Surgical Outcomes Following Neoadjuvant Treatment for Locally Advanced and Borderline Resectable Pancreatic Ductal Adenocarcinoma

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Objective: To assess overall survival (OS), compare the effects of neoadjuvant treatment, and describe surgical outcomes for patients undergoing pancreatic resection following chemotherapy and/or chemoradiotherapy (CRT) for borderline resectable (BR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC).

Background: We approach BR/LA PDAC using chemotherapy followed by selective CRT to the primary site of disease where either the surgical margin remains radiologically threatened following chemotherapy or as a further downstaging treatment.

Methods: Retrospective study of patients between December 2005 and June 2023 at the Royal Marsden Hospital, London, United Kingdom.

Results: A total of 54 patients were included. The OS between R1 and R0 patients was significantly different: 7.5 versus 23 versus 42 versus 51 months for R1 chemo, R1 chemo and CRT, R0 chemo and R0 chemo, and CRT groups, respectively, $P < 0.001$. Similarly, 9 versus 18 versus 42 versus 41 months for N1 chemo, N1 chemo and CRT, N0 chemo and N0 chemo, and CRT groups, respectively, $P = 0.0026$. Multivariable Cox regression model demonstrated that perineural invasion (hazard ratio: 2.88, 95% confidence interval: 1.06–7.81; $P = 0.038$) and perivascular invasion (PVI) (HR: 2.76, 95% CI: 1.24–6.13; $P = 0.013$) were associated with significantly worse OS. Chemo and CRT conferred OS benefit compared to chemo only (7 vs 23 months, $P = 0.004$) in PVI-positive patients.

Conclusions: Neoadjuvant chemotherapy followed by CRT compared to chemotherapy alone for resected BD and LA PDAC was demonstrated to significantly improve median OS, in particular, in patients with R1 resection margins, ypN1 nodal status, and perivascular invasion.

Keywords: chemoradiation, neoadjuvant treatment, pancreatic cancer

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related deaths globally. In the United States, the 5-year survival of PDAC has increased from 5% in 2020 to 11% currently.[1] However, the incidence of PDAC is also increasing in those aged 55 or younger[2] and particularly in females.[2] Due to the lack of specific symptoms, almost 50% of patients already have advanced disease at the time of diagnosis.[3] Similar trends are observed in the United Kingdom.[4] The modest improvement in survival is due to a variety of factors including improved surgical techniques, improved perioperative care, and the use of multimodal systemic neoadjuvant chemotherapy and other oncological treatments including radiotherapy.[5]

At the time of diagnosis, PDAC is classified into 4 categories: upfront resectable, borderline resectable (BR), locally advanced (LA), or metastatic disease. The National Comprehensive Cancer Network guidelines[6] describe resectable disease as no arterial contact and less than 180-degree tumor-venous interface with no contour irregularity. BR and LA disease are classified according to the presence and degree of involvement with adjacent major venous (portal vein, superior and inferior mesenteric vein, and splenic vein) and arterial structures (aorta, hepatic artery, superior mesenteric artery, and celiac axis) as well as the potential for resection and reconstruction.

Surgical resection followed by adjuvant chemotherapy is the recognized standard of care for resectable disease.[7] The ESPAC-5 trial results supported the role of neoadjuvant chemotherapy for BR PDAC,[8] and the use of neoadjuvant treatment in the LA PDAC setting has also contributed to the improved rates of complete resection and subsequent overall survival (OS).[9]

Neoadjuvant treatment serves to downstage advanced disease for local control, improve complete resection rates, treat presumed occult micro-metastasis for systemic control, and serves as a test of tumor biology, selecting against those with biologically aggressive disease where major resectional surgery may not contribute to improved outcomes. Ultimately, the only realistic route to a cure is radical resection with clear margins (R0).[10] For patients with LA PDAC, with the appropriate neoadjuvant strategies, it is possible to achieve survival rates of over 3 years[11–13]; however, the optimal neoadjuvant strategy is yet to be fully established.

The PREOPANC-1 trial demonstrated that neoadjuvant chemoradiation followed by surgery and adjuvant gemcitabine improved long-term OS when compared to upfront surgery alone in patients with BR or resectable PDAC.[14] The Alliance A021501 trial reported no difference in OS between preoperative mFOL-FIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy for BR PDAC.[15] The recently reported PREOPANC-2 trial also found no difference in OS when comparing neoadjuvant FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) to gemcitabine-based chemoradiation in patients with BR or resectable PDAC[16]; however, no patients were treated in a combined manner with chemotherapy followed by chemoradiation.

Neoadjuvant chemoradiation has been demonstrated to improve R0 resection rates.[17,18] The Conko-007 trial also reported that neoadjuvant chemotherapy followed by chemoradiation in LA PDAC improved R0 rates but surprisingly this did not demonstrate an impact on OS.[19] Finally, in the nonsurgical setting, the Lap07 trial only demonstrated progression-free benefit and not OS benefit in patients with LA nonresectable PDAC treated with chemotherapy versus chemotherapy and chemoradiation.[20]

At our institution, we approach BR/LA PDAC using chemotherapy followed by selective chemoradiation to the primary site of disease where either the surgical margin remains radiologically threatened following chemotherapy or as a further downstaging treatment to give patients with advanced disease the best chance of reaching resectability, achieve complete margins, and a potential chance at a cure.

We hereby present our single UK tertiary institution experience of patients undergoing pancreatic resection following chemotherapy and/or chemoradiotherapy for BR or LA PDAC.

METHODS

Study Description

This is a retrospective study of a prospectively maintained database. Approval for the study was provided by the Royal Marsden NHS Foundation Trust (CCR5615). It includes all patients undergoing pancreatic resection following chemotherapy or chemotherapy followed by chemoradiotherapy for BR or LA PDAC between December 2005 and June 2023 at the Royal Marsden Hospital, London, United Kingdom. The time of analysis was January 2024. Clinical, biochemical, and radiological investigations relevant to each patient's case are discussed weekly in a dedicated pancreatic multidisciplinary team at each stage of the treatment pathway. The primary aim of this study was to assess OS, and secondary aims include comparing the effects of neoadjuvant treatment, describing surgical outcomes, and identifying factors that improve OS. OS is calculated from the day of surgery to nullify any bias caused by variations in the duration of neoadjuvant treatment.

Informed Consent Statement

All patients provided informed consent at the time of surgery, and the manuscript contains no patient-identifiable data. Informed consents were conducted in accordance with the ethical standards of the Helsinki Declaration of 1975.

Treatment Protocol

All pancreatic masses are assessed with triple-phase computed tomography (CT) imaging and staged as per National Comprehensive Cancer Network 2019 guidelines.[6,21] [18]Fluorodeoxyglucose-positron emission tomography (FDG-PET) is utilized routinely at our institution to exclude metastatic disease. Magnetic resonance imaging is utilized only in select cases, mainly as an adjunct to assess for the presence of liver or adrenal metastasis. A histological diagnosis of PDAC was required before the commencement of systemic anticancer treatments. This is obtained via endoscopic ultrasound-guided fine needle biopsy or endoscopic retrograde cholangiopancreatography. Biliary drainage in patients with jaundice is achieved using a self-expanding metal biliary stent. Patients' serum Ca19-9 levels are also monitored throughout the treatment pathway.

The standard neoadjuvant chemotherapy regimen is 12 cycles of FOLFIRINOX. Following completion of treatment, restaging CT imaging is reviewed by a dedicated pancreatic radiologist at multidisciplinary team. If there is still arterial or venous abutment with potentially resectable and reconstructable disease, or if the R1 risk remains high, patients are then treated with chemoradiation. The current regimen is 45 Gy in 15 fractions with oral capecitabine as a radiosensitizer.

Further, reassessment is taken at 4 weeks post chemoradiation. To proceed with surgical resection, patients should have no evidence of disease progression on CT imaging, a sustained Ca19-9 response if the tumor was secretory at diagnosis, and exhibit a sustained metabolic response on FDG-PET imaging. Finally, the patient's Eastern Cooperative Oncology Group performance status (ECOG PS) following neoadjuvant treatment is assessed and cardiopulmonary exercise testing is utilized to objectively assess fitness for major surgical resection.

Follow-Up

The follow-up protocol consists of 3-monthly clinical reviews with blood tests in the first 2 years postoperatively followed by 6 monthly reviews thereafter. CT thorax, abdomen, and pelvis imaging is performed every 6 months during the first 2 years of follow-up and then on an annual basis. Patients are discharged after 5 years of follow-up.

Statistical Analysis

Continuous data are presented as median (with interquartile range), and categorical data as the absolute number (percentage). Univariate analysis is as follows, paired t-test for parametric paired data, Wilcoxon rank sum test for paired nonparametric data, and Mann–Whitney U test for unpaired nonparametric data. Pearson chi-square test or Fisher exact test was used to compare groups of categorical data. Kaplan–Meier curves were produced to analyze OS. Comparison between groups was performed using a log-rank test. Univariate and multivariable Cox proportional hazard models were used to evaluate the effect of multiple factors on OS. Statistical significance was defined by $P \leq 0.05$. All statistical analysis and graphics were performed and produced using RStudio (Boston, MA, US, version 2023.12.1 + 402).

RESULTS

Patient Demographics

A total of 54 patients were included in this series. Thirty-seven received neoadjuvant chemotherapy followed by chemoradiation and 17 received neoadjuvant chemotherapy alone prior to surgical resection. The groups will be abbreviated respectively as "CRT" and "Chemo" for the purposes of discussion (Table 1). There were no significant differences between the 2 groups' baseline demographics including age, body mass index, American Society of Anaesthesiologist grade, and ECOG PS. Twenty-two (59%) and 15 (88%) patients had elevated Ca19-9 at the point of diagnosis, respectively, defined as over 37 units/mL.

Neoadjuvant Treatment

As per our institution's treatment protocol, 73% and 82% of patients were treated with FOLFIRINOX in the CRT and Chemo groups, respectively. Second-line chemotherapy was gemcitabine and capecitabine (Supplemental Figure 1, see http://links.lww.com/AOSO/A400). Chemoradiation regimes are listed

Comparison of Patient Demographics for Each Study Group

	CRT	Chemo	*P*
n	37	17	NA
Age, yr	65.0 (57.5.0-72.5)	70.0 (64.5-75.5)	0.59
BMI, kg/m^2	23.0 (20.5-25.5)	23.0 (20.6-25.4)	0.86
Female:male, n	17:20	7:10	NA
ASA, n (%)			0.45
1	4 (11)	2 (12)	
2	29 (78)	11 (65)	
3	4 (11)	3 (24)	
ECOG PS, n (%)			0.77
0	16 (43)	7 (41)	
1	20 (54)	10 (59)	
2	1 (3)	0 (0)	
Diabetes, n (%)	28 (76)	7 (41)	0.34
Patients with elevated Ca19-9 at diagnosis, n (%)	22 (59)	15 (88)	0.15
Ca19-9 at Diagnosis, units/ml	319.5 (175.0-2142.0)	1097.0 (448.0-1918.5)	0.27
BR, n (%)	14 (38)	7 (41)	1.00
LA, n (%)	23 (62)	10 (59)	

ASA indicates American Society of Anaesthesiologist; BMI, body mass index; NA, not applicable.

in Supplemental Table 1, see http://links.lww.com/AOSO/A400. Only 22 (59.5%) and 6 (35.4%) patients completed the planned cycles of chemotherapy within the CRT and Chemo groups, respectively. The median time from diagnosis to completion of neoadjuvant treatment (NAT) was 8 (5–11) months for CRT and 5 (4–6) months for chemotherapy only. The median time from completion of NAT to surgical resection was 12 (5–19) weeks for CRT and 8 (4–12) weeks for chemo only.

Surgical Outcomes

The majority of patients underwent classic Whipple's pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy (for full breakdown of procedures, see Supplemental Figure 2, http://links.lww.com/AOSO/A400). Six (16.2%) and 2 (11.7%) operations were performed minimally invasively, and 20 (54.1%) and 10 (58.8%) involved venous resection with or without reconstruction for CRT and Chemo groups, respectively.

There were no statistically significant differences in critical care unit days, length of stay, inpatient transfusion rate, Clavien–Dindo complication rates, postoperative pancreatic fistula rate, delayed gastric emptying, and 30-day reintervention, readmission, and mortality rates between the 2 groups (Table 2). There were two 30-day mortalities in this study. Within the CRT group (n = 1), the patient passed away in the critical care unit despite maximal support due to postoperative liver failure with no radiological evidence of impaired arterial or venous blood

Comparison of Perioperative and Pathology Outcomes for Each Study Group

	CRT	Chemo	P
Critical care unit, d	3.0 (1.5–3.5)	2.0 (1.0–3.0)	0.45
LOS, d	12.0 (5.0–19.0)	13.0 (9.0–17.0)	0.59
Preoperative hemoglobin, g/L	128.0 (114.0–141.0)	121.0 (113.5–128.5)	0.26
IP transfusion (%)	11 (29.8)	1 (5.9)	0.08
Hb on discharge	104.0 (94.0–114.0)	101 (93.0–109.0)	0.72
CD			0.62
II (%)	12 (32.4)	8 (47.1)	
III (%)	4 (10.8)	1 (5.9)	
IV (%)	2 (5.4)	2 (11.8)	
POPF			1.0
Grade A (%)	2 (5.4)	0 (0)	
Grade B (%)	0 (0)	1 (5.9)	
Delayed gastric emptying	4 (10.9)	2 (11.8)	1.0
30-d reintervention (%)	5 (13.5)	2 (11.8)	1.0
30-d readmission (%)	6 (16.2)	2 (11.8)	0.99
30-d mortality (%)	1 (2.7)	1 (5.9)	0.54
Adjuvant chemotherapy	9 (24.3)	7 (41.1)	0.35
Postoperative pathology			0.17
Poorly differentiated (%)	11 (29.7)	8 (47.0)	
Moderately differentiated (%)	14 (37.8)	4 (23.5)	
Well differentiated (%)	1 (2.7)	0 (0)	
Mucinous differentiation (%)	1 (2.7)	2 (11.8)	
Complete pathological response (%)	10 (27.0)	3 (17.6)	
Perineural invasion (%)	11 (29.7)	7 (41.2)	0.60
Perivascular invasion (%)	12 (32.8)	4 (23.5)	0.73
R1 (%)	14 (37.8)	4 (23.5)	0.47

CD indicates Clavien–Dindo classification; Hb, hemoglobin; IP, inpatient; LOS, length of stay; R1, positive resection margin.
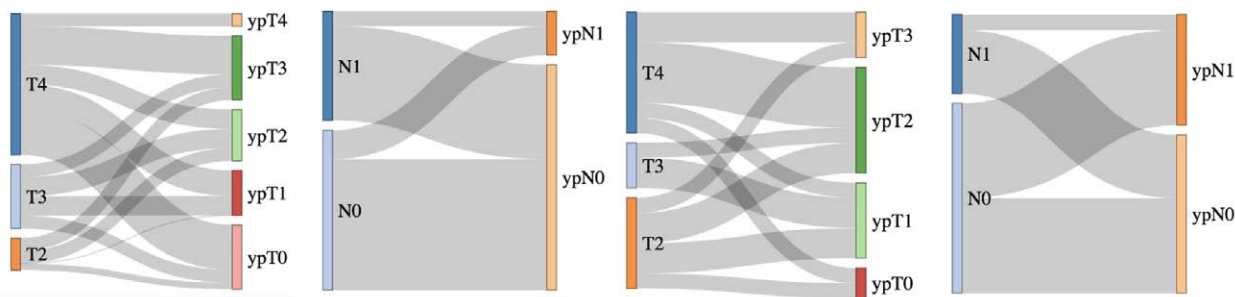
FIGURE 1. Sankey diagram illustrating downstaging effects of NAT, preoperative radiological staging compared to postoperative histological staging (left to right: chemotherapy and CRT: T staging, N staging; chemotherapy only: T staging, N staging).

flow. Within the Chemo group (n=1), 1 patient passed away due to an out-of-hospital cardiac arrest after discharge from the hospital.

Preoperative tumor and nodal staging are compared to post neoadjuvant treatment and surgical resection histological findings in Figure 1 (for full breakdown, see Supplemental Table 2, see http://links.lww.com/AOSO/A400). The median lymph node yield was 20 (13–27) nodes in the CRT group and 22 (10.5–32.5) nodes in the Chemo group. There were no statistically significant differences in postoperative histopathology, perineural invasion (PNI) rates, perivascular invasion (PVI) rates, and R1 resection rates between the 2 groups (Table 2).

Survival Analysis

The median OS was 36 months in the CRT group and 26 months in the Chemo group, although this was not statistically significant with log-rank testing ($P = 0.32$) (Supplemental Figure 3, see http://links.lww.com/AOSO/A400). The OS between those who achieved R0 versus R1 was significantly different, 7.5 months R1 chemo only group, 23 months R1 CRT group, 42 months R0 chemo only group, and 51 months R0 CRT group (Fig. 2, $P < 0.001$). Similarly, the OS between those who achieved N0 versus N1 status was also significantly different, 9 months N1 chemo only group, 18 months N1 CRT group, 42 months N0

chemo only group, and 41 months N0 CRT group (Fig. 3, $P = 0.0026$).

Univariate Cox regression analysis was performed to identify factors that affect OS. A multivariable Cox regression model was then utilized to evaluate the simultaneous effect of significant factors on OS. PNI (hazard ratio [HR]: 2.88, 95% confidence interval [CI]: 1.06–7.81; $P = 0.038$) and PVI (HR: 2.76, 95% CI: 1.24–6.13; $P = 0.013$) was associated with significantly worse OS (Table 3).

The OS between those with PNI-0 versus PNI-1 was significantly different, 15 months PNI-1 chemo only group, 13 months PNI-1 CRT group, 42 months PNI-0 chemo only group, and 36 months PNI-0 CRT group ($P < 0.001$, Supplemental Figure 4, see http://links.lww.com/AOSO/A400). The OS between those with PVI-0 versus PVI-1 was also significantly different, 7 months PVI-1 chemo only group, 23 months PVI-1 CRT group, 42 months PVI-0 chemo only group, and 38 months PVI-0 CRT group (Fig. 4, $P = 0.0004$).

DISCUSSION

This is the largest series of patients undergoing surgical resection following NAT for BR or LA PDAC reported to date from the United Kingdom. There were no significant differences in baseline demographics between the chemotherapy alone (Chemo) or chemotherapy followed by chemoradiotherapy (CRT) study groups.
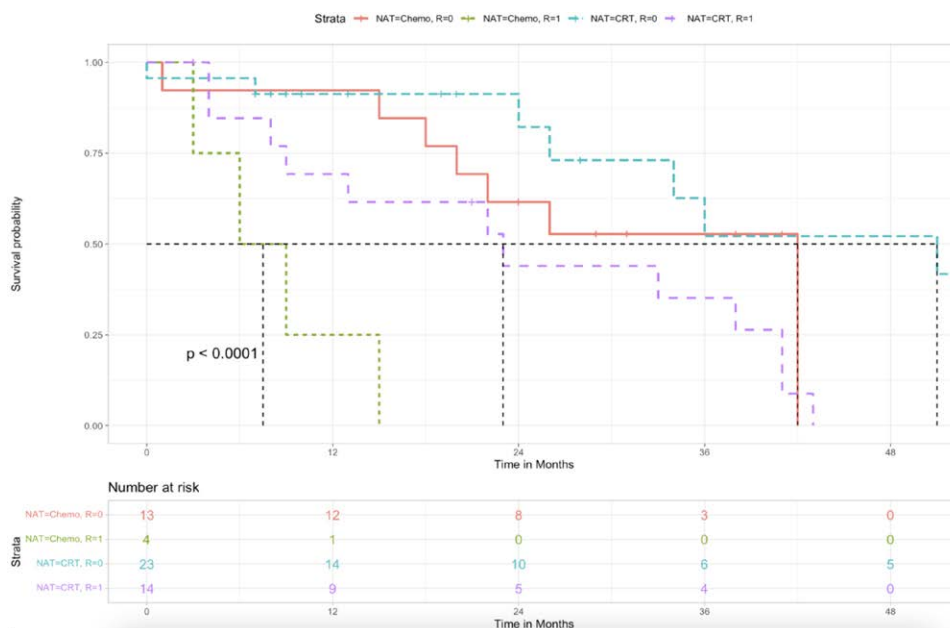

FIGURE 2. Kaplan–Meier plot: R0 versus R1 median overall survival: chemo R1 (green) 7.5 months versus CRT R1 (purple) 23 months versus Chemo R0 (red) 42 months versus CRT R0 (blue) 51 months, $P < 0.0001$.
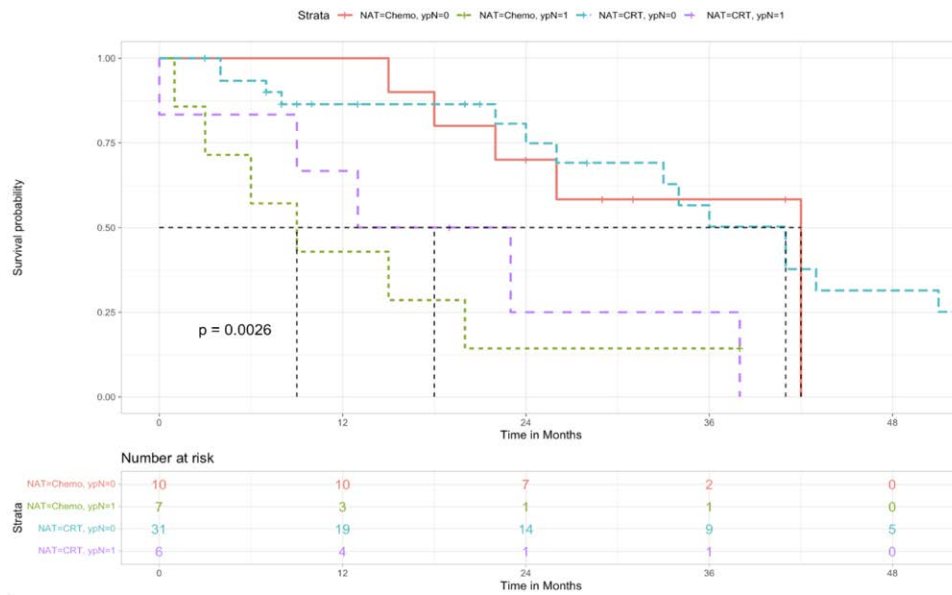
FIGURE 3. Kaplan–Meier plot: N0 versus N1 median overall survival: chemo N1 (green) 9 months versus CRT N1 (purple) 18 months versus chemo N0 (red) 42 months versus CRT N0 (blue) 41 months, *P* = 0.0026.

TABLE 3.

Multivariate Cox Regression, Hazard Ratio for Factors Contributing to Overall Survival in Study Cohort

Characteristic	Hazard Ratio	95% Confidence Interval	*P*
Neoadjuvant treatment			
Chemotherapy	—	—	—
Chemotherapy and CRT	0.42	0.14–1.24	0.12
Ca19-9 at diagnosis	1.0	1.00–1.00	0.40
Ca19-9 following NAT	1.0	1.00–1.00	0.70
R	1.39	0.44–4.41	0.60
ypT	1.34	0.87–2.07	0.20
ypN	1.46	0.47–4.53	0.50
PNI	2.88	1.06–7.81	0.038
PVI	2.76	1.24–6.13	0.013

CRT indicates chemoradiation; R, resection margin status; ypN, postoperative lymph node status following neoadjuvant therapy; ypT, postoperative histological tumor stage following neoadjuvant therapy.
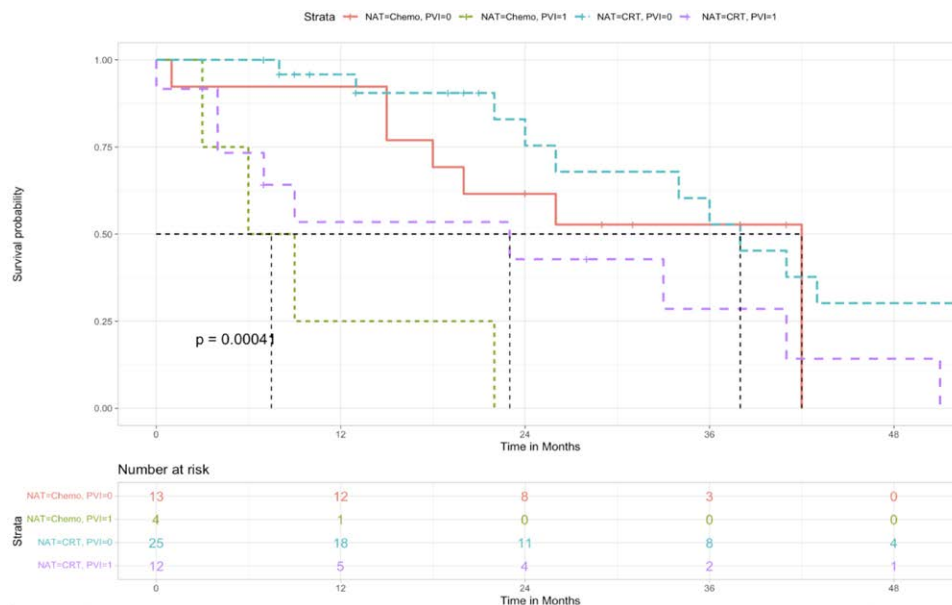

FIGURE 4. Kaplan–Meier plot: PVI median overall survival: chemo PVI-1 (green) 7 months versus CRT PVI-1 (purple) 23 months versus chemo PVI-0 (red) 42 months versus CRT PVI-0 (blue) 38 months, *P* = 0.0004.

When considering surgical OS, the duration of NAT is often overlooked and not included in the conventional calculation of OS, which typically begins from the date of surgery. However, in reality, the duration of treatment does contribute to a patient's survival from the point of diagnosis. In this study, the median time from diagnosis to the completion of NAT was 8 months for the CRT group and 5 months for the chemotherapy group. When including the median time from the completion of NAT to surgery, the total median duration extends to almost 10 months for the CRT group and 8 months for the chemotherapy group. Given the poor 5-year survival rates for PDAC, this duration is not insignificant.

It is also important to discuss that while 12 cycles of FOLFIRINOX is our institution's first-line chemotherapy regime, a large proportion of patients did not complete the planned cycles of treatment due to reported toxicities. A recent meta-analysis and systemic review comprising 2930 patients reviewed neoadjuvant chemotherapy regimens for BR or LA PDAC and reported that OS was superior with neoadjuvant FOLFIRINOX, but patients who eventually underwent surgical resection were found to have similar outcomes when comparing FOLFIRINOX to gemcitabine-based regimens.[22] With the higher side effect profile, there is an argument to utilize less toxic neoadjuvant chemotherapy regimens, particularly in the BR resectable setting if patients are expected to undergo surgical resection. Recent evidence suggests that undergoing 12 cycles of FOLFIRNOX does not lead to additional survival benefits compared to 8 to 11 cycles in cases of BR PDAC followed by surgical resection.[23] Therefore, the optimal treatment duration still needs to be defined. Ultimately, the ability to predict a patient's response to treatment or grade how aggressive tumor biology is will be invaluable in the future to guide personalized treatment plans.

The primary endpoint median OS was 36 months in the CRT group compared to 26 months in the Chemo group, although this was not statistically significant ($P = 0.32$). The OS in the Chemo group was similar to those recently reported in the NORPACT-2 study where patients who underwent systemic chemotherapy followed by surgical resection were found to have a median survival of 24.4 months for BR PDAC and 28.4 months for LA PDAC.[24]

On further analysis, several key factors have a significant influence on the reported OS. Resection margin status is a well-established prognostic factor for resected PDAC.[25] In this study, R1 patients who received chemotherapy only achieved a median OS of only 7.5 months. Patients who received chemotherapy followed by chemoradiotherapy, despite an R1 resection, had a median OS of 23 months. At the same time, the median OS for R0 was 42 months and 51 months, respectively. Over half of the patients within both study groups required venous resection and/or reconstruction, similar to a recently published Dutch nationwide study for surgically resected LA PDAC.[26] The R1 rates reported in this study are not inferior to studies reporting similar neoadjuvant treatments followed by surgical resection.[22,27,28] A recently large study from the United States comprising over 10,000 PDAC patients who underwent surgical resection reported adjuvant chemoradiotherapy improved OS for R1 patients if adjuvant systemic treatment was delayed.[29] The underlying therapeutic mechanisms of which chemoradiation confers survival benefit may be similar in both scenarios and will require further investigation.

Similarly, the median OS for patients with ypN1 disease was only 9 months in the chemo only group compared to 18 months in the CRT group. Those with N0 have a significantly higher median OS of 42 and 41 months. The CRT group had a higher proportion of ypN0 nodal status and this is in keeping with neoadjuvant chemoradiation's effect on reducing lymph node positivity[17,30] but in this study, CRT also seems to confer improved OS despite ypN1 status.

There were also no significant differences in perioperative outcomes including critical care days, length of stay, and rates of significant complications. A higher proportion of patients from the CRT group required an inpatient blood transfusion (29.8% vs 5.9%, $P = 0.08$). Rates of postoperative pancreatic fistula (POPF) were low in both groups and the only grade B pancreatic fistula occurred in the chemo only group. It is the experience of the authors that NAT, in particular, chemoradiation is associated with lower POPF rates due to the effects on pancreatic texture. This finding was also reported by a Dutch systematic review comprising 25,389 patients treated with NAT followed by surgical resection for PDAC.[31] Our perioperative findings are also in keeping with the PREOPANC trial that reported no increased incidence of surgical complications in patients who received preoperative chemoradiotherapy and a lower incidence of POPF.[32]

Using multivariable Cox regression analysis, regardless of treatment group, PNI (HR: 2.88, 95% CI: 1.06–7.81; $P = 0.038$) and PVI (HR: 2.76, 95% CI: 1.24–6.13; $P = 0.013$) were associated with significantly worse OS. Other factors known to be associated with OS were not found to be statistically significant in multivariable Cox regression analysis. These factors include postoperative tumor staging (ypT) (HR: 1.34, 95% CI: 0.87–2.07; $P = 0.20$), postoperative nodal status (ypN) (HR: 1.46, 95% CI: 0.47–4.53; $P = 0.50$), and resection margin status (R) (HR: 1.39, 95% CI: 0.44–4.41; $P = 0.60$). Although, the HR values for each factor demonstrate expected trends, the possibility of type II statistical error due to low sample size must be considered.

The median OS difference between those with and without PNI was not dissimilar between the study groups. However, for those with positive PVI, CRT again seemed to confer a survival significant advantage compared to the chemotherapy alone (7 months versus 23 months). The negative prognostic value on OS by PNI and PVI has been previously reported[33] with neoadjuvant chemoradiation shown to reduce lymph and vascular invasion.[17] The current challenge is that both PNI and PVI are a postoperative histological diagnosis. In the future, if preoperative imaging,[34] biomarkers,[35] or even combined artificial intelligence models[36] can accurately detect PNI and PVI in the preoperative setting, then more aggressive treatments including CRT can be tailored for the individual patient. While a retrospective study cannot establish causality, it does provide evidence for further investigation. These findings also raise the question of whether the presence of PVI may also be considered as an indicator for patients to undergo adjuvant chemoradiation.

Finally, the assessment of response following NAT and the decision to proceed to surgical resection is of significant importance. Within our institution, it is now established within our pathway that following NAT, the disease should exhibit radiological stability, a sustained Ca19-9 response, and a sustained metabolic response on PET-CT before proceeding with surgical resection.

Ca19-9 is by no means an ideal biomarker but until a better biomarker is discovered and widely validated, it is still the only biomarker commonly utilized in PDAC. Circulating tumor DNA and other proteomic guided markers[37] shows promise as a biomarker for assessing response to neoadjuvant chemotherapy,[38] but until then, a combination of serum Ca19-9, CT, or magnetic resonance imaging in combination with FDG-PET is still the best modalities of assessing response to treatment and determination of resectability.[39,40] This study contributes to the now increasing evidence that the addition of chemoradiotherapy or radiotherapy after induction chemotherapy leads to improved local control and pathological response for PDAC,[41] but furthermore perhaps in specific patient groups such as those with R1 resection risk, nodal disease, and perivascular invasion. However, the reported clinical benefits of chemoradiation in particular translation to improve OS are still conflicting and require investigation further in a clinical trial setting with a treatment arm of combined neoadjuvant chemotherapy and chemoradiation.[42] Further studies should also aim to investigate the optimal duration of NAT

as well as factors such as completion of planned chemotherapy cycles and the effect of chemotherapy dose density on OS.

There are limitations to this study. It is a single-center retrospective series. Due to the extended timeframe, adjustments have been made to treatment pathways and thus not all NATs are identical. The statistical findings need to be validated with larger and international cohorts. Not all patients have reached 5 years follow-up yet, so the long-term effects of the treatments discussed are not fully established yet. Finally, the total number of patients who underwent NAT for PDAC regardless of progression to surgical resection was not available so the resection rate could not be calculated. The resection rates reported in the literature are between 46.9% and 60.6% (BR) or 13.0% and 28.0% (LA) PDAC.[13,22,24]

CONCLUSION

In summary, neoadjuvant chemotherapy followed by chemoradiation compared to chemotherapy alone for resected BR and LA PDAC was demonstrated in this series to significantly improve median OS, in particular, in patients with R1 resection margins, ypN1 nodal status, and perivascular invasion.

ACKNOWLEDGMENTS

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