Use and outcomes of chemotherapy for metastatic pancreatic cancer in Australia

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Introduction

There have been incremental improvements in survival for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) since the 1990s.

The earliest trial showing survival benefit demonstrated 5-fluorouracil (5FU) /leucovorin (LV) +/- etoposide improved survival compared with best supportive care and delayed deterioration in quality of life [(1)]. Subsequently, gemcitabine was shown to have a modest survival benefit over 5FU alone (median OS 5.7 vs. 4.4 months) [(2)]. More recently, combination regimens have provided survival benefit in advanced pancreatic cancer. Compared to gemcitabine alone, FOLFIRINOX (median OS 11.1 vs. 6.8 months) [(3)], and gemcitabine-nab-paclitaxel (median OS 8.5 vs. 6.7 months) [(4)] provide small survival advantages in the first line setting [Table 1]. In the limited subset of patients with BRCA gene mutations, maintenance therapy with olaparib improved progression free survival (PFS) from 3.8 months to 7.4 months in patients who had previously had disease control with platinum based chemotherapy [(5)].

Modest survival benefits have been observed with second line chemotherapy [Table 1]. Oxaliplatin in combination with 5FU initially showed benefit using the OFF regimen; however a later trial using the FOLFOX regimen failed to confirm this [(6-8)]. FOLFIRI (5FU/LV/irinotecan) has been evaluated only

in phase II or observational studies and appears to have a modest benefit similar to oxaliplatin based regimens [9]. Nano-liposomal irinotecan plus 5FU has been shown in a phase III trial to have a modest survival benefit compared with 5FU alone [10]. Of note, none of these regimens have shown a survival benefit of more than 3 months compared with best supportive care (OFF regimen) or compared with 5FU/LV (all later trials).

There are practical considerations in the choice of chemotherapy, with reimbursement requirements and patient fitness influencing management decisions. The Pharmaceutical Benefits Scheme (PBS) in Australia provides reimbursement for gemcitabine-nab-paclitaxel only for first line use, contributing to decreased uptake of FOLFIRINOX in this setting. Furthermore, neither olaparib in the maintenance setting nor nanoliposomal irinotecan in the second line setting is currently reimbursed in Australia. Prior to the advent of combination regimens, chemotherapy was prescribed in only a third of patients in our state, Victoria[11]. Our study seeks to establish current practice in Australia and subsequent survival outcomes.

Methods:

This study utilised data from six Victorian sites who contribute to the PURPLE (**P**ancreatic cancer: **U**nderstanding **R**outine **P**ractice and **L**ifting **E**nd **R**esults) registry (ACTRN12617001474347). The PURPLE registry is a prospective, multi-centre, electronic database enrolling consecutive patients with pancreatic cancer across Australasia. This federated web-based platform is maintained by participating oncology units and allows de-identified data to be combined and analysed with the aim to encourage collaboration, standardise treatment and improve outcomes for pancreatic cancer. Key data points pertaining to patient and disease characteristics, treatment and outcomes are collected at the point of care. Data from the PURPLE registry is audited quarterly, regularly updated and has

been cross validated against state level outcomes from the Victorian Integrated Cancer Services. ECOG performance status is recorded onto the electronic database and cross checked against medical records.

For this analysis, all patients with mPDAC treated at the participating sites from January 2016 until June 2019 were included. Patients with an initial diagnosis of unresectable localised disease were excluded due to their different disease pattern and the use of palliative chemotherapy for localised disease in these patients. Patients with initially resectable or borderline resectable disease who progressed with distant metastases at a later date were included, with the date of recurrence/progression recorded as the date of diagnosis of mPDAC. Data collection, storage and use is approved by the Melbourne Health Office for Research, reference number HREC/16/MH/216. This project was approved by the Office of Research and Ethics at Eastern Health, approval number QA19/019.

Information regarding demographics, ECOG performance status (PS), chemotherapy regimens and OS were evaluated. Charlson comorbidity index (CCI), a validated prognostic score, was utilised to assess fitness. This score gives a weighting to common comorbid conditions and patients' age to predict mortality, a higher score reflects a higher risk of death [(12)]. We chose the score of ≥3 as a cut-off for binary comparison of groups, as this confers a 77% or less 10 year survival (moderate competing risk of death). In analyses where age was a significant predictor of outcome, we assessed age-unadjusted CCI (uCCI) to reflect comorbidities alone. Descriptive analysis was undertaken. Survival outcomes were compared using Kaplan-Meier methods. Survival was calculated from the date of diagnosis of metastatic disease. Nonparametric tests were used to compare baseline characteristics. Categorical variables were compared using Fisher's exact test and continuous variables using the Mann-Whitney U test.

Results:

Baseline characteristics

As of June 2019, 749 patients with PDAC were included in the PURPLE database. A total of 363 patients with mPDAC were identified, 260 with metastases at diagnosis, 84 with initially resectable disease and 19 with initially borderline resectable disease (Figure 1). The date of diagnosis of mPDAC ranged from October 2012 to May 2019. Patients receiving chemotherapy were younger (median age 69 vs. 73 years, p<0.01) with better ECOG PS (89% vs. 66% ECOG 0-1, p=<0.01) compared with the chemotherapy-untreated group. Age-adjusted CCI was lower in the chemotherapy-treated than the chemotherapy-untreated group (37% vs. 63% with CCI ≥3, p<0.0001). Unadjusted CCI (uCCI) was similar between groups (7% vs. 11% uCCI ≥3, p=0.13), as was the rate of prior primary tumour resection, adjuvant chemotherapy and biliary stent utilisation [Table 2].

Of 363 patients, 103 (28%) had initially resectable or borderline resectable localised disease and of these 82 (79%) of these underwent resection. Of those who did not undergo surgery, 11 patients were considered initially borderline resectable but progressed prior to surgery (median time to progression 4.9 months). Ten patients were considered initially resectable, but were diagnosed with distant metastases prior to surgery (median time to progression 24 days). Of those who underwent surgery, 70/82 (85%) received adjuvant chemotherapy. Median time to recurrence was 10.3 months from diagnosis.

Treatment received

After diagnosis of metastatic disease, 195 patients (54%) received chemotherapy. The commonest first line regimen was gemcitabine-nab-paclitaxel (71%), followed by gemcitabine alone (10%) and

FOLFIRINOX (6%) [Figure 2]. Twelve patients (6%) were enrolled on clinical trials for first line treatment.

Data regarding the reason patients weren't commenced on chemotherapy was available for 74 (44%) patients who did not receive systemic therapy. Of these, 62 (83%) were considered unsuitable for treatment or died prior to commencement, 5 (7%) refused offered treatment and the remainder had treatment planned which was not commenced at the time of data entry. Of those unfit for or who died prior to treatment, 35/62 (56%) had a recorded ECOG PS of 0 or 1.

Of those who received chemotherapy, 62 of 195 (32%) proceeded to second line treatment. Second line regimens included oxaliplatin-fluoropyrimidine (37%), irinotecan-fluoropyrimidine (26%) and gemcitabine-nab-paclitaxel (15%). Seven patients (11%) were enrolled on clinical trials for second line treatment. Compared to patients who only received first line chemotherapy, those who later received second line chemotherapy were younger (median age 65 vs. 70 years, $p<0.01$), but had comparable ECOG PS and uCCI to those who received first line treatment alone [Table 3].

Treatment outcomes

Median PFS on first line chemotherapy was 4.4 months. Compared to patients who only received first line chemotherapy, patients who later received second line chemotherapy experienced a numerically longer median PFS on first line treatment (5.6 months vs. 3.5 months HR 0.88 (0.64-1.2) p=0.43), which was not statistically significant.

Median OS from diagnosis of metastases was 5.1 months in the entire cohort. Compared with any chemotherapy, patients receiving best supportive care alone had shorter survival (9.3 vs. 2.4 months, HR 2.7 (2.06-3.50), p<0.0001) [Figure 3]. Compared to patients who received only first line chemotherapy, patients who received second line chemotherapy and beyond appeared to derive a survival benefit (median OS 14.3 vs. 5.9 months, HR 0.48 (0.34-0.67), p<0.0001) [Figure 3]. Due to the high proportion of patients receiving gemcitabine-nab-paclitaxel as the first line treatment, statistical comparison of outcomes according to treatment regimens was not performed.

From commencement of second line therapy, median PFS was 3 months and median OS was 6.3 months.

Of those who have not proceeded to second line treatment, 69% (92 patients) are deceased. Of the 31% (41 patients) with no date of death recorded, 14% (19 patients) were seen in the last year and remain on first line therapy. 17% (22 patients) were censored >1 year ago and their disease status is unknown.

Discussion

Chemotherapy provides a survival benefit in patients with mPDAC who are fit for systemic treatment. However, our analysis of the current treatment landscape in a community setting demonstrates that only half of patients with mPDAC proceed with chemotherapy. Poor PS

accounted only in part for patients who did not receive any systemic treatment. Of those who did receive chemotherapy, approximately half again deteriorated within months of commencement and did not receive second line chemotherapy.

Of the data available regarding the reasons chemotherapy was not given, we found that the majority of patients were considered unsuitable for treatment by their treating physicians, and only a small minority (7%) declined offered treatment. We also found that many of the patients considered unsuitable for treatment had a recorded ECOG PS of 0 or 1, possibly reflecting the dynamic nature of this variable and difficulty of accurately capturing changes in a registry setting. Given the short median survival of less than a year even in patients who are able to receive treatment, best supportive care remains an appropriate treatment choice for a subset of patients with this disease, and the goal is not to provide systemic treatment to all patients.

Our analysis demonstrated comparable survival outcomes to those of recent clinical trial populations, with patients receiving one or more lines of chemotherapy achieving a median OS of 9.3 months. Patients enrolled in the MPACT trial treated with gemcitabine-nab-paclitaxel experienced a similar median OS of 8.5 months, suggesting that our patients are appropriately selected for treatment [(4)].

Overall, the treatment pattern observed in our cohort is similar to that seen in published data of international registries, suggesting that unsuitability for chemotherapy for a large number of patients precludes any chemotherapy, and that patients deteriorate rapidly with less than half of those fit for chemotherapy at diagnosis being able to proceed to second line treatment. A Swedish cancer registry study of patients with unresectable or metastatic pancreatic cancer published in 2019 found that 35% of patients with advanced pancreatic cancer in their cohort received best supportive care alone, compared with 46% of patients in our cohort[(13)]. The higher uptake of

chemotherapy in their cohort may reflect the inclusion of patients with locally advanced disease. Survival outcomes for patients with metastatic disease were similar to those seen in our cohort, with a median survival of 9.8 months seen for patients receiving gemcitabine-nabpaclitaxel. A large European multi-registry study looking at outcomes by type of chemotherapy confirmed better survival with combination regimens than single agent gemcitabine[14]. Interestingly they noted overall survival was slightly worse than that observed in clinical trials, which was not the case in our patient group. Second line chemotherapy use was similarly low, offered to less than 50% of patients treated with first line therapy.

Our cohort experienced a median PFS of only 4.4 months on first line chemotherapy. Given most patients do not receive second line chemotherapy, optimal regimen selection with the highest depth and duration of response is important. In the ACCORD 11/0402 study, an overall response rate of 32% to FOLFIRINOX was observed compared with 9.4% in the comparator arm of gemcitabine alone. There was a corresponding longer PFS observed with FOLFIRINOX of 6.4 months, compared with 3.3 months on gemcitabine [3]. Contrastingly, the MPACT trial observed an overall response rate of 23% to gemcitabine-nab-paclitaxel compared to 7% with gemcitabine alone, with a median PFS of 5.5 months for the combination and 3.7 months for the single agent arm [4]. However, it is difficult to draw definitive cross-trial comparisons. Despite the suggestion of a higher response rate and longer PFS on FOLFIRINOX, uptake of this regimen in Australian practice has been low, potentially limited by toxicity concerns and the PBS restricting the reimbursement of nab-paclitaxel in mPDAC to the first line treatment setting.

The proportion of patients for whom chemotherapy is prescribed has increased in recent years in our state. A Victorian study of patients treated between 2002-2003 observed that 185/578 (32%) of patients with advanced disease had received palliative chemotherapy [11], compared with 54% in our

study (2016-2019). In the 2002-2003 study, 15% of patients initially considered for chemotherapy did not proceed with treatment, the major contributing reason being patients declining the offered treatment, followed by disease progression and functional decline. A median OS of 6.6 months was observed in patients who received gemcitabine (83% of patients who received systemic therapy) [(11)]. It is sobering to observe, that for patients eligible to receive systemic therapy in Victoria, the progress of nearly two decades and the addition of at least one further chemotherapeutic agent have resulted in only a modest gain in survival.

In our cohort, , only 32% of patients who received chemotherapy and 17% of all patients were able to proceed to second line treatment. It has been shown that the percentage of patients receiving second line chemotherapy can be increased by optimisation of care pathways [(15)]. Improvements in multidisciplinary care may therefore allow more patients to receive the incremental survival benefit provided by second line treatment.

Our study has demonstrated that survival in mPDAC remains short, even for patients able to be treated with combination chemotherapy. Despite this, clinical trial participation in our cohort was low, with only 6% of treated patients (3% of all patients) participating in first line trials, and 2% of all patients participating in second line trials. This is in line with estimates of trial participation in the USA (where it is estimated about 4.6% of mPDAC patients participate in trials) [(16)]. There are major difficulties with trial design for pancreatic cancer patients, in particular the clinical urgency to start treatment after diagnosis. The other significant concern is the high rate of negative trials and the importance of appropriately designing trials to be of maximum potential benefit to patients [(17)]. The difficulty in identifying agents with activity in pancreatic cancer also means that few agents progress beyond phase I trials in this disease, further limiting trial availability and concentrating it in centres with phase I trials units. To achieve major improvements in overall survival, new treatments are

needed. For this to occur in a timely fashion, a higher proportion of patients need to be involved in clinical trials. Ongoing observational research is also important, given the barriers to trial participation. Registries such as the PURPLE registry aim to systematically collect data on patients in routine care to drive quality improvement and better inform future research [(18)]. In addition to observational data, there is increasing experience with randomised registry-based trials, which aim to answer pragmatic clinical questions (for example, optimal treatment sequencing) in a cost-effective manner, while allowing patient enrolment from the standard care setting [(19)]. This approach is particularly attractive in pancreatic cancer, allowing optimisation of existing therapeutics, and bringing trials into standard care for a cohort with otherwise low participation.

Other measures which can improve survival and quality of life for our patients include system improvements and better delivery of existing treatments. A United Kingdom study evaluated centralisation in pancreatic cancer care, [(15)]. The main features of the care model included a team of specialised hepatobiliary oncologists, regular access to a hepatobiliary specialist nurse and streamlined referral pathways for medical and allied health interventions. The study demonstrated that centralisation reduced time to treatment, improved utilisation rates of both first and second line therapy and improved OS (from a median of 3 to 5 months, HR 0.785, p=0.045). Similarly, a national cancer registry study in the Netherlands found that patients treated with palliative chemotherapy in high volume centres had a reduced risk of death (HR 0.76, 95 % CI 0.67–0.87) compared to those treated in lower volume settings [(20)]. These approaches could inform further quality improvement efforts in Australia.

A further area potentially able to improve survival and quality of life is the use of predictive biomarkers. Benefits could include more judicious use of systemic therapy with improved response

rates and avoidance of unnecessary toxicity. It has been suggested that physical properties of the tumour, such as stroma, vascularity and immune infiltrate play a part in treatment response and could be potential predictive biomarkers [21]. BRCA mutations in mPDAC [22] and other tumour types [23, 24] are associated with response to platinum agents and this has also been noted with the associated gene PALB2 [25]. The most common genetic mutations in pancreatic cancers are KRAS mutations (>90% of PDAC [26]), however a drug to successfully target these remains elusive. Currently, predictive biomarkers have a limited clinical role. However, as identified in our study, there is a broad range of survival outcomes ranging from less than 3 months in those unable to receive systemic treatment to more than 14 months for those who received second line therapy. Registries are well placed to identify outliers at both ends of the spectrum, and could inform future biomarker trial design.

There were limitations of our study, including the restricted detail available to ascertain the rationale for treatment decisions. The nature of a registry is that data is recorded in categories which may not fully represent the clinical complexity of a treatment decision. This limits the ability to assess whether treatment opportunities have been missed, or whether those patients who did not receive treatment appropriately received best supportive care only. Previous research into treatment decisions has used in depth clinician surveys, which have the benefit of detail but the limitation of incomplete representation of the population and long delays in collating data. Our findings will be applied to fine-tune our own registry, and can also inform survey design for targeted qualitative research. A further limitation was that this study focused on Victorian sites only. While this provides an in depth assessment of our local situation, our state is relatively small with higher population density than other parts of Australia. It is likely that there are increased barriers to treatment in other states and outcomes may not be comparable.

Future funding for research should focus on making the known incremental gains from centralisation and treatment uptake available to all patients, while facilitating future trials to continue to search for better therapies. A systems approach with development of a semi-centralised model, allowing patient treatment close to home but open communication between clinicians on a statewide level may be able to achieve this aim. In order to provide ongoing improvements, a strong focus on clinical trials is essential, as well as ongoing real-world data collection to inform research design and ensure advances are reaching the whole population. In the first instance, funding to develop and evaluate feasibility of better communication channels between stakeholders (for example, through a statewide metastatic pancreatic cancer treatment group) would progress this aim. The recent widespread uptake of Telehealth for routine oncological management could also allow shared care between high-volume centres and local hospitals, providing subspecialist oversight even for patients treated in regional and remote locations, and could improve clinical trial access regardless of location, as shown recently by development of successful Teletrials models [(27)].

Conclusions

There are significant challenges to overcome in the optimisation of chemotherapy treatments for patients with metastatic pancreatic ductal adenocarcinoma. This analysis suggests that Australian patients are most likely to receive gemcitabine-nab-paclitaxel in the first line setting. Survival outcomes for this real world cohort were comparable to those seen in clinical trials.

Pancreatic cancer in Australia remains a disease with high morbidity and mortality. The fittest patients in our cohort (those able to receive second line chemotherapy) survived a median of only 14 months from diagnosis, while those unable to receive systemic treatment survived less than 3 months. Accessible, high quality palliative care remains of utmost importance to patients and

families while research into more effective treatments continues. Ongoing drug and biomarker development is required to find treatments with a high response rate, good tolerability and durable disease control for patients with this disease.

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Figures

Figure 1. Inclusion of patients from the PURPLE database

Figure 2. Choice of first line chemotherapy

<see separate document for figure>

Figure 3. Survival according to lines of chemotherapy received

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Table 1: Chemotherapy regimens

Regimen	Comparator	Regimen survival	Comparator survival	% alive at 1 year	Quality of life benefit?	ECOG cut-off
First line regimens						
5 FU/LV +/- etoposide[1]	Best supportive care	6 months	2.5 months	Not reported	Better with chemotherapy	Karnofsky PS ≥50 (approx. ECOG ≤3)
Gemcitabine[2]	5FU	5.6 months	4.4 months	18% vs. 2%	Better with gemcitabine	Karnofsky PS ≥50 (approx. ECOG ≤3)
FOLFIRINOX[3] (ACCORD 11/ 0402 trial)	Gemcitabine	11.1 months	6.8 months	48.4% vs. 20.6%	Better with FOLFIRINOX	≤1
Gemcitabine-nab-paclitaxel[4] (MPACT trial)	Gemcitabine	8.5 months	6.7 months	35 vs. 22%	Not measured	≤2
Second line regimens						
OFF (stopped	Best	4.8	2.3	Not	Not reported	Karnofsky

early due to accrual issues)[7]	supportive care			reported		PS ≥60 (approx. ECOG ≤2)
OFF[6]	5FU/LV	5.9	3.3	Not reported	Not reported	Karnofsky PS ≥70 (approx. ECOG ≤2)
FOLFOX[8]	5FU/LV	6.1	9.9	Not reported	Similar both arms	≤2
FOLFIRI[9]	Compared to OFF/FOLFOX in meta-analysis	5.5	5.3	Not reported	Not reported	NA- meta analysis
Nanoliposomal irinotecan/ 5FU[10]	5FU/LV	6.1	4.2	Not reported	Similar both arms	Karnofsky PS ≥70 (approx. ECOG ≤2)

Table 2. Baseline characteristics: Patients receiving any chemotherapy vs. those receiving no chemotherapy

	Any chemotherapy (n=195)	No chemotherapy (n=168)	P value
Age	Median = 69 years (20-94 years)	Median = 73 years (33-85 years)	<0.00001
Gender	Male 101 (51%)	Male 90 (53%)	0.83
ECOG PS 0-1	175 (89%)	110 (66%)	0.0002
Private hospital	93 (65%)	49 (35%)	0.0004
Age-adjusted Charlson comorbidity index ≥3	75 (37%)	127 (63%)	<0.0001
Unadjusted Charlson comorbidity index ≥3	13 (7%)	19 (11%)	0.13
Prior resection of localised disease	43 (22%)	39 (23%)	0.8
Prior adjuvant chemotherapy	40 (21%)	40 (24%)	0.82
Biliary stent required	50 (26%)	42 (22%)	0.9

Table 3: Baseline characteristics: Patients receiving 1 line of chemotherapy compared with 2 or more lines of chemotherapy

	1st line chemotherapy only (n= 133)	2 or more lines of chemotherapy (n= 62)	P value
Age	70 years (33-85 years)	64.6 years (42-84 years)	0.0028
Gender	Male n=69 (52%)	Male n= 32 (52%)	>0.99
ECOG PS 0-1	118 (89%)	56 (90%)	0.8
Private hospital	63 (47%)	30 (48%)	>0.99
Age-adjusted Charlson comorbidity index ≥3	94 (71%)	28 (45%)	0.0008
Unadjusted Charlson comorbidity index ≥3	11 (8%)	2 (3%)	0.23

Figure 1. Patient inclusion from the PURPLE database

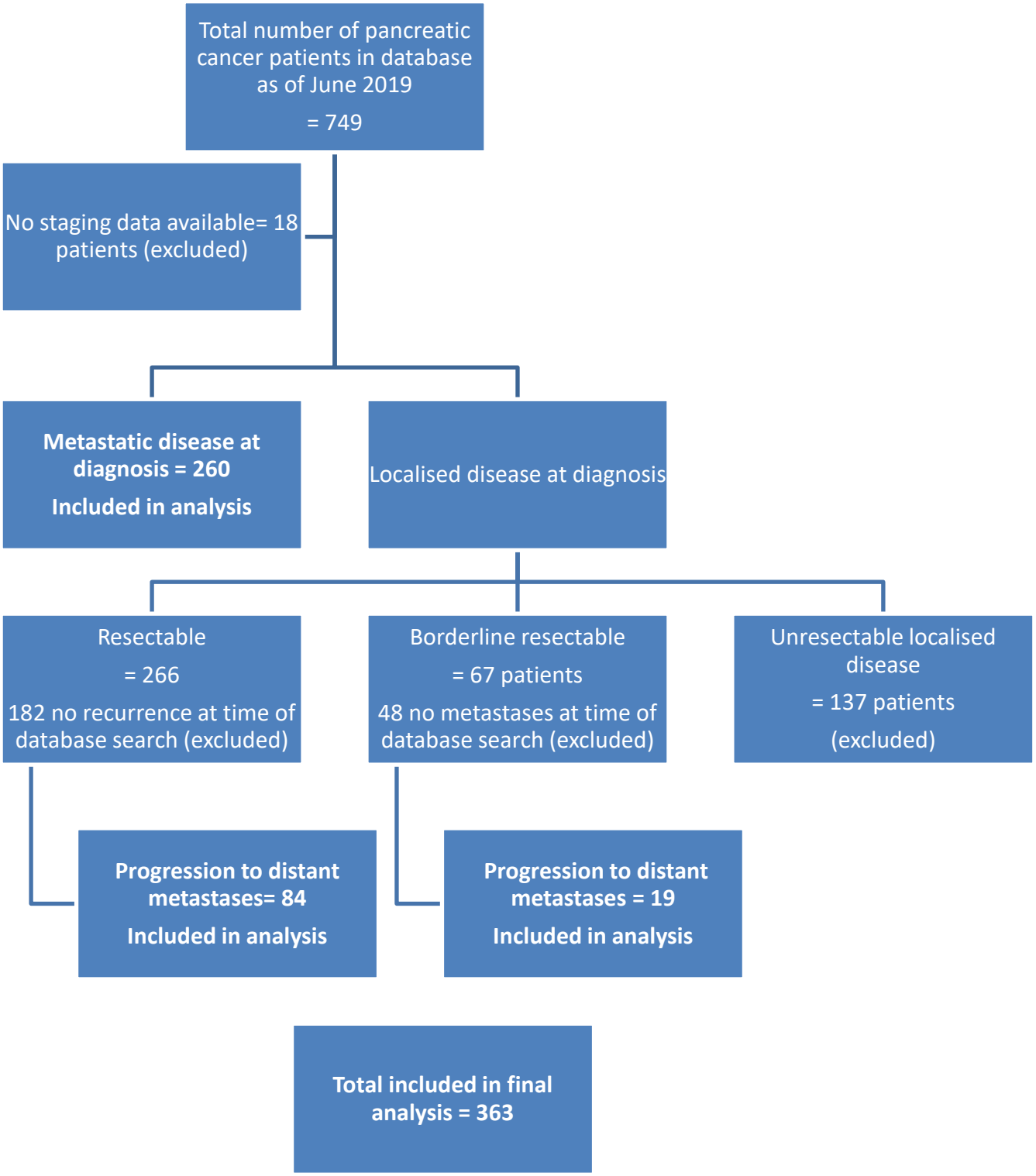

Figure 2. Choice of first line chemotherapy

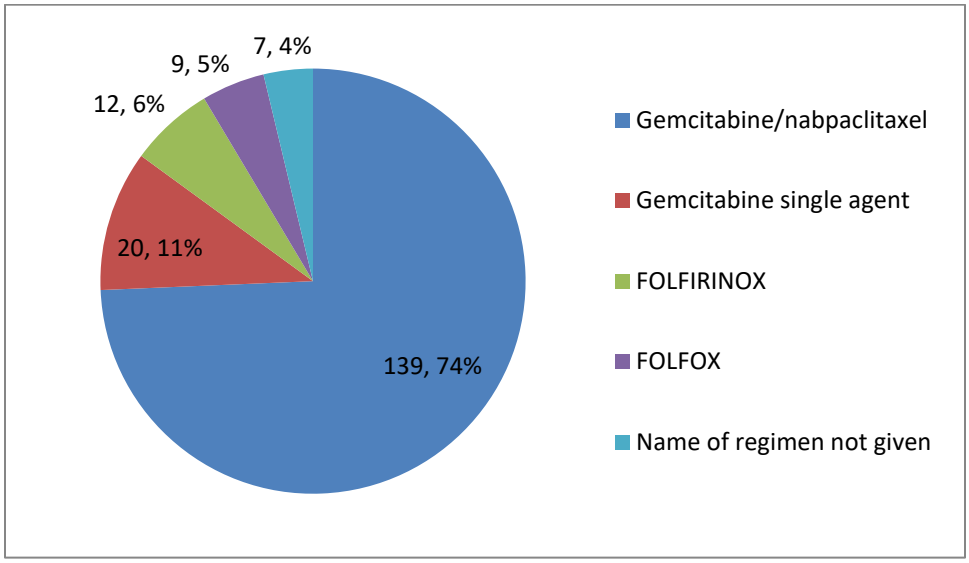

Figure 3. Survival according to lines of chemotherapy received