Surgery 165 (2019) 307–314

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Understaging of clinical stage I pancreatic cancer and the impact of multimodality therapy ☆,☆☆

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ARTICLE INFO

Article history:
Accepted 6 August 2018
Available online 20 September 2018

ABSTRACT

Background: Although current guidelines recommend multimodal therapy for all patients with pancreatic ductal adenocarcinoma, it is unclear the extent to which clinical stage I patients are accurately staged and how this may affect management.

Methods: In this retrospective cohort study of 4,404 patients aged 18–79 years with clinical stage 1 (ie, T1N0 or T2N0) pancreatic ductal adenocarcinoma treated with upfront resection in the National Cancer Database (2004–2014), understaging was ascertained by comparing pretreatment clinical stage with pathologic stage. The association between adjuvant treatment and overall risk of death among true stage I and understaged patients was evaluated using multivariable Cox regression.

Results: Upstaging was identified in 72.6% of patients (62.8% T3/4, 53.9% N1) of whom 69.7% received adjuvant therapy compared with 47.0% with true stage I disease. Overall survival at 5 years among those with true stage I disease was significantly higher than those who had been clinically understaged (42.9% vs 16.6%; log-rank, $p < 0.001$). For true stage I patients, adjuvant therapy was not associated with risk of death (hazard ratio: 1.07, 95% confidence interval: 0.89–1.29). For understaged patients, adjuvant therapy significantly decreased risk of death (hazard ratio: 0.64, 95% confidence interval: 0.55–0.74).

Conclusion: The majority of clinical stage I pancreatic ductal adenocarcinoma patients actually have higher-stage disease and benefit from multimodal therapy; however, one third of understaged patients do not receive any adjuvant treatment. Clinicians should discuss all potential treatment strategies with patients (in the context of the acknowledged risks and benefits), including the utilization of neoadjuvant approaches in those presenting with potentially resectable disease.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is estimated to be responsible for more than 40,000 deaths in the United States and is the fourth leading cause of cancer death.[1] In large part, this is because patients often present with advanced disease at diagnosis, and PDAC typically responds poorly to available systemic therapy regimens. Because of its aggressive nature, current recommendations for the management of PDAC include the use of multimodal therapy (MMT).[2] However, despite recent advancements in the chemotherapeutic agents available to treat patients with PDAC, 5-year survival rates remain poor (<10% overall and <30% for those with localized disease), with a slight increase in the mortality rate over the past decade.[1,3,4]

The traditional paradigm for the curative management of patients presenting with early-stage and/or potentially resectable disease has been upfront surgical resection followed by adjuvant therapy.[5] However, although the benefit of adjuvant systemic therapy has been clearly established, between 40% and 50% of patients in PDAC trials failed either to initiate or to complete all intended cycles of adjuvant therapy, and only 50% of patients in the general

☆ Presented as a poster at the Society of Surgical Oncology Annual Cancer Symposium in Chicago, IL in March 2018.

☆☆ This material is based on work supported by the National Institutes of Health (T32 HL 92332-15 [KAB]) and by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and the Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413 [NNM]). The funding body played no part in the design and/or conduct of this study, had no access to the data or a role in data collection, management, analysis, or interpretation, and had no role in preparation, review, or approval of the article.

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https://doi.org/10.1016/j.surg.2018.08.003
0039-6060/Published by Elsevier Inc.

community receive postoperative adjuvant therapy.[6-9] In addition, recent data suggest half of clinically node-negative patients treated with upfront surgery are in fact node positive on final pathology; furthermore, nodal downstaging occurs in 38% of patients treated with neoadjuvant therapy.[10] As such, because of the low rate of MMT completion in the postoperative setting, if clinical staging modalities consistently understage PDAC patients believed to have early-stage or potentially resectable disease, a number of patients who might otherwise be considered for neoadjuvant therapy could be treated with a surgery-first approach, resulting in underutilization of MMT in a significant proportion of those who may be likely to benefit from it.

At present there are 2 important, but as yet unanswered questions regarding the optimal management of patients with stage I PDAC: First, the extent to which current clinical staging modalities are associated with understaging is unclear. Second, because only ~10% of patients in published adjuvant trials have stage I disease, the generalizability of the benefit of adjuvant therapy in these patients has not been well characterized. In this context, the goals of this study are to (1) describe the frequency with which clinical stage I patients are understaged (ie, in actuality have more advanced disease on final pathology); and (2) evaluate whether there is a benefit associated with adjuvant therapy among patients with true stage I disease. Our hypotheses were that the majority of patients with stage I disease are understaged and that adjuvant therapy is beneficial in all patients with PDAC.

Methods

Data

This was a retrospective cohort study using the National Cancer Data Base (NCDB). The NCDB is a prospectively maintained, hospital-based registry collecting data on more than 70% of incident cancers diagnosed annually. Data are contributed from more than 1,500 Commission on Cancer–accredited centers in the United States. The NCDB is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. This study was approved by the institutional review board of the Baylor College of Medicine and the Michael E DeBakey VA Medical Center Research & Development Committee. This study is reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Study subjects

Between 2004 and 2014, 242,240 patients between 18 and 79 years of age with a diagnosis of PDAC were identified. Standard sequential exclusions when using NCDB data were then applied and are illustrated in Fig. 1. The exclusion based on treatment at the reporting facility was to enhance the accuracy of treatment ascertainment. Exclusions regarding death within 30 days of diagnosis and patients for whom definitive surgical resection was not performed were to ensure that our cohort included patients who were potential candidates for curative treatments. Our decision to exclude patients who underwent non-oncologic resections or in whom this could not be ascertained also served to ensure that the value of adjuvant therapy as part of multimodal curative treatment could be evaluated. Patients treated neoadjuvantly ($n = 483$) were excluded because prior work has indicated poor negative predictive value for clinical nodal staging in PDAC patients, and a 38% rate of nodal downstaging is observed after neoadjuvant treatment.[10] As such, it would not be possible to ascertain which neoadjuvantly treated patients were truly stage I on final pathology. Therefore, this exclusion was to allow the accurate identification of patients as having true stage I or having been understaged.

Variables

The NCDB provides information on demographic, clinical, and tumor data, as well as all forms of cancer-directed therapy. Education and income are derived from the 2012 American Community Survey. A Charlson-Deyo index is provided and used to quantify the burden of comorbid conditions. Two forms of staging data are also provided: (1) *clinical*—based on the best available staging data prior to the initiation of the first course of treatment—and (2) *pathologic*. As all patients in the study were considered to have clinical stage I disease, pathologic staging information was used to categorize patients as having true stage I disease or having been clinically understaged.

All patients were categorized based on the types of treatment they received. Primarily, patients were categorized as having undergone surgery alone or surgery plus adjuvant therapy. As all patients in this cohort underwent upfront resection, the definition of adjuvant therapy was chemotherapy or radiation therapy administered postoperatively. MMT was defined as the use of both surgery and any form of adjuvant therapy. NCDB does not provide information on whether patients who received radiation were treated with systemic therapy followed by concurrent chemotherapy and radiation or only concurrent chemotherapy and radiation. Therefore, as is routinely done using NCDB data, patients were categorized as having received radiation or not.

Analysis

Standard descriptive statistics were used to evaluate categorical and continuous variable distributions. A nonparametric test of trend was used to evaluate proportional changes over time. The primary outcome of interest was overall survival (OS). The Kaplan-Meier method and log-rank test were used to compare OS distributions. The association between the use of adjuvant treatment and risk of death was evaluated using multivariable Cox regression. Risk of death among those with true stage I disease and those patients who were clinically understaged were evaluated using 2 separate models. Model covariates were selected in a nonparsimonious fashion and included age, sex, race, insurance type, income, education, comorbidity, rurality, treatment facility type, tumor site, histologic grade, and margin status. The assumption of proportional hazards was evaluated graphically. To address underlying survivor treatment bias, a 90-day landmark was applied.[11]

Our cohort included 14.1% of patients with at least 1 missing covariate data point. To address missing values, modeling was conducted in a case-complete fashion and by using multiple imputations by chained equations. Similar results were obtained, and thus, imputed results are presented. Statistical comparisons were 2-sided and considered significant at P values $< .05$. All analyses were performed using STATA Version 14.0 (StataCorp, College Station, TX).

Results

A total of 4,404 surgically resected patients with clinical stage I disease were identified. Demographic and clinical characteristics of the study cohort are presented in the Table 1. The distribution of men and women was nearly equal. Roughly 84% were white and 10.4% were black. Most (80.3%) of the patients had proximal tumors. The majority (82.8%) had moderate or poor histologic differentiation. More than one third (36.5%) of patients were treated with surgery alone. Among those who received adjuvant treatment, 49.3% received radiation (with or without chemotherapy), 66.2% received single-agent chemotherapy, and 26.7% received multiagent chemotherapy.

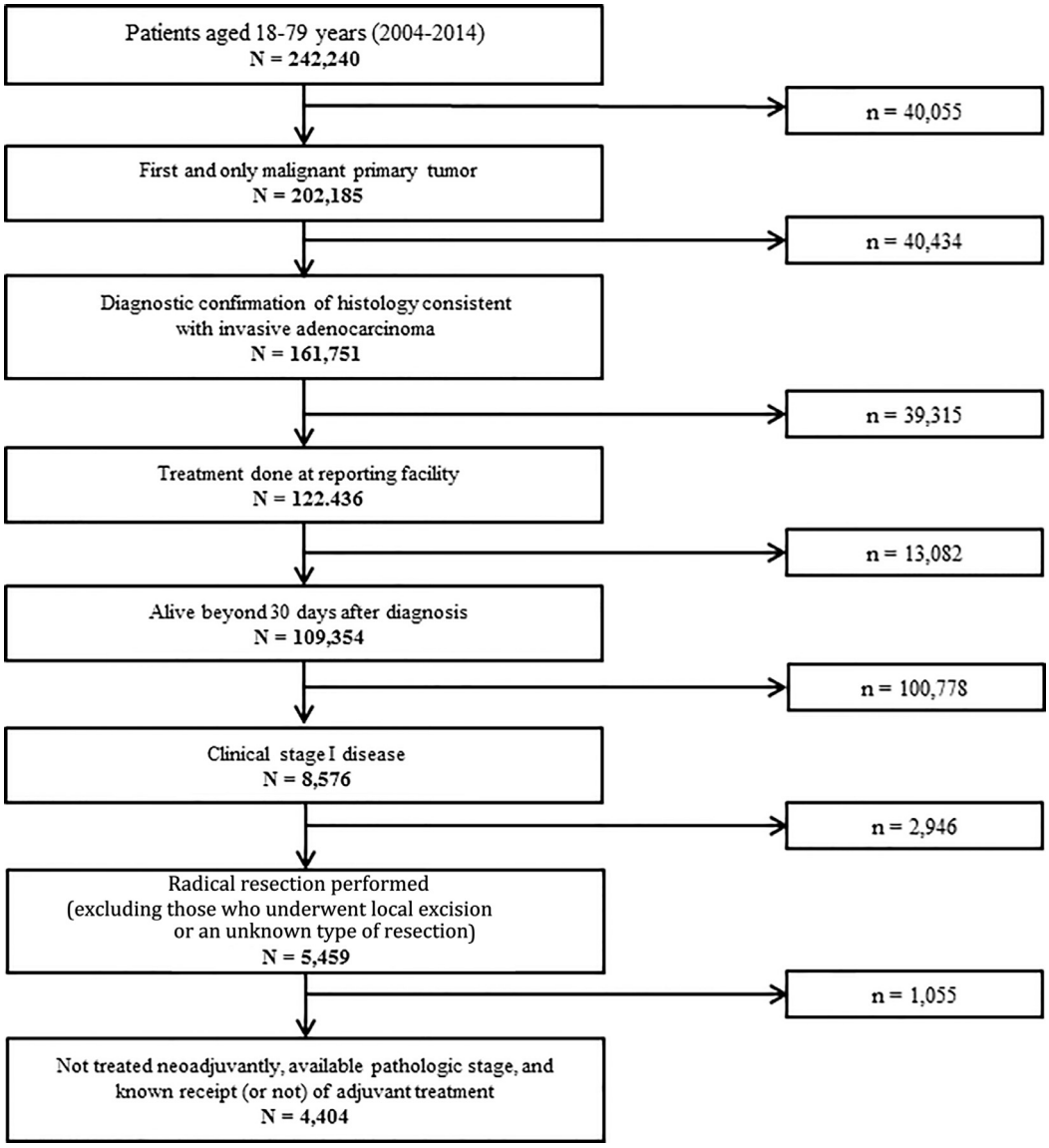


Fig. 1. Flow diagram of study cohort definition.

The proportion of patients who were clinically understaged (ie, final pathology was not consistent with stage I) and the type of understaging (ie, T or N stage) are illustrated in Fig. 2. Higher-stage disease on final pathology was identified in 72.6%. With respect to T stage, 62.5% had been clinically understaged, with 97.4% having T3 and 2.6% having T4 tumors. For N stage, 53.7% had been clinically understaged. The MMT strategies used are illustrated in Fig. 3 and significantly differed ($P < .001$) between patients with true stage I disease and those who were upstaged. Among patients who were truly stage I, 53.0% received no adjuvant therapy, 23.2% adjuvant chemotherapy only, 20.6% both adjuvant chemotherapy and radiation, and 1.2% adjuvant radiation without chemotherapy (ie, chemotherapy was not reported as having been administered). For patients who had been clinically understaged, 30.3% received no adjuvant therapy, 34.9% adjuvant chemotherapy, 33.8% both adjuvant chemotherapy and radiation, and 1.0% adjuvant radiation without chemotherapy. Among patients who truly had pT1/2 tumors but had nodal disease on final pathology (ie, upstaged based on nodal status), adjuvant therapy was used in 69.8%. Among patients who were truly node negative but had upstaging of their primary on final pathology, adjuvant therapy was used in 65.1%. During the study period, the proportion of patients with true stage I disease who received MMT was unchanged (44.1% vs 39.8%, trend test: $P = .38$). By comparison, the proportion of understaged patients treated with MMT significantly decreased (70.9% vs 65.3%, trend test: $P = .004$).

The 5-year OS among those with true stage I disease was significantly higher than that of those who had been clinically understaged (42.9% vs 16.6%, log-rank: $P < .001$). Among those who were truly stage I, 5-year OS was not significantly different (Fig. 4) whether adjuvant therapy was or was not used (47.7% no adjuvant vs 41.5% adjuvant, log-rank: $P = .07$). The use of adjuvant therapy was not significantly associated with risk of death in these patients (hazard ratio: 1.07, 95% confidence interval: 0.89–1.29). Among those who had been clinically understaged, 5-year OS was significantly improved with the use of adjuvant therapy (15.3% no adjuvant vs 18.4% adjuvant, log-rank: $P < .001$). Similarly, adjuvant therapy was associated with a significant 36% decrease in the risk of death (hazard ratio: 0.64, 95% confidence interval: 0.55–0.74). We performed 2 sensitivity analyses. First, we compared the OS between true stage I patients who were treated with adjuvant chemotherapy only and those treated only with resection. Second,

Table 1
Demographic and clinical characteristics of the study cohort

	Overall (n = 4,404)	True stage I (n = 1,207)	Understaged (n = 3,197)
Demographics			
Mean age ± SD, y	64.5 ± 9.6	64.1 ± 10.0	64.6 ± 9.4
Age (%)			
≤60 y	32.4	33.5	32.0
61–65 y	17.4	16.6	17.7
66–70 y	19.0	18.8	19.1
71–75 y	17.7	17.8	17.6
>75 y	13.5	13.3	13.5
Male sex (%)	48.7	47.1	49.3
Race (%)			
White	84.3	83.8	84.5
Black	10.4	11.2	10.1
Other	4.3	4.1	4.4
Missing	1.0	0.9	1.0
Insurance status (%)			
Insured	40.9	40.9	40.8
Medicare/Medicaid	54.9	54.3	55.2
Uninsured	2.4	2.7	2.4
Other	1.2	1.4	1.1
Missing	0.6	0.8	0.6
Income* (%)			
≥$63 000	34.1	32.7	34.6
Missing	1.9	2.4	1.8
Education* (%)			
<7%	24.9	23.5	25.5
Missing	1.9	2.4	1.8
Rurality (%)			
Metropolitan	52.4	47.3	54.3
Urban	28.4	30.9	27.4
Rural	15.3	16.9	14.7
Missing	4.0	4.9	3.6
Comorbidity index (%)			
0	62.7	63.5	62.4
1	29.0	28.7	29.2
≥2	8.3	7.9	8.5
Facility			
Hospital type (%)			
Academic/Research	59.4	57.0	60.3
Comprehensive Cancer Center	26.1	28.6	25.2
Community Cancer Center	2.7	2.3	2.8
Other	10.9	10.5	11.0
Missing	1.0	1.6	0.8
Clinical			
Grade (%)			
Well	9.7	16.9	7.0
Moderate	49.8	43.2	52.2
Poor/undifferentiated	33.0	23.2	36.6
Missing	7.6	16.7	4.1
Surgical margin (%)			
Positive	19.1	7.8	23.4
Missing	1.0	1.3	0.9
Primary location (%)			
Proximal	80.3	71.3	83.8
Distal	18.0	25.9	15.0
Unknown	1.7	2.8	1.2
Surgical resection (%)			
Whipple	70.2	61.1	73.6
Distal	16.5	23.9	13.7
Total	13.4	15.1	12.7

* Based on 2008–2012 American Community Survey data. For income, the percentage of patients whose area of residence (based on ZIP code) had a median household income ≥$63,000 (adjusted for 2012 inflation) is presented. For education, the percentage of patients whose area of residence (based on ZIP code) had <7% adults who did not attain a high school education is presented.

we compared the OS between true stage I patients whose adjuvant therapy included radiation and those treated only with resection. There were no significant differences for either comparison.

Discussion

Despite the advent of new systemic therapies and an increasing appreciation for the importance of MMT in the management of PDAC patients, there has been little improvement in survival over time.[1,3-5] The reasons for this are multifactorial and include aggressive tumor biology, a predilection for early metastasis that is often occult at the time of presentation, and resistance to current adjuvant therapy regimens. However, pretreatment staging is also an important factor that is used to inform clinical decision making at the time of presentation, and as such, the accuracy of this information can greatly influence the sequence of treatments patients receive. Whereas in prior work we evaluated nodal staging for PDAC and the degree to which neoadjuvant therapy is

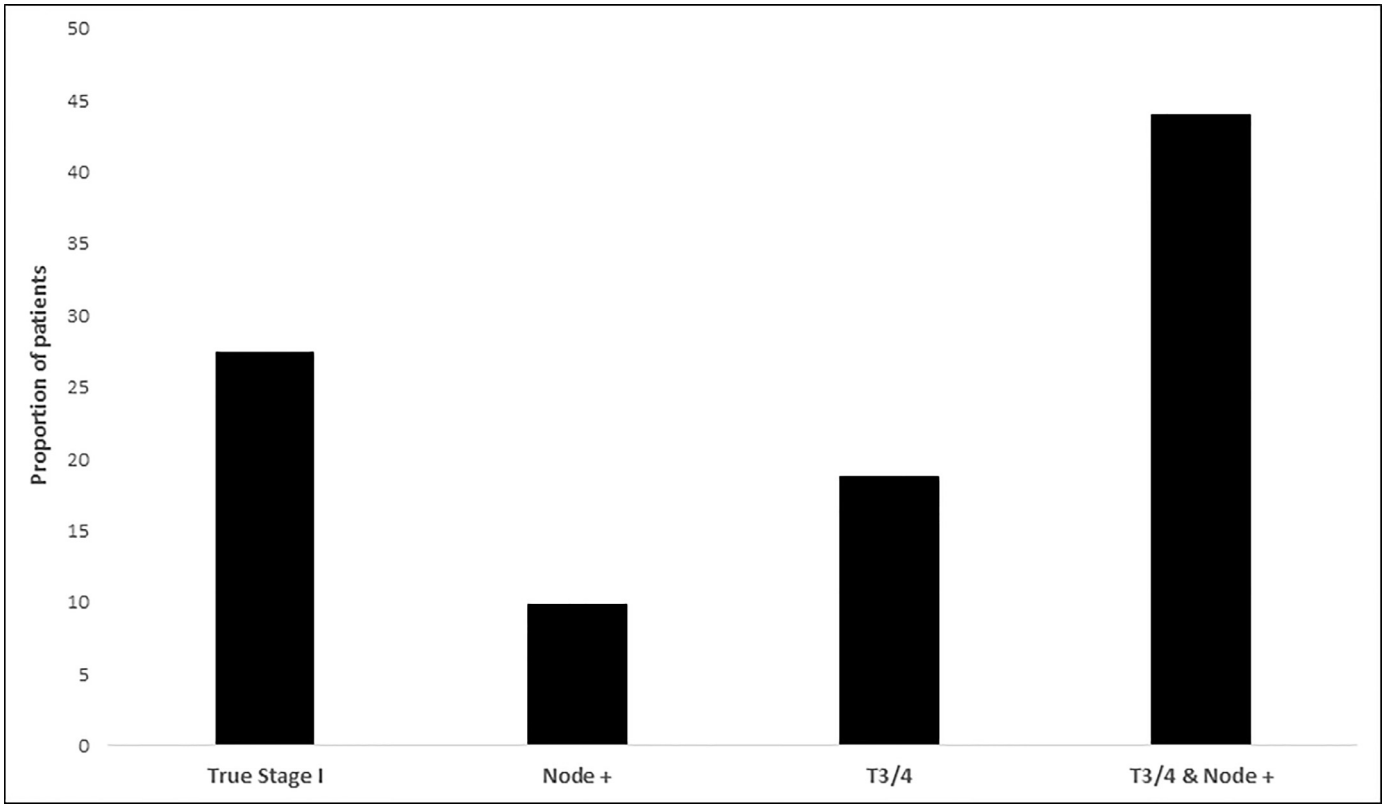


Fig. 2. Final pathologic stage among clinical stage I patients.

associated with nodal downstaging, in our current study we aimed to characterize the extent to which patients presenting with clinical stage I disease (ie, patients who traditionally have been managed with upfront resection) actually have true stage I disease and the benefit associated with MMT.[10] Because data from the existing adjuvant trials are based on a very small proportion of stage I patients, our current study of more than 1,200 PDAC patients with true stage I disease provides 2 novel and important conclusions. First, nearly three quarters of clinical stage I patients actually have higher-stage disease on final pathology, nearly half of whom are node positive. Second, although adjuvant therapy is currently recommended in the management of all PDAC patients, our findings suggest it may not be beneficial in those who truly have stage I disease.

Currently, adjuvant therapy is considered an important and beneficial part of MMT for patients with PDAC and is recommended for all patients, regardless of stage.[2] CONKO-001 demonstrated a 5-year OS survival benefit among patients treated with adjuvant gemcitabine relative to resection alone (20.7% and 10.4%).[6,12] ESPAC-4 reported a survival benefit associated with the use of a multiagent adjuvant regimen (ie, gemcitabine and capecitabine) compared with single-agent gemcitabine alone (28.8% vs 16.3%).[13] However, only a small proportion of enrolled patients in these 2 trials had early-stage disease—T1/T2 tumors accounted for only 14% of the CONKO-001 cohort, and only 3% of patients in ESPAC-4 had stage I disease. These small numbers of patients with early-stage PDAC in these trials are likely attributable to the fact that greater than 80% of incident PDAC cases present as regional or distant disease.[1] Given the extremely low accrual of patients with stage I disease in existing PDAC adjuvant trials, it seems unlikely a randomized trial to further evaluate this topic among such patients could ever be performed.

Decisions regarding the use of MMT in the management of patients with PDAC, including the use of neoadjuvant therapy, are typically based on the best available information regarding stage of disease at presentation. It is therefore important to understand how well contemporary clinical staging modalities perform in patients for whom upfront resection is being considered. Currently, computed tomography or magnetic resonance imaging paired with adjunctive endoscopic ultrasound are recommended as part of preoperative or pretreatment staging.[5] However, paramount to accurate staging and, thus, determination of resectability is precise discernment of primary measurements, vascular invasion, and nodal status. Recent meta-analyses have found relatively poor positive predictive value for computed tomography in determining resectability ranging from 61% to 81% (ie, between 19% and 39% of patients have more advanced disease than is detected by this modality alone).[14,15] Endoscopic ultrasound is another commonly used preoperative staging modality that provides local anatomic details and offers the added benefit of tissue biopsy. However, among patients believed to have resectable disease on CT, it does not clearly provide additional information or value in ascertaining resectability—an estimated 13% of those with an endoscopic ultrasound predicting unresectable disease are actually resectable, and 20% of those with an endoscopic ultrasound predicting resectable disease are actually unresectable.[15] Our finding that T understaging was detected in nearly two thirds of patients would appear to corroborate these data regarding the limitations of contemporary clinical staging modalities. Another likely contributory factor is in prior iterations of the American Joint Committee on Cancer (AJCC) pancreatic cancer staging guidelines distinguishing between T1/2 and T3 tumors was dependent on the identification of extra-pancreatic extension. By comparison, in the most recent edition of the AJCC staging guidelines, this same distinction is based purely on the size of the primary tumor. It seems likely this change will improve the accuracy of T staging and help to more clearly identify patients who may have stage I disease—at least, based on the status of their primary tumor. With respect to regional nodal staging, our group

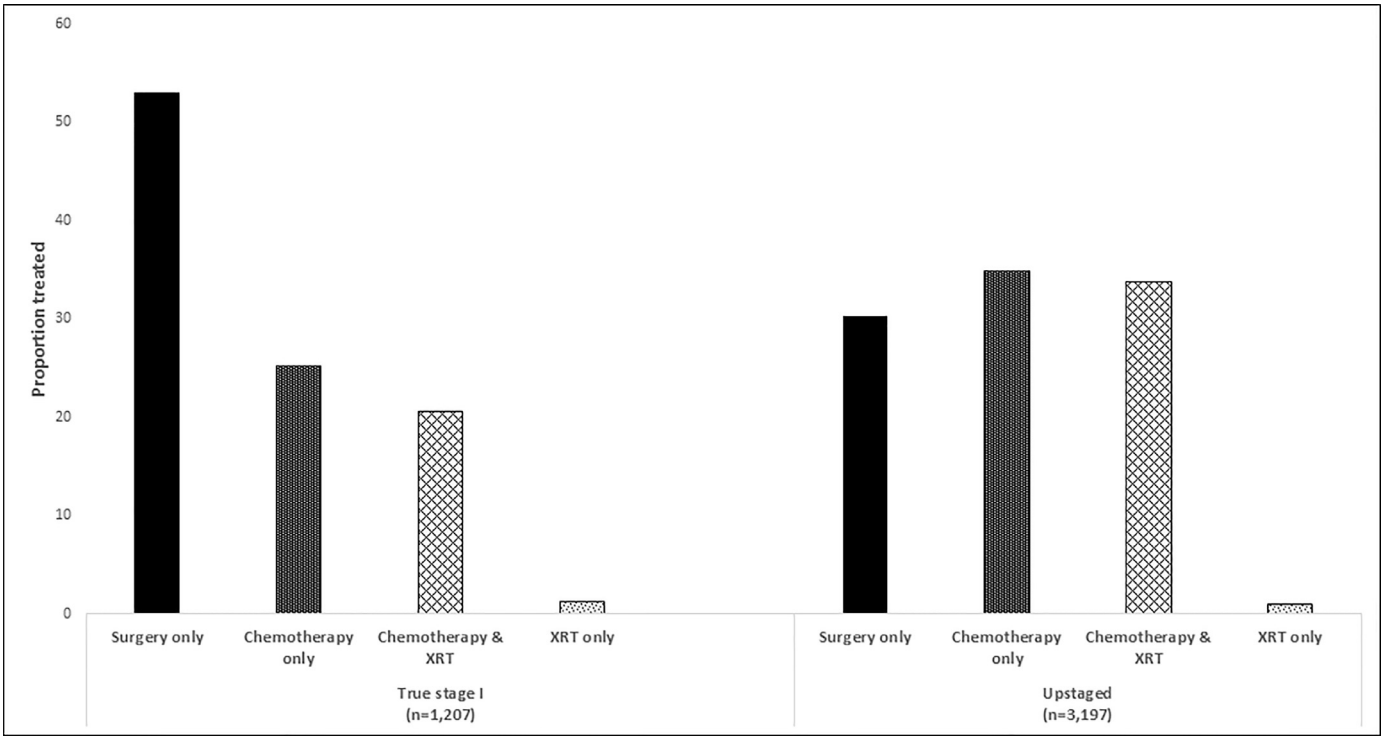
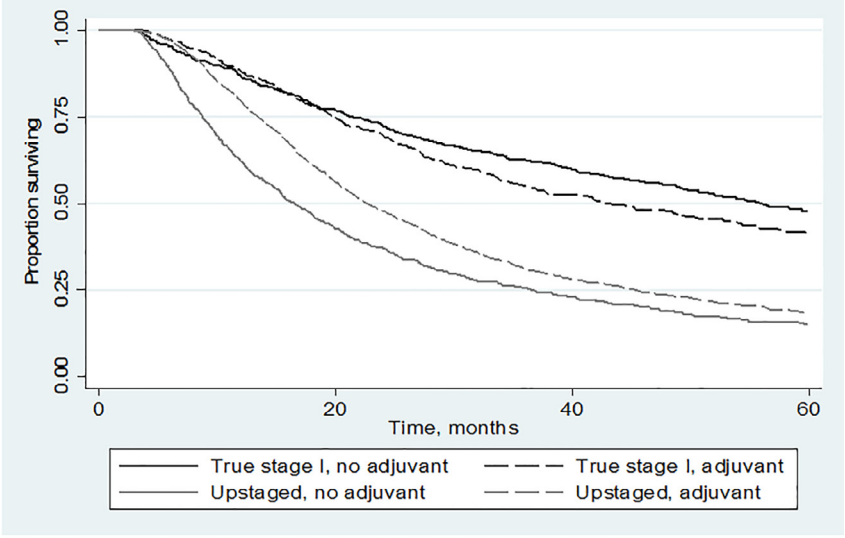


Fig. 3. Treatment strategies utilized among true stage I and upstaged patients. *XRT,* radiation therapy.



Number at risk

True stage I, no adjuvant	599	423	258	151
True stage I, adjuvant	564	403	232	133
Upstaged, no adjuvant	804	314	123	45
Upstaged, adjuvant	2,220	1,176	442	197

Fig. 4. Overall survival of true stage I and upstaged patients stratified by the use of adjuvant therapy.

recently evaluated a large cohort of PDAC patients with stage I–II disease and found contemporary preoperative staging modalities have poor negative predictive value (49.8%), indicating nearly half of patients found to be clinically node negative are actually node positive.[10]

Taken together, these data suggest that clinicians are frequently treating "early-stage" PDAC patients who actually have more advanced disease than suggested by preoperative staging modalities. Given the high degree of clinical understaging among our cohort of clinical stage I patients, an important question emerges: What is the optimal approach to the management of patients who present with clinical stage I disease? Our data suggest that ~73% of these patients will actually have higher-stage disease on final pathology and clearly benefit from the use of MMT. However, our data also indicate that MMT is underused in these patients, with roughly 30% not receiving adjuvant therapy after upfront resection. Between half and two thirds of patients in CONKO-001, ESPAC-1, ESPAC-3, and ESPAC-4 completed all intended cycles of adju-

vant therapy.[6-7,12-13,16] Not surprisingly, this is also an issue in the general community, where over the past 2 decades, less than 50% of patients received adjuvant treatment after resection.[9,17] As such, an ongoing debate regarding the optimal management of PDAC patients presenting with potentially resectable disease is how best to use MMT—upfront resection followed by adjuvant treatment or neoadjuvant treatment?

Although neoadjuvant treatment is increasingly used in the management of patients presenting with borderline resectable disease, it is now also included in the recently released American Society of Clinical Oncology management guidelines for patients presenting with resectable disease.[18] In this regard, greater utilization of neoadjuvant treatment could be a feasible approach to increase the proportion of patients who complete MMT. In fact, because of the traditionally high rate of noncompletion of adjuvant therapy after upfront resection and because the majority patients believed to have early-stage disease in actuality have more advanced disease, a strong argument should be made that presently all patients presenting with PDAC, regardless of perceived stage, should be considered for neoadjuvant therapy, preferably in the context of a clinical trial. This is particularly relevant given that our findings on the lack of benefit of adjuvant therapy in patients with true stage I disease cannot be extrapolated to imply a lack of benefit for neoadjuvant therapy. Although recent changes to the AJCC staging system may improve the accuracy of T staging, in the absence of contemporary clinical staging modalities that are more robust for identifying nodal metastases, it is unclear that additional efforts to identify patients who could have true stage I disease on the basis of T stage will help to inform decisions about the need for adjuvant therapies. By comparison, in patients for whom upfront resection is performed and are found on final pathology to have true stage I disease, our data suggest older adjuvant regimens are unlikely to be beneficial and more modern regimens should be considered instead. Many patients in our cohort may have been treated with older systemic therapy regimens (given our study period), and as such, our findings regarding the lack of benefit for adjuvant therapy in patients with true stage I disease may not generalize to newer, more efficacious regimens. However, although more effective, these regimens can be more difficult for patients to tolerate, especially in the postoperative setting; thus, when being considered, they may be best administered and tolerated as neoadjuvant therapy.

These findings need to be interpreted in the context of several limitations. The NCDB does not indicate the type of preoperative imaging modality used to ascertain clinical staging for each patient. However, NCDB clinical staging data are based on the best available information used by the care team for treatment planning and therefore likely provide an accurate reflection of actual clinical practice and the real-world effectiveness of contemporaneous clinical staging modalities used in the general community. Information on the specific chemotherapy regimen used and the number of cycles of chemotherapy received is not available, which could have influenced our findings regarding the lack of benefit of adjuvant therapy in true stage I patients. However, in trials comparing single-agent gemcitabine with multiagent regimens in both the metastatic and adjuvant settings, the observed difference in median overall survival was limited to between 2 and 4 months.[3-4,13] Data regarding the intent of treatment, clinical decision-making, and patient preferences are not provided. Postoperative complications are not reported by the NCDB. Because of the retrospective nature of the study, selection bias in estimating the associated benefit of adjuvant therapy (specifically, survivor-treatment bias; ie, patients who did well postoperatively, did not have complications, and survived the perioperative period would be more likely to receive adjuvant treatment) is a potential concern. However, we applied a 90-day landmark in all survival analyses to help mitigate (to the extent possible) the impact of such bias. Finally, NCDB does not provide any information on disease recurrence or disease-free survival.

Data from ongoing trials investigating preoperative FOLFIRINOX and gemcitabine/nab-paclitaxel with or without radiation treatment for resectable PDAC will likely provide important information that can help to optimize MMT for patient with PDAC.[19-22] But, because stage I patients represent a very small proportion of those enrolled in randomized PDAC adjuvant trials and because of the previously described nodal downstaging effect of neoadjuvant treatment, these studies will be unlikely to truly address the benefit of MMT in this subgroup of patients. As such, our results add important information to the ongoing conversation around the use of neoadjuvant treatment, rather than upfront surgical resection, in patients presenting with resectable disease. Because a future randomized trial focused on stage I patients seems unlikely, our work provides useful data that should be used at the point of care to inform discussions with patients about the likelihood of upstaging, the benefits of MMT, and the possibility of over- or undertreatment and to better personalize MMT for PDAC patients in the context of their personal preferences and risk tolerance.

Acknowledgments

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, Baylor College of Medicine, or the American College of Surgeons Commission on Cancer. The data used in this study are derived from a de-identified National Cancer Database file. 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.

Conflict of interest

The authors have no conflicts of interest to disclose.

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