Textbook Oncologic Outcomes Among Pancreatic Cancer Patients Who Receive Neoadjuvant Versus Adjuvant Therapy

Kevin Zhao[†1], Gregory Wu[2], Katie Frank[2], Rebecca Lynn Hoffman[2], and Joseph Alfred Blansfield[2]
[1]Geisinger Commonwealth School of Medicine, Scranton, PA 18509
[2]Geisinger Medical Center, Danville, PA 17822
[†]Doctor of Medicine Program
Correspondence: kzhao@som.geisinger.edu

Abstract

Background: Textbook oncologic outcome (TOO) is a quality measure defined by the receipt of an idealized baseline level of care in cancer patients undergoing curative surgical resection. The patient achieves TOO if they receive a surgery in which adequate lymph nodes (LN) are resected, negative surgical margins are achieved, the postoperative stay does not exceed expected length, there are no unplanned hospital readmissions, and adjunct guideline concordant chemotherapy with or without radiation is delivered. Each requirement has been shown to individually improve survival. While literature has shown TOO to be associated with improved survival in patients with pancreatic cancer, it is achieved at low rates in this population. Additionally, the lack of clinical practice guidelines for the medical management of pancreatic cancer in the setting of multimodal therapy complicates the consistent achievement of TOO. The aim of this study was to compare TOO attainment among patients who received neoadjuvant therapy and those who received adjuvant therapy for pancreatic cancer.

Methods: Patients who underwent neoadjuvant or adjuvant therapy and surgical resection for pancreatic cancer between 2014 and 2018 were identified using the National Cancer Database (NCDB). The four requirements used to define TOO were: 12 or more lymph nodes examined, R0 resection, non-length-of-stay (LOS) outlier (>16 days), and no 30-day hospital readmission. Univariate analysis was used to identify factors associated with TOO. Cox proportional hazards was used to identify factors associated with survival.

Results: A total of 12,510 patients were included. Over half (51.0%) were male (n=6,383), 85.4% were Caucasian (n=10,689), and 53.6% were treated at an academic facility (n=6,708). Most patients received adjuvant therapy at 76% (n=9,498) and just over half of all patients (50.4%, n=6,306) achieved TOO. Patients who received neoadjuvant therapy had a significantly higher rate of achieving TOO than those who received adjuvant therapy (59% vs 48%, p<0.001). Each of the four requirements for TOO were independently associated with receipt of neoadjuvant therapy. Positive lymph nodes were observed more often in patients who received adjuvant therapy (67% vs 55%, p<0.001). On COX analysis, survival was not significantly increased in patients who had TOO, although R0 resection (p<0.001) and non-LOS outlier (p<0.001) were both associated with improved survival.

Conclusion: Despite the inconclusive survival benefits of TOO, receipt of neoadjuvant therapy was associated with TOO attainment in pancreatic cancer patients. The shorter LOS and lower readmission rates may represent a considerable net positive perioperative outcome for patients. For these reasons, we recommend neoadjuvant therapy in the multimodal approach to curative pancreatic cancer therapy.

Introduction

While a multimodal approach of surgery and chemotherapy is the only curative approach to pancreatic cancer, variable patient outcomes indicate the need for a high-quality care measure (1). Textbook oncologic outcomes (TOO) is an aggregate quality metric composed of no unplanned readmissions, non-prolonged postoperative stay, negative margin status, adequate lymph node yield, and receipt of guideline concordant chemotherapy (2, 3). Each measure independently offers an essential glimpse into patient care and is associated with improved oncologic outcomes (4–11). As a composite, TOO retains much of the generalizability of its constituent metrics and is applicable to different malignancies. It also adds the benefit of scope, with medical management, surgery, and perioperative performance concisely integrated. Lastly, TOO has been shown to improve survival in patients undergoing surgery for pancreatic cancer and be associated with other markers of quality, including surgical volume (3, 12–14).

Despite these positive associations, this patient population qualifies for TOO at low rates. Aquina et al. compared TOO rates among pancreas, rectal, gastric, and colon cancer, with the lowest rate in pancreatic cancer at 25.0%, compared to the next lowest at 31.8% in gastric cancer (12). Kulshrestha et al. and Sweigert et al. also identified low rates in patients specifically undergoing pancreaticoduodenectomy at 21.5% and 16.8%, respectively (3, 14). Sweigert et al. also compared TOO in patients undergoing open and minimally invasive pancreatectomy, but rates were still low in both groups at 23.5% and 24.7%, respectively (13).

A possible explanation for this finding may be found within the measures that compose TOO. Qualification for receipt of chemotherapy depends on recommendations afforded by the National Comprehensive Cancer Network (NCCN) (15). However, chemotherapy sequencing recommendations for pancreatic cancer remain a subject of debate (10, 16–18). Survival outcomes have been observed in receipt of neoadjuvant and adjuvant therapy, yet the relationship between sequence and textbook outcomes is still underdeveloped. Thus, receipt of guideline concordant chemotherapy is a potential source of resistance to TOO achievement in this patient population. Sweigert et al. utilized adjuvant therapy within 12 weeks of surgery as TOO criteria, while Aquina et al. included patients who received neoadjuvant and adjuvant treatment (3, 12, 14). In both circumstances however, receipt of chemotherapy was the criteria achieved at the lowest rate at 48.2–49.3% and 65.4%, respectively.

Improving the achievement of desired patient outcomes is the goal and controlling for variables most likely to limit the attainment of a composite measure may be the first step. This study aimed to compare TOO rates in pancreatic cancer patients who receive neoadjuvant and adjuvant therapy. The secondary objectives were to identify other factors associated with TOO and to characterize any survival benefits TOO might afford.

Methods

Study Design

This retrospective cohort study utilized the National Cancer Database (NCDB), a joint project between the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. The database consists of information from approximately 1,500 CoC-accredited hospitals. It includes treatment, demographics, tumor traits, and outcome data from more than 70% of newly diagnosed cancer patients in the United States. Data used in this examination were de-identified, and IRB approval was exempted. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator. Facility-type designations were based on those listed by the National Cancer Database (19). Rural-Urban Commuting Area Codes (RUCA) codes classify census tracts or zip codes as urban or rural based on census data from the 2010 decennial census and the 2006-2010 American Community Survey (21).

Patients with invasive primary pancreas cancers diagnosed between 2014 and 2018 and underwent chemotherapy and surgery with a documented treatment sequence were included in the analysis. Metastatic disease, missing endpoint data, and cancers of non-pancreas histology or site were reasons for exclusion. Patients with missing TOO component data were also excluded.

Patients qualified for TOO if they met the four non-controlled criteria: no readmissions within 30 days of surgery, a non-outlier postoperative length of stay (LOS), tumor resection with microscopically negative (R0) margins, and American Joint Committee on Cancer (AJCC) compliant lymph node resection. According to the AJCC, 12 or more lymph nodes were considered a compliant resection at the time of surgery (2010-2015, AJCC 7th) [20]. Outlier LOS were based on Tukey's interquartile range *(Q3 + 1.5 × IQR)* as applied by Aquina et al (12). All patients in the study population were concordant with guideline recommendations for chemotherapy since the inclusion criteria were for patients who had undergone neoadjuvant or adjuvant chemotherapy with surgery.

Statistical Analysis

Demographic information was categorized by frequency using univariate analysis. Chi-square and Wilcoxon rank sum tests were used to compare neoadjuvant and adjuvant treatment groups. Factors associated with receipt of TOO were identified using logistic regression analysis. An odds ratio greater than one indicated an increased likelihood of TOO achievement. Survival analysis was used to estimate point survival and confidence intervals for each group while log-rank tests were used to assess the null hypothesis that there was no difference in survival probability between the two treatment groups. Overall survival (OS) was defined as the number of months between treatment initiation and the date of death from any cause. Cox proportional hazards was used to identify the effect of potential factors on survival probability. A hazards ratio greater than one indicated an improved likelihood of survival. Statistical analysis was conducted using R Version 4.0.5 (R Core Team, 2021). Results were considered statistically significant if the $p \leq 0.05$.

Results

Demographics

This report identified 12,510 patients who met inclusion criteria from the original 498,987 in the NCDB file (Table 1). The mean age was 65.8 ± 9.5 years, and approximately half were male (n=6,383; 51.0%). The sample was predominantly White (n=10,689; 85.4%) and located in metropolitan areas, assigned codes 1–3 under the RUCA schema (n=10,740, 85.9%) (21). Most patients were covered by government insurance (n=7,374; 58.9%) and were treated at academic or research programs (n=6,708; 53.6%). The most common procedure was Whipple (n=8,928; 71.4%), followed by distal pancreatectomy (n=2,056; 16.4%), and total pancreatectomy (n=1,408; 11.3%).

Only a quarter of the sample received neoadjuvant therapy (n=3,012; 24.1%). While demographic features between the neoadjuvant and adjuvant therapy groups were similar, tumor characteristics varied between the treatment groups. Higher rates of distal pancreatectomies were achieved in the adjuvant therapy group compared to the neoadjuvant therapy group (17.9% vs. 12.0%; $p < 0.001$). Whipple procedures were more common in the neoadjuvant therapy group (75.2% vs. 70.2%; $p < 0.001$). Patients who received adjuvant therapy had higher rates of all documented histologic grades, while those who received neoadjuvant had higher rates of a histologically ungraded or undocumented tumor ($p < 0.001$). A higher proportion of patients who received adjuvant therapy were pathologically staged as 2A or 2B (86.5% vs. 77.3%; $p < 0.001$) compared to the neoadjuvant therapy group, in which patients were staged 1A or 1B more frequently (22.6% vs. 13.5%; $p < 0.001$). Lastly, positive lymph node rates (67.4% vs. 55.3%; $p < 0.001$) and median lymph node ratio (0.09 vs. 0.04; $p < 0.001$) were higher in patients who received adjuvant therapy.

Virtually half of all patients qualified for all four TOO criteria (n=6,306; 50.4%). Individually, 91.6% had no unplanned readmission within 30 days of surgery (n=11,453), 89.8% had a non-outlier LOS (n=11,230), 80.8% had R0 margins (n=10,111), and 74.3% had ≥12 lymph nodes examined (n=9,290).

There was a significant difference in all TOO metrics between patients who received neoadjuvant and adjuvant chemotherapy. A higher proportion of patients who received neoadjuvant therapy had no unplanned 30-day readmission (93.0% vs. 91.1%; $p = 0.001$), a non-outlier LOS (91.4% vs. 89.2%; $p < 0.001$), and negative surgical margins (83.0% vs. 80.1%; $p < 0.001$) compared to those who received adjuvant therapy. The component measure achieved at the lowest rate in both groups was adequate lymph node yield (81.3% vs. 72.0%; $p < 0.001$). Overall, patients who received neoadjuvant therapy qualified for TOO significantly more frequently than patients who received adjuvant therapy (58.4% vs. 47.9%; $p < 0.001$).

	Overall (n = 12,510)	Treatment Group		p-value[1]
		Adjuvant (n= 9,498)	Neoadjuvant (n = 3,012)	
Year of Diagnosis, median (IQR)	2016 (2009, 2017)	2016 (2008, 2017)	2016 (2016, 2017)	< 0.001
Year of Diagnosis, mean (SD)	2014 (4)	2014 (4)	2016 (3)	< 0.001
Age at Diagnosis, mean (SD)	66 (9)	66 (10)	65 (9)	< 0.001
Gender, n (%)				0.732
Male	6,383 (51.0%)	4,838 (50.9%)	1,545 (51.3%)	
Female	6,127 (49.0%)	4,660 (49.1%)	1,467 (48.7%)	
Race, n (%)				0.460
White	10,689 (85.4%)	8,095 (85.2%)	2,594 (86.1%)	
Black	1,208 (9.7%)	929 (9.8%)	279 (9.3%)	
Asian, Hawaiian, or Native American	398 (3.2%)	313 (3.3%)	85 (2.8%)	
Other or Unknown	215 (1.7%)	161 (1.7%)	54 (1.8%)	
Insurance Status at Diagnosis, n (%)				0.001
Private or Managed Care	4,813 (38.5%)	3,567 (37.6%)	1,246 (41.4%)	
Government	7,374 (58.9%)	5,675 (59.7%)	1,699 (56.4%)	
Not Insured/Unknown	323 (2.6%)	256 (2.7%)	67 (2.2%)	
Facility Type, n (%)				< 0.001
Community Cancer Program	307 (2.5%)	238 (2.5%)	69 (2.3%)	
Comprehensive Community Cancer Program	3,011 (24.1%)	2,506 (26.4%)	505 (16.8%)	
Academic/Research Program	6,708 (53.6%)	4,818 (50.7%)	1,890 (62.7%)	
Integrated Network Cancer Program	2,484 (19.9%)	1,936 (20.4%)	548 (18.2%)	
Metro/Non-Metro, n (%)				< 0.001
Metro (RUCA 1-3)	10,740 (86%)	8,218 (87%)	2,522 (84%)	
Non-Metro (RUCA 4-9)	1,770 (14%)	1,280 (13%)	490 (16%)	
Charlson-Deyo Score, n (%)				0.343
0	7,973 (63.7%)	6,027 (63.5%)	1,946 (64.6%)	
1	3,161 (25.3%)	2,400 (25.3%)	761 (25.3%)	
2	864 (6.9%)	670 (7.1%)	194 (6.4%)	
≥ 3	512 (4.1%)	401 (4.2%)	111 (3.7%)	
Procedure Type, n (%)				< 0.001
Distal	2,056 (16.4%)	1,696 (17.9%)	360 (12.0%)	
Whipple	8,928 (71.4%)	6,663 (70.2%)	2,265 (75.2%)	
Total Pancreatectomy	1,408 (11.3%)	1,049 (11.0%)	359 (11.9%)	
Pancreatectomy, NOS	118 (0.9%)	90 (0.9%)	28 (0.9%)	
Histologic Grade, n (%)				< 0.001
1	997 (8.0%)	771 (8.1%)	226 (7.5%)	
2	5,215 (41.7%)	4,289 (45.2%)	926 (30.7%)	
3	3,228 (25.8%)	2,672 (28.1%)	556 (18.5%)	
4	141 (1.1%)	116 (1.2%)	25 (0.8%)	
Missing	2,929 (23.4%)	1,650 (17.4%)	1,279 (42.5%)	
AJCC Pathological Stage, n (%)				< 0.001
1A	756 (6.0%)	389 (4.1%)	367 (12.2%)	
1B	1,208 (9.7%)	894 (9.4%)	314 (10.4%)	
2A	2,500 (20.0%)	1,824 (19.2%)	676 (22.4%)	
2B	8,046 (64.3%)	6,391 (67.3%)	1,655 (54.9%)	
Positive Lymph Node Yield, n (%)				< 0.001
0	4,437 (35%)	3,092 (33%)	1,345 (45%)	
≥ 1	8,073 (65%)	6,406 (67%)	1,667 (55%)	
Ratio between Positive and Examined Lymph Nodes, median (IQR)	0.08 (0.00, 0.20)	0.09 (0.00, 0.22)	0.04 (0.00, 0.13)	< 0.001
Non-outlier LOS (i.e., < 16 days), n (%)				0.001
Outlier LOS	1,280 (10.2%)	1,022 (10.8%)	258 (8.6%)	
Non-Outlier LOS	11,230 (89.8%)	8,476 (89.2%)	2,754 (91.4%)	
R0 Resection, n (%)				< 0.001
No R0 resection	2,399 (19.2%)	1,887 (19.9%)	512 (17.0%)	
R0 resection	10,111 (80.8%)	7,611 (80.1%)	2,500 (83.0%)	
12 or More Lymph Nodes Removed and Examined, n (%)				< 0.001
<12 LNs	3,220 (25.7%)	2,656 (28.0%)	564 (18.7%)	
≥12 LNs	9,290 (74.3%)	6,842 (72.0%)	2,448 (81.3%)	
No 30-Day Hospital Readmission, n (%)				0.001
Unplanned readmission	1,057 (8.4%)	847 (8.9%)	210 (7.0%)	
No unplanned readmission	11,453 (91.6%)	8,651 (91.1%)	2,802 (93.0%)	
Textbook Oncologic Outcome (TOO), n (%)				< 0.001
No TOO	6,204 (49.6%)	4,950 (52.1%)	1,254 (41.6%)	
TOO	6,306 (50.4%)	4,548 (47.9%)	1,758 (58.4%)	

[1]Wilcoxon rank sum test; Pearson's Chi-squared test, IQR: Interquartile range, SD: Standard deviation, TOO: textbook oncologic outcome

Table 1. Demographics. 1Wilcoxon rank sum test; Pearson's Chi-squared test, IQR: Interquartile range, SD: Standard deviation, TOO: textbook oncologic outcome, RUCA: Rural-urban commuting area code, NOS: Not otherwise specified, LOS: Length-of-stay

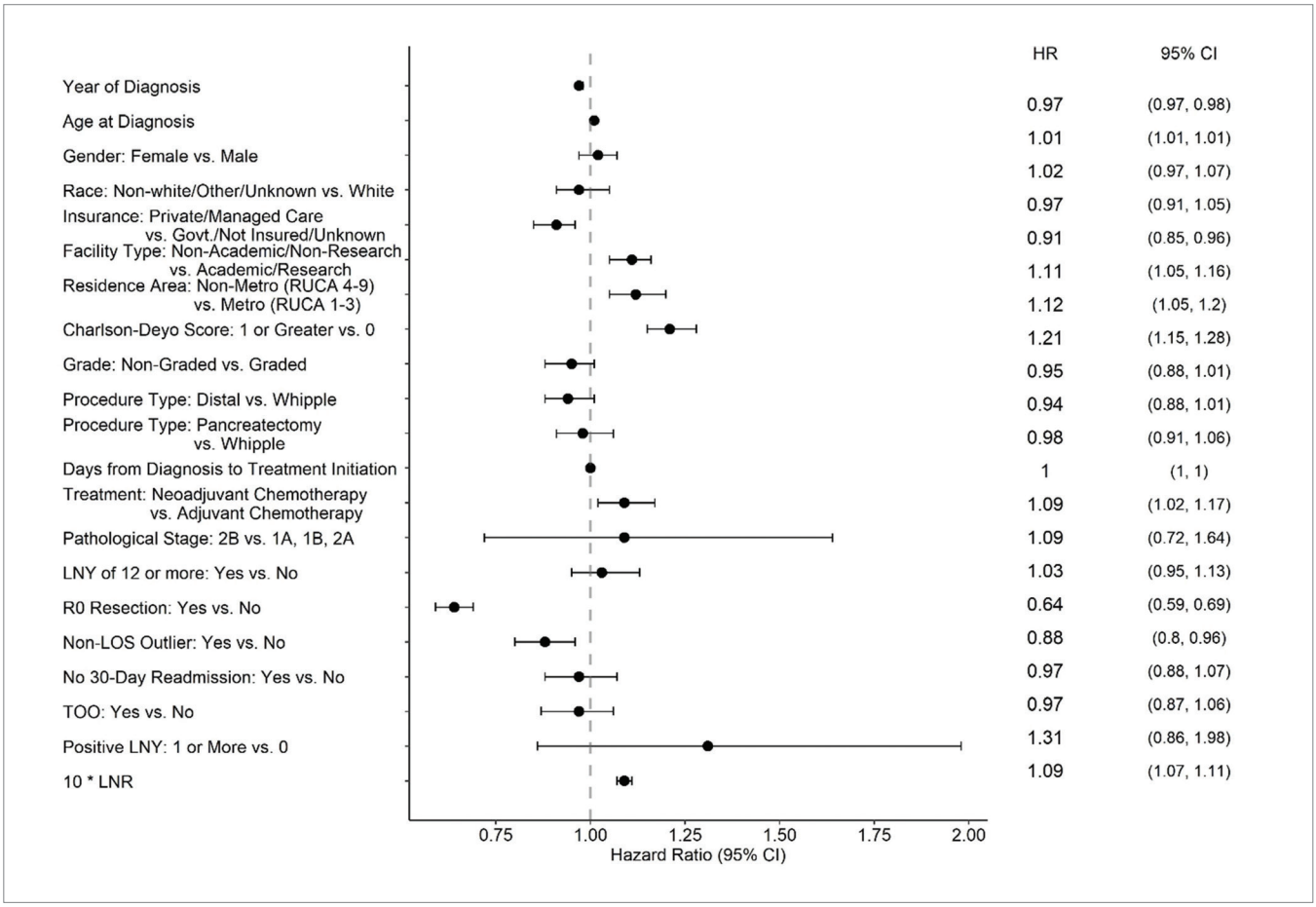

Figure 1. Forest plot of factors associated with overall survival in pancreatic cancer patients. A hazards ratio of less than one is associated with decreased likelihood of survival and a ratio greater than one is associated with increased likelihood of survival. Data from the National Cancer Database includes patients who received treatment between 2014 and 2018. RUCA: Rural-urban commuting area code, LNY: Lymph node yield, LOS: Length-of-stay, TOO: Textbook oncologic outcomes

Survival

Cox analysis identified several factors associated with survival. All factors analyzed for survival are listed in (Figure 1). In this analysis, TOO was not significantly associated with survival (HR, 0.965; 95% CI, 0.875–1.065). Individually, both non-outlier LOS (HR, 0.880; 95% CI, 0.804–0.964) and negative microscopic margins (HR, 0.638; 95% CI, 0.586–0.693) were associated with improved survival regardless of treatment. Worse survival was predicted by an older age of diagnosis (HR, 1.010; 95% CI, 1.007–1.014), treatment at a non-academic/non-research facility (HR, 1.107; 95% CI, 1.053–1.164), residence in a non-metropolitan area (HR, 1.122; 95% CI, 1.047–1.204), a higher comorbidity burden (HR, 1.214; 95% CI, 1.153–1.278), receipt of neoadjuvant chemotherapy (HR, 1.092; 95% CI, 1.023–1.166), and a higher lymph node ratio (LNR) (HR, 1.089; 95% CI, 1.072–1.106). Other factors associated with improved survival were a more recent year of diagnosis (HR, 0.972; 95% CI, 0.966–0.977) and having private insurance or managed care coverage (HR, 0.906; 95% CI, 0.852–0.964).

Factors Associated with TOO

As expected of a composite measure, TOO was multifactorial (Figure 2). Multivariate analysis revealed neoadjuvant therapy to be the strongest predictor of TOO qualification of all variables analyzed in this study (OR, 1.297; 95% CI, 1.175–1.433). Earlier diagnosis (OR, 1.100; 95% CI, 1.089–1.111), female gender (OR, 1.129; 95% CI, 1.042–1.224), and having private insurance or managed care coverage (OR,1.144; 95% CI, 1.036–1.263) were all additionally shown to be associated with qualifying for TOO. Factors associated with not receiving TOO included: non-White or unknown race (OR, 0.874; 95% CI, 0.779–0.982), treatment at a non-academic/non-research facility (OR, 0.712; 95% CI, 0.656–0.772), histologically non-graded disease (OR, 0.840; 95% CI, 0.760–0.929), and distal pancreatectomy (OR, 0.804; 95% CI, 0.720–0.897).

Discussion

To our knowledge, this was the first investigation to compare the achievement of textbook outcomes in pancreatic cancer patients with different treatment sequences. This study demonstrates that pancreatic cancer patients who receive neoadjuvant therapy are more likely to qualify for TOO than those who receive adjuvant therapy. Neoadjuvant therapy-treated patients were also more likely to achieve the individual component measures of no 30-day unplanned readmission, non-LOS outlier, negative surgical margins, and adequate lymph

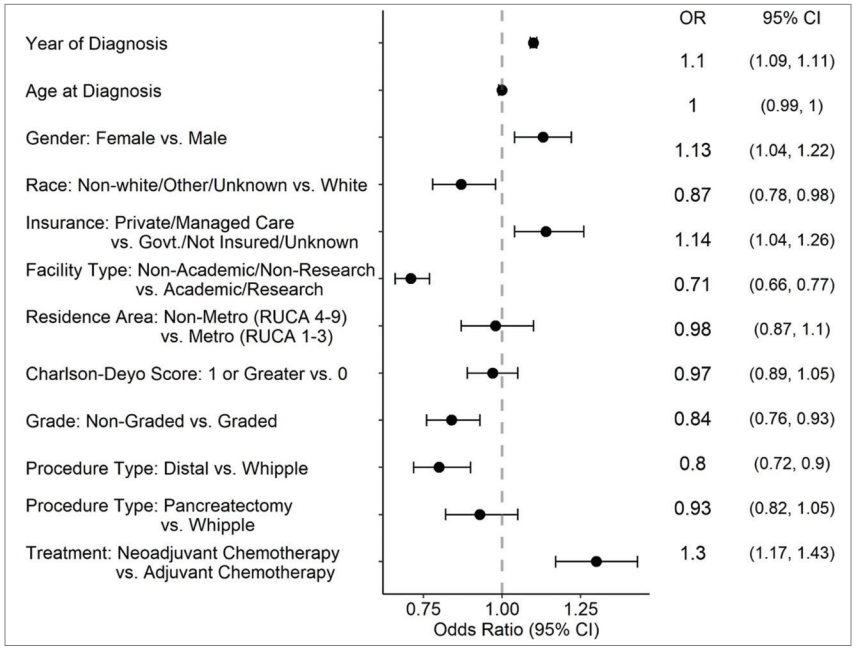

Figure 2. Forest plot of factors associated with Textbook Oncologic Outcomes in pancreatic cancer patients. An odds ratio less than one is associated with a decreased likelihood of achieving TOO and an OR greater than one is associated with increased odds of achieving TOO. Data from the National Cancer Database includes patients who received treatment between 2014 and 2018. RUCA: Rural-urban commuting area code

node yield. While this report did not find a significant correlation between TOO and survival, patients with a non-LOS outlier and negative microscopic margins following surgery demonstrated improved survival compared to those without.

Quality improvement efforts in care have improved the experiences of innumerable patients (22). The increased reliance of the healthcare industry on care guidelines has been driven by the increased use of quality metrics for decades (23). Composite measures have particularly been utilized in quality assessment for their ability to summarize multiple statistics and convey the information in a more digestible format for physicians, patients, and payers alike (24). Patients have also shown a preference for surgery-specific, quality-of-care information when evaluating a hospital's performance (25) and summarized but comprehensive evidence rather than detailed or individual measures when contemplating this information (26). TOO is definitionally a single quality metric that delivers a condensed report in a binary, "all-or-nothing" format (27). Whether a patient is weighing facilities for potential treatment, or a stakeholder is assessing a hospital's interventional efficacy, TOO offers critical insight into the achievement of specific, ideal patient outcomes.

The role of neoadjuvant therapy in pancreatic cancer is still not well-defined. Without addressing specific regimens, multiple options and modalities have been shown in prior literature to share positive associations with survival (28–30). As our study did not find a survival association between neoadjuvant therapy and TOO, the primary benefit of this modality may exist in its effects on other measures of patient outcome. Margin status and lymph node resection may be assessed as pathologic responses to chemotherapy treatment before surgery. Some studies have shown no or questionable effects of neoadjuvant therapy in resectable disease, but improvement in resectability of borderline resectable or locally advanced disease through tumor shrinkage and control of micrometastases (31–33). Merkow et al. found neoadjuvant therapy decreased the likelihood of margin involvement in pancreatic cancer patients undergoing surgery (34). In this study, higher rates of adequate lymph node resection, lower positive lymph nodes, and lower LNRs among patients treated with neoadjuvant therapy may represent a favorable post-operative profile and one of the benefits of neoadjuvant therapy. The relationship between lymph node yield and oncologic outcomes is well established (4, 5, 35–37). The number of positive lymph nodes and the lymph node ratio are also powerful prognostic indicators (38–40). Given the pronounced disparity in adequate lymph node resection and negative surgical margin rates compared to that of other TOO metrics, future exploration of factors that influence their achievement in the context of textbook outcomes may be warranted.

Avoidance of 30-day readmission and LOS outlier was accomplished in the overwhelming majority of patients in this study regardless of therapy sequence. Readmission and prolonged LOS have both been linked to worse prognoses and increased costs in pancreatic cancer patients (9, 41). In these studies, procedure-related complications were the most common reason for readmission within 30 days of surgery, but the reasons for and frequency of readmission changed beyond this period. Studies in textbook outcomes that have utilized Medicare data offer an extended 90-day observation. Readmission rates dropped as low as 71.9% and 67.5% in minor and major pancreatic operations, respectively (27). Readmission rates are likely higher, and the 30-day window captured by NCDB is insufficient to assess the actual frequency of clinically significant readmits. However, extending the discussion of ideal patient outcomes to include a more accurate assessment of true readmissions calls for an alternate data pool to be employed.

Limitations

This study has several limitations. The retrospective and observational nature of this research limits its level of evidence. Additionally, the data sourced for this project through the NCDB offers good insight into patient demographics and surgical outcomes but lacks the granularity to capture comorbidity, operative, and complication details that undoubtedly influence immediate and long-term patient well-being.

The focus of this investigation was also directed toward the facility level. Surgeon-specific features such as experience and patient-provider management decisions are important

factors in discussions on outcomes but are excluded due to the availability of such information. Facilities not captured by the NCDB and not accredited by the CoC make up a substantial proportion of the healthcare system. Patients at these facilities comprise roughly 30% of newly diagnosed malignancies. Accreditation status has shown some evidence to play a role in patient satisfaction and quality of care (42–44). Thus, this study's findings may not be applicable to patients receiving care at non-accredited facilities.

Conclusion

In conclusion, TOO rates were higher in pancreatic cancer patients who received neoadjuvant therapy compared to those who received adjuvant therapy. While TOO was not significantly associated with survival in this study, its component measures of margin status and post-operative stay were independently so. Furthermore, the lower readmission rates and LOS outliers seen in the neoadjuvant therapy group may additionally contribute to a considerable net positive outcome. We recommend receipt of neoadjuvant therapy for pancreatic cancer patients who require surgical management for their disease.

Disclosures

The authors declare no conflicts of interest. The research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors. All authors made substantial contributions to either the concept and/or design of this study. KF collected and analyzed the data for the present study. KZ, GW, KF, RH, and JB all interpreted the data and drafted and/or edited the manuscript. KZ, GW, KF, RH, and JB reviewed the manuscript for errors and provided feedback for changes. All authors approved this version of the manuscript and agreed to be accountable for all aspects of the article.

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