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Original Research Article

Need for a paradigm shift? Survival post-pancreatoduodenectomy remains poor despite surgical and oncological advances

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ABSTRACT

Background: Despite advances in surgical techniques and chemotherapy, poor outcomes persist in pancreatic malignancy. This study aimed to investigate clinical outcomes and describe the impact of factors like the closest resection margin on overall survival following open pancreatoduodenectomy at a tertiary referral centre over a ten-year period.
Methods: Patients who underwent a pancreaticoduodenectomy at a tertiary hospital in South Australia between 2009-2019 were included in this retrospective study. Patient demographics, systemic treatments, complications, and histological features were analysed for their role in overall survival. Kaplan-Meier survival curves were used to assess patient survival and estimate median survival time.
Results: There were 134 open pancreaticoduodenectomy procedures during 2009-2019. Majority of patients were male (54.7%) between 65-75 years of age (41%) with an ASA physical status classification grade of 3 (63.3%). 56.7% of patients experienced a complication with 5 in-hospital deaths recorded and 12 ISPGF grade B or C pancreatic anastomotic leaks (n=5, n=7 respectively). 88% of resected specimens were malignant with an overall 5-year survival of 32%. A resection margin of >2 mm had a significantly improved overall survival compared to 0 mm (p=0.01). There was no survival benefit for a resection margin of <1 mm or 1-2 mm compared 0mm margin (p=0.6 and p=0.2 respectively). 65 patients (54.6%) experienced either local or distal disease recurrence by the end of the study period.
Conclusions: There has been no improvement in overall survival post pancreatoduodenectomy for pancreatic malignancy. Further research into the clinical significance of the R status classification is required.

Keywords: Pancreatoduodenectomy, Pancreatic cancer, Resection margin, Overall survival

INTRODUCTION

The incidence of pancreatic cancer is increasing globally with 5 year survival rates amongst the lowest of all cancers.[1] The majority of patients are not suitable for curative intent treatment at presentation; either due to a primary that is locally unresectable, metastatic disease or poor performance status. For patients with lesions in or near the head of the pancreas only 15-20% are suitable to undergo curative intent treatment in the form of pancreaticoduodenectomy or 'Whipples' procedure at the time of diagnosis.[2] Pancreatic ductal adenocarcinoma (PDAC) is by far the most common solid pancreatic neoplasm (70-95%) and despite treatment advancing in recent years, these carcinomas continue to have poor long-term outcomes with a 5-year survival remaining less than 10%.[3,4] In those few patients eligible to have a pancreatoduodenectomy for PDAC, outcomes remain poor with 5-year survival less than 20%, high morbidity rates of greater than 50%, and early rates of recurrence with almost

40% developing disease recurrence within 12 months of upfront surgery.[5-7]

The closest surgical margin is one parameter used to determine the extent of resection and can demonstrate surgical quality and possible risk of local recurrence.[8] Moreover, margin status is an independent predictor of local recurrence.[9,10] Surgical margins in pancreatic cancer are classified using the R status, however, inconsistencies in the definition and reporting of R0 and R1 resections has led to international debate and a call to standardise the criteria. Historically an R0 resection, or clear margin, was defined as no direct tumour involvement. Recently the definition of R0 has been revised to state the R0 margin should be clear by >1 mm. This definition was endorsed by the International study group of pancreatic surgery (ISGPS), however, this is not universally accepted.[11] Studies have even reported that patients may only experience significant benefits from tumour free margins of 2mm, thus creating a dynamic and important space for research.[12]

Cancer in the head of the pancreas carries a high morbidity not only from its typically aggressive tumour biology but also the highly complex surgical resection required to attempt to cure the disease. Pancreatoduodenectomy,

a technically demanding operation, is associated with a high rate of complications including a pancreatic anastomotic leak, post-operative haemorrhage, delayed gastric emptying and significant surgical site infections.[13,14] There is a paucity of studies describing long term survival following pancreaticoduodenectomy in the Australian context. This study aimed to investigate clinical outcomes and describe the impact of factors like the closest resection margin on overall survival following open pancreatoduodenectomy at a tertiary referral centre over a ten-year period.

METHODS

All patients who underwent a pancreatoduodenectomy at a Flinders Medical Centre between 2009-2019 were included in this retrospective study and in the analysis of post-operative complications. Patients who were intended for pancreatoduodenectomy but underwent a palliative bypass surgery were excluded from the study. Only patients with malignancy were included in the analysis of resection margins, type of malignant histology and systemic treatments on overall survival. Patient demographics including age, gender and ASA physical status classification were retrieved from online medical records and previous databases collected for auditing. Tumour histological subtype (pancreatic ductal adenocarcinoma, ampullary carcinoma, neuroendocrine tumour or benign lesions), histological features (tumour size, perineural invasion, lymphovascular invasion), closest resection margin (0 mm, <1 mm, 1-2 mm and >2 mm) and portal vein involvement were analysed to determine their role in overall survival. The survival benefits of neoadjuvant (NACT) and adjuvant (ACT) chemotherapy were also compared to those who underwent surgical resection only. The study examined the incidence and type of postoperative complication which were categorised based on Clavien-Dindo criteria. Anastomotic leaks were defined as per the ISGPS classifications, and the use of octreotide in their prevention was also analysed. This study was submitted to the South Australian department for health and wellbeing human research ethics committee (HREC) for ethics approval. This study was deemed by HREC as low/negligible risk and it was exempt from formal ethics processing.

Statistical analysis

All statistical analyses were conducted using R version 4.2.2. Patients' demographic and clinical characteristics were expressed as percentages of the respective denominator. Survival was measured from the date of surgery to the date of death, or individuals were censored at date of loss to follow-up or end of follow-up. The end of follow-up was assigned on 31 December 2019. Cox proportional hazard models were applied to examine the survival outcomes. The estimates were calculated using the likelihood ratio method and were expressed as hazard ratios (HRs) - lower the HR, longer the survival. Proportional hazard assumption was tested by log-log plot of survival and Schoenfeld residuals. Survival curves for patient survival were evaluated by standard Kaplan-Meier survival curves and patient cohorts were compared by log-rank test. The survival curves were restricted to 5 years' death, or the time of last follow-up or loss to follow-up. The median survival time was estimated from Kaplan-Meier survival curves as the smallest survival time for which the survivor function is less than or equal to 0.5. The two-sided test was performed for all analysis, 95% confidence intervals were reported, and the level of significance was set at α=0.05.

RESULTS

Demographics and postoperative complications

Between 2009-2019 there were 134 open pancreaticoduodenectomy procedures completed at a tertiary South Australian Centre. The patient demographics are cited in Table 1. Within this cohort, 56.7% of patients experienced some form of complication ranging from Clavien Dindo classification grades 1-5 (grade 3a, 3b, 14.5%, grade 4, 4a, 4b, 10.5%, and grade 5, 6.6%). 5 in-hospital deaths were recorded and 12 ISPGF grade B or C pancreatic anastomotic leaks (n=5, n=7 respectively). Octreotide was administered as per surgeon preference to 77 patients to prevent pancreatic anastomotic leaks. There was no significant difference in the rate of pancreatic anastomotic leaks between patients who received octreotide, 8/77 (10.4%), compared to those that did not, 4/56 (7.1%) (p=0.5). Other notable complications included delayed gastric emptying (3.7%), postoperative

ileus (11.9%), sepsis (7.5%) and post-operative haemorrhage requiring return to theatre (7.5%) (Table 2).

Table 1: Patient demographics who underwent pancreatoduodenectomy between 2009-2019.

Characteristics	N (%)
Total patients	134
Age (years)	
<65	50 (37.3)
65-75	55 (41.0)
>76	29 (21.6)
Gender	
Male	73 (54.5)
Female	61 (45.5)
ASA classification	
1	6 (4.5)
2	37 (27.6)
3	85 (63.4)
4	6 (4.5)

Table 2: Surgical complications post pancreatoduodenectomy.

Characteristics	N (%)
Any complication	
Yes	76 (56.7)
No	58 (43.3)
Number of complications	
0	58 (43.3)
1	38 (28.4)
2	14 (10.4)
3	13 (9.7)
>4	11 (7.4)
Complication	
In hospital mortality	5 (3.7)
Pancreatic anastomotic leak (grade B, C)	12 (9)
Delayed gastric emptying	5 (3.7)
Post-operative ileus	16 (11.9)
Septicaemia	10 (7.5)
Post-operative haemorrhage	10 (7.5)
Clavien Dindo classification	
1	13 (17.1)
2	39 (51.3)
3a, 3b	11 (14.5)
4, 4a, 4b	8 (10.5)
5	5 (6.6)

25 patients (28.7%) underwent portal vein or superior mesenteric vein resection (PV/SMV) (Table 3). Of those who underwent PV/SMV resection, 21 patients had pancreatic adenocarcinoma histology (PDAC). PV/SMV resection did not result in an overall survival difference in the PDAC population compared to those who did not undergo venous resection (p=0.98).

Table 3: Histopathological features of benign and malignant resected specimens.

Characteristics (all specimens)	N (%)
Malignant	
Yes	119 (88.8)
No	15 (11.2)
Histology	
Pancreatic adenocarcinoma	66 (49.3)
Ampullary	21 (15.7)
Neuroendocrine	6 (4.5)
Other	26 (19.4)
Benign	15 (11.2)
Tumour size (cm)	
<2	27 (20.1)
2-3	41 (30.6)
>3	59 (44.0)
Other	7 (5.2)
Portal vein resected	
Yes	25 (28.7)
No	109 (81.3)
Characteristics: all malignancy	
Lymph node positivity	
0	48 (40.2)
1-2	33 (27.7)
3-4	23 (19.3)
>5	15 (12.6)
Lymphovascular invasion	
Yes	63 (52.9)
No	56 (47.1)
Perineural invasion	
Yes	69 (58)
No	50 (42)
Surgical resection margin (mm)	
0	17 (14.5)
<1	29 (24.8)
1-2	18 (15.4)
>2	53 (45.3)

Histopathological features of resected specimens and their influence on overall survival

Of the 134 specimens, histology was malignant for 88% (n=119) of specimens. Benign histology included normal pancreatic tissue, chronic pancreatitis, tubulovillous adenoma, microcystic cystadenoma or non-invasive intraductal papillary mucinous neoplasm (IPMN). Combined malignant and benign tumours were most commonly >3 cm in size (44%) compared to 2-3 cm or less than 2 cm (30.6% and 20.1%). Malignant tumours included PDAC (n=66), ampullary carcinomas (n=21), neuroendocrine tumours (NET) (n=6) and other cancers (metastatic renal cell carcinoma, gastrointestinal stromal tumour, primary biliary melanoma, duodenal cancers, cholangiocarcinoma, intramucosal carcinoma, acinar cell carcinoma, carcinosarcoma, hepatoid carcinoma and invasive intrapapillary mucinous neoplasia (IPMN)

(n=26)). Histology significantly influenced overall survival for patients who underwent pancreatoduodenectomy.

The overall 5-year survival for patients with any malignancy was 32% (Figure 1). Patients who underwent resection for PDAC had poorer survival (17% at 5 years) compared to ampullary (62% at 5 years), NET (67% at 5 years) and other malignancies (46% at 5 years) (p=0.03) (Figure 2). Lymphovascular invasion (LVI) and perineural invasion (PNI) were present in the majority of malignant specimens (52.9% and 58% respectively). There was no significant difference in overall survival of PDAC patients with positive or negative LVI or PNI (p=0.39 and p=0.70). In patients with malignancy, the closest resection margin was recorded. The majority were >2 mm (45%), followed by <1 mm (24.8%), 1-2 mm (15.5%) and 0 mm (14.5%) (Table 3).

A resection margin of <1 mm or 1-2 mm did not show any overall survival benefit compared to a positive, 0 mm margin (p=0.6 and p=0.2). A resection margin of >2 mm had a significantly improved overall survival compared to 0 mm (Figure 3, p=0.01). The median survival for a resection margin of >2 mm was more than triple (6.8 years) compared to 1-2 mm (3 years), <1 mm (2.8 years) and 0 mm (2.1 years).

Neoadjuvant and adjuvant chemotherapy

Most patients with malignancy received some form of chemotherapy, with only 6 patients receiving neoadjuvant treatment. 63% of patients with malignancy received adjuvant chemotherapy (80% of PDAC, 41.5% of other malignancies). Patients with PDAC who received adjuvant chemotherapy achieved a statically significant improved overall 5-year survival compared to those who underwent surgical resection only (Figure 4, p=0.033). Despite surgical and medical therapies for these pancreatic malignancies, 65 patients (54.6%) experienced either local or distal disease recurrence by the end of the study period.

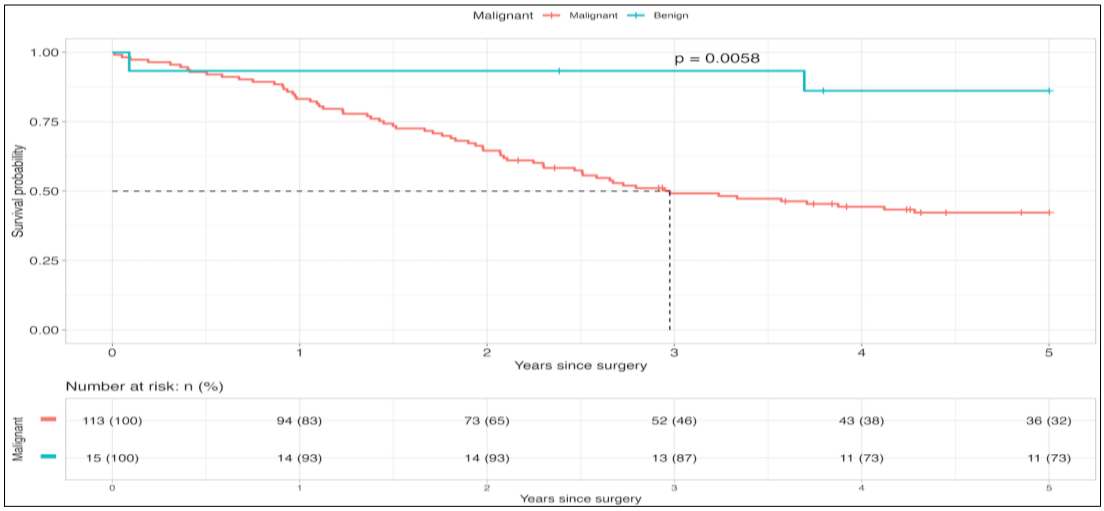

Figure 1: Comparison of overall survival for patient with pancreatic malignancies compared to benign tumours with NET excluded.

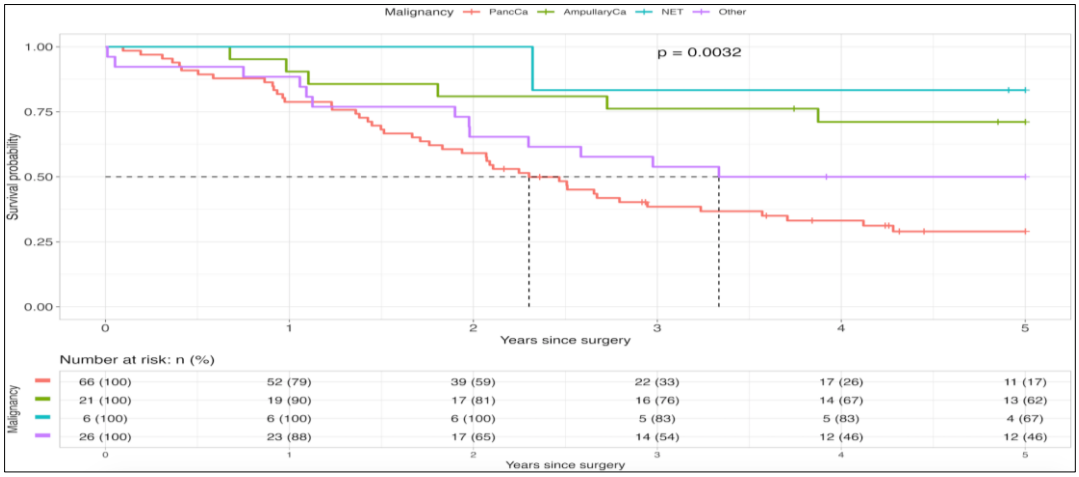

Figure 2: Comparison of overall survival for pancreatic adenocarcinoma (red), ampullary carcinoma (green), neuroendocrine tumours (blue) and other malignancies (purple).

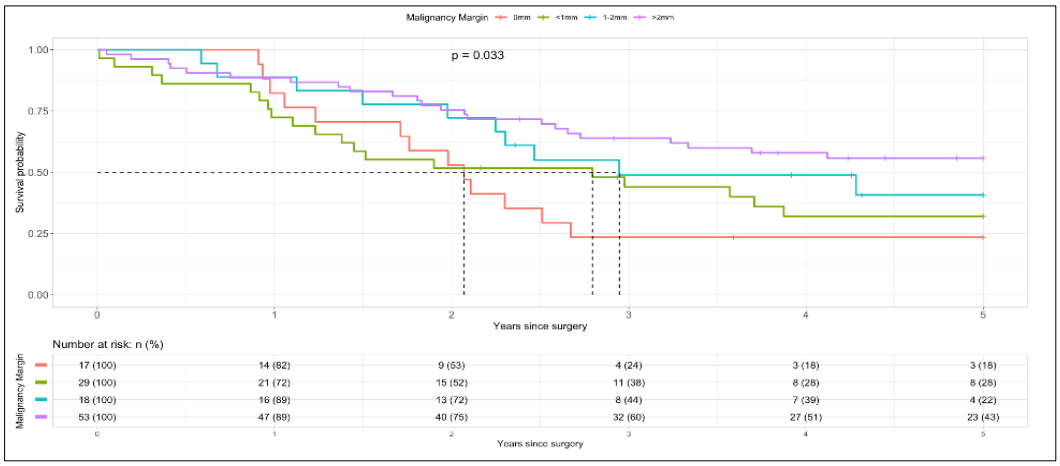

Figure 3: Comparison of overall survival based on resection margins (0 mm, <1 mm, 1-2 mm, >2 mm) in malignancy (p=0.01 for 0 mm versus >2 mm).

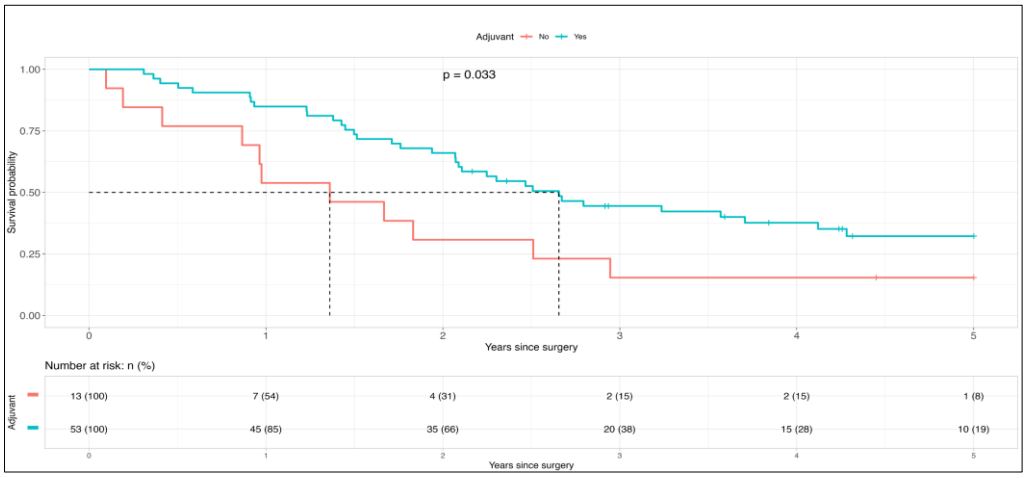

Figure 4: Comparison of overall survival in pancreatic malignancy (PDAC) in patients who received adjuvant chemotherapy compared to no adjuvant chemotherapy.

DISCUSSION

This study provides some of the only long-term survival data for Australian patients undergoing an open pancreatoduodenectomy. Our 1-, 3- and 5- year survival rates from 1998-2008 and 2009-2019 were 62%, 31% and 27% and 79%, 33% and 17% respectively.[15] The improvement in 1-year overall survival reflects the advances in surgical and perioperative techniques. Unfortunately, a decrease in 5-year survival was found in our study, however, this is consistent with data published from other Australian centres from the same time period where 5-year overall survival is quoted between 14.7 and 22%.[16-19] The lack of improvement in 5-year overall survival may be attributed to small volume of patients who received neoadjuvant chemotherapy (NACT) (n=6). NACT was increasingly used towards the end of the study period, thus its benefit, it not likely to be reflected in the results. The majority of patients with pancreatic malignancy received adjuvant chemotherapy (Figure 4) which has previously been shown to improve overall survival. ESPAC-1, published in 2004, was the first landmark trial to demonstrate that surgery with adjuvant chemotherapy is superior to surgery alone.[20] It reported a 5-year overall survival improvement of 16% with the addition of adjuvant chemotherapy(20). This was confirmed in our results which demonstrated that PDAC patients who received adjuvant chemotherapy had superior overall survival compared to surgery alone (Figure 4, p=0.033). Furthermore, ESPAC-4 demonstrated superior outcomes with combination multi-agent adjuvant chemotherapy compared to monotherapy.[21] 5-year overall survivals for patients who received multi-agent adjuvant chemotherapy was 40%, however it is important to note that the patients in this trial had both low biological and surgical risk. Following ESPAC-4, PRODIGE 24 set the standard of care with superior outcomes with adjuvant FOLFIRINOX compared to capcitabine/gemcitabine.[22] Clinical equipoise exists with regards to chemotherapy treatment sequencing for resectable PDAC (i.e. NACT versus ACT) and practise at our institution continues to evolve. Despite the clear survival benefit for adjuvant chemotherapy, only 50-60% of patients receive it, even in

patients with excellent pre-operative fitness. This is largely due to the high postoperative functional/physiological burden that follows pancreaticoduodenectomy.

Multiple phase 2 studies have demonstrated high rates of tolerance to NACT with 90% completing the intended course, compared to only 60% of the 50-60% who actually receive adjuvant chemotherapy.[23] In our study, neoadjuvant chemoradiotherapy is unlikely to have demonstrated a significant impact upon our results as only 5% of patients with malignancy received neoadjuvant therapy. NACT allows assessment of tumour biology and patient robustness. There are promising studies that demonstrate favourable serological response with drop in CA 19.9 with this approach, however there is a paucity of data to suggest improved outcomes.[24] The ESPAC5 study demonstrated that patients who received short course NACT (8 weeks) in borderline resectable PDAC had improved survival compared to those who underwent immediate surgery, however, there was no difference in resection rates.[25] The theoretical disadvantages of NACT for resectable PDAC include a possible increase in surgical morbidity and mortality related to the chemotherapy. Chemotherapy can cause malnutrition and functional decline, both of which are associated with poor surgical outcomes. The prep-02/JSAP-05 PII/III RCT assessed outcomes of NACT versus ACT for resectable PDAC.[26] The same percentage of patients between arms proceeded to resection. Overall, 11 patients in the NACT arm did not proceed to the operating table, but of those who did, a higher rate of proceeding to curative resection was achieved compared to the upfront surgery arm.[26] The most recent SWOG S1505 demonstrated that patients can tolerate modern NA systemic therapy and then undergo successful surgical resection without prohibitive perioperative complications.[27] It also demonstrated a promising 30% major pathological response. Moreover, 85% of patients completed the NA treatment regimen, though, 30% of patients did not proceed to resection.

The rate of R0 resection is considered an important indicator of the quality of the oncological surgical resection.[28] Local recurrences most commonly occurs along the adventitia of cardinal visceral vessels (i.e. superior mesenteric artery (SMA) or common/proper hepatic artery). This occurs in concordance with the known biological behaviour of PDAC in that it tends to propagate along the neurovascular structures on a histological level.[29] An involved pancreatic, or R1, resection margin is associated with early recurrence and decreased overall survival.[6] However, the definition of an R1 resection; R1 direct margin involvement versus R1<1 mm clearance, and the impact this has upon survival is a matter of international debate. From a technical standpoint, achieving a routine 1 mm margin may be challenging, largely due to the intrinsic nature of the local anatomy - an area confined by critical vasculature. As such, one of the most common sites for local recurrence occurs is within the adventitia of the SMA or the adjacent mesopancreatic tissue. Several operative approaches have been described to achieve superior oncological clearance. These include the artery first approach (determine arterial involvement and improve access for SMA skeletonisation), peri-arterial SMA divestment, TRIANGLE dissection (clearance of tissue from SMA to CT), vascular resection and extended lymphadenectomy. The risk to benefit ratio of performing more extensive dissection needs to be carefully considered. Moreover, peri-arterial divestment can result in severe intractable diarrhoea (stripping of autonomic nerves from SMA), which can significantly reduce functional/physiological outcomes following pancreaticoduodenectomy. Additionally, enthusiasm for SMA resection and reconstruction has 'waxed and waned' over the years, predominantly due to unacceptably high morbidity and mortality rates without a clear improvement in oncological outcomes.[30] All procedures that involve close SMA dissection/reconstruction can increase the risk of post-pancreatectomy haemorrhage in the presence of a postoperative pancreatic fistula. The optimal combination of neoadjuvant treatment and surgical technique to achieve R0 resection is currently not well understood. Neoadjuvant chemo-radiotherapy (NACRT) is another approach to improve R0 resection rates, however, it is yet to show a consistent survival or resection benefit.[31-33] The revised R0 definition (>1 mm margin) was endorsed by the International study group of pancreatic surgery (ISGPS), however it is not universally accepted because it has not been prospectively validated as an indicator of survival.[11] Several studies have failed to demonstrate that R1 <1 mm conveys a prognostic benefit, whereas others have shown that resection margin is an independent risk factor.[9,10,34,35-38] A meta-analysis by Chandrasgaram et al demonstrated that reported R0 resection rates in the literature varied between 15% and 83%. They also highlighted the need for uniform pathological processing and reporting.[39] The lack of a commonly accepted definition of R status has hampered its ability to be assessed and used as an indicator of prognosis. Recent evidence is mounting to support the new R status definition. A recent cohort study by Strobel et al confirmed that resection status is independently associated with survival. R0 and R1 (<1 mm) versus R1 (direct margin involvement) was associated with median survival times of 41.6, 27.5, and 23.4 months and 5-year survival rates of. 37.7%, 30.1% and 20.3% respectively ($p<0.0001$).[12] This study did not include the locations of the positive margin. The importance of resection margin vs circumferential margins is not well understood. A retrospective study by Jamieson et al indicated that a close transection margin was associated with poorer survival whereas anterior and posterior margins were not.[40] Our series demonstrated the surgical margin only achieved a statistically significant survival benefit once the margin was >2 mm ($p>0.01$), Interestingly, <1 mm and 1-2 mm margin did not have a statistically significant impact on survival ($p=0.6$ and $p=0.2$ respectively) (Figure 3). This is supported by several other studies showing survival benefit was only seen in margins greater than 1.5 or 2 mm.[36,40-42] We have previously published our results with sequential margin analysis revealing that long term

survival difference only became significant when the margin was clear by 2 mm ($p<0.01$).[15]

This project has been limited by the number of patients who did not undergo neoadjuvant chemotherapy. This likely reflects the shift in treatment approach over the past decade at this institution where patients towards the end of the study received neoadjuvant therapy and those a decade prior did not. The study was also limited by the small sample size resulting in the inclusion of non PDAC patients in some figures to ensure adequate statistical analysis. With a greater sample size, histological subtypes could be analysed independently which would improve assessment of overall survival given different pancreatic neoplasms can vary significantly in morbidity and recurrence. A greater sample size could be achieved with a national clinical quality registry which would combine the data of many individual centres.[43,44]

CONCLUSION

Despite advances in adjuvant chemotherapy and surgical technique, outcomes are strikingly unchanged since our previous audit published in 2009. In order to accurately describe and comment on the significance resection margins, a consistent R status definition needs to be established internationally such that R0 >1 mm. This study has shown a 2 mm margin is required to show a survival benefit and it is possible that this may be achieved with the use of NACT. Thus, a paradigm shift towards NACT for upfront and borderline resectable pancreatic cancer with a 2 mm resection margin should be explored. There is a lack of quality long term survival data for Australian PDAC patients, with most studies focusing on short term survival outcomes. Therefore, a national clinical quality registry could be key to improving the management of PDAC in Australia.

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