Original article

Impact of delay between imaging and treatment in patients with potentially curable pancreatic cancer

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Background: **Locoregional pancreatic ductal adenocarcinoma (PDAC) may progress rapidly and/or disseminate despite having an early stage at diagnostic imaging. A prolonged interval from imaging to resection might represent a risk factor for encountering tumour progression at laparotomy. The aim of this study was to determine the therapeutic window for timely surgical intervention.**

Methods: **This observational cohort study included patients with histologically confirmed PDAC scheduled for resection with curative intent from 2008 to 2014. The impact of imaging-to-resection/reassessment (IR) interval, vascular involvement and tumour size on local tumour progression or presence of metastases at reimaging or laparotomy was evaluated using univariable and multivariable regression. Risk estimates were approximated using hazard ratios (HRs).**

Results: **Median IR interval was 42 days. Of 349 patients scheduled for resection, 82 had unresectable disease (resectability rate 76·5 per cent). The unresectability rate was zero when the IR interval was 22 days or shorter, and was lower for an IR interval of 32 days or less compared with longer waiting times (13 *versus* 26·2 per cent; HR 0·42, $P = 0·021$). It was also lower for tumours smaller than 30 mm than for larger tumours (13·9 *versus* 32·5 per cent; HR 0·34, $P < 0·001$). Tumours with no or minor vascular involvement showed decreased rates of unresectable disease (20·6 per cent *versus* 38 per cent when there was major or combined vascular involvement; HR 0·43, $P = 0·007$). However, this failed to reach statistical significance on multivariable analysis ($P = 0·411$), in contrast to IR interval ($P = 0·028$) and tumour size ($P < 0·001$).**

Conclusion: **Operation within 32 days of diagnostic imaging reduced the risk of tumour progression to unresectable disease by half compared with a longer waiting time. The results of this study highlight the importance of efficient clinical PDAC management.**

Paper accepted 7 October 2015
Published online 17 November 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10046

Introduction

Pancreatic ductal adenocarcinoma (PDAC) will probably be the second leading cause of cancer death by the year 2020[1]. Reasons for the dismal prognosis include absence of symptoms at early stages, inability of imaging to detect precursor lesions and lack of adequate screening procedures[2]. A decade during which the tumour remains asymptomatic and undetectable may be required for an initiating mutation to develop into an infiltrating carcinoma[3]. Increasingly rapid tumour progression leads to symptomatic PDAC exhibiting lymphovascular invasion and/or metastases[4]. More than 80 per cent of diagnosed PDACs present at late stages and are not amenable to curative therapy[5]. Complete surgical resection combined with adjuvant chemotherapy within multimodal treatment protocols is offered to patients with limited locoregional disease[6].

Diagnosis, staging and assessment of resectability are generally done on the basis of imaging[7]; additionally, laparoscopy and serum levels of biomarkers such as carbohydrate antigen 19-9 may provide important diagnostic information in selected patients[8,9]. Contrast-enhanced multidetector CT (MDCT) using a pancreatic protocol is currently the imaging modality of choice for staging PDAC[10]. However, staging based on radiology is suboptimal, in part owing to technical limitations and lack of consensus regarding assessment of resectability despite

the existence of established cancer staging systems[11–13]. A better understanding of the heterogeneity of the disease and increasing surgical experience with vascular reconstructions have blurred the border between resectability and unresectability[14,15].

The dilemma of imaging-based resectability assessment in pancreatic cancer is illustrated by a constant risk of disease understaging owing to inaccurate diagnostic methods[16]. Additionally, determining the resectability of tumours at an early stage cannot preclude rapid progression or dissemination as a result of aggressive tumour biology once the diagnosis has been made[17,18]. Up to 30 per cent of PDACs considered resectable at imaging are unresectable at the time of exploratory laparotomy owing to locoregional progression or metastasis[19]. It is currently unknown what the safe time window is for surgical intervention in PDAC.

The aim of the present study was to analyse whether the interval between diagnostic imaging and surgical exploration had an impact on the tumour resectability rate. The secondary aim was to assess the impact of this time interval relative to tumour stage at the time of diagnosis.

Methods

This single-centre observational cohort study included patients with pancreatic tumours evaluated by the multidisciplinary pancreatic tumour board (MPTB) at Karolinska University Hospital between 2008 and 2014. Tumour stage and resectability were assessed after review of diagnostic imaging (pancreatic protocol MDCT or MRI). Patients with resectable tumours were included in the study cohort; those who had completed neoadjuvant treatment for initially unresectable or borderline tumours had to have stable disease or remission according to the Response Evaluation Criteria In Solid Tumours (RECIST) at restaging[20]. Histological confirmation of PDAC was required in all patients. Before resection, patients underwent preoperative evaluation and signed consent for the planned procedure. Patients who refused surgical treatment or were not surgical candidates were excluded from the analysis. The conduct of the study was approved by the institutional review board.

Reassessment of tumour resectability was done surgically at the time of laparotomy or by preoperative reimaging. Two subgroups were defined: an unresectable group consisting of patients whose disease was confirmed to have progressed to locally advanced/metastasized disease at the time of reassessment; and a resection group consisting of patients who proceeded to resection with curative intent after reassessment. Further imaging was undertaken if initial diagnostic imaging was older than 42 days. Patients who still had resectable tumours at the time of reassessment proceeded to surgery. If tumours were deemed unresectable at this time, the planned surgery was abandoned, and neoadjuvant or palliative oncological therapy was initiated after ultrasound- or endoscopic ultrasound-guided biopsy for histological confirmation of PDAC. These patients were included in the unresectable group.

At laparotomy, the liver and abdominal cavity were inspected and suspicious lesions were sampled for frozen-section biopsy. In the absence of metastases or peritoneal carcinomatosis, the locoregional stage was evaluated, with assessment of the tumour in relation to mesenteric and hepatic vessels. Patients were included in the unresectable group after histological verification of locally advanced or metastatic PDAC. Patients who underwent a successful resection were included in the resection group after PDAC had been diagnosed in the surgical specimen (*Fig. 1*).

The imaging-to-resection/reassessment (IR) interval was defined as the time interval between the date of diagnostic imaging (the basis for MPTB assessment) until the date of reassessment (reimaging or surgical assessment at laparotomy). In patients who had stable disease or tumour remission following neoadjuvant treatment, the IR interval was defined from the date of restaging imaging until date of reassessment. Tumour size was recorded as the largest diameter of the primary mass. The resectability of pancreatic tumours was determined by their relation to the superior mesenteric vein (SMV), portal vein (PV), superior mesenteric artery (SMA) or hepatic arteries. Vascular involvement was classified as: none; minor isolated venous (tumour–SMV/PV interface less than 180° circumference, maximum involvement less than 2 cm in length); major isolated venous (tumour–SMV/PV interface exceeding 180° circumference, maximum involvement less than 2 cm in length); and major combined arteriovenous (tumour–SMV/PV interface exceeding 180° circumference, maximum involvement more than 2 cm in length and/or tumour–SMA interface less than 180° circumference, maximum involvement less than 2 cm in length). Tumours without vascular invasion or with isolated venous involvement were considered primarily resectable, whereas those with combined arteriovenous involvement were considered unresectable; however, the latter tumours could potentially become resectable after neoadjuvant therapy (systemic gemcitabine-based combination chemotherapy). The response was evaluated according to RECIST[20]; surgical exploration was undertaken and resection attempted if the classification was stable disease or a partial response. Tumours with more extensive

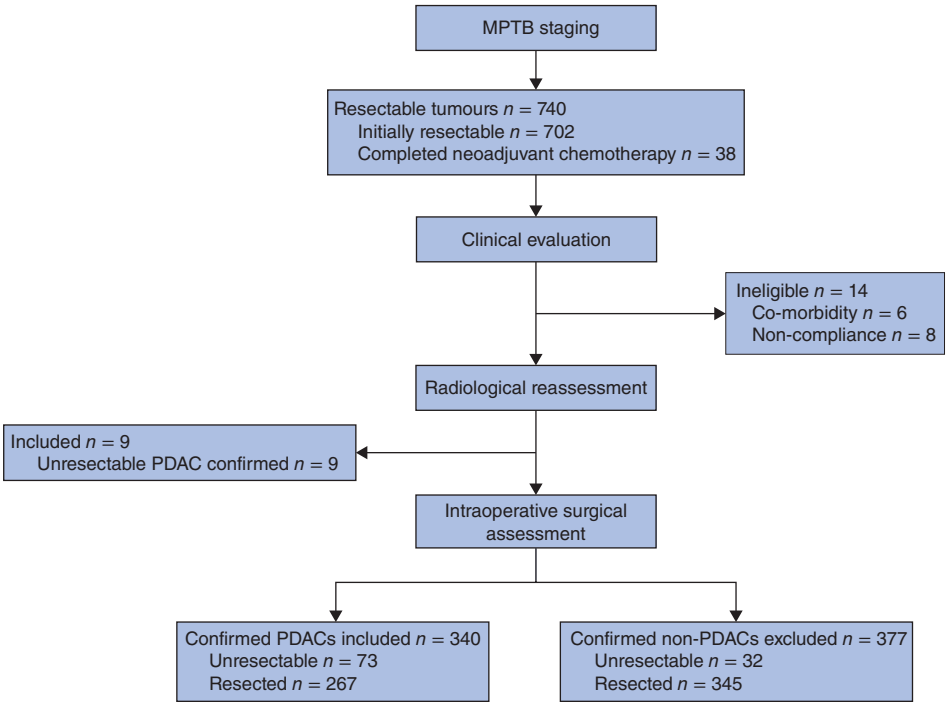


Fig. 1 Flow diagram showing selection of patients for inclusion in the study. Confirmation refers to a histological verification of the pancreatic ductal adenocarcinoma (PDAC) diagnosis. MPTB, multidisciplinary pancreatic tumour board

vascular involvement that did not fall into one of the four groups defined above were considered locally advanced and not amenable to curative therapy. The assessment of vascular involvement according to this protocol was considered reproducible[21].

Radiological assessments were done at the MPTB by at least two senior radiologists together with two pancreatic surgeons. Postoperative morbidity was graded according to the Dindo–Clavien classification[22]. Associated mortality was calculated as in-hospital death (Dindo–Clavien V), and deaths within 30 and 90 days. Overall survival was defined as the interval from date of surgery until death excluding in-hospital and 30-day mortality. Patient data were obtained from the institution's prospectively maintained pancreatic cancer database. Radiological and operative reports were used to obtain details regarding resectability assessment and reassessment. Pathology and cytology reports from specimen examination, frozen sections and biopsies provided information on the histological characteristics of the tumour.

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous variables had a non-normal distribution (Kolmogorov–Smirnov test) and were analysed using the Mann–Whitney *U* test; median values are presented with as 95 per cent c.i. unless indicated otherwise. Progressive trends were analysed by linear and logistic regression. Hazard ratios (HRs) were calculated by means of Cochran–Mantel–Haenszel statistics and Cox regression analysis. Variables in multivariable regression were entered in a single step. Survival analysis was performed by the method of Kaplan and Meier. Survival and hazard distributions were compared using the log rank test. The level of statistical significance was set at $P < 0{\cdot}050$ (2-tailed). Statistical analyses were performed in SPSS® version 22 (IBM, Armonk, New York, USA).

Results

Three hundred and forty-nine patients with histologically confirmed PDAC met the inclusion criteria and were included in the analysis (*Fig. 1*). Two hundred and sixty-seven successfully underwent resection with curative intent (resection group; resection rate 76·5 per cent); 82 patients were assessed to have unresectable disease (unresectable group; 22 locally advanced, 35 liver metastases, 25 carcinomatosis), nine at follow-up imaging and 73 at laparotomy (53 underwent double bypass surgery). Demographics are shown in *Table 1*. The 30- and 90-day mortality rates were 2·2 and 5·6 per cent respectively

Table 1 Patient demographics and operative data

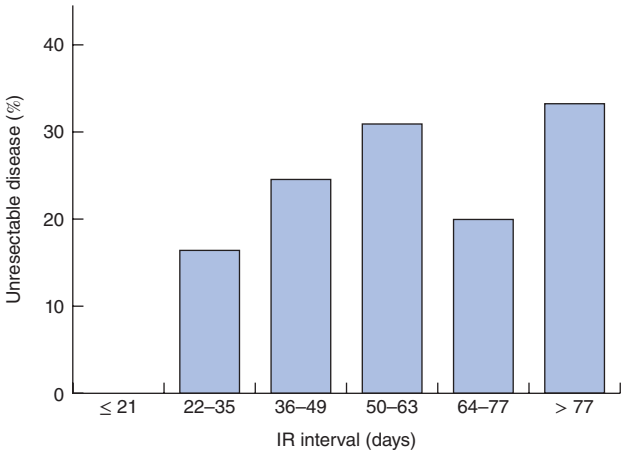
	No. of patients* ($n = 349$)
Age (years)†	68 (42–86)
Sex ratio (F : M)	153 : 196
Symptoms leading to PDAC diagnosis	
Jaundice	207 (59·3)
Abdominal pain	75 (21·5)
Fatigue	16 (4·6)
Weight loss	16 (4·6)
Nausea/loss of appetite	13 (3·7)
Diarrhoea	11 (3·2)
Other	11 (3·2)
Resected	267 (76·5)
Whipple/PPPD	231 (66·2)
Total pancreatectomy	14 (4·0)
Distal pancreatectomy	22 (6·3)
Duration of surgery (min)†	371 (30–705)
Blood loss (ml)†	700 (10–9000)
Morbidity grade‡	
I	193 (55·3)
II	91 (26·1)
IIIa	27 (7·7)
IIIb	26 (7·4)
IVa	4 (1·1)
IVb	1 (0·3)
Mortality	
30 days	11 (3·2)
90 days	38 (10·9)
In hospital	7 (2·0)

*With percentages in parentheses unless indicated otherwise; †values are median (range). ‡Dindo–Clavien classification. PDAC, pancreatic ductal adenocarcinoma; PPPD, pylorus-preserving pancreaticoduodenectomy.

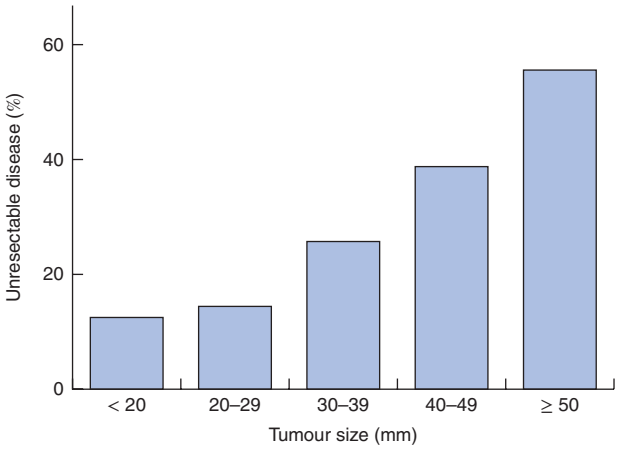
following resection, and 7 and 33 per cent for patients with unresectable PDAC. Median overall survival was 20·4 (95 per cent c.i. 17·6 to 23·2) months in the resection group and 6·7 (4·2 to 9·1) months in the unresectable group ($P < 0·001$).

Complete data sets were obtained for IR interval and vascular involvement; however, data on tumour size were missing for 18 of 349 patients owing to insufficient visualization of tumour borders on preoperative imaging (10 previously stented, 5 solely double-duct sign, 3 cystic tumours with PDAC histology).

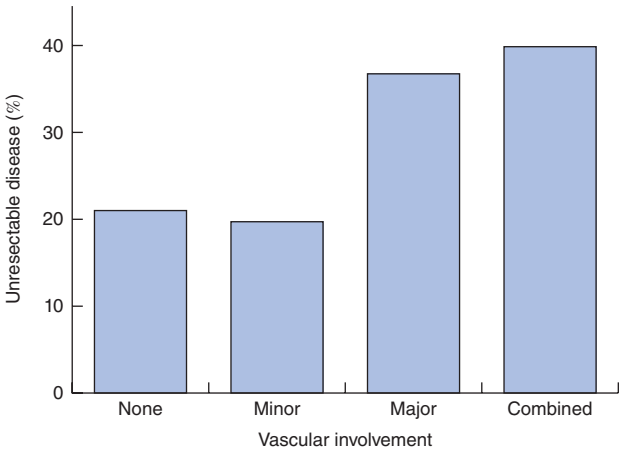
The IR interval ranged from 10 to 159 (median 42) days. None of the eight patients who underwent laparotomy within an IR interval of 22 days had unresectable disease. For those with an IR interval longer than 22 days, a progressive trend was noted between the IR interval and unresectable disease (*Fig. 2a*), and hazard analysis showed an increased risk of unresectability with increasing IR interval (*Fig. 3a*). Hazard comparisons for all IR intervals revealed a cut-off at 32 days to denote the greatest impact on unresectable disease; 274 patients had an IR interval exceeding 32 days (*Table 2*).



a By IR interval



b By tumour size



c By vascular involvement

Fig. 2 Incidence of unresectable pancreatic cancer at reassessment, according to: **a** imaging-to-resection/reassessment (IR) interval, **b** tumour size and **c** vascular involvement at preoperative imaging

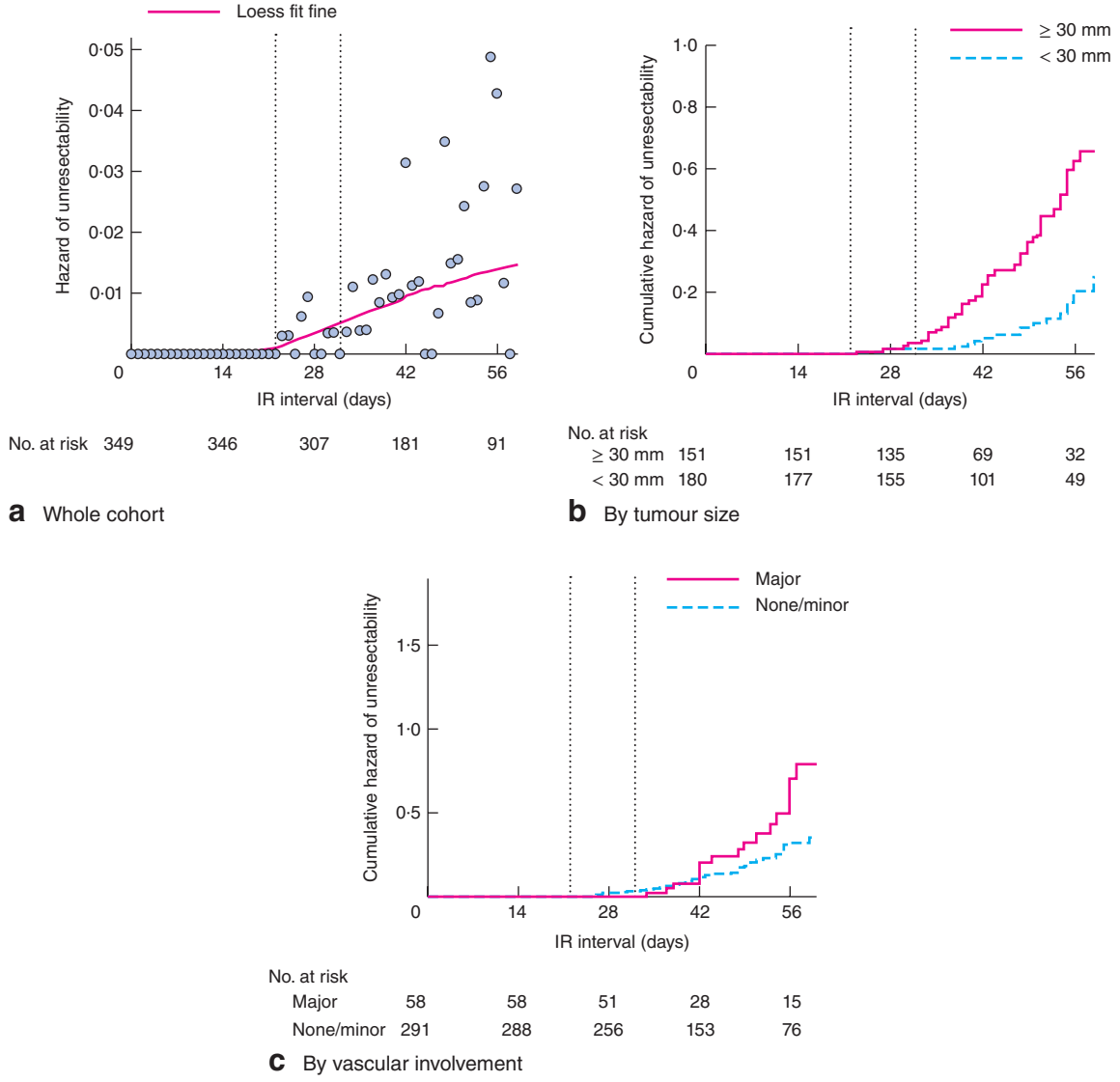


Fig. 3 Risk of unresectable pancreatic cancer at reassessment in relation to the imaging-to-resection/reassessment (IR) interval: **a** in the whole cohort, and grouped according to **b** tumour size and **c** vascular involvement at preoperative imaging. Reference lines at 22 and 32 days are shown

Tumour size ranged from 10 to 70 (median 25) mm. A progressive linear trend was observed between increasing lesion size and unresectable disease (*Fig. 2b*). Subgroups with tumour sizes ranging from 10 to 19 mm and 20–29 mm had unresectability rates of 13 per cent (6 of 48) and 14·4 per cent (19 of 132), whereas larger tumours of 30–39 mm and 40 mm and above had unresectability rates of 26 per cent (25 of 97) and 44 per cent (24 of 54) respectively ($P < 0·001$). A comparison of hazard ratios showed the lowest risk for unresectability at a tumour size below 30 mm on preoperative imaging (*Table 2*).

Before surgery, 170 patients had tumours without vascular involvement, 121 with minor and 38 with major isolated venous involvement. Twenty patients had been considered to have resectable tumours after neoadjuvant therapy according to RECIST; unresectability patterns in these patients were similar to those in the whole cohort (0 of 8 patients developed unresectable disease with an IR interval of 32 days or less; $P = 0·047$). Tumours with no or only minor isolated venous involvement had comparable unresectability rates (21·2 per cent (36 of 170) and 19·8 per cent (24 of 121) respectively), as did those with major isolated venous or combined vascular involvement

Table 2 Risk of progression from resectable to unresectable locally advanced or metastasized disease at reassessment

	No. of patients	Unresectable disease (%)	Hazard ratio	*P**
Tumour size (mm)				
≥ 30	151	32·5	1·00 (reference)	
< 30	180	13·9	0·34 (0·16, 0·58)	< 0·001
Vascular involvement				
Major or combined	58	38	1·00 (reference)	
None or minor	291	20·6	0·43 (0·23, 0·78)	0·007
IR interval (days)				
> 32	274	26·2	1·00 (reference)	
≤ 32	75	13	0·42 (0·21, 0·89)	0·021

Values in parentheses are 95 per cent c.i. IR, imaging-to-resection/reassessment. *Fisher's exact test (2-sided).

(37 per cent (14 of 38) and 40 per cent (8 of 20) respectively) (*Fig. 2c*). The unresectability rate for the combined group of tumours with no vascular involvement and minor venous involvement was 20·6 per cent, whereas that for lesions with major venous involvement plus those with combined vascular involvement was 38 per cent (*Table 2*).

In multivariable regression, no or minor vascular involvement did not contribute to the logistic model predicting unresectable disease (regression coefficient −0·340; HR 0·71, 95 per cent c.i. 0·32 to 1·60; $P = 0·411$), in contrast to preoperative tumour size smaller than 30 mm (regression coefficient −1·235; HR 0·27, 0·14 to 0·53; $P < 0·001$) and IR interval 32 days or less (regression coefficient −1·040; HR 0·35, 0·14 to 0·90; $P = 0·028$).

Additional tests showed that a composite factor of preoperative tumour size smaller than 30 mm and IR interval of 32 days or less could not outperform either of these as independent factors (unresectability rate 8 per cent for tumours smaller than 30 mm and IR interval of 32 days or less *versus* 19·8 per cent for larger tumours and a longer IR interval; HR 0·35, 95 per cent c.i. 0·10 to 1·18; $P = 0·109$). Logistic regression did not show any differences between the incidence of locally advanced disease, liver metastases or peritoneal carcinomatosis in relation to the IR interval ($P = 0·751$).

The relationships between tumour size and vascular involvement on preoperative imaging and IR interval are illustrated in *Figs 3b* and *3c* respectively. The cumulative risk of unresectable disease was significantly different for tumours smaller than 30 mm *versus* larger tumours ($P = 0·001$); a similar trend was noted for no or minor *versus* major vascular involvement ($P = 0·001$). In the resection group, the analysis of patients with an IR interval of at least 70 days (90th percentile, 29 patients) showed that 27 had no or minor vascular involvement and 22 had tumours smaller than 30 mm.

Table 3 Overall survival in patients who had successful resection of pancreatic cancer

	No. of patients	Median overall survival (months)	Hazard ratio	*P**
Tumour size (mm)				
≥ 30	102	17·5 (12·0, 23·0)	1·00 (reference)	
< 30	155	21·9 (18·1, 25·8)	0·63 (0·45, 0·87)	0·006
Vascular involvement				
Major or combined	36	10·5 (5·6, 15·4)	1·00 (reference)	
None or minor	231	22·8 (20·0, 25·6)	0·51 (0·33, 0·80)	0·002
IR interval (days)				
> 32	202	20·8 (17·4, 24·1)	1·00 (reference)	
≤ 32	65	21·9 (16·1, 27·7)	0·88 (0·61, 1·26)	0·486

Values in parentheses are 95 per cent c.i. IR, imaging-to-resection/reassessment. *Log rank test.

Tumour size and vascular involvement on diagnostic imaging had a significant impact on overall survival in successfully resected PDAC, but IR interval did not (*Table 3*).

Discussion

The present study addressed the therapeutic importance of the interval between diagnostic imaging and planned surgery with curative intent in patients with resectable pancreatic cancer. This interval was investigated from the standpoint of successful surgical resection and impact on patient outcome. Both tumour size and vascular involvement influenced the rate of resection. In addition, an increased risk of resectable tumours progressing to unresectability was noted when the interval between diagnostic imaging and planned surgery exceeded 32 days. In these patients, the risk of progression to unresectable disease at laparotomy was double that for patients in whom surgery with curative intent was planned within 32 days; for surgery scheduled within 22 days of diagnostic imaging, the risk was negligible.

The tumorigenesis of PDAC has been estimated to require more than 20 years[3]. After slow initial tumour development, disease progression is rapid in the later stages, taking 14 months for a T1 pancreatic cancer to progress to T4 category[17]. PDAC is usually in a phase of exponential growth at the time of clinical diagnosis[23]. In this respect, few studies have explored the sustainability of imaging-based PDAC staging, and the importance of the time interval between diagnosis and treatment, and the resulting clinical consequences on tumour resectability. The frequency of unanticipated metastases has been demonstrated to increase linearly with the interval between imaging and operation[18]. This linear increase in risk has

been questioned by a recent study[10], which suggested that an initially stable tumour situation after imaging was followed by an increased need for further imaging after 25 days. Monitoring the risk of both locoregional tumour progression and systemic dissemination, the present study confirmed an increasing need for reimaging after 22 days, and the risk of tumour progression after imaging seemed to depend on tumour stage at diagnosis, specifically lesion size and vascular involvement.

In the present study, patients who had presented with severe jaundice or cholangitis underwent biliary drainage before surgery. Similar practice has been incorporated in many centres[24]. Recently, it has been acknowledged that preoperative biliary drainage may lead to an increased rate of complications[25] and should not be performed routinely[26]. The results of the present study suggest the need for timely surgical resection once the diagnosis of resectable PDAC has been made, whenever possible without prior biliary drainage.

The exponential growth of PDAC at clinical diagnosis[23] might suggest that the growth slope is determined by tumour stage at the time of diagnosis. In resectable PDAC, even after controlling for different pathways of progression, it appears that the time interval to unresectability decreases with increasing tumour stage. Here, tumour size and vascular involvement were associated with different increases in the unresectability rate over time. Hazard distributions showed an increasing incidence of unresectable disease for tumours of 30 mm or larger and major vascular involvement at similar risk levels for locoregional unresectability and metastatic disease. The varying risk of unresectability may reflect non-linear tumour progression, as almost all patients who underwent successful resection, despite long waiting times, had tumours smaller than 30 mm and no or only minor vascular involvement.

In the resection group, tumour size of at least 30 mm and major vascular involvement were associated with shorter median survival following resection, consistent with previous observations[23]. In contrast, the IR interval had no prognostic significance in terms of overall survival. This may be because tumour size and vascular involvement represent aspects of tumour stage, whereas the IR interval is a modifiable factor.

The present study has a number of limitations. Its retrospective nature may have introduced selection and misclassification bias, and radiological and surgical assessments of local unresectability were not validated by pathological examinations. Resectable PDAC of 30 mm or more on preoperative imaging was associated with a time-independent risk of encountering unresectable disease at laparotomy. This may reflect the issue of radiological understaging and diagnostic inaccuracy. In previous reports, the overall sensitivity of MDCT was estimated at 75 per cent for liver metastases, and 7–50 per cent for low-volume peritoneal carcinomatosis (metastatic lymphadenopathy 73 per cent)[27]. Newer MDCT scanner technology and the use of diffusion-weighted MRI and/or hepatobiliary-specific contrast agents may be able to increase diagnostic accuracy, especially for small liver metastases[27,28]. However, the risk of not recognizing metastatic PDAC remains, despite comprehensive surgical assessment at the time of laparotomy. As a consequence, false-negative metastasized PDAC might have been included in the resection group, resulting in a falsely high resection rate. However, substantial alteration in group distributions as a result of this detection error is unlikely. Patients with PDAC who had received neoadjuvant treatment were included in the study when the response was classified as stable disease or partial response according to RECIST, and the tumour considered resectable by the MPTB. Their inclusion was supported by the fact that PDAC is considered a heterogeneous disease with varying progression even in chemotherapy-naive patients, and that the effects of chemotherapy on tumour progression have not been investigated sufficiently to justify the exclusion of these patients from the analysis.

The interval from diagnosis to treatment has been regarded as a reflection of the availability of hospital resources and the efficiency of the overall healthcare system[29]; this can be extended to serve as a proxy indicator of quality of cancer care[30]. Although concerted efforts have been made in recent years to shorten healthcare waiting times, it remains a challenging national responsibility to provide all patients with prompt access to efficient cancer services and introduce standard treatment pathways. In resectable pancreatic cancer, regardless of tumour size or vascular involvement, the risk of progression to unresectable disease may be minimized by operating within 22 days and decreased by half if surgery takes place within 32 days of diagnostic imaging. The results of the present study highlight the need for efficiency and streamlining in the management of pancreatic cancer, and for improvements in health services that can facilitate timely diagnosis and treatment.

Disclosure

The authors declare no conflict of interest.

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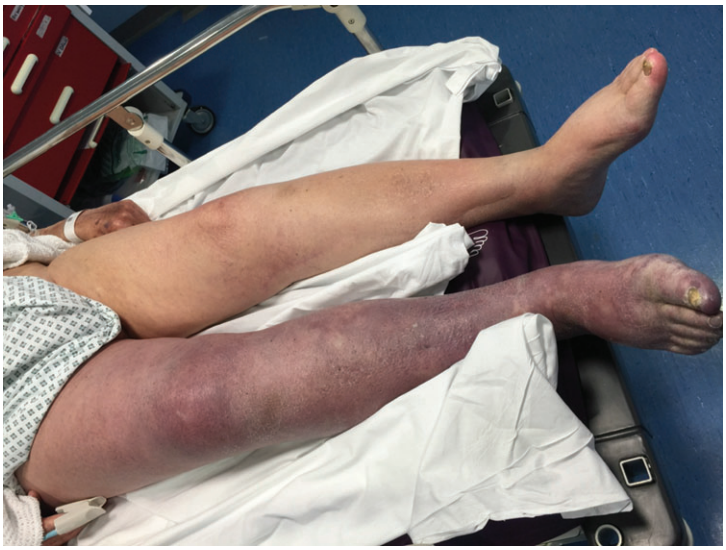
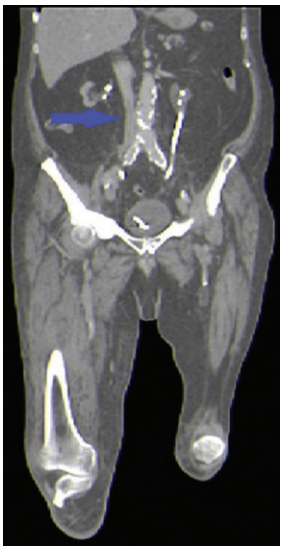
Snapshot quiz

Snapshot quiz 16/2

Question: This man has a painful swollen leg with a palpable foot pulse. What is the diagnosis?



a



b

The answer to the above question is found on p. 283 of this issue of *BJS*.

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