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Mini Review Article

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Survival and quality of life following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

Thomas B Russell[1], Peter L Labib[1], Somaiah Aroori[1*]

[1]*Department of HPB Surgery, University Hospitals Plymouth NHS Trust, Derriford Road, Plymouth, PL6 8DH, UK*

[*]Corresponding author
Somaiah Aroori, Consultant HPB and Transplant Surgeon, University Hospitals Plymouth NHS Trust, Derriford Road, Plymouth, PL6 8DH, UK,

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) most commonly affects the head of the pancreas. This condition has a dismal prognosis. Patients with early disease may be candidates for pancreaticoduodenectomy (PD). This is a high-risk operation which is associated with considerable morbidity. Whilst perioperative mortality rates have fallen in recent times, the risk remains significant and long-term survival is poor, even in those who make an uncomplicated recovery. Furthermore, PD is known to affect quality of life (QoL) negatively. Most studies suggest it takes up to six months before a patient's QoL returns to baseline. This is a considerable amount of time for a patient who is unlikely to achieve long-term survival. This short review discusses the recent literature surrounding mortality rates, long-term survival and QoL following PD for PDAC. A comprehensive understanding of these topics will allow clinicians and patients to consider the risks and benefits before surgical resection is considered.

Keywords: Pancreatic ductal adenocarcinoma, pancreatic cancer, pancreaticoduodenectomy, Whipple, mortality, survival, quality of life

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has the lowest survival of all common cancers; current United Kingdom (UK) one-year and five-year survival rates are 23.7% and 6.9% respectively[1]. Approximately 80% of PDAC cases in the UK are diagnosed at stage III or IV, and around 20% are diagnosed at stage I or II[1]. Surgical resection in the form of pancreaticoduodenectomy (PD) is usually recommended in patients with stage I/II disease providing they have an appropriate performance status and acceptable co-morbidity profile. Median survival following PD in PDAC patients is around 24 months[2]. Those with stage III disease are usually not offered surgery since it rarely provides cure and does not prolong survival.

Surgical resection is a major undertaking and morbidity/mortality rates may be under-estimated due to publication bias. Therefore, it is important that both clinicians and patients have a comprehensive understanding regarding mortality, survival, and impact on quality of life (QoL) following PD for PDAC, so that informed decisions can be made regarding treatment. This short review consolidates the recent literature on these topics.

Resection for early disease

No large studies have compared outcomes of patients with resectable PDAC (stage I/II) who have undergone PD to those who have not. A retrospective study by Lee et al. analysed the outcomes of PDAC patients at a single Korean centre between 2007-2014 (n=1,646). 475 (28.9%) had resectable PDAC, 129 (7.8%) had borderline resectable disease, 384 (23.3%) had locally-advanced disease, and 658 (40.0%) had metastatic PDAC[3]. Among those with resectable disease, 91.4% underwent curative-intent surgery, 3.6% underwent chemotherapy only, and 5.1% received palliative care. Median survival was 22 months in the surgery group, 8 months in the chemotherapy group ($p<0.001$), and 11 months in the palliative care group ($p<0.001$)[3]. In the borderline group, 34.9% underwent surgery without neoadjuvant therapy (NAT), 21.7% underwent up-front surgery followed by adjuvant chemotherapy, 33.3% received chemotherapy alone, and 10.1% received palliative care. In those who underwent PD, patients who received NAT had a significant survival advantage (24 months vs. 16 months, $p=0.049$)[3].

PD without NAT was associated with a longer median survival (16 months) when compared with chemotherapy alone (12 months), but this was not significant ($p=0.091$)[3]. In those with locally advanced disease, there was also no significant difference in median survival between those who underwent PD (with or without adjuvant therapy, 10 months), NAT prior to PD (19 months), and

chemotherapy alone (13 months)(p=0.142)[3]. The authors did not specify why patients with resectable disease did not undergo PD, although they were likely to represent patients who were not fit enough to undergo surgery. This study highlights the survival benefit of PD in those with resectable disease. The picture is less clear in those with borderline disease, and PD does not improve survival in those with locally advanced disease.

Chakraborty et al. carried out a survival analysis of patients diagnosed with stage I/II PDAC (i.e. those without vascular invasion) between 1973-2009 using the Surveillance, Epidemiology, and End Results Program (SEER) database (n=1,759). This study was not limited to tumours affecting the head of the pancreas and considered all forms of pancreatic resection. 92.6% underwent curative-intent surgery[4]. Resection was associated with longer overall survival (OS) (18 months vs. 7 months, p<0.0001). Other factors associated with improved OS were age less than 50 years, maximum tumour diameter less than 20 mm, absence of positive lymph nodes, radiation therapy, and a well-differentiated tumour[4].

Elderly patients are more likely to have a poor performance status and may not be appropriate surgical candidates, even if they have early stage PDAC. Older patients also have lower OS rates when all causes of death are considered. In another Korean study, Park et al. investigated whether PD provided a survival benefit to patients aged over 75 years. Only those with resectable disease were included and patients were excluded if they had another malignancy or a history of another malignancy. Thirty-eight patients underwent PD and 11 did not; three of these could not undergo surgery due to poor performance status, and eight elected to decline all forms of treatment[5]. 40.7% of those who underwent PD were alive at two years following diagnosis, whereas all those who did not undergo surgery had died[5]. The authors concluded that an aggressive surgical approach could provide a significant survival benefit in older patients[5].

Major outcomes

Mortality

Perioperative mortality following PD has traditionally been quoted at 5%, although this has decreased in recent years due to improved patient selection, advances to surgical techniques, centralisation of services, and increased attention to peri-operative care[6]. High-volume centres have been shown to have reduced mortality rates when compared with low-volume centres, but optimum volume has not been defined. A series published by Narayanan et al. studied 551 PDs at a single USA centre from 2007-2016 (all pathologies, including PD for other cancers and benign disease). Thirty-day, 90-day, and one-year mortality rates were 1.1%, 3.6%, and 16.5%, respectively [7]. The most common causes of death were multi-organ failure secondary to sepsis or aspiration, post-pancreatectomy haemorrhage, myocardial infarction, and pulmonary embolus [7].

Whilst some single-centre studies have reported very low mortality rates, studies using national data report higher rates. A less recent (but larger) multi-centre UK study looked at 90-day mortality in PD patients from 2001-2016 (n=14,935). In-hospital, 30- and 90-day mortality rates were 4.7%, 3.7%, and 6.5%, respectively[8]. The authors concluded that 90-day mortality was highest in very low-volume centres, but no additional benefit was obtained once a centre performed more than 36 procedures per year. Another highlight was that 90-day mortality fell dramatically from 10.0% in 2001-2004 to 4.1% in 2013-2016[8].

Merath et al. studied 9,639 PDs at multiple USA hospitals from 2004-2014 (all pathologies included). Inpatient mortality was 3.2%, regardless of histological diagnosis[9]. Unlike the UK study, smaller hospitals did not have higher mortality rates. No significant difference was observed between “rural” and “urban non-teaching” hospitals. Inpatient mortality was significantly lower at “urban teaching” hospitals, but the difference was marginal[9]. Patients who died as an inpatient were more likely to be male, have chronic obstructive pulmonary disease (COPD), liver disease, chronic kidney disease (CKD), peripheral vascular disease (PVD), or congestive cardiac failure (CCF)[9].

Table 1: Thirty- and 90-day mortality following pancreaticoduodenectomy (PD) and coronary artery bypass grafting (CABG).

Study	Operation	Number of patients	30-day mortality (%)	90-day mortality (%)
Narayanan et al., 2018[7]	PD	551	1.1	3.6
Liu et al., 2018[8]	PD	14,935	3.7	6.5
Mittel et al., 2020[10]	CABG	72,398	2.2	3.7

To put these figures into perspective, they can be compared to those from another commonly performed non-emergency operation which is considered high-risk e.g., coronary artery bypass grafting (CABG) (Table 1). A 2020 study by Mittel et al. looked at 72,398 CABGs carried out at multiple USA centres from 2008-2014. 30-day mortality was 2.16% and 90-day mortality was 3.69%[10]. Whilst the two operations cannot be directly compared, this data suggests PD can be grouped with other non-emergency operations that are considered high-risk.

Long-term survival

Although PD is performed for early PDAC with curative intent, the vast majority of patients develop recurrent disease. Disease-free survival (DFS) refers to the length of time between treatment and the point at which a patient develops signs and/or symptoms of recurrent cancer. Following PD for PDAC, DFS is usually defined as the time at which recurrent disease is identified on surveillance imaging. However, definitions vary and it is more challenging to measure than other endpoints. Hence, few recent studies have at-

tempted to calculate DFS. A multicentre retrospective study by Lubrano et al. followed up 942 PDs from multiple European centres from 2004-2009 (PDAC only). Patients were excluded if they died in the peri-operative period. In the remaining patients, median DFS was 19 months[11].

A severe complication was associated with significantly reduced DFS. The authors suggested that this was likely because a severe complication can result in a delay to adjuvant chemotherapy. DFS is also heavily influenced by the completeness of the resection. A retrospective study by Roessel et al. studied 531 PDs from 2000-2014 from centres in the USA and the Netherlands (PDAC only). Patients who received NAT and those with who had an incomplete resection were excluded. DFS was 12.9, 15.4, and 24.1 months for surgical margin clearances of 0, <1, and ≥1 mm, respectively.

Overall survival refers to the length of time between the date of diagnosis and death. A recent single-centre USA study by Pugalenthi et al. studied 596 PDs from 2001-2009 (PDAC only). Median OS was 24 months[12]. Further data is available from recent studies regarding five-year survival (Table 2). A German single-centre retrospective study by Luu et al. looked at 167 PDs from 2007-2014. Median five-year survival was 20.4%[2]. A prospective observational study by Acedo et al. studied patients who underwent PD with total mesopancreatic excision at a single Spanish centre between 2008-2014 (n=114, PDAC only). Five-year survival was 26.6% [13]. A less-recent Taiwanese study by Hsu et al. looked at 223 PDs from 1995-2010 (PDAC only). Three- and five-year survival rates were 21.4% and 10.1%, respectively[14]. A large retrospective study by Huang et al. used the USA SEER database and the national cancer registries of Slovenia, the Netherlands, Belgium and Norway to compare the OS of PDAC patients who underwent resection with OS of all PDAC patients[15]. Five-year OS for operated patients with stage I-II disease in the most recent cohort (2009-2011) ranged from 11% in Slovenia to 20% in Norway, with the Netherlands and Belgium both having 5-year OS of 18% (5-year OS for the USA was not available). In conclusion, patients who undergo curative-intent resection for PDAC have a predicted 5-year OS of around 15-20%.

Table 2: Five-year survival following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma.

Study	Number of patients (n)	Five-year survival (%)
Luu et al., 2020[2]	167	20.4
Acedo et al., 2019[13]	114	26.6
Hsu et al., 2018[14]	223	10.1
Huang et al., 2018[15]	125,183	11-20

Quality of life

Since PD is associated with high morbidity rates and poor long-term survival, it is important that a patient's quality of life (QoL) following the procedure is considered. A recent systematic review (SR) by van Dijk et al. evaluated all prior studies which assessed QoL using validated questionnaires in patients who underwent PD for PDAC. The authors concluded that PD negatively affects QoL in the short term but that a recovery to baseline is made 3-6 months post-operatively (Figure 1)[16]. Most of the included studies reported that physical functioning initially declined but then recovered to baseline at 3-6 months, and that emotional functioning initially declined before recovering to baseline at 3-12 months[16]. Results regarding social functioning were highly variable between the included studies. Except for one, all studies which reported on fatigue suggested an increase before recovery to baseline by 6-month follow-up[16]. All studies which reported on nausea showed an initial increase before a return to baseline by 6-month follow-up[16]. Most studies reported on pain, although the results were highly variable. Six studies reported on dyspnoea and five on insomnia, all suggested a return to baseline by 6-month follow-up[16]. The results for loss appetite, diarrhoea, and constipation were highly variable; no studies suggested these symptoms were worse than baseline at 6-month follow-up[16].

Table 3 : Summary of the key findings from the meta-analysis performed by van Dijk et al.[16], QoL = quality of life, PD = pancreaticoduodenectomy.

Aspect of QoL/symptom	Time to recovery to baseline after PD (months)
Physical functioning	3-6
Fatigue, nausea, dyspnoea, insomnia, loss of appetite, change of bowel habit	6
Emotional functioning	3-12
Social functioning, pain	Highly variable

Discussion

Most patients diagnosed with PDAC are not appropriate surgical candidates. Around one fifth present with resectable disease. This is only appropriate in patients with a reasonable performance status and acceptable co-morbidity profile. Whilst PD is high-risk, it can improve survival in those with resectable disease. It is less clear if PD improves survival in those with borderline resectable disease. Perioperative mortality rates have fallen considerably in recent years. This is because of better patient selection, improved surgical technique, and better peri-operative care. The centralisa-

tion of services may also have contributed. Peri-operative mortality was traditionally quoted at 5%; a figure between 1-3% is likely more up-to-date. Excluding patients who die in the peri-operative period, median OS is around two years, and between 15-20% of patients achieve five-year survival[15].

PD has a profound impact on a patient's QoL. Physical, emotional, and social functioning are all likely to be affected in the early post-operative phase. Most studies suggest a return to baseline between 3-6 months. Many patients also suffer with considerable pain, dyspnoea and insomnia post-operatively. Whilst results from prior studies are highly variable, most suggest these return to baseline by six months. It is important to remember that only patients who survived the peri-operative period will have taken part in these studies, and that 3-6 months is a considerable amount of time for patients who have a median OS of 24 months.

Conclusion

Perioperative mortality following PD for PDAC has fallen considerably in recent years. However, the risk remains significant. Of those who survive the peri-operative period, between 15-20% will achieve five-year survival. PD has a profound negative impact on a patient's QoL; this may take six months or more to return to baseline. It is important that clinicians and patients with resectable disease have a comprehensive understanding of these issues before PD is considered.

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Declaration of competing interests

TR, PL, and SA declare that there are no conflicts of interest.

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Authorship statement

Conceptualisation: TR, PL, SA, Investigation: TR, Study design: TR, PL, SA, Writing – Original Draft: TR, Writing – Review & Editing: PL, SA, Supervision: SA, Project Administration: TR

References

1. UK, P.C. (2021) Pancreatic cancer statistics 2021.
2. Andreas Minh Luu, Chris Braumann, Orlin Belyaev, Janot M, Henrik Rudolf, et al. (2020) Long-term survival after pancreaticoduodenectomy in patients with ductal adenocarcinoma of the pancreatic head. Hepatobiliary & Pancreatic Diseases International, 2020.
3. Doo ho Lee, Jin Young Jang, Jae Seung Kang, Jae Ri Kim, Youngmin Han, et al. (2018) Recent treatment patterns and survival outcomes in pancreatic cancer according to clinical stage based on single-center large-cohort data. Annals of hepato-biliary-pancreatic surgery, 22: 386-396.
4. Chakraborty S, S Singh (2013) Surgical resection improves survival in pancreatic cancer patients without vascular invasion- a population based study. Annals of gastroenterology, 26:346-352.
5. Hyeong Min Park, Sang Jae Park, Sung Sik Han, Seoung Hoon Kim (2019) Surgery for elderly patients with resectable pancreatic cancer, a comparison with non-surgical treatments: a retrospective study outcomes of resectable pancreatic cancer. BMC Cancer, 19: 1090.
6. J D Birkmeyer, A E Siewers, Emily Finlayson (2002) Hospital volume and surgical mortality in the United States. N Engl J Med, 346:1128-1137.
7. Sowmya Narayanan, Allison N Martin, Florence E Turrentine, Todd W Bauer, Reid B Adams, et al. (2018) Mortality after pancreaticoduodenectomy: assessing early and late causes of patient death. J Surg Res, 231: 304-308.
8. Z Liu, I S Peneva, Felicity Evison, S Sahdra, D F Mirza, et al. (2018) Ninety day mortality following pancreatoduodenectomy in England: has the optimum centre volume been identified? HPB, 20:1012-1020.
9. Katiuscha Merath, Rittal Mehta, Diamantis I Tsilimigras, Ayesha Farooq, Kota Sahara, et al. (2020) In-hospital Mortality Following Pancreatoduodenectomy: a Comprehensive Analysis. Journal of Gastrointestinal Surgery, 24:1119-1126.
10. Aaron Mittel, Dae Hyun Kim, Zara Cooper, Michael Argenziano, May Hua, et al. (2020) Use of 90-day mortality does not change assessment of hospital quality after coronary artery bypass grafting in New York State. The Journal of Thoracic and Cardiovascular Surgery 2020.
11. Jean Lubrano, Philippe Bachelier, François Paye, Yves Patrice Le Treut , Laurence Chiche, et al. (2018) Severe postoperative complications decrease overall and disease free survival in pancreatic ductal adenocarcinoma after pancreaticoduodenectomy. Eur J Surg Oncol, 44:1078-1082.
12. Amudhan Pugalenthi, Mladjan Protic, Mithat Gonen, T Peter Kingham, Michael I D Angelica, et al. (2016) Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Surg Oncol, 113: 188-193.
13. Pablo Sanchez Acedo, Javier Herrera Cabezón, Cruz Zazpe Ripa, Antonio Tarifa Castilla (2019) Survival, morbidity and mortality of pancreatic adenocarcinoma after pancreaticoduodenectomy with a total mesopancreas excision. Rev Esp Enferm Dig, 111(8):609-614.
14. Chih Po Hsu, Jun Te Hsu , Chien Hung Liao, Shih Ching Kang, Being Chuan Lin, et al. (2018) Three-year and five-year outcomes of surgical resection for pancreatic ductal adenocarcinoma: Long-term experiences in one medical center. Asian Journal of Surgery, 41:115-123.
15. Lei Huang, Lina Jansen, Yesilda Balavarca, Masoud Babaei, Lydia van der Geest, et al. (2018) Stratified survival of resected and overall pancreatic cancer patients in Europe and the USA in the early twenty-first century: a large, international population-based study. BMC Medicine,16: 125.
16. Sven M van Dijk, Hanne D Heerkens, Dorine S J Tseng, Martijn Intven, I Quintus Molenaar, et al. (2018) Systematic review on the impact of pancreatoduodenectomy on quality of life in patients with pancreatic cancer. HPB, 20:204-215.