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ORIGINAL ARTICLE

# Is early-stage pancreatic adenocarcinoma truly early: stage migration on final pathology with surgery-first versus neoadjuvant therapy sequencing

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## Abstract

**Background:** Neoadjuvant therapy (NT) remains controversial in early-stage pancreatic ductal adenocarcinoma (PDAC), defined as clinical (c)Stage I-II. Our aim was to analyze rates of pathologic upstaging/downstaging for resectable PDAC treated with surgery-first (SF) vs. NT.

**Methods:** Utilizing the National Cancer Data Base (NCDB), patients with cStage I-II PDAC who underwent pancreatoduodenectomy in 2006–2013 were pathologically staged using the AJCC 8th edition and compared by treatment sequencing.

**Results:** Among 13,871 patients, 15.3% received NT. Despite higher pre-treatment T-stage (cT2: 71.9% vs. 56.3%, $p < 0.001$), NT patients had lower rates of pathologic nodal metastases (46.2% vs. 69.2% in SF, $p < 0.001$), suggesting higher rates of pathologic downstaging. In cStage II, 33.0% were upstaged to stage III after SF, vs. only 14.0% after NT. In cStage I, 65.5% were upstaged following SF, vs. 46.7% after NT (all $p < 0.001$). Patients with NT (HR-0.77, $p < 0.001$) or downstaging (HR-0.80, $p < 0.001$) had improved overall survival (OS).

**Conclusion:** NT is associated with reduction in unexpected upstaging, reduction in nodal positivity, and improved OS, compared to SF approach in putatively early-stage PDAC. Because clinical staging underestimates the underlying disease burden in resectable PDAC, patients with cStage I-II should be considered for NT.

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## Introduction

In 2018, over 55,000 people will be diagnosed with pancreatic adenocarcinoma in the United States, most of whom die of the disease, making pancreatic cancer the third leading cause of cancer death.[1] While surgical resection offers the best chance for cure in pancreatic cancer, less than 20% of the patients present with potentially resectable disease, while patients who present with distant metastasis or with locally advanced disease involving critical visceral vasculature are much more common. Even in the minority of the patients who undergo surgery for potentially resectable disease, early systemic or local disease recurrences are common, which result in a median overall survival (OS) of less than 2 years.[2,3]

Due to poor survival outcome with surgery alone, multimodality treatment approaches have been established as the standard in pancreatic cancer, or pancreatic adenocarcinoma (PDAC). Prospective randomized trials such as CONKO 001 and ESPAC 1–4 have shown that adjuvant chemotherapy can improve OS after resection.[4–7] The benefit of adjuvant chemoradiotherapy is more controversial with conflicting trial results, ranging from significant improvement[8] to worse outcomes.[5] Based on these results, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the

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European Society for Medical Oncology (ESMO) all recommend the use of adjuvant chemotherapy, and in some instances chemoradiotherapy, for patients with resected PDAC.[9–11]

Despite the incremental improvement in OS with multimodality therapy, long-term survival remains rare in PDAC, and better therapeutic strategies are needed. More recently, preoperative, or neoadjuvant, therapy has been gaining traction, particularly in patients with locally advanced or borderline resectable disease. In this setting, neoadjuvant therapy has been accepted as a treatment option to convert patients into resection candidates and/or to increase the likelihood of margin-negative resection. However, in the "early-stage," potentially resectable setting, neoadjuvant therapy has not been widely adopted, despite studies demonstrating potential benefits.[12,13]

The aim of this national cohort study was to analyze the U.S. utilization rates of neoadjuvant therapy in Stage I-II PDAC and to analyze rates and impact of pathologic stage migration for Stage I-II PDAC treated with surgery-first versus neoadjuvant approaches. The hypothesis was that the rate of neoadjuvant therapy use would be low in early-stage PDAC, but neoadjuvant therapy positively affects oncologic outcomes by reducing rates of final pathologic upstaging.

## Patients and methods

### Data source

We performed a retrospective cohort study using the National Cancer Data Base (NCDB), which is a nationwide oncology outcomes database jointly sponsored by American College of Surgeons Commission on Cancer and the American Cancer Society.[14] As of 2016, NCDB is the largest clinical oncology database in the world with more than 34 million patient records, and captures more than 70% of all cancer cases in the United States. The available variables in the NCDB have been nicely summarized by Boffa *et al.*.[15] The specific pancreatic cancer NCDB Participant User File (PUF) 2014 was obtained by the principal investigator after a formal application process. This study was granted an exemption by The University of Texas MD Anderson Cancer Center institutional review board since it utilized a publicly available de-identified patient dataset.

### Study cohort

We identified a total of 239,390 patients with PDAC in the NCDB between 2004 and 2014, using histology codes 8140, 8480, 8481 and 8500. We selected for the minority of the patients who were eligible to undergo pancreatoduodenectomy between 2006 and 2013, using surgery codes 35, 36, 37 and 70. This particular study period was selected since treatment sequencing data was only recorded from 2006. We excluded patients diagnosed in 2014 due to limited follow-up. We then selected for patients with clinical stages I and II. The patients in our database had been staged according to AJCC 6 and AJCC 7 definitions.[16,17] Of note, there is no difference in definition of TNM and stage groupings between AJCC 6 and AJCC 7. However, AJCC 8 has significant updates for pancreatic adenocarcinoma with new definitions for both T and N classifications.[18]

First, T-staging in AJCC 8 has been revised from descriptive to size-based classification with the elimination of extra-pancreatic extension as a staging criteria. T3 stage, which previously defined tumors with extra-pancreatic extension, is now defined as tumors greater than 4 cm, based on published studies demonstrating size as an important prognosticator.[19] We re-classified our patient cohort according to AJCC 8, utilizing the PUF data item "TUMOR_SIZE."[20] Second, N-staging has been revised to a number-based system depending on the extent of involved lymph nodes (LNs), with N1 being defined as 1–3 positive regional LNs and the new N2 category being defined as 4 or more positive LNs. We therefore re-classified our cohort according to AJCC 8, utilizing the available lymphadenectomy variables in NCDB. We utilized the PUF data items "REGIONAL-NODES_EXAMINED" and "REGIONAL_NODES_POSITIVE" to define N-stage for our cohort according to AJCC 8. Codes 01-89 defined the number of lymph nodes that were examined or positive. During the re-classification, patients with missing tumor or LN variables were identified and classified as unknown staging and were excluded from further analysis. Patients with unclear treatment sequencing information were also excluded. In all, 13,871 patients were included in our overall cohort (Fig. 1). The overall cohort was divided into surgery-first and neoadjuvant therapy groups. Patients who received any form of preoperative chemotherapy and/or radiotherapy were included in the neoadjuvant group. Adjuvant therapy data were utilized during the survival analysis.

### Statistical analysis

Patient characteristics were reported as count data and percentages, and differences between the groups were compared using the $\chi^2$ test. A $p$-value of $<0.05$ was defined as statistically significant, and all tests were two-sided. OS was estimated using the Kaplan–Meier method. OS among subgroups treated with various treatment sequencing approaches were compared using univariate Cox regression. All analyses were performed using SAS version 9.4 (Cary, NC).

## Results

### Neoadjuvant therapy trends in Stage I-II PDAC

A total of 13,871 patients with clinical Stage I or II PDAC had undergone pancreatoduodenectomy during the study period. Of those, 11,750 (84.7%) patients underwent surgery-first sequencing, and only 2,121 (15.3%) patients received neoadjuvant therapy before resection (Fig. 1). While the proportion of patients receiving neoadjuvant therapy remained low, neoadjuvant therapy usage in Stage I-II PDAC increased throughout the study period, from 11% in 2006 to 21% in 2013 (Fig. 2).

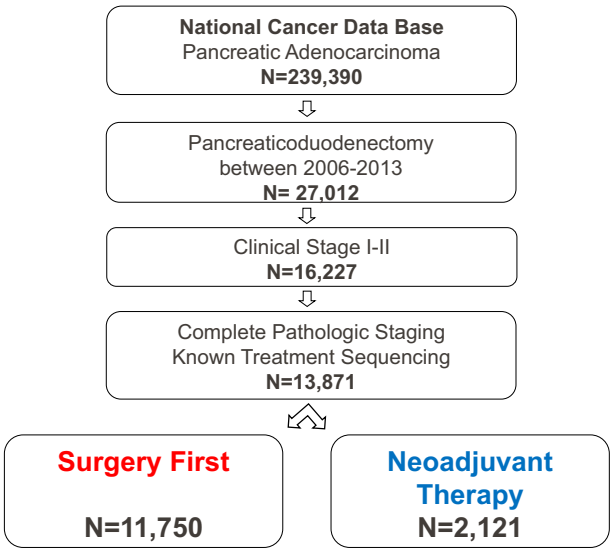



**Figure 1** Patient selection

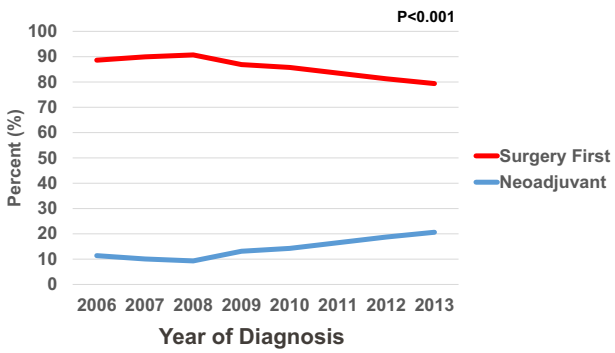



**Figure 2** Trend of neoadjuvant therapy use in early stage pancreatic adenocarcinoma

## Patient characteristics stratified by treatment sequencing

The mean age of our overall cohort was 66, and 51.2% of the patients were male. We compared the preoperative factors between the patients who underwent surgery-first approach to patients undergoing neoadjuvant therapy. Patients who received neoadjuvant therapy were more likely to be younger ($p < 0.001$), have received treatment at higher volume hospitals and academic centers ($p < 0.001$), and have clinical stage II disease ($p < 0.001$) (Table 1). As expected, the neoadjuvant therapy group had higher pre-treatment clinical T stages compared to surgery first group (Fig. 3a), but with similar clinical N stage (Fig. 3b). There was no difference in sex of the patients ($p = 0.742$) or Charlson-Deyo comorbidity score ($p = 0.574$) between surgery-first and neoadjuvant patients.

On pathologic assessment, the neoadjuvant group had higher rates of margin-negative resection (R0) (88.7% vs. 83.2%, $p < 0.001$), and higher rates of node-negative disease (N0, 53.8% vs. 30.9%, $p < 0.001$) compared to surgery-first. When the overall pathologic stages were compared, the neoadjuvant group was more likely to have lower final pathologic stages compared to the surgery-first group (IA: 9.5% vs. 8.3%, IB: 34.1% vs. 17%, IIA: 7.9% vs. 4.8%, IIB: 33.5% vs. 40.1%, III: 12.2% vs. 27.5%, $p < 0.0001$) (Table 1).

## Rates of pathologic downstaging after neoadjuvant therapy

Despite the fact that neoadjuvant patients had more advanced pre-treatment clinical staging, they had lower rates of lymph node metastasis and less advanced disease on final pathologic staging compared to surgery-first patients. Therefore, we examined impact of therapy sequencing on the rates of unexpected stage migration from initial clinical staging to final pathologic staging. The overall rate of down-staging on final pathology was significantly higher in the neoadjuvant group compared to the surgery-first group (40.1% vs. 18.3%, $p < 0.001$) (Fig. 4). When clinical Stage I patients underwent surgery upfront, 65.5% were up-staged as Stage IIA or higher on final pathology. In comparison, after neoadjuvant therapy, the up-staging rate was 46.7%. For clinical Stage II patients, 33.0% were up-staged as Stage III or higher after surgery-first approach compared to only 14.0% after neoadjuvant therapy.

## Overall survival with pathologic downstaging

The pathologic down-staging was associated with improved OS (HR 0.80, 95% CI 0.75–0.86) (Fig. 5a). In addition, the median OS was 26.5 months in the neoadjuvant group, which was better than both the surgery-only group at 14.2 months and the surgery plus adjuvant therapy group at 23.4 months (Fig. 5b). Using univariate Cox regression, patients with neoadjuvant therapy (HR 0.77, 95% CI 0.73–0.82) had improved overall survival (OS). While the difference in OS between neoadjuvant therapy plus surgery vs. surgery-first plus adjuvant therapy cohorts seemed small, the effect size was statistically significant (HR 1.13, 95% CI 1.07–1.20, reference group: neoadjuvant therapy). Importantly, 34.4% (4,041 of 11,750) patients in the surgery-first group did not receive a single dose of adjuvant therapy, and thus this "surgery-first plus adjuvant group" is only two-thirds of the surgery-first group.

## Overall survival by treatment sequencing groups

Of the 2,121 neoadjuvant sequencing patients, only 53 patients (2.5%) received preoperative radiation therapy alone, which makes any analysis on this subgroup difficult. Neoadjuvant chemotherapy alone was given to 843 patients (39.7%), and 1225 patients (57.8%) received both neoadjuvant chemotherapy and radiation therapy. When compared to patients with surgery alone (as the reference group), neoadjuvant chemotherapy alone and neoadjuvant chemotherapy plus radiation cohorts had HR 0.52 (95% CI 0.47–0.59) and HR 0.59 (95% CI 0.54–0.64), respectively. The neoadjuvant

**Table 1** Patient demographics of the overall cohort, grouped by surgery first and neoadjuvant treatment groups

| | All | | Treatment Groups | | | | p-value |
|---|---|---|---|---|---|---|---|
| | | | Surgery First | | Neoadjuvant | | |
| | N | % | N | % | N | % | |
| **Age** (mean, standard deviation) | 66 (10.4) | | 67 (10.4) | | 64 (9.8) | | <0.001 |
| **Sex** | | | | | | | 0.742 |
| Female | 6769 | 48.8 | 5741 | 48.86 | 1028 | 48.47 | |
| Male | 7102 | 51.2 | 6009 | 51.14 | 1093 | 51.53 | |
| **Race** | | | | | | | 0.004 |
| White | 11,572 | 83.43 | 9773 | 83.17 | 1799 | 84.82 | |
| Black | 1171 | 8.44 | 978 | 8.32 | 193 | 9.1 | |
| Hispanic | 599 | 4.32 | 531 | 4.52 | 68 | 3.21 | |
| Asian | 35 | 0.25 | 28 | 0.24 | 7 | 0.33 | |
| Other | 342 | 2.47 | 303 | 2.58 | 39 | 1.84 | |
| Unknown | 152 | 1.1 | 137 | 1.17 | 15 | 0.71 | |
| **Charlson-Deyo Score** | | | | | | | 0.574 |
| 0 | 9246 | 66.66 | 7816 | 66.52 | 1430 | 67.42 | |
| 1 | 3712 | 26.76 | 3164 | 26.93 | 548 | 25.84 | |
| 2 | 913 | 6.58 | 770 | 6.55 | 143 | 6.74 | |
| **Clinical Stage** | | | | | | | <0.001 |
| Stage I | 5735 | 41.35 | 5139 | 43.74 | 596 | 28.1 | |
| Stage II | 8136 | 58.65 | 6611 | 56.26 | 1525 | 71.9 | |
| **Grade** | | | | | | | <0.001 |
| Well differentiated | 1190 | 8.58 | 1028 | 8.75 | 162 | 7.64 | |
| Moderately differentiated | 6645 | 47.91 | 5831 | 49.63 | 814 | 38.38 | |
| Poorly differentiated | 4672 | 33.68 | 4185 | 35.62 | 487 | 22.96 | |
| Undifferentiated | 128 | 0.92 | 111 | 0.94 | 17 | 0.8 | |
| Not determined | 1236 | 8.91 | 595 | 5.06 | 641 | 30.22 | |
| **Positive Margin** | | | | | | | <0.001 |
| R0 | 11,664 | 84.09 | 9782 | 83.25 | 1882 | 88.73 | |
| R1 | 2207 | 15.91 | 1968 | 16.75 | 239 | 11.27 | |
| **T Stage** | | | | | | | <0.001 |
| T1 | 2418 | 17.43 | 2105 | 17.91 | 313 | 14.76 | |
| T2 | 8512 | 61.37 | 7171 | 61.03 | 1341 | 63.22 | |
| T3 | 2732 | 19.7 | 2343 | 19.94 | 389 | 18.34 | |
| Unknown | 209 | 1.51 | 131 | 1.11 | 78 | 3.68 | |
| **N Stage** | | | | | | | <0.001 |
| N0 | 4769 | 34.38 | 3627 | 30.87 | 1142 | 53.84 | |
| N1 | 5566 | 40.13 | 4850 | 41.28 | 716 | 33.76 | |
| N2 | 3536 | 25.49 | 3273 | 27.86 | 263 | 12.4 | |
| **AJCC 8th Stage** | | | | | | | <0.001 |
| IA | 1181 | 8.51 | 979 | 8.33 | 202 | 9.52 | |
| IB | 2723 | 19.63 | 2000 | 17.02 | 723 | 34.09 | |
| IIA | 737 | 5.31 | 569 | 4.84 | 168 | 7.92 | |
| IIB | 5501 | 39.66 | 4791 | 40.77 | 710 | 33.47 | |
| III | 3489 | 25.15 | 3230 | 27.49 | 259 | 12.21 | |
| IV | 149 | 1.07 | 134 | 1.14 | 15 | 0.71 | |
| Unknown | 91 | 0.66 | 47 | 0.4 | 44 | 2.07 | |

Table 1 (*continued*)

| | All | | Treatment Groups | | | | p-value |
|---|---|---|---|---|---|---|---|
| | | | Surgery First | | Neoadjuvant | | |
| | N | % | N | % | N | % | |
| **Hospital Volume** | | | | | | | <0.001 |
| <= 5 patients/year | 5942 | 43.12 | 5238 | 44.76 | 704 | 33.9 | |
| 6–20 patients/year | 5783 | 41.97 | 4756 | 40.64 | 1027 | 49.45 | |
| 21–40 patients/year | 1608 | 11.67 | 1338 | 11.43 | 270 | 13 | |
| >40 patients/year | 447 | 3.24 | 371 | 3.17 | 76 | 3.66 | |
| **Facility Type** | | | | | | | <0.001 |
| Community Cancer Program | 428 | 3.11 | 389 | 3.32 | 39 | 1.88 | |
| Comprehensive Community Cancer Program | 3632 | 26.36 | 3224 | 27.55 | 408 | 19.64 | |
| Academic/Research Program | 8094 | 58.74 | 6668 | 56.98 | 1426 | 68.66 | |
| Integrated network cancer program | 1511 | 10.97 | 1331 | 11.37 | 180 | 8.67 | |
| Unknown | 115 | 0.83 | 91 | 0.78 | 24 | 1.16 | |
| **Treatment Sequence** | | | | | | | <0.001 |
| Neoadjuvant radiotherapy | 14 | 0.1 | | | 14 | 0.66 | |
| Neoadjuvant chemotherapy | 622 | 4.48 | | | 622 | 29.33 | |
| Neoadjuvant radiotherapy + chemotherapy | 1225 | 8.83 | | | 1225 | 57.76 | |
| Neoadjuvant radiotherapy + adjuvant chemotherapy | 39 | 0.28 | | | 39 | 1.84 | |
| Neoadjuvant chemotherapy + adjuvant radiotherapy | 221 | 1.59 | | | 221 | 10.42 | |
| Adjuvant radiotherapy | 97 | 0.7 | 97 | 0.83 | | | |
| Adjuvant chemotherapy | 3871 | 27.91 | 3871 | 32.94 | | | |
| Adjuvant radiotherapy + chemotherapy | 3741 | 26.97 | 3741 | 31.84 | | | |
| Surgery Only | 4041 | 29.13 | 4041 | 34.39 | | | |

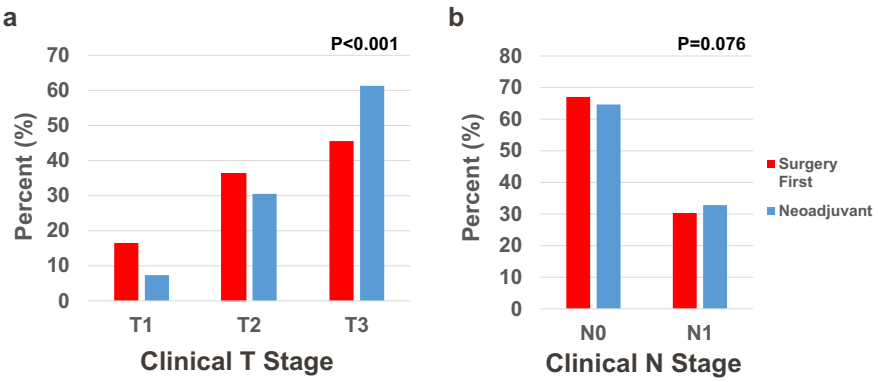
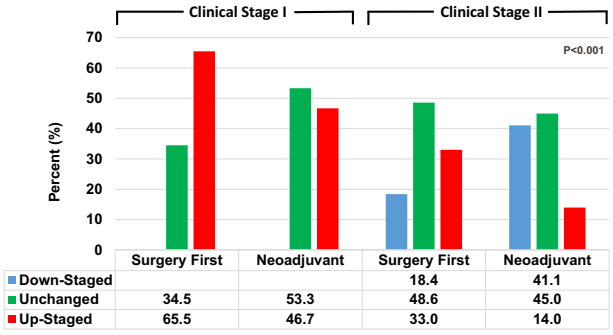



Figure 3 Frequency of neoadjuvant therapy utilization stratified by a) clinical T-Stages and b) Clinical N-Stages

radiation-only patients had HR 1.32 (95% CI 0.73–2.39) – no difference vs. surgery alone. Compared to surgery alone, the neoadjuvant chemotherapy plus postoperative radiation cohort had HR 0.54 (95% CI 0.46–0.65), similar to the HR 0.52 and HR 0.59 above for the totally neoadjuvant groups above. The neoadjuvant radiation alone plus postoperative chemotherapy group had HR 0.75 (95% CI 0.53–1.07) – a wide confidence interval due to low numbers in this unusual treatment combination.

## Discussion

In this study, we analyzed patients with clinical stage I-II PDAC and compared the final pathologic staging between patients who underwent neoadjuvant therapy before resection and patients who had surgery first. The NCDB documented a national, real-world, trend in the use of neoadjuvant therapy in "early-stage" PDAC. While the overall proportion of patients receiving neoadjuvant therapy remains low, its usage in clinical stage I-II



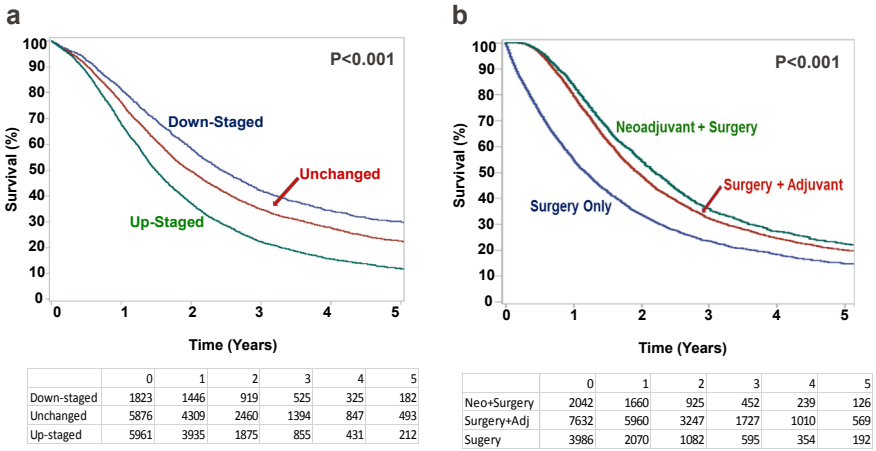

| | Surgery First | Neoadjuvant | Surgery First | Neoadjuvant |
|---|---|---|---|---|
| Down-Staged | | | 18.4 | 41.1 |
| Unchanged | 34.5 | 53.3 | 48.6 | 45.0 |
| Up-Staged | 65.5 | 46.7 | 33.0 | 14.0 |

**Figure 4** Rates of pathologic stage migration stratified by treatment sequencing

PDAC increased to 21% between 2006 and 2013. Even though the neoadjuvant patients started off with more advanced disease, including higher clinical T-stage and higher overall clinical stage, the neoadjuvant group had higher rates of negative LN disease on final pathologic assessment. Clinical stage II patients who received neoadjuvant therapy had higher rates of pathologic down-staging. Pathologic down-staging and neoadjuvant therapy were associated with improved OS. Finally, for both clinical stage I and II groups, neoadjuvant therapy resulted in decreased rates of unexpected upward stage migration compared to the surgery-first group.

Overall, the rates of pathologic upstaging were extremely high in our entire cohort, with 65% of clinical stage I patients getting up-staged on final pathology following surgery first. Certainly, the aggressive biology of PDAC and its propensity for infiltrative locoregional disease account for much of the upward stage migration rates. However, it also highlights the frequent preoperative clinical under-staging of PDAC patients. While quality contrast-enhanced computed tomography (CT) scan is a critical component of preoperative staging and provides relatively accurate information regarding presence of distant metastasis and local resectability, the ability of CT imaging to assess lymph node involvement is poor.[21] Using an additional imaging modality such as endoscopic ultrasound (EUS) does not improve preoperative nodal staging.[22] On the other hand, accurate assessment of nodal stage has been emphasized in the latest AJCC 8th edition staging system, with the introduction of N2 stage, representing 4 or more positive nodes. Therefore, due to difficulty in assessing nodal status pre-operatively, it is now possible for a clinical stage I patient with a small tumor <2 cm on imaging to be up-staged to Stage III on final pathology if there are ≥4 positive nodes (N2). Underscoring the importance of pathologic up-staging, it is notable that N2 patients share the same Stage III prognosis with T4 patients who have locally advanced, unresectable disease. While this might trigger calls for better preoperative imaging modalities, the reality is that it might be easier to just assume that most Stage I-II PDAC patients are node-positive at diagnosis and treat them accordingly.

Neoadjuvant therapy has many theoretical and tangible advantages compared to a surgery-first approach. First, PDAC is widely believed to be a systemic disease at diagnosis with undetectable micrometastasis, leading to poor survival outcomes despite "successful" R0 resection. Therefore, it makes sense to start systemic therapy with minimal delay. Under the surgery-first approach, by the time patients undergo surgery and recover, often 2 months have passed before systemic therapy is initiated (if it is even initiated at all). Second, neoadjuvant therapy decreases locoregional tumor burden and facilities likelihood of R0 resection. Third, improved pathologic outcome likely translates to better OS. In a propensity-matched analysis of NCDB, Mokdad *et al.* showed a modest survival advantage in neoadjuvant patients.[23] Finally, the ultimate goal of pancreatic cancer care should be the delivery and completion of multimodality therapy, which results in best outcome. However, under the surgery first approach, up to 50% of patients never actually receive adjuvant chemotherapy, largely due to postoperative complications and/or deconditioning.[7,24,25] In our study, 34.4% of the surgery first group did not receive any adjuvant therapy,




| | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Down-staged | 1823 | 1446 | 919 | 525 | 325 | 182 |
| Unchanged | 5876 | 4309 | 2460 | 1394 | 847 | 493 |
| Up-staged | 5961 | 3935 | 1875 | 855 | 431 | 212 |

| | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Neo+Surgery | 2042 | 1660 | 925 | 452 | 239 | 126 |
| Surgery+Adj | 7632 | 5960 | 3247 | 1727 | 1010 | 569 |
| Sugery | 3986 | 2070 | 1082 | 595 | 354 | 192 |

**Figure 5** Overall survival stratified by a) stage migration and b) Treatment sequencing

consistent with previous reports. It is important to note that when surgery first patients do not receive adjuvant therapy, they have similar OS to patients who receive neoadjuvant sequencing but are unable to undergo resection.[24] Proponents of surgery-first often quote highly selected randomized trials of efficacy, such as the PRODIGE 24/CCTG PA.6 trial (median OS of 54.4 months with postoperative mFOLFIRINOX),[26] but ignore the reality that the majority of surgery-first patients outside of specialty centers and clinical trials don't receive any adjuvant therapy within 4 months of resection. So while adjuvant therapy is beneficial if routinely delivered, that is not the pragmatic reality. In contrast, neoadjuvant therapy offers a real-world strategy that demonstrably maximizes the likelihood of delivery of multimodality therapy. There are several ongoing phase II/III trials comparing the neoadjuvant approach to surgery first approach, including NEPAFOX (NCT02172976)[27] and NEONAX (NCT02047513).[28] The results of these trials may clarify the optimal treatment strategy for clinically early-stage PDAC.

There are potential study limitations which reflect our use of the NCDB. In order to ensure accuracy of the reported data, the NCDB has implemented standardized registry manuals with instructions for data collection. For instance, with regards to the staging information, Facility Oncology Registry Data Standards (FORDS) which was in effect from 2003 to 2017, provides the hospital registrar with specific instructions for recording the stage information and for resolving any discrepancies found in the medical records.[29] However, even with these efforts, as with any large administrative database, one must assume the accuracy of the reported variables, such as staging information. In addition, due to lack of granular detail, we also assume that clinical staging was based on similar radiologic modalities across all patients. However, the greater numbers available from such a national database provide power for statistical analyses not possible with single- or even multi-institutional studies. Naturally, we cannot extrapolate the clinical reasons patients were chosen for surgery-first vs. neoadjuvant therapy. On the surface, it seems that patients with worse clinical disease presentation were more likely to receive neoadjuvant therapy. However, our results emphasize that clinicians are rarely correct in ascertaining the "true" underlying stage of the patient when they clinically stage patients at presentation. The data is this study show that the assessment of "early-stage" PDAC is more often wrong than right. We do not have details of chemotherapy regimens before or after surgery, which limits any regimen-to-regimen comparisons. However, despite these limitations, this database demonstrates strong national trends in both use of neoadjuvant therapy and its effects on both mitigating unexpected upward stage migration and improving survival (with HR ranging 0.52–0.59, with precise confidence intervals) compared to surgery alone. And these national data also remind us that 34% patients who are "surgery-first" end up as "surgery-alone" with not a single dose of postoperative chemo. It is important to acknowledge that patients in our study were all clinically staged using either AJCC 6th or AJCC 7th criteria, in which T3 includes descriptive extra-pancreatic extension criteria. It is possible that patients with small tumors were defined as having T3 disease under the old staging systems, but were "down-staged" under the new size-based criteria in AJCC 8th edition. This may explain somewhat higher than expected rate of down-staging seen in the SF group in our analysis. However, when we pathologically staged patients using the AJCC 7th criteria, the NT group still had significantly higher rates of downstaging compared to the SF group (data not shown).

In conclusion, in this national database analysis, there was a statistically significant and clinically relevant final pathologic up-staging in clinical stage I-II PDAC patients. Neoadjuvant therapy was associated with reductions in unexpected upstaging, reduction in nodal positivity, and improved OS, compared to SF approach in putatively early-stage PDAC. Because clinical staging underestimates the underlying disease burden in potentially resectable PDAC, these data suggest that patients with clinical Stage I-II PDAC should be considered for neoadjuvant therapy.

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## Authors' contributions

A.J.L., E.S and C.D.T. contributed for study concept and design. A.J.L., Y.J.C., and C.D.T. performed statistical analysis. A.J.L., Y.J.C., and C.D.T drafted the manuscript. A.J.L., E.S., Y.S.C., J.E.L., M.P.K., T.A.A., J.N.V., M.H.K. and C.D.T. critically revised the article.

## Disclosures

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

## Conflicts of interest

None declared.

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