Use and Outcomes from Neoadjuvant Chemotherapy in Borderline Resectable Pancreatic Ductal Adenocarcinoma in an Australasian Population

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Acknowledgements: The authors wish to thank the Walter and Eliza Hall Institute and contributors to the PURPLE database without with, this research would not be possible.

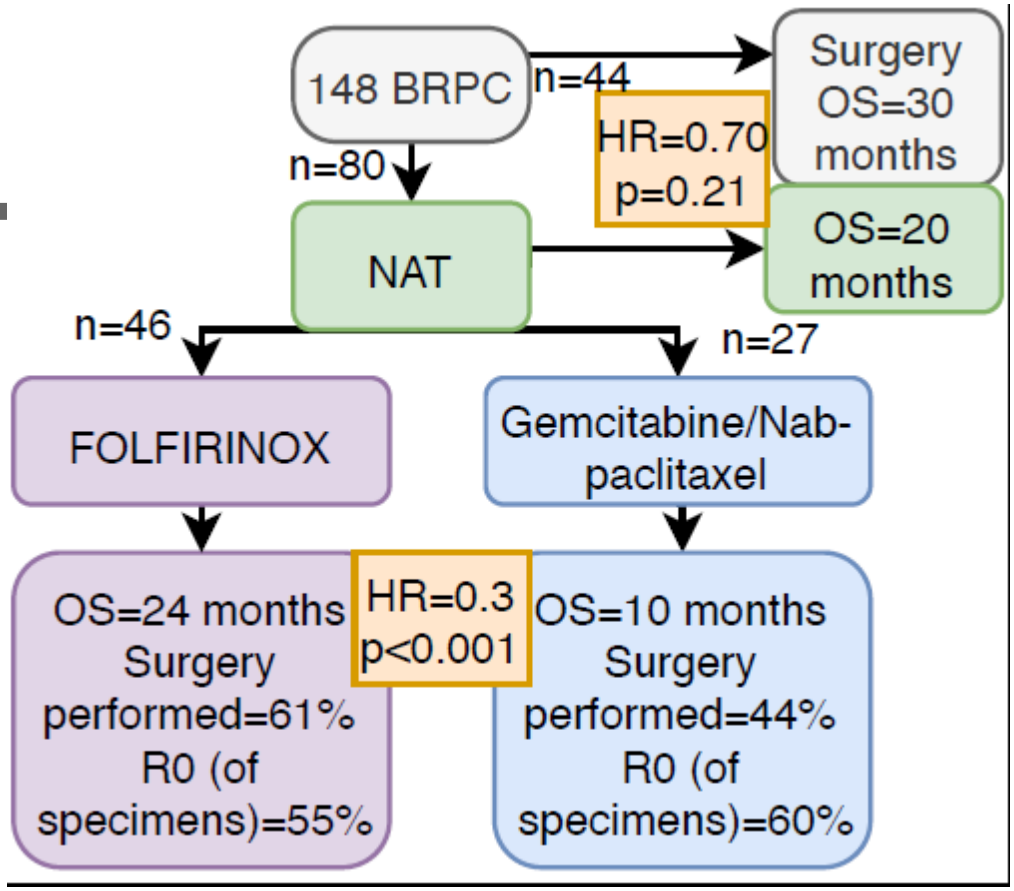
Conflicts of Interest: No conflicts of interest to declare.

Data Availability Statement: Data available on request from the authors

Ethics Approval Statement: The PURPLE registry has ethics approval at the sites at which data is collected. Further information is available through the Australian and New Zealand Clinical Trials Registry: ACTRN12617001474347.

Funding Statement: PURPLE receives funding from the Hemstritch Foundation, and Pancare Foundation. Dr Lee is the recipient of the Hemstritch Centenary Research Fellowship.

Background: Use of neoadjuvant (NA) chemotherapy is recommended when pancreatic ductal adenocarcinoma (PDAC) is borderline resectable. **Method**: Retrospective analysis of consecutive patients with localized PDAC between January 2016 until March 2019 within the Australasian Pancreatic Cancer Registry (PURPLE: Pancreatic cancer: Understanding Routine Practice and Lifting end results) was performed. Clinicopathological characteristics, treatment, and outcome were analysed. Overall survival (OS) comparison used Log-rank and Kaplan-Meier analysis. **Results**: There were 754 PURPLE cases with localized PDAC, including 148 (20%) as borderline resectable (BRPC). Of 148 BRPC, 44 (30%) underwent immediate surgery, 80 (54%) received NA chemotherapy and 24 (16%) were inoperable. Median age of NA therapy patients was 63yrs and FOLFIRINOX (53%) was more often used as NA therapy versus Gemcitabine/Nab-paclitaxel (31%). Patients who received FOLFIRINOX were younger vs Gemcitabine/Nab-paclitaxel (60 vs 67 yrs p=0.01). Surgery was performed in 54% (43 of 80) of BRPC patients receiving NA chemotherapy, with 53% (16 of 30) achieving R0 resections. BRPC undergoing surgery had a median OS of 30 months and 38% (9 of 24) achieved R0 resection. NA chemotherapy patients had a median OS of 20 months, improving to 24 months versus 10 months for patients receiving FOLFIRINOX compared to gemcitabine/nab-paclitaxel (HR 0.3 p<0.0001). **Conclusions**: NA chemotherapy use in BRPC is increasing in Australia. One half of patients receiving NA chemotherapy proceed to curative resection, with 53% achieving R0 resections. Patients receiving FOLFIRINOX had increased survival than Gemcitabine/Nab-paclitaxel. Treatment strategies are being explored in the MASTERPLAN and DYNAMIC-Pancreas trials.



This study aimed to describe the current practice in Australasia in managing potentially resectable pancreatic cancer. Description of neoadjuvant chemotherapy (NAT), surgical and survival outcomes in borderline resectable pancreatic cancer (BRPC) using real world data was extracted from PURPLE: Pancreatic cancer: Understanding Routine Practice and Lifting end results.

Keywords: Drug Therapy, General Surgery, Mortality, Neoadjuvant Therapy, Pancreatic Neoplasms

Word Count: 3442

Introduction:

Pancreatic ductal adenocarcinoma (PDAC) has high mortality even when primary surgical excision is possible. In 2019, 3599 new cases of pancreatic cancer were diagnosed in Australia (11.6 per 100000 persons) (1) and 3051 people died of pancreatic cancer. It is currently the 13th leading cause of death in Australia and is the cancer with the 5th highest mortality (1, 2). The mortality rate has not significantly changed since 1982 (1). Only 15-20% of patients have a surgical resection though still with a poor overall survival (OS) (18-20% 5 year stage I-II, 4-6% stage III-IV) (3, 4). R0 resection is the only patient subgroup with better long-term survival (5, 6). Chemotherapy post-surgery improves survival. Research into more effective treatments to improve R0 resection of pancreatic cancer is necessary, particularly when in locally advanced PDAC (LAPC) an improved chance of R0 resection may improve historically poor survival.

Patients with borderline resectable pancreatic cancer (BRPC) are a heterogenous group due to variation in definition and are a subset of LAPC. The best approach to downstage patients with BRPC to enhance operative success is unclear. The use of induction chemotherapy prior to surgery or radiotherapy selects out patients poorly responsive to chemotherapy which can guide further management (7). Current international guidelines suggest using a period of neoadjuvant (NA) treatment but there is no clear consensus on the best regimen (3, 8). Neither, has there been consensus on the use of chemotherapy versus chemoradiotherapy to improve response, resectability and survival.

R0 resections have been shown to correlate with improved OS and are used as a surrogate marker (5, 6, 9). Surgical conversion and R0 rate is improved by multimodality therapy (6, 10-26). However, the use of combined chemoradiotherapy in BRPC has not shown OS benefit compared to chemotherapy alone (5, 27-30) and confers greater toxicity (27, 28, 30-33). Combination chemotherapy, although increasing toxicity (34, 35) has been associated with a higher response and resectability (25). FOLFIRINOX as the chemotherapy backbone has been most effective (11, 12, 16, 35, 36) but recent data suggests similar survival with Gemcitabine/nab-paclitaxel in both localised and BRPC (37, 38). Current evidence includes various combinations of radiotherapy, surgery and chemotherapy with different types of chemotherapy regimens being used. Often different amounts of resectable and borderline resectable pancreatic cancer patients are included within studies. This

makes clear consensus about approach to BRPC patients difficult as clear superiority data is lacking. Data is mostly retrospective and LAPC is confined to small subgroup analysis of patients in studies of metastatic disease (35, 39).

Currently there is a lack of data surrounding LAPC and BRPC management and outcomes in the Australasian population. This is particularly true for the use of NA treatments. This study provides real world data on the use of NA chemotherapy in BRPC in the Australasian population.

Methods:

The aim of this study was to describe the current practice in Australasia in managing potentially resectable pancreatic cancer. This included describing the use of neoadjuvant therapies, surgical and survival outcomes in BRPC using real world data. A retrospective analysis was performed on data extracted from the prospective, PURPLE Pancreatic Cancer Registry (PURPLE: Pancreatic cancer: Understanding Routine Practice and Lifting end results) (ACTRN12617001474347), for consecutive patients with borderline resectable disease who received NA chemotherapy or proceeded to immediate surgery. This international multi-site prospective database collates key clinicopathological, treatment and outcome data across all stages of pancreatic cancer from Australia, New Zealand and Singapore. This database has been set up to capture all patients with PDAC at participating sites in Australasia to reflect current, real-world practice in an audit-type approach. Strict inclusion criteria are therefore not provided to sites who make determinations in resectability, stage, pathology and treatment as per local practice.

The selection of patients into categories of resectable, borderline resectable and unresectable were determined at the local site by initial imaging assessment at each institution's local multidisciplinary meeting (MDM). Definition of surgical standards for pancreatic cancer developed by the Australasian Gastro-intestinal Trials Group denote standard practice for sites in Australasia involved in this study (40). BRPC is subdivided into those requiring venous vascular resection, reconstruction and/or resection of adjacent organs (not typically included in pancreatic resection) and requiring for arterial resection and/or reconstruction (40). From this consensus statement this would include patients with (40):

- Venous involvement of the superior mesenteric vein or portal vein with venous distortion. Safe resection/replacement must be possible due to vessel availability proximal and distal.
- Gastroduodenal artery encasement up to hepatic artery with limited encasement or abutment of the hepatic artery without coeliac axis involvement.
- Tumour abutment inclusive of <180 degrees of circumference of superior mesenteric artery.

Within this consensus R0 resection is considered if all surgical margins are clear by >/=1mm (40). Further detailed information can be found in this consensus report (40). Data entry into the PURPLE registry is performed at the local site and reflects real-world interpretation of the staging categories and surgical resection criteria. Due to this, further review of patient information and imaging at MDM may subsequently have reclassified some patients as unresectable. Neoadjuvant chemotherapy choice was based on investigator discretion at local site and within the Pharmaceutical Benefits Scheme (PBS) reimbursement rules within Australia.

Patient characteristics, tumour characteristics, staging (according to the American Joint Committee on Cancer 7th edition), treatment administered including chemotherapy regimens, surgical outcomes and survival were reported. Survival outcomes were analysed based on staging categories and grouped by treatment approaches. OS was defined as date from diagnosis until death, and date from diagnosis until disease recurrence respectively. OS was generated using Kaplan-Meier analysis and compared using the Log-rank model. One-way ANOVA was used for comparison between multiple groups and Fisher's exact test or chi squared test was used for contingency analysis between groups. A p value of <0.05 was considered significant. This study was approved by the ethics committees of all the hospitals that contributed to the data collected.

Results:

Baseline Characteristics

Seven hundred and fifty-four patients registered from 21 participating cancer centres received a diagnosis of localised PDAC between January 2016 till March 2019. Overall, the median follow up was 16 months from time of diagnosis to database lock for analysis (23 November 2021). Nine patients were excluded from further analysis (1 patient with intraductal papillary mucinous neoplasm and 8 patients with incomplete details which precluded further analysis). Of these patients, 148 were classified as borderline resectable disease (20%), 350 as resectable disease (47%)

and 247 as locally advanced unresectable disease (33%) (Figure 1). Eighty patients who had BRPC received NA chemotherapy (Figure 1). Patients who received NA chemotherapy were younger as seen in Table 1 (63 years vs 65 years vs 73 years p<0.0001). Ninety-eight percent of those receiving NA chemotherapy had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Table 1). Further details are outlined in Table 1.

Surgical Outcomes and Neoadjuvant Therapy

The most common NA regimen was FOLFIRINOX (53%). This was followed by Gemcitabine combined with Nab-paclitaxel in 31% of patients. The most common adjuvant chemotherapy regimen was gemcitabine (43%), followed by GEMCAP (31%). NA chemotherapy was more common from 2016 onwards (78% from 2016-2018). Patients who received FOLFIRINOX were younger than those receiving gemcitabine/nab-paclitaxel (60 years vs 67 years p=0.01) (Table 2). Performance status defined by ECOG, was 0 or 1 for most patients in both groups (Table 2). Surgery was performed in 54% of patients who had NA chemotherapy and 65% (44 of 68) of those who did not (p=0.19). Sixty-one percent of patients receiving FOLFIRINOX went on to surgical resection compared to 44% receiving gemcitabine/nab-paclitaxel (p=0.23). Within patients deemed BRPC two patients were recorded as receiving radiotherapy (one chemoradiotherapy). For those receiving NA chemotherapy, where surgery was not performed, reasons included disease being determined as inoperable (25/37, 68%), patient declined surgery (3/37, 8%) or reason not recorded (9/37, 24%). For those who did not receive NA therapy, reasons recorded for surgery not being performed were inoperability (9/24, 38%), patient declined (5/24, 21%) or was not recorded (10/24, 42%).

Those who received NA chemotherapy had a longer interval to surgery being performed (165 days vs 28 days p<0.0001) with an average of 100 days receiving chemotherapy. FOLFIRINOX patients received chemotherapy for an average of 98 days (7 cycles) and those receiving gemcitabine/nab-paclitaxel patients for 92 days (4.4 cycles) (p=0.66, Table 2). Intraoperative diagnosis of metastatic disease not detected on preoperative imaging was not significantly different between the NA and surgery groups (19% vs 20% p>0.99, respectively). Fourteen percent of patients had progressive disease on NA therapy (Table 1). Disease progression on FOLFIRINOX was 11% and on gemcitabine/nab-paclitaxel was 22% (p=0.31, Table 2). In patients whose disease was resected with histology recorded, average nodes examined, was similar (Table 1).

The R0 resection rate for those who received NA chemotherapy was 53% of those with histology specimens recorded in the database, compared to 38% as described in Table 1 (p=0.28). In patients who received FOLFIRINOX neoadjuvantly, the R0 resection rate was 55%. In those receiving gemcitabine/nab-paclitaxel the rate was 60% (p=>0.99). The fraction of patients who received palliative chemotherapy following progression was similar (25% vs 20% p=0.23, Table 1).

Survival Analysis

The median follow up of patients with BRPC was 9 months in those who received NA chemotherapy. With additional follow up data added to the analysis median follow up of BRPC was 12 months for OS. Median OS for patients with unresectable, borderline resectable and resectable disease was 12, 20 and 26 months respectively (p<0.001, Figure 2A). Those receiving supportive care alone had a median OS of 8 months (Figure 1).

Patients with BRPC receiving NA chemotherapy had a median OS of 20 months compared to 30 months for those who underwent upfront surgery (HR 0.70 p=0.21, Figure 2B). RFS was 3 and 6 months respectively (p=0.33). Median OS for patients receiving FOLFIRINOX was 24 months compared to 10 months in those receiving gemcitabine/nab-paclitaxel (HR 0.3 p<0.0001, Figure 2C). Median RFS was 9 months compared to 2 months respectively (p=0.01, Table 2).

Discussion:

Studies evaluating NA therapy especially in borderline resectable disease are varied. Most recent studies use FOLFIRINOX as NA chemotherapy of choice *(11, 14, 15, 17-20, 35)*. This is in line with our findings, that 53% patients who underwent NA chemotherapy received FOLFIRINOX. Given most of these studies also include patients who have had radiotherapy (see Table 3) it confounds what modality has conferred benefit. The use of chemoradiation was less frequent in the centres participating in the PURPLE registry with only 1 patient receiving chemoradiotherapy. This reflects local practice in Australasia and provided insight into outcomes with NA chemotherapy is used as a single modality. Inclusion criteria for studies of chemotherapy are heterogenous with few studies dedicated to BRPC alone (Table 3). Studies of BRPC patients tend to have smaller numbers and are retrospective. Pietrasz et al 2019 was a retrospective study including 203 patients with BRPC and

LAPC who received FOLFIRINOX (50% also received CRT) (11). Our study with 148 patients within an Australasian population adds to this body of literature, although only 80 received neoadjuvant chemotherapy.

Most studies in BRPC and LAPC focus on achieving resectability in order to obtain cure in this patient subset. This study achieved surgical resection in 54% of patients receiving neoadjuvant chemotherapy. This was 61% in patients who received FOLFIRINOX neoadjuvantly (compared to 44% in patients receiving gemcitabine/nab-paclitaxel). This compares favourably with other studies, particularly those using FOLFIRINOX which shows a surgical resection rate of 15-61% (table 3) (14, 15, 17-20, 35). All of these studies used radiotherapy to some extent. Achieving similar outcomes without the use of radiotherapy is promising given the increased toxicity conferred with chemoradiotherapy (27, 28, 30-33). Prospective studies into this area are necessary to confirm this.

The R0 rate is used as a surrogate for OS in many studies given greater number of positive resection margins has been negatively correlated with survival (6). This was also shown in an analysis of patients in the ESPAC-1 study, where patients with R0 resection had a median OS of 17 months vs 11 months (R1 resection) (5). Eighty-two percent of patients in the ESPAC-1 study had an R0 resection (42). It should be noted that this was a study of adjuvant therapy in resected pancreatic cancer. Our study achieved an R0 rate of 53% in patients receiving neoadjuvant therapy overall, 55% in patients receiving FOLFIRINOX and 60% in those receiving Gemcitabine/nab-paclitaxel. Previous studies using FOLFIRINOX show a range of 33-89% (table 3) (11, 14, 15, 17-20, 35). A contempory study with a similar number of patients (72 patients, 52 FOLFIRINOX, 20 Gemcitabine/nab-paclitaxel) showed R0 resection rates of 73% and 75% (p=1.00) (38). Response rates to NA therapy were not different between groups (38). Our results are comparable to this contempory study but direct comparison is limited.

The AJCC 8th edition staging system for pancreatic cancer shows the survival of patients with larger tumours or node positive disease to be 11-22 months (43). The median OS of BRPC in this study who underwent upfront surgery was 30 months. In the PRODIGE study, patients receiving adjuvant FOLFIRINOX had median OS of 54 months and 35 months in the gemcitabine group (44). In the ESPAC-4 trial patients receiving adjuvant GEMCAP had a median OS of 28 months vs 26 months in the gemcitabine group (45). The median OS of BRPC patients in this study who underwent adjuvant

chemotherapy was also 30 months. This is comparable with the ESPAC-4 study. Most of the patients in our study received adjuvant gemcitabine or GEMCAP. The improved median OS in the PRODIGE study of patients receiving FOLFIRINOX may be influenced by selection bias in this study as FOLFIRINOX is perceived as a toxic regimen suitable for fitter patients. The data from our study however reflects real world practices and patients who are likely less fit nor appropriate for clinical trial selection.

The median OS of 20 months in BRPC receiving NA chemotherapy is comparable to resectable patients receiving surgery alone (Figure 1). The median OS of patients receiving NA FOLFIRINOX in prior studies was 16-36 months (11, 14, 15, 17). The majority of patients in this study received FOLFIRINOX neoadjuvantly (53%), with the remaining 47% of patients received alternate chemotherapy regimens like gemcitabine/nab-paclitaxel. Wolfe et al, showed survival rates of 33 and 27 months respectively (FOLFIRINOX vs Gemcitabine/nab-paclitaxel, p=0.105) (38). The median OS of patients post NA FOLFIRINOX in this study was 24 months and 20 months for patients undergoing resection post any NA therapy (Figure 2). Our results of median OS of 10 months for patients who received NA gemcitabine/nab-paclitaxel is lower than is reflected in a recent data of retrospectively enrolled patients (38). The improved OS may be due to the higher rate of surgery in the FOLFIRINOX vs gemcitabine/nab-paclitaxel groups. The RFS results of patients receiving gemcitabine/nab-paclitaxel of 2 months is lower than seen in the original study of metastatic disease (PFS of 5.5 months) (46). However median overall survival was 8.5 months which is comparable to the median OS of 10 months this our population (46).

Difference in our results may reflect local interpretation and practice with regards to the selection for resectability based on first imaging assessment. It may also reflect bias in patient selection to gemcitabine/nab-paclitaxel based on older age or borderline performance status as gemcitabine/nab-paclitaxel is a more tolerable regimen than FOLFIRINOX. PBS prescribing limitations in Australia limit nab-paclitaxel to the first line metastatic setting. Patients receiving this regimen may have had more advanced disease at imaging to access this. The median OS in our population receiving gemcitabine/nab-

paclitaxel being similar to that in a metastatic setting probably reflects this prescribing practice and the limitation of local classification of resectability on initial MDM assessment.

Data collation of the baseline radiological clinical Tumour Node Metastasis staging upon initial categorisation into the PURPLE registry would help to further delineate this heterogenous group of tumours that fall into the borderline resectable category. This clinical radiological staging data is now being collected in the recently updated version of the PURPLE registry database. Both more advanced disease and poorer performance status would influence survival outcomes as outcomes for patients receiving gemcitabine/nab-paclitaxel is lower than expected in current literature. Although, reportedly 96% of patients receiving gemcitabine/nab-paclitaxel had an ECOG of 0-1 as assessed by the local site. The majority of patients receiving NA chemotherapy completed the expected standard of care duration of chemotherapy treatment as reflected by the average time patients received NA therapy (7 cycles for FOLFIRINOX and 4.4 cycles for gemcitabine/nab-paclitaxel). This would suggest differences in outcomes are not related to reduced exposure to chemotherapy.

Eleven percent of BRPC patients had disease progression on NA chemotherapy (11% FOLFIRINOX, 22% gemcitabine/nab-paclitaxel). BPRC patients who received NA chemotherapy who did not go onto surgical resection had a median OS of 12 months. This is similar to NA studies of FOLFIRINOX, gemcitabine and GEMOX which showed an OS of 9-12 months (14, 17, 21, 24). NA chemotherapy offers the advantage of assessing tumour biology and avoiding futile invasive procedures if early metastatic disease is detected. A previous study using NA chemotherapy to select responders to go onto further consolidative therapy showed improved OS in responders (7). This is reflected in the above results in our database.

Most patients receiving NA chemotherapy were undergoing treatment from 2016-2018 (78%). NA chemotherapy became more common in the more recent years. This reflects a change in practice in Australasia over this period of time. BRPC patients who underwent surgery had statistically similar outcomes to those who received NA chemotherapy (30 months vs 20 months p=0.21, Figure 2). This may be reflective of the median follow up duration of 12 months and small sample size. However, given the aggressive nature of PDAC this follow up should have been adequate to detect progression and death. Other considerations include the incorporation of more advanced patients into the initial

surgery group in the years before NA chemotherapy was more commonly used. There is also the potential inclusion of patients with more advanced disease in the NA group in the later years with hope of downstaging.

We acknowledge this study has significant limitations. This includes the retrospective nature of the data analysed and small numbers of BRPC patients within the database. However, it should be noted that most studies (Table 3) of this cohort of patients use small numbers. The categories of resectability were determined by local site at first MDM imaging review. Strict database inclusion criteria were not mandated to order to capture patients and reflect the current day to day practice within Australasia. This means the categorisation may have changed when further information was available leading to unresectable patients being included in the BRPC category (Figure 1). This reflects real-world practice and the challenges that face MDM review in categorising these patients initially but is a limitation in drawing conclusions from this study. The outcomes may have been influenced by including the categorisation of patients in an intention-to-treat type fashion. The definition of R0 resection was also assessed at the site level meaning there may be some differences in application. Data integrity and completeness was limited by clinicians at sites uploading the most up to date data at time of analysis. The small numbers of patients with histology data recorded in the database at analysis was likely affected by incomplete records as direct access to pathology by database personnel is not available. Lastly, there is an inherent bias of younger, fitter patients receiving FOLFIRINOX or more aggressive therapy even potentially despite more advanced disease at diagnosis.

This study reports a snapshot of current real world practice and outcomes in our Australian population. This study supports emerging evidence for the use of neoadjuvant therapy in BRPC. Given this is a retrospective study with limitations, this needs to be confirmed in prospective trials. This approach should be explored further in randomised control trials including the currently recruiting DYNAMIC-Pancreas trial and the MASTERPLAN trial.

Conclusion:

This study reflects the real practice of managing pancreatic cancer in the Australasian setting. Eighty patients with BRPC received NA chemotherapy, with 54% undergoing surgical excision and R0

resection in 53%. Presumably fitter patients received FOLFIRINOX and 61% underwent surgical excision, with an R0 resection of 55%. This translated to a median OS of 24 months. The R0 resection rate for patients receiving gemcitabine/nab-paclitaxel was 60% although median OS was only 10 months. The inferior outcomes of patients receiving gemcitabine/nab-paclitaxel reflects bias in local prescribing as per government guidelines and local assessment of disease resectability. Although, this real-world data is promising, this study has significant limitations and further prospective randomised controlled trials in this area are needed to further establish best practice.

Acknowledgements: The authors wish to thank the Walter and Eliza Hall Institute and contributers to the PURPLE database without with, this research would not be possible.

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Table 1. Baseline characteristics and surgical outcomes of patients with Borderline Resectable Pancreatic Cancer stratified based on receiving Neoadjuvant Chemotherapy

Variable	NA Chemotherapy (n=80)	Surgery (n=44)	Supportive Care (n=24)	p Value
Female	37 (46%)	12 (27%)	13 (54%)	p=0.051
Age at diagnosis (years)	63	65	73	p<0.0001
ECOG 0 or 1	78 (98%)	42 (95%)	19 (79%)	p=0.004
Surgery Performed	43 (54%)	44 (100%)	-	-
Average Interval to Surgery (Days)	165	28	-	p<0.0001
Metastases found Intraoperatively	8 (19%)	9 (20%)	-	p>0.99
Disease Progression on NA therapy	11 (14%)	-	-	-
Histology Specimen Recorded	30 (70%)	24 (55%)	-	p=0.19
R status R0 R1	 16 (53%) 9 (30%)	 9 (38%) 7 (29%)	-	 p=0.28 p>0.99
Average Nodes Examined	22	21	-	p=0.76
Palliative Chemotherapy upon Disease Progression	20 (25%)	9 (20%)	2 (8%)	p=0.22

Table 2. Baseline characteristics and outcomes for patients receiving Neoadjuvant Chemotherapy based on regimen received

Variable	FOLFIRINOX (n=46)	Gemcitabine/Nab paclitaxel (n=27)	p Value
Female	19 (41%)	12 (44%)	p=0.81
Age at Diagnosis (years)	60	67	p=0.01
ECOG 0 or 1	45 (98%)	26 (96%)	p>0.99
Surgery Performed	28 (61%)	12 (44%)	p=0.23
Histology Specimen Recorded	22 (79%)	5 (42%)	p=0.03
R status R0	12 (55%)	3 (60%)	p=>0.99
Median OS (Months)	24	10	HR 0.30 p<0.0001
Median RFS (Months)	9	2	p=0.01
Average Time Receiving NA Chemotherapy (days)	98	92	p=0.66
Disease Progression on NA therapy	5 (11%)	6 (22%)	p=0.31

Table 3. Summary of evidence for patients receiving Neoadjuvant intent therapies in Borderline Resectable and Locally Advanced Pancreatic cancer

ulation	Type of Study	Number of patients	Chemotherapy	Radiotherapy (patients)	Response Rate (%)	Median OS (months)	Resection rate (%)
C and metPC	Phase II	31 LAPC 44 metPC	mFOLFIRINOX	17 LAPC	17.2% LAPC 35.1% metPC	10.2mths met PC 26.6mths LAPC	41.9% LAPC
LAPC	Retrospective	101	FOLFIRINOX	63	29%	11mths if progression post CT 26mths if further therapy	15% with CT 31% with RT post C
LAPC	Retrospective	25 (13 unresectable, 12 BR)	FOLFIRINOX	9	-	-	43% (64% BR, 20% LAPC)
ectable/BRPC	Phase II	35 (16 BR)	Gemcitabine and S1		69%	19.7mths (all) 34.7mths (resected) 10mths (no resection or mets)	86%
LAPC	Retrospective	18	FOLFIRINOX	10 (only post CT if not resectable)	-	NR	39%
C and metPC	Phase III	313 (157 GEMOX 156 GEM)	GEMOX vs GEM	29.8% GEM 21.6% GEMOX	17.3% GEM 26.8% GEMOX P=0.04	7.1mths GEM 9mths GEMOX P=0.13 (10.3mths for LAPC in both)	4.3% (2/47 pt with LAPC in GEM arm)
C and metPC	Phase I	47 (76% metPC)	FOLFIRINOX	-	26%	10.2mths	-
C and metPC	Phase III	342 (173 IRINOGEM 169 GEM)	IRINOGEM vs GEM		16.1% IRINOGEM 4.4% GEM P<0.001	6.3mths IRINOGEM 6.6mths GEM P=0.789	-

ectable and esectable	Metaanalysis	707 from 20 studies (366 resectable, 341 unresectable)	NA GEM	18 studies	12% resectable 27% unresectable	16.4mths (all) 28.2mths (resected) 8.8mths (not resected) 17.8mths in unresectable pt who become resectable	91% resectable 39% unresectable
C	Retrospective	77	FOLFIRINOX	70%	28%	22mths	36%
LAPC	Retrospective	43 (18 BR 25 LA)	mFOLFIRINOX	54% (44% BR 60% LA)	23%	21.2mths (NR resected, 12.7mths not resected)	51% (61% BR 44% LA)
LAPC	Retrospective	203	FOLFIRINOX	50%		57.8mths CRT 35.5mths CT alone P=0.007	
LAPC	Phase II	33 (18 unresectable 15 BR)	GEMOX	-	-	22mths resected 12 mths no resection p=0.046	39%
LAPC	Retrospective	72	FOLFIRINOX, Gem/nab-paclitaxel	65% FOLFIRINOX, 55% Gem/nab-pac	31% FOLFIRINOX, 5% Gem/nab-pac p=0.028	33mths (FOLFIRINOX), 27mths (Gem/nab-pac) p=1.05	-

BRPC=borderline resectable pancreatic cancer LAPC=locally advanced pancreatic cancer metPC=metastatic pancreatic cancer CT=chemotherapy RT=radiotherapy CRT=chemoradiotherapy RR=response rate R0=margin negative resect

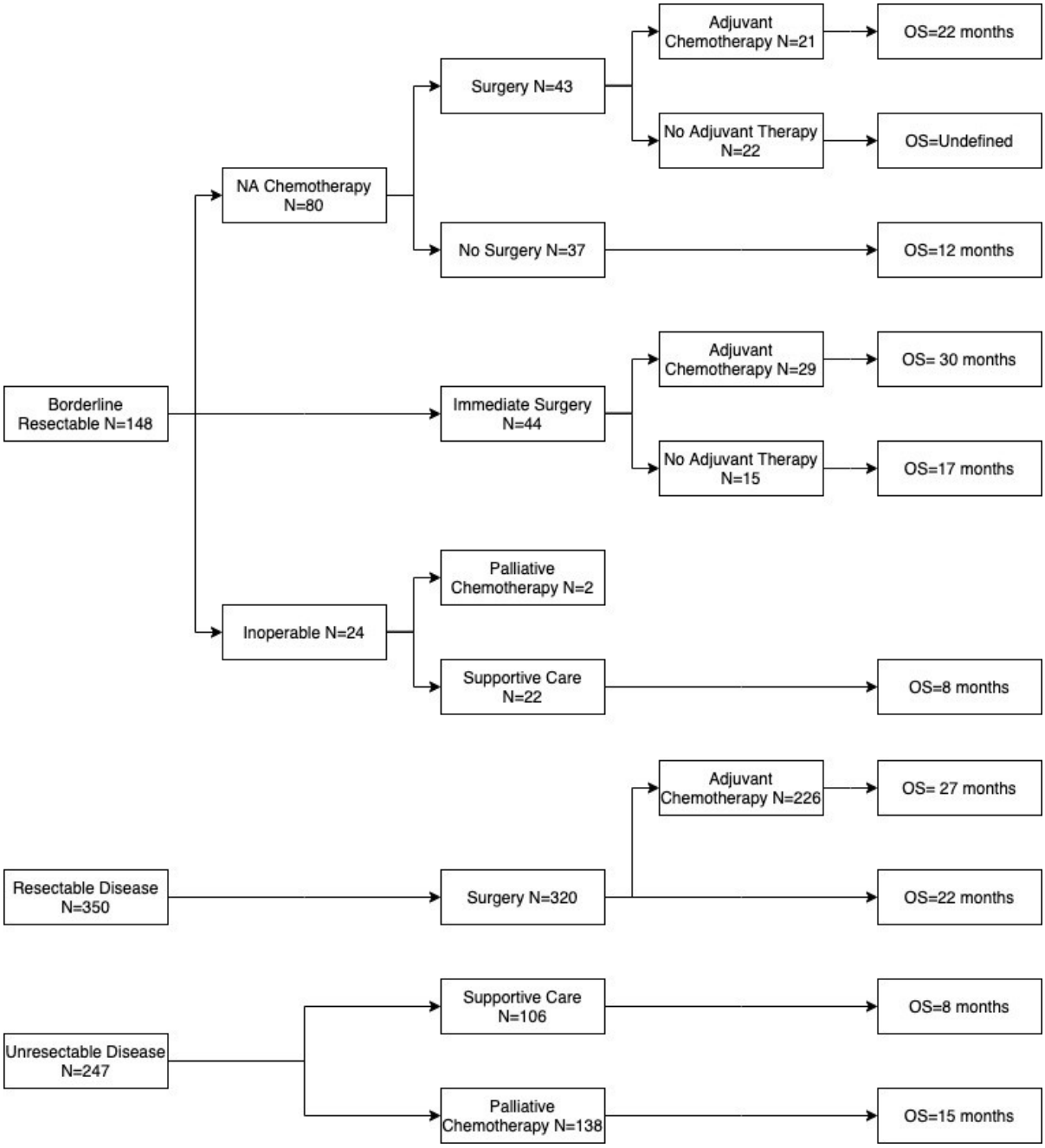

Figure 1. Flow diagram of patients with Localised Pancreatic Adenocarcinoma in the PURPLE database, management strategies and subsequent median survival outcomes.

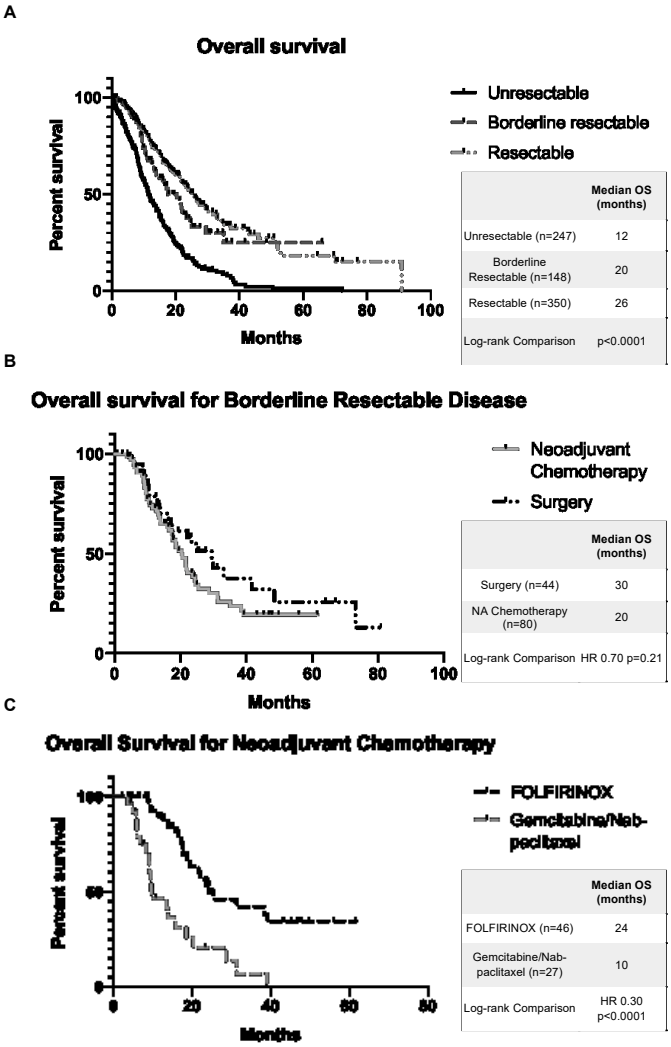

Figure 2. Overall Survival in patients with pancreatic adenocarcinoma. A: Overall survival of patients with unresectable, borderline resectable and resectable disease. B: Overall survival of patients with borderline resectable receiving neoadjuvant chemotherapy compared to upfront surgery. C: Overall survival of patients receiving neoadjuvant chemotherapy based on regimen.