Original Article

Overall survival and treatment modalities in pancreatic adenocarcinoma: a retrospective analysis of a single centre in Western Australia

Alice Talbot[1], Thomas Talbot[1], Emma Shaughnessy[1], Aisling Glass[1], Adarsh Das[1], Yuki Watanabe[2], Daniel Cheng[3], Mikael Johansson[2], Samarth Rao[3], Ian Yusoff[3], Colin Tang[4], Rohen White[4], Andrew Dean[1]

[1]Department of Oncology, St. John of God Hospital, Subiaco, WA, Australia; [2]Department of Surgery, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Department of Gastroenterology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [4]Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

Contributions: (I) Conception and design: A Dean, A Talbot; (II) Administrative support: A Dean; (III) Provision of study materials or patients: Y Watanabe, D Cheng, M Johansson, S Rao, I Yusoff, C Tang, R White, A Dean; (IV) Collection and assembly of data: A Talbot, T Talbot, E Shaughnessy, A Glass, A Das; (V) Data analysis and interpretation: A Talbot, T Talbot, A Das; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alice Talbot, MB, BCh, BAO, LRCP & SI. Department of Oncology, St. John of God Subiaco Hospital, 12 Salvado Road, Subiaco, WA 6008, Australia. Email: alicetalbot@rcsi.ie.

Background: Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of approximately 10.7% in Australia. It is becoming an increasingly common cause of cancer mortality. The therapeutic model for PDAC remains limited, especially for those with metastatic disease on presentation.

Methods: We completed a retrospective cohort study including all patients with PDAC presenting between April 2008 and October 2021 to St. John of God Subiaco Hospital in Western Australia. Overall survival (OS) was calculated via Kaplan-Meier method.

Results: We identified 251 patients treated for PDAC. Of these, 134 patients (53%) had resectable, borderline resectable or locally advanced (LA) disease at diagnosis and 117 patients (47%) had metastatic disease. The median age of all patients was 66 years (range, 25–87 years). OS in PDAC was 26 months [95% confidence interval (CI): 23–30]. In the non-metastatic group OS was 34 months (95% CI: 30–39). In the metastatic group OS was 19 months (95% CI: 14–22). Treatment modalities varied between patients. Overall 123 patients were treated with chemotherapy alone, 55 patients had chemoradiotherapy, 34 patients had chemotherapy and surgery and 37 had tri-modality treatment including chemotherapy, surgery and radiotherapy. Two patients received cyberknife radiation alone.

Conclusions: This retrospective study shows a significant prolonged survival for PDAC patients. Further studies are needed to validate second- and third-line regimens in PDAC.

Keywords: Chemotherapy; survival; pancreatic cancer; pancreatic ductal adenocarcinoma (PDAC); Australia

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of approximately 10–12% in Australia (1,2). This 5-year survival has increased from 4–5% in 2007, possibly due to advancements in standard of care chemotherapy (2). Improvements in general healthcare and emergence of personalised treatments for cancer have resulted in vast improvements in 5-year survival for most cancers. This is not the case for locally advanced (LA) and metastatic PDAC as treatments options beyond first and second line chemotherapy remain limited (3). Surgical resection of the pancreatic tumour is the only curative option; however, up to 85% of cases are unresectable at the time of presentation (4). Poor outcomes in PDAC also result from late stage at diagnosis due to vague initial symptoms and early disease spread with over 50% of patients presenting with metastatic disease at diagnosis (2). Historically, gemcitabine was used as standard of care chemotherapy for LA and metastatic cancer (5). In recent years combination regimens including gemcitabine with nab-paclitaxel (Gem/NabP) and FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin) have demonstrated survival advantage over gemcitabine monotherapy (6,7). These regimens have since become standard of care first line treatments. Despite progression on first line treatment, a number of patients have sufficient performance status for further systemic chemotherapy. There are currently no established guidelines for second- and third-line treatment of metastatic PDAC. We aim to describe the survival outcomes in PDAC in our centre over a 13-year period to further our understanding of the current landscape of pancreatic cancer care in Australia. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-488/rc).

Highlight box

Key findings

- This centre reported median overall survival of 19 months in metastatic pancreatic cancer and 34 months in patients with no metastasis at diagnosis.
- The median age of all patients was 66 years (range, 25–87 years).
- Gemcitabine with nab-paclitaxel was the first line chemotherapeutic regimen of choice for the majority of patients followed by FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin).

What is known and what is new?

- Pancreatic cancer patients often have poor survival outcomes in advanced disease compared to other solid organ tumours and limited treatment options beyond first- and second-line chemotherapy.
- Western Australia has shown favourable treatment outcomes in patients with pancreatic cancer.
- A number of patients may have performance status to tolerate third line treatment.

What is the implication, and what should change now?

- This is a retrospective review of a single centre that shows prolonged survival in pancreatic cancer patients.
- More randomised control trials are needed to assess the optimal treatment regimens after second line in this population.

Methods

Study design

We completed a retrospective cohort study of all patients with PDAC presenting to St. John of God Subiaco Hospital in Western Australia between April 2008 and October 2021. All treatment modalities and outcomes were reviewed for all patients in this cohort. This information was extracted from an on-site electronic patient chart system using 'Genie' medical database software.

Eligibility criteria

All patients with PDAC that attended for systemic treatment from April 2008 to October 2021 were eligible. This included patients with resectable, borderline resectable, LA or metastatic disease.

Data collection

Demographic data including age at diagnosis and gender. Clinical data included disease extent at diagnosis, type of therapy, treatment related adverse events, chemotherapy dates, date of progression, date of death. Data was collected over a 6-month period. Data was deidentified and input into an excel database for analysis. Data input and calculations were subsequently verified by a second reviewer.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Low risk ethical approval and a waiver of consent were granted from St. John of God Healthcare Ethics Committee on 19 Sept 2022 (No. 1986).

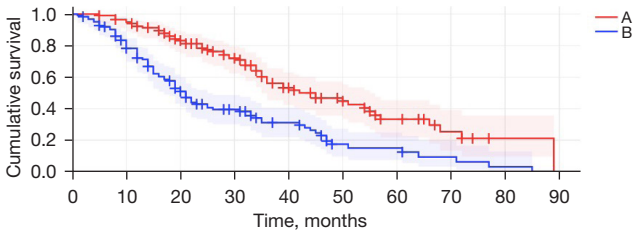

Figure 1 Overall survival in metastatic *vs.* non-metastatic PDAC. A, patients with non-metastatic disease at diagnosis; B, patients with metastatic disease at diagnosis. PDAC, pancreatic ductal adenocarcinoma.

Statistical analyses

Statistical analyses were completed using R statistics (R version 4.1.3 for macOS®; R Foundation for Statistical Computing, Vienna, Austria). Demographic and clinical characteristics were summarised using standard descriptive summaries such as median and range for continuous variables and percentages for nominal and ordinal data. Only patients with complete data were included in the analysis. Overall survival (OS) was calculated from the date of diagnosis to the date of death or commencement of study via Kaplan-Meier method. OS was compared between non-metastatic and metastatic cancer patient groups as well as comparisons between differing first and second line chemotherapy regimens. We did not believe there was rationale for subdata analysis, such as logistic regression investigating predictors of outcome, given the data is heterogenous and retrospective.

Results

Between April 2008 and October 2021, 251 patients were diagnosed and treated for PDAC at a single oncology centre in Western Australia. Of this cohort, 134 had non-metastatic disease at diagnosis, including 37 with initially resectable disease presenting for adjuvant chemotherapy. There were 97 with borderline resectable or LA disease, precluding upfront surgical intervention. Of these, 34 had neoadjuvant chemotherapy and subsequently had surgical resection. There were 117 found to have metastatic disease at diagnosis. Three patients had incomplete data on their medical oncology record and were not included in further analysis. Median overall survival (mOS) in non-metastatic PDAC was 34 months (95% CI: 30–39) and 19 months (95% CI: 14–22) in metastatic disease *(Figure 1)*.

The median age of all patients was 66 years (range, 25–87 years) (*Table 1*). Those that presented with non-metastatic disease had a median age of 67 years (range, 34–87 years) with metastatic disease at diagnosis had a median age of 64 years (range, 25–85 years). Overall there were 120 females (48%) and 131 males (51%) in this study. Of those that had non-metastatic disease at diagnosis, 60 were female (45%) and 74 were male (54%). Of those presenting with metastatic disease, there were 60 females (51%) and 57 males (49%).

Treatment modalities varied broadly between patients depending on age, disease extent, performance status at diagnosis, patient preferences regarding intensity of therapy and suitability for clinical trials. Between all stages there were 123 patients (49%) that received chemotherapy alone, 55 patients (22%) had chemoradiotherapy, 34 patients (14%) had chemotherapy and surgery and 37 had tri-modality treatment (15%) including chemotherapy, surgery and radiotherapy (*Table 1*). Two patients received cyberknife radiation alone. The median length of time on chemotherapy was 4 months for first line treatment (range, 1–38 months), 3 months for second line therapy (range, 1–39 months) and 3 months for third line therapy (range, 1–21 months). There were 34 patients who received neoadjuvant chemotherapy (31 Gem/NabP, 3 FOLFIRINOX). The median length of neoadjuvant therapy was 4 months (range, 2–11 months).

Of the non-metastatic patient group (n=134, 53.3%), 43 had chemoradiation, 37 had tri-modality treatment (adjuvant/neo-adjuvant chemotherapy, surgery, radiotherapy), 34 had chemotherapy (adjuvant/neo-adjuvant) and surgery, 18 had chemotherapy alone and 2 patients had cyber-knife radiotherapy with no other treatment. Of these patients, 74 patients (55%) had 3 or more lines of chemotherapy. There were 71 patients who had surgery as part of treatment. Of these, 43 had a Whipple's procedure, 8 had a distal pancreatectomy and one patient had total pancreatectomy. Surgical details were not recorded for 19 patients.

Gem/NabP was the first line chemotherapeutic regimen of choice for the majority of patients with non-metastatic disease (n=103, 76.9%), followed by FOLFIRINOX (n=20, 15%). Gemcitabine was commenced at starting dose 1,000 mg/m^2 and nab-paclitaxel at 125 mg/m^2 per EVIQ guidelines (3). A modified FOLFIRINOX dose was used and involved a dose intensity of 65% for oxaliplatin, 68% for irinotecan, 18% for bolus 5-fluorouracil (5-FU) and 68% for infusional 5-FU. FOLFIRINOX was the

Table 1 Demographics and survival outcomes based on therapy received

Therapy type	n	Age, years (median)	Male (n)	Female (n)	OS, months (median)
Total (n=251)					
Chemotherapy only	123	66	57	66	18
Chemotherapy plus radiation	55	66	31	24	32
Chemotherapy plus surgery	34	68	15	19	45
Cyberknife	2	79	2	0	17
Trimodality	37	65	26	11	49
Metastatic (n=117)					
Chemotherapy only	105	65	49	56	18
Chemotherapy plus radiation	12	63	8	4	24.5
Chemotherapy plus surgery	0	N/A	N/A	N/A	N/A
Cyberknife	0	N/A	N/A	N/A	N/A
Trimodality	0	N/A	N/A	N/A	N/A
Non-metastatic (n=134)					
Chemotherapy only	18	69	8	10	23
Chemotherapy plus radiation	43	66	23	20	34
Chemotherapy plus surgery	34	68	15	19	45
Cyberknife	2	79	2	0	17
Trimodality	37	65	26	11	47

OS, overall survival; N/A, not applicable.

most commonly used second line regimen in those who progressed following first line treatment and had adequate performance status to undertake further therapy (n=53, 39.6%). Although Gem/NabP and FOLFIRINOX were the two most commonly employed treatment approaches, multiple other regimens were utilised on a patient specific basis (*Table 2*).

The vast majority of those diagnosed with metastatic PDAC at our centre underwent palliative chemotherapy alone (n=105, 88.9%), with a small number receiving chemoradiotherapy (n=12, 10.2%). As was the case in the non-metastatic group, Gem/NabP was the most frequently used first line chemotherapeutic regimen (n=92, 78.6%) (*Table 2*). Beyond this, the first line treatment options varied widely, with a significant number of patients being enrolled in both national and international clinical trials (n=20, 16.9%) (*Table 2*). FOLFIRINOX was rarely used as first line intervention in metastatic disease in our centre (n=3, 2.5%), however was the most frequently utilised second line strategy (n=58, 49.6%). There were 33 patients (28%) with metastatic disease at diagnosis that had three or more lines of chemotherapy.

Discussion

The survival outcomes we report in this study echo the previously demonstrated favourable survival figures in Western Australia published in the 2019 *Lancet* review of global PDAC outcomes (4). The reasons for this likely include access to modern therapies and diagnostic technology. Improvements in healthcare facilities in recent years have also enabled more timely diagnoses and treatment. These are essential factors in the management of PDAC. At least one third of patients with PDAC present with LA disease, usually due to extensive vascular invasion which precludes the possibility of curative surgical resection (5). Following treatment with platinum-based chemotherapy or gemcitabine combination therapy, a minority of cases subsequently achieve sufficient downstaging to allow surgical resection. The role of chemoradiotherapy in

Table 2 Variable treatment modalities for non-metastatic and metastatic disease

Disease stage	Treatment approach		Chemotherapy regimen (1st line)		Chemotherapy regimen (2nd line)	
	Approach	n	Regimen	n	Regimen	n
Non-metastatic (n=134)	Chemotherapy, radiation	43	Gem/NabP	103	FOLFIRINOX	53
	Tri-modality	37	FOLFIRINOX	20	5-FU (with radiotherapy)	41
	Chemotherapy, surgery	34	Gemcitabine monotherapy	4	Gem/NabP	12
	Chemotherapy alone	18	Gemcitabine, capecitabine	2	Gemcitabine, capecitabine	4
	Cyber-knife only	2	Cisplatin, etoposide	1	Carboplatin, nab-paclitaxel	3
			Carboplatin, nab-paclitaxel	1	Gemcitabine monotherapy	2
			NALIRIFOX (NAPOLI-2 phase II trial)	1	Carboplatin, gemcitabine	1
			Did not receive first line chemotherapy	2	FOLFOX	1
					Did not receive second line chemotherapy	17
Metastatic (n=117)	Chemotherapy alone	105	Gem/NabP	92	FOLFIRINOX	58
	Chemotherapy, radiation	12	Anetumab ravtansine, gemcitabine (phase Ib trial)	6	Gem/NabP	9
			Gem/NabP (NAPOLI-3 phase III trial)	6	Carboplatin, nab-paclitaxel	5
			NALIRIFOX (NAPOLI-3 phase III clinical trial)	3	5-FU (with radiotherapy)	5
			Gemcitabine, nab-paclitaxel, CEND-1 (phase I trial)	3	FOLFOX	1
			FOLFIRINOX	3	Did not receive second line chemotherapy	39
			Gemcitabine monotherapy	1		
			NALIRIFOX (NAPOLI-2 phase II trial)	1		
			Carboplatin, nab-paclitaxel	1		
			Gemcitabine, nab-paclitaxel, demicizumab (YOSEMITE phase II trial)	1		

Gem/NabP, gemcitabine and nab-paclitaxel; FOLFIRINOX, fluorouracil leucovorin irinotecan oxaliplatin; NALIRIFOX, liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin; 5-FU, 5-fluorouracil.

those with LA disease remains controversial, with research yielding mixed results. A 2011 Eastern Cooperative Oncology Group (ECOG) trial demonstrated improved OS in those with LA PDAC who received gemcitabine and radiotherapy versus those who received gemcitabine alone (11.1 *vs.* 9.2 months) (6). The LAP07 trial however yielded conflicting findings, with no significant difference in OS seen between those who received chemoradiotherapy versus chemotherapy alone (7). Chemotherapy remains at the forefront of most treatment regimens for PDAC.

In this study, 134 patients were treated for non-metastatic PDAC over a 13-year period with an mOS of 34 months, compared to international figures of 14–23 months (8,9). The most common treatment modality was chemoradiotherapy (n=43). The most common chemotherapy regimen in the non-metastatic group was Gem/NabP utilised in 103 patients (76.8%). FOLFIRINOX was used as first line therapy in non-metastatic disease in only 20 cases (15%). It was, however, the most commonly used second line treatment regime, used in 40% of patients who received second line therapy. There is limited data directly comparing the relative efficacy of gemcitabine containing regimens with FOLFIRINOX in LA PDAC. The choice of first line regimen often depends on patient

and clinician preferences with regards to intensity of treatment and performance status at diagnosis. More recently, the presence or absence of pathogenic or likely pathogenic mutations in a gene associated with homologous recombination repair (HRR) has been used to guide first line therapy (5). A retrospective analysis of 485 patients treated for potentially resectable, borderline resectable or LA PDAC with either FOLFIRINOX or Gem/NabP found no significant difference in OS between both cohorts (mOS 21 *vs.* 20 months) (10). In recent times FOLFIRNOX has established itself as the favoured first line regimen in younger patients with a more favourable performance status (11). In our centre Gem/NabP was the preferred first line agent in the majority of cases. This was likely due to clinician preference towards Gem/NabP given preferable safety profile in an older population (median age 67 years) and non-inferiority to FOLFIRINOX in terms of OS (12). A formal non-inferiority study should be completed in this area to further evaluate the risk-benefit profile associated with each regimen.

In the metastatic setting, FOLFIRINOX and Gem/NabP regimens both have a well-established survival benefit when compared to gemcitabine alone (13,14). Prior to the availability of these platinum-based and gemcitabine combination therapies, gemcitabine monotherapy was standard of care chemotherapy for metastatic disease (5). In 2011, FOLFIRINOX was shown to be superior to gemcitabine monotherapy with an mOS of 11.1 *vs.* 6.7 months in the arm treated with gemcitabine alone (14). The use of Gem/NP was also shown to have superior survival outcomes compared to gemcitabine monotherapy (mOS 8.5 vs 6.7 months) (13). To date, no head to head clinical trial has been carried out directly comparing survival outcomes in those treated with FOLFIRINOX versus Gem/NabP in metastatic disease. Our centre demonstrates real-time data of 117 patients treated for metastatic PDAC with an mOS of 19 months, compared to 6–11 months globally (13,14). The most frequently used first line chemotherapy was Gem/NabP, used in 103 patients (76.8%). Despite metastatic disease, many patients have sufficient performance status for further chemotherapy however evidence for second line chemotherapy in progressive metastatic disease is limited (15). The only second line treatment option that has proven survival advantage in a phase 3 clinical trial is fluorouracil plus leucovorin with nanoliposomal irinotecan (16). However modified FOLFIRINOX has been used historically in the second line setting (2). Use of modified FOLFIRINOX has shown an improved side effect profile without compromising efficacy (17,18). Of those who received second line chemotherapy for metastatic disease in this study, 75% (n=58) received modified FOLFIRINOX. Patients are often excluded from use of second line FOLFRINOX due to concerns regarding toxicity. Previous studies have recognized safe use of mFOLFIRINOX in patients with ECOG performance status 0–1 and age below 75 years, however there is a limited evidence for other patient populations (19,20). A previous review from our centre in 2019 which documented a durable response for second line mFOLFIRINOX in patients with an ECOG of 2 or less (21). There is a paucity of evidence for third line chemotherapy in advanced disease. This is due in part to the aggressive nature of PDAC resulting in advanced disease at diagnoses and short OS compared to other solid tumours. Anecdotally, platinum-based regimens or gemcitabine combination therapies have been used in those patients that have an adequate performance status (e.g., ECOG <3) to tolerate third line treatment after an informed discussion regarding potential risks and benefits.

There were 42 patients (16.7%) in our study that received treatment as part of a clinical trial. PDAC has a relatively low number of available clinical trials compared to other solid tumours such as lung and breast. PDAC is the third most common cause of cancer death in Australia preceding prostate and breast cancer (22). Despite this, the number of interventional clinical trials that are active or recruiting for PDAC in Australia is significantly lower than prostate and breast cancer (28 studies *vs.* 102 and 133 studies respectively) (23). The relatively low number of clinical trials may be due to the poor prognosis associated with PDAC meaning many patients do not have sufficient performance status to meet eligibility criteria. Pancreatic tumours tend to grow at an aggressive rate with a characteristically dense fibrotic stroma which acts as a barrier to chemotherapeutic agents. There were 12 patients in this group that were treated as part of the CEND-001 study. These molecular therapies such as iRGD have been developed to aid penetration of current chemotherapy agents into the pancreatic tissue and show promising early efficacy results (24). For most solid tumours many clinical trials in recent years involve immunotherapy and targeted therapy. Immunotherapy in PDAC has not yielded promising results in trials to date (25). The pancreatic tumour microenvironment does not classically express high numbers of $CD8^+$ T lymphocytes and consequently have had poor response to immunotherapies. This is not

the case for patients with high microsatellite instability such as in Lynch syndrome or patients with high PD-1 expression. In recent years, pembrolizumab, nivolumab and dostarlimab have been approved for patient with mismatch repair deficient tumours (25). However, genotyping and subsequent targeted therapies for PDAC have also been limited due to poor prognosis. Next generation sequencing with subsequent identification of suitable targeted treatment is a time-consuming process which many PDAC patients cannot afford. Recently PARP inhibitors for BRCA mutant PDAC have been investigated for use in PDAC. The POLO study in patients with platinum sensitive mPDAC with a germline BRCA variant showed significantly increased median progression-free survival with olaparib group compared to placebo (7.4 *vs.* 3.8 months) (26). This has not yet been implemented into clinical practice. PDAC is underrepresented in the clinical trial space for patients that have suitable ECOG and favourable prognosis.

There were inherent limitations in this study. It is a retrospective cohort study with associated bias and no direct comparative arm to confirm the difference in survival outcomes compared with global figures. All data was taken from a single centre in a metropolitan area. This does not reflect the survival outcomes of PDAC in regional areas with poor access to chemotherapy, radiation therapy and surgical treatment. Thirdly, favourable OS in this study may be accounted for by selection bias, given the patients that went on to have second- and third-line therapy would have ECOG scores rendering them fit for these lines of treatment. As such they were more likely to have superior survival outcomes.

Conclusions

Western Australia has shown favourable survival outcomes in the treatment of PDAC. Many patients have sufficient performance status to have second- and third-line chemotherapy in PDAC. Further studies are needed to assess survival and quality of life outcomes prior to implementation of third line chemotherapy into standard of care treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-488/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-488/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-488/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Low risk ethical approval and a waiver of consent were granted from St. John of God Healthcare Ethics Committee on 19 Sept 2022 (No. 1986).

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