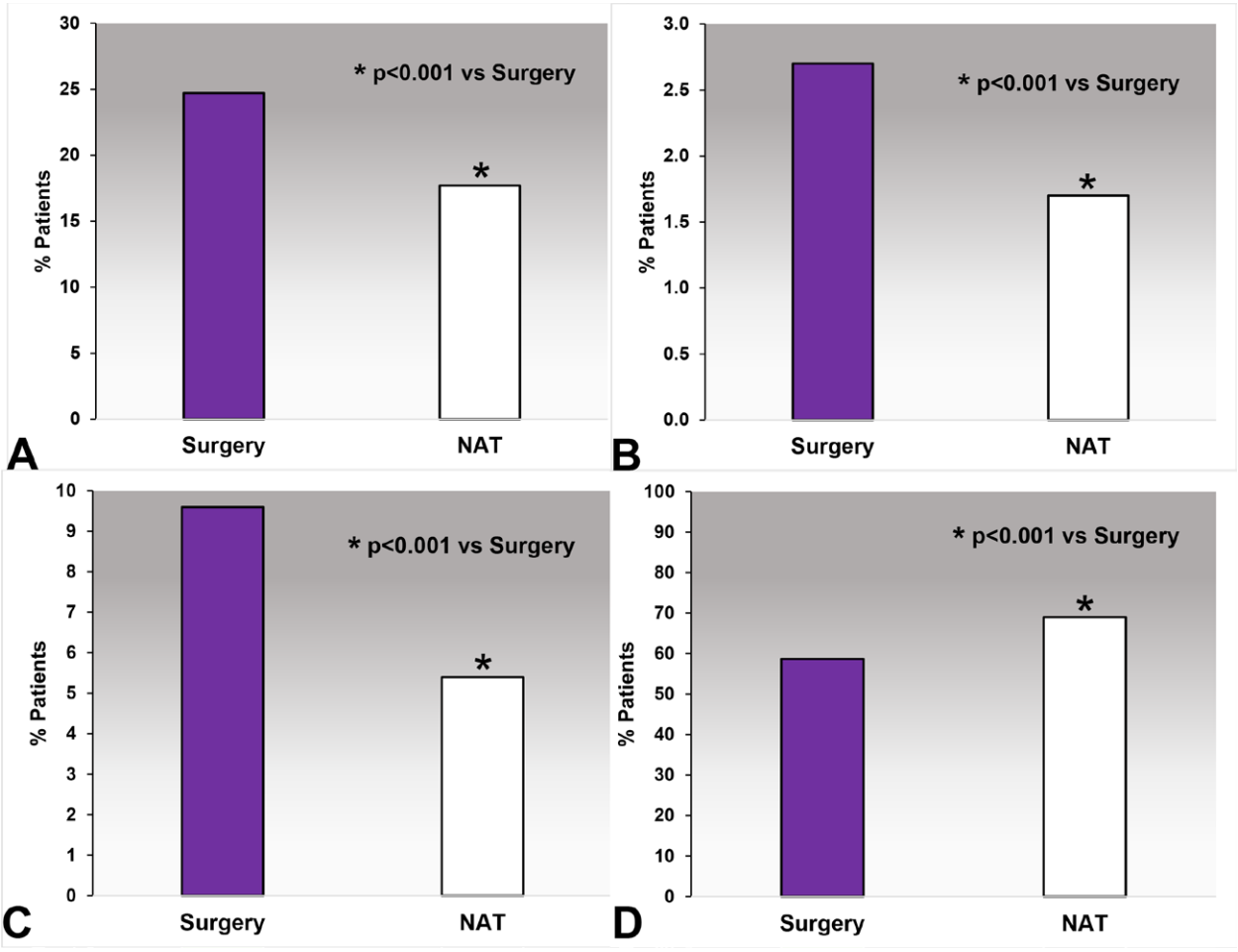


**Figure 2.** (A) Serious morbidity in patients receiving upfront surgery or neoadjuvant therapy (NAT). (B) Mortality in patients receiving upfront surgery or NAT. (C) Clinically relevant-postoperative pancreatic fistula in patients receiving upfront surgery or NAT. (D) Ideal outcomes in patients receiving upfront surgery or NAT.

In a multivariable analysis of factors associated with serious morbidity, NAT was the only protective factor (OR 0.69, p < 0.001; Table 3). In comparison, increased age (OR 1.31, p < 0.001), a soft gland (OR 1.72, p < 0.001), a small duct (OR 1.27, p < 0.001), and vascular resection (OR 1.13, p < 0.001) all were associated with increased serious morbidity. In a sensitivity analysis of patients undergoing vascular resection, patients receiving NAT had significantly lower rates of serious morbidity (20.7% vs 25.8%, p = 0.007) and CR-POPF (4.5% vs 7.5%, p < 0.001), as well as a higher rate of IO (64.9% vs 56.9%, p < 0.001; Table 4). Finally, in a sensitivity analysis of patients treated in Europe, many outcomes trended to favor the use of NAT, but only 1, CR-POPF (4.2% vs 8.5%, p = 0.002), reached statistical significance due to the lower power when excluding the North American data (**Supplemental Digital Content 1**, Table 1, http://links.lww.com/JACS/A353).

## DISCUSSION

This study demonstrates that the use of NAT for patients with pancreatic cancer (PDAC) undergoing PD has increased significantly in a transatlantic analysis from 2018 to 2020. However, use of NAT varied widely by country with the US and the Netherlands using NAT most frequently. On multivariable analysis, NAT was significantly associated with reduced rates of serious morbidity and CR-POPF, as well as increased IO. These short-term outcome associations remained in the sensitivity analysis of patients undergoing vascular resection. On a multivariable analysis with serious morbidity as the outcomes, NAT was the only protective factor.

The use of NAT in PDAC has increased steadily over time in the US. An analysis of the ACS NSQIP Pancreatectomy Demonstration Project, which was performed in 2012, demonstrated that 12.7% of patients with PDAC undergoing pancreatectomy had received NAT.[1] At that time, NAT consisted of chemotherapy

**Table 3.** Multivariable Analysis of Factors Associated with Serious Morbidity

| Factor | Odds ratio | p Value |
|---|---|---|
| Age | 1.31 | <0.001 |
| Diabetes | 0.95 | 0.445 |
| American Society of Anesthesiologists classification (1 ref) | | |
| 2 | 1.13 | 0.689 |
| 3 | 1.54 | 0.167 |
| 4 | 1.96 | 0.046 |
| Biliary stent | 0.96 | 0.468 |
| Neoadjuvant therapy | 0.69 | <0.001 |
| Soft gland | 1.72 | <0.001 |
| Small duct | 1.27 | <0.001 |
| Vascular resection | 1.13 | <0.001 |
| T1 (T0 ref) | 0.86 | 0.547 |
| N1 (N0 ref) | 0.88 | 0.060 |

ref, reference.

**Table 4.** Sensitivity Analysis: Outcomes in Patients Undergoing Vascular Resection

| Outcomes | Upfront surgery (n = 1,606) | Neoadjuvant therapy (n = 1,324) | p Value |
|---|---|---|---|
| Serious morbidity | 412 (25.8) | 274 (20.7) | 0.001 |
| Mortality | 53 (3.3) | 27 (2.0) | 0.037 |
| Delayed gastric emptying | 228 (14.4) | 197 (14.9) | 0.693 |
| Clinically relevant postoperative pancreatic fistula | 119 (7.5) | 59 (4.5) | 0.001 |
| Surgical site infection | 193 (12.3) | 131 (10.0) | 0.044 |
| Pneumonia | 81 (5.1) | 44 (3.3) | 0.019 |
| Reoperation | 128 (8.0) | 91 (6.9) | 0.241 |
| length of stay <75th percentile | 1,083 (67.4) | 1,072 (81.0) | <0.001 |
| Readmission | 235 (14.8) | 209 (15.8) | 0.436 |
| Ideal outcomes | 895 (56.9) | 854 (64.9) | <0.001 |

Data presented as n (%).

alone in 6.3% of patients and radiation with or without chemotherapy in 6.4% of patients. A more recent ACS NSQIP analysis of trends in patients with PDAC treated between 2014 and 2019 found that the use of NAT increased steadily from 24.2% in 2014 to 42.7% in 2019.[3] Combining these 2 reports, more than a 3-fold increase in the use of NAT in patients with PDAC occurred in North America during the past decade. Despite higher rates of NAT usage in the US, this practice is not universal across North America. A study comparing patients with pancreas cancer from the Ontario Cancer Registry to the Surveillance, Epidemiology, and End Results-Medicare databases from 2006 to 2015 found that 12.0% of resected patients in the US received NAC as compared with only 3.2% of patients in Ontario.[4]

A few landmark trials performed in North America have informed practice regarding the feasibility and use of NAT in patients with PDAC. First, the Alliance A021101 trial demonstrated the feasibility of NACRT.[13] Twenty-two patients with borderline-resectable PDAC were treated in a single-arm fashion with 4 cycles of mFOLFIRINOX after 5.5 weeks of chemoradiation. Sixty-eight percent of patients underwent pancreatectomy, 93% of whom had an R0 resection. Next, a phase 2 clinical trial from Massachusetts General Hospital studied 43 patients with borderline-resectable PDAC undergoing 8 cycles of neoadjuvant FOLFIRINOX and CRT.[14] Seventy-nine percent of patients were able to complete the NAC, and 91% of patients had NART. R0 resection was achieved in 65% of patients and 2-year overall survival was 56%. The SWOG S1505 trial randomized 147 patients with resectable PDAC to mFOLFIRINOX vs gemcitabine and nab-paclitaxel.[15] Seventy-six percent of patients completed preoperative therapy and underwent pancreatectomy, 85% of whom had an R0 resection. Finally, the Alliance A021806 randomized controlled trial (NCT04340141) is currently ongoing to address the role of NAT in patients with resectable PDAC. In another retrospective analysis of 415 locally advanced patients treated at a single institution from 2013 to 2017, FOLFIRINOX-based chemotherapy and stereotactic body radiation therapy were associated with increased probability of resection and improved survival.[16]

European institutions have likewise been engaged in multiple high-quality clinical trials aiming to assess the benefit of NAT in PDAC. First, the Dutch PREOPANC trial (2013 to 2017) randomized patients to preoperative gemcitabine and NART vs upfront surgery with adjuvant gemcitabine.[5] This trial reported a significant improvement in median overall survival for borderline-resectable patients (17.6 vs 13.2 months, p = 0.029) and a 5-year overall survival of 20.5% vs 6.5%, respectively.[5] The ESPAC-5F study from the UK and Germany was a 4-armed randomized controlled trial in patients with borderline-resectable PDAC studying upfront surgery vs preoperative GEMCAP vs preoperative FOLFIRINOX vs NACRT.[17] In a combined analysis of the neoadjuvant groups vs the upfront surgery group, 1-year overall survival was 77% in the NAT group compared with 40% in the upfront surgery group. Next, the PREOPANC-2 trial from the Netherlands recently reported no overall survival difference between total neoadjuvant FOLFIRINOX vs neoadjuvant gemcitabine-based CRT with adjuvant gemcitabine in borderline-resectable patients.[6]

The NorPACT-1 trial from Norway recently has been reported, and the NEONAX phase II trial from Germany is currently underway.[18] Two additional major European trials on resectable patients are awaiting completion, including the French PANACHE-01-PRODIGE-48 study, which has randomized patients to 2-drug neoadjuvant FOLFOX vs 3-drug neoadjuvant FOLFIRINOX, and the Dutch PREOPANC-3 trial (NCT04927780), which is still enrolling patients to perioperative vs adjuvant mFOLFIRINOX.[19] Finally, the French PANDAS-PRODIGE-44 study is currently randomizing patients to preoperative mFOLFIRINOX vs preoperative mFOLFIRINOX and NACRT (NCT02676349). Despite these multiple trials evaluating NAT vs upfront surgery for borderline-resectable PDAC, convincing long-term survival data supporting NAT has yet to be published.

NAT refers to a wide spectrum of treatments using chemotherapy, radiotherapy, or CRT. However, a wide variety of systemic therapy and radiation therapy regimens exist. Chemotherapeutic regimens may be single or multiagent and may be 5-FU- or gemcitabine-based. An additional layer of the debate over NAT for PD is the use of radiotherapy. In theory, radiation assists in local control of the tumor. In a retrospective review from 2020 of 341 patients with localized PDAC who received NAT, patients who received NAC alone had poorer histopathologic response as compared with patients who received NART.[20] Importantly, pathologic response, which may in part be driven by chemoradiation, was associated with improved overall survival. A second retrospective cohort study of 531 patients from the Trans-Atlantic Pancreatic Surgery Consortium compared borderline-resectable patients who received NAC vs NACRT in a matched 1:1 manner. NACRT was associated with more node-negative disease and better pathologic response in patients who underwent resection, yet no difference in overall survival was found.[21] Total NAT, which has become popular in other disease processes, particularly in rectal cancer also has been explored in pancreatic cancer.[22] A retrospective study by

Kim and colleagues[23] compared 541 patients with resectable and borderline-resectable PDAC receiving total NAT to traditional NAT. Patients undergoing total NAT were more likely to receive all intended nonsurgical therapy as compared with the traditional NAT group (67% vs 45%, $p < 0.01$).

The current transatlantic study demonstrates that NAT was associated with more favorable postoperative outcomes, including reduced rates of serious morbidity, and clinically relevant pancreatic fistulae, as well as improved IO. Similar findings have been found in the North American literature: an analysis of 13,257 patients undergoing PD for PDAC between 2014 and 2019 showed in a multivariable analysis that NAT was associated with reduced serious morbidity (OR 0.83, $p < 0.001$), clinically relevant pancreatic fistulae (OR 0.52, $p < 0.001$), organ space infections (OR 0.74, $p < 0.001$), percutaneous drainage (OR 0.73, $p < 0.001$), reoperation (OR 0.76, $p = 0.005$), and prolonged LOS (OR 0.63, $p < 0.001$).[3] Likewise, another study of the ACS NSQIP database from 2014 to 2017 demonstrated an advantage to NAC for perioperative morbidity (40.4% vs 49.5%, $p < 0.001$) as well as lower rates of CR-POPF (9.0% vs 14.5%, $p < 0.001$).[2] Finally, a recent systematic review and meta-analysis of patients with PDAC likewise demonstrated significantly lower rates of CR-POPF in patients receiving NAT before PD (OR 0.55, $p < 0.001$).[24]

The ultimate goal while caring for patients with PDAC is to achieve superior overall care, including adequate tumor resection, avoidance of postoperative complications, and discharging the patient home in a timely manner so they may recover and return to intended oncologic therapy. To measure this goal, composite outcomes are particularly helpful. In this study, the composite outcome, "IO," was used to incorporate the variables available across Global Audits on Pancreatic Surgery Group collaborative registries.[12] This study demonstrated in a transatlantic analysis that 69.0% of patients who received NAT achieved IO, as compared with 58.4% of patients who received upfront surgery. OPS is a second composite outcome that has been measured in the North American literature.[2,3] An increase in OPS was demonstrated by Beane and colleagues[2] for patients with any histologic diagnosis undergoing either PD (+3%) or distal pancreatectomy (+5%) from 2014 to 2017. In a more recent study on PD alone, surgeons achieved OPS increasingly over time from 2014 to 2019 (50.7% to 56.6%, $p < 0.001$).[3] "Textbook oncologic outcome" is a third composite measure that additionally incorporates margin status, receipt of systemic therapy, as well as long-term oncologic survival.[25] In a study of National Cancer Database patients undergoing PD for PDAC from 2006 to 2016, only 16.8% of patients achieved textbook oncologic outcomes.[25]

The results of this study should be interpreted within the context of several limitations. First, the lack of intention-to-treat data eliminates patients started on NAT who never come to surgery, which results in a patient selection bias. Second, the study is limited to PD, and therefore, the findings are not generalizable to all pancreas procedures. Third, no specific information on the type of chemotherapy, number of doses, or radiation regimens was available nor was it possible to determine if patients received adjuvant therapy postoperatively. Fourth, whether patients were initially resectable, borderline resectable, or potentially unresectable before NAT is not known across the 4 registries. Fifth, due to the nature of these databases that focus on postoperative outcomes within 30 days, long-term and oncologic outcomes are unknown. As such, reporting composite outcomes that include long-term survival, including textbook oncologic outcomes, is not possible using these 4 registries. Additional limitations relate to the collaborative nature of this study. Sixth, 2 of the participating registries (NSQIP and StuDoQ) are voluntary and not nationwide, and a risk exists that the participating centers might have different patient selection, volume, and results compared with those not represented. Seventh, the inconsistency of some variables and missing data among registries may make comparisons difficult. Among the more important variations to mention are tumor characteristics including the TNM stage, where the registries collect data using different scoring systems. Nevertheless, the Global Audits on Pancreatic Surgery Group collaboration provides a unique opportunity to evaluate and compare current practices and outcomes of pancreatic surgery in different countries in a large number of patients with detailed data regarding the pre-, intra-, and postoperative courses.

## CONCLUSIONS

This transatlantic analysis of NAT before PD for pancreatic cancer demonstrates an increase of 26% during 3 years. NAT was associated with improved perioperative outcomes, confirming previous findings from North American patients and a Dutch randomized trial.

### Author Contributions

Conceptualization: Davis, Augustinus, de Graaf, Wellner, Johansen, Andersson, Beane, Björnsson, Busch, Gleeson, van Santvoort, Tingstedt, Williamsson, Keck, Besselink, Koerkamp, Pitt

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