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Impact of time interval between multidisciplinary team meeting and intended pancreatoduodenectomy on oncological outcomes

M. W. Steen[1,2], L. B. van Rijssen[2], S. Festen[1], O. R. Busch[2], B. Groot Koerkamp[3], L. G. van der Geest[4], I. H. de Hingh[5], H. C. van Santvoort[6], M. G. Besselink[2] and M. F. Gerhards[1], on behalf of the Dutch Pancreatic Cancer Group

[1]Department of Surgery, Onze Lieve Vrouwe Gasthuis (OLVG), [2]Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam,[3]Department of Surgery, Erasmus Medical Centre, Rotterdam, [4]Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), [5]Regional Academic Cancer Centre Utrecht, St Antonius Hospital Nieuwegein and University Medical Centre, Utrecht Cancer Centre Utrecht, and [6]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands

Correspondence to: Dr M. F. Gerhards, Department of Surgery, OLVG, Oosterpark 9, 1090 HM Amsterdam, the Netherlands
(e-mail: m.f.gerhards@olvg.nl)

Background: **Dutch guidelines indicate that treatment of pancreatic head and periampullary malignancies should be started within 3 weeks of the multidisciplinary team (MDT) meeting. This study aimed to assess the impact of time to surgery on oncological outcomes.**

Methods: **This was a retrospective population-based cohort study of patients with pancreatic head and periampullary malignancies included in the Netherlands Cancer Registry. Patients scheduled for pancreatoduodenectomy and who were discussed in an MDT meeting from May 2012 to December 2016 were eligible. Time to surgery was defined as days between the final preoperative MDT meeting and surgery, categorized in tertiles (short interval, 18 days or less; intermediate, 19–32 days; long, 33 days or more). Oncological outcomes included overall survival, resection rate and R0 resection rate.**

Results: **A total of 2027 patients were included, of whom 677, 665 and 685 had a short, intermediate and long time interval to surgery respectively. Median time to surgery was 25 (i.q.r. 14–36) days. Longer time to surgery was not associated with overall survival (hazard ratio 0·99, 95 per cent c.i. 0·87 to 1·13; $P = 0·929$), resection rate (relative risk (RR) 0·96, 95 per cent c.i. 0·91 to 1·01; $P = 0·091$) or R0 resection rate (RR 1·01, 0·94 to 1·09; $P = 0·733$). Patients with pancreatic ductal adenocarcinoma and a long time interval had a lower resection rate (RR 0·92, 0·85 to 0·99; $P = 0·029$).**

Discussion: **A longer time interval between the last MDT meeting and pancreatoduodenectomy did not decrease overall survival.**

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Introduction

The best chance of long-term survival for patients with cancer of the pancreatic head and periampullary region is obtained by radical resection. In patients with pancreatic cancer, systemic chemotherapy is administered preferentially[1,2]. However, up to 80 per cent of patients with pancreatic cancer are not eligible for curative resection owing to locally advanced stage or distant metastases[3].

Delay in treatment may contribute to poor prognosis. Surgery may be postponed for valid reasons, such as neoadjuvant therapy or preoperative biliary drainage in case of jaundice. Postponement of surgery for logistical reasons is undesirable. Hypothetically, a prolonged time to surgery may lead to progression of the disease, a lower resection rate, and worse survival. Current studies[4–11] in the literature on time to surgery have focused on pancreatic cancer, and the results are somewhat conflicting.

Dutch guidelines recommend that treatment be started within 3 weeks of the final multidisciplinary team (MDT) meeting[12]. The aim of this study was to evaluate the impact

of the time interval between the final MDT meeting and surgery on overall survival, resection rate and R0 resection rate in patients with resectable periampullary malignancies.

Methods

This was a retrospective population-based study with data retrieved from the Netherlands Cancer Registry (NCR), the Dutch nationwide registry covering all 17 million inhabitants of the Netherlands that includes data on all patients with cancer. The NCR is linked to the nationwide pathology database (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA)). Completeness of inclusion is estimated to be at least 95 per cent. The TNM classification of malignant tumours (7th edition)[13] was used to record clinical and pathological tumour stages. Data on the vital status of patients were obtained by annual linkage with the Municipal Personal Records Database, a database containing personal details collected by the federal government (such as address) for the whole population of the Netherlands.

All patients diagnosed with invasive periampullary malignancies (including pancreatic head cancer, duodenal cancer, ampullary cancer and distal cholangiocarcinoma, ICD-O-3: C25·0, C17·0, C24·1 and C24·0-distal respectively[14]), and who were discussed in an MDT meeting and subsequently scheduled for pancreatoduodenectomy, were included. Patients treated between May 2012 and December 2016 were eligible. Patients with missing data on the date of the preoperative MDT meeting were excluded. In 2013, the NCR did not record the dates of preoperative MDT meetings, so patients scheduled for pancreatoduodenectomy in 2013 were excluded. Patients with hyperbilirubinaemia underwent preoperative biliary drainage. Patients who were scheduled for and underwent staging laparoscopy for diagnostic reasons were excluded. Patients who received neoadjuvant chemo(radio)therapy before pancreatoduodenectomy were excluded as this was not standard treatment during the study period; patients had neoadjuvant treatment for pancreatic ductal adenocarcinoma (PDAC) only in studies such as the PREOPANC RCT[15], which was conducted in the Netherlands. Approval of a medical ethics committee was not required under Dutch law, as all data were anonymized.

Data collection

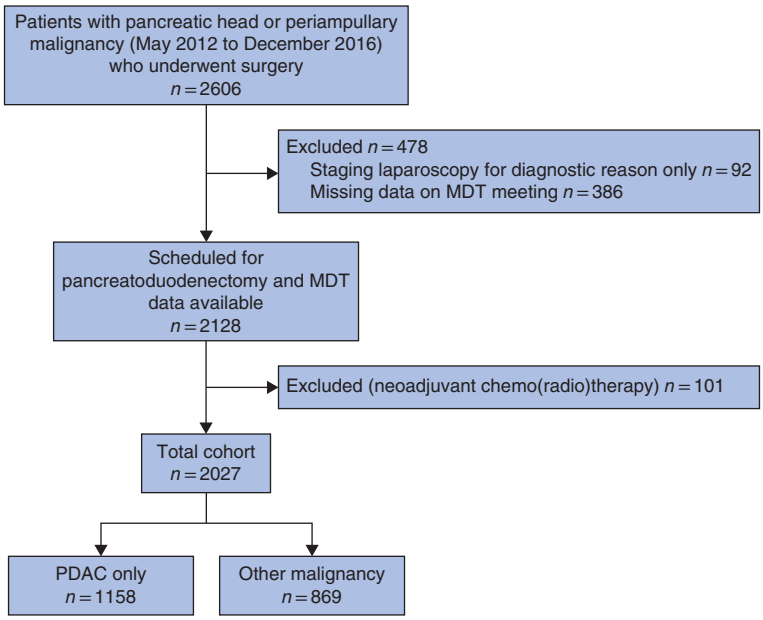
Data that were collected routinely included age, sex, location of the last MDT meeting (treating or referring hospital), preoperative biliary drainage, annual hospital volume, time interval from the preoperative MDT meeting and date of surgery, clinical TNM stage, pathological TNM stage, and margin status in patients who had a resection, whether a resection was performed or not, postoperative chemo(radio)therapy (including both adjuvant therapy in patients who had a resection and palliative therapy in those who had no resection), 30- and 90-day mortality, and overall survival.

Outcomes and definitions

Outcomes were overall survival, resection rate and R0 resection rate. Overall survival was defined as time in days between surgery and death or alive vital status at 1 February 2018. Resection rate was defined as the proportion of pancreatoduodenectomies carried out in all patients who had surgical exploration. R0 resection rate was defined as the proportion of R0 resections of all resections. Margin status was recorded as reported by the assessing pathologist. A margin of less than 1 mm was considered a non-radical resection.

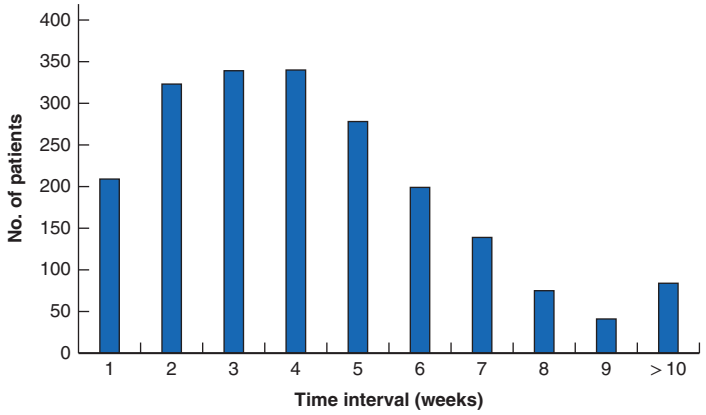
Time interval was defined as the number of days between the date of the last preoperative MDT meeting and the date of surgery, and was categorized in tertiles (18 days or less; 19–32 days; 33 days or more). Surgery included both pancreatoduodenectomy and surgical exploration only, when no resection was performed. Pathological diagnoses were categorized according to the WHO classification of tumours[12] and included pancreatic ductal adenocarcinoma of the pancreatic head (PDAC, including ICD-O-3 morphology codes 8010, 8012, 8020, 8070, 8140, 8144, 8163, 8452, 8453, 8480, 8481, 8490, 8500, 8510, 8560 and 8570), other tumours of the pancreatic head (including ICD-O-3 morphology codes 8000 and 8550), carcinoma of the papilla of Vater (including ICD-O-3 morphology codes 8010, 8013, 8140, 8144, 8163, 8260, 8261, 8263, 8480, 8481, 8490 and 8500), duodenal carcinoma (including ICD-O-3 morphology codes 8010, 8012, 8013, 8140, 8144, 8255, 8261, 8263, 8480, 8481 and 8490) and cholangiocarcinoma (including ICD-O-3 morphology codes 8000, 8012, 8013, 8082, 8140, 8144, 8160, 8163, 8249, 8255, 8260, 8263, 8480 and 8500). Thirty- and 90-day mortality was defined as death from any cause within 30 and 90 days of surgery respectively. Hospital volume classification was based on the number of pancreatoduodenectomies performed for malignancy, as registered in the NCR. Hospital volume was categorized in two categories: 19 or less and 20 or more procedures per year. In the Netherlands, a minimum hospital volume of 20 pancreatoduodenectomies annually has been set since December 2011.

Fig. 1 Diagram showing patient selection



MDT, multidisciplinary team; PDAC, pancreatic ductal adenocarcinoma.

Fig. 2 Time interval from multidisciplinary team meeting to surgery for patients with pancreatic ductal adenocarcinoma and periampullary malignancy



Statistical analysis

Data were analysed using IBM SPSS® Statistics for Windows® version 22.0® (IBM, Armonk, New York, USA). Non-normally distributed continuous data are presented as median (i.q.r.) values and analysed with the Kruskal–Wallis test. Categorical (binary, ordinal and nominal) data are presented as frequencies with percentages and analysed with the χ^2 test and Fisher's exact test as appropriate. Survival was determined by Kaplan–Meier analysis. The association between time interval and survival was analysed by Cox proportional hazards models and expressed as hazard ratios (HRs) with 95 per cent confidence intervals. Associations between time interval and the outcomes resection rate and R0 resection rate were analysed by generalized linear models and expressed as relative risks (RRs) with 95 per cent confidence intervals. If applicable, the sandwich method with robust estimators was

Table 1 Characteristics of patients scheduled for pancreatoduodenectomy with a short, intermediate or long time interval to surgery

	Total cohort ($n = 2027$)	Time interval to surgery (days)			P‡
		≤ 18 ($n = 677$)	19–32 ($n = 665$)	≥ 33 ($n = 685$)	
Patient and tumour characteristics					
Age (years)*	68 (61–74)	67 (60–73)	68 (62–74)	69 (62–75)	< 0·001§
Male sex	1144 (56·4)	386 (57·0)	366 (55·0)	392 (57·2)	0·672
Multidisciplinary team meeting at treating hospital	1658 (81·8)	555 (82·0)	547 (82·3)	556 (81·2)	0·313
Missing	76				
Pathological diagnosis†					< 0·001
PDAC of pancreatic head	1158 (57·1)	373 (55·1)	385 (57·9)	400 (58·4)	
Carcinoma of papilla of Vater	343 (16·9)	107 (15·8)	119 (17·9)	117 (17·1)	
Cholangiocarcinoma	343 (16·9)	108 (16·0)	110 (16·5)	125 (18·2)	
Duodenal carcinoma	166 (8·2)	87 (12·9)	44 (6·6)	35 (5·1)	
Other carcinoma of pancreatic head	17 (0·8)	2 (0·3)	7 (1·1)	8 (1·2)	
pT category					0·147
pT0	1 (0·1)	0 (0)	0 (0)	1 (0·2)	
pT1	89 (5·3)	22 (3·9)	28 (5·1)	39 (7·1)	
pT2	257 (15·4)	91 (16·1)	87 (15·7)	79 (14·5)	
pT3	1124 (67·5)	378 (66·8)	369 (66·6)	377 (69·0)	
pT4	182 (10·9)	72 (12·7)	64 (11·6)	46 (8·4)	
pTX	13 (0·8)	3 (0·5)	6 (1·1)	4 (0·7)	
Missing	361				
pN category					0·071
pN0	510 (30·5)	170 (29·8)	168 (30·3)	172 (31·3)	
pN1	1111 (66·4)	373 (65·4)	372 (67·1)	366 (66·7)	
pN2	45 (2·7)	25 (4·4)	10 (1·8)	10 (1·8)	
pNX	7 (0·4)	2 (0·4)	4 (0·7)	1 (0·2)	
Missing	354				
pM category					0·692
pM0	1787 (88·2)	600 (88·6)	589 (88·6)	598 (87·3)	
pM1	240 (11·8)	77 (11·4)	76 (11·4)	87 (12·7)	
Tumour differentiation grade					0·820
Well	171 (11·5)	56 (10·5)	55 (11·0)	60 (13·0)	
Moderate	765 (51·3)	272 (51·2)	260 (52·2)	233 (50·3)	
Poor	554 (37·1)	203 (38·2)	182 (36·5)	169 (36·5)	
Undifferentiated	2 (0·1)	0 (0·0)	1 (0·2)	1 (0·2)	
Missing	535				
Treatment characteristics					
PD volume of treating hospital					0·077
< 20	344 (17·0)	132 (19·8)	106 (16·1)	106 (15·5)	
≥ 20	1664 (82·1)	534 (80·2)	554 (83·9)	576 (84·5)	
Missing	19 (0·9)				
Preoperative biliary drainage	913 (45·0)	231 (34·1)	318 (47·8)	364 (53·1)	< 0·001
Postoperative chemotherapy	97 (4·8)	36 (5·3)	29 (4·4)	32 (4·7)	0·704
Postoperative radiotherapy	7 (0·3)	3 (0·4)	2 (0·3)	2 (0·3)	0·868
30-day mortality	84 of 2021 (4·2)	33 of 674 (4·9)	22 of 662 (3·3)	29 of 685 (4·2)	0·352
90-day mortality	203 of 2021 (10·0)	76 of 674 (11·3)	58 of 662 (8·8)	69 of 685 (10·1)	0·311

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Basis for pathological diagnosis: histological confirmation of primary tumour, including autopsy (1772 patients, 87·4 per cent); histological confirmation of distant metastasis only, including autopsy (150, 7·4 per cent); haematological or cytological confirmation, but unclear whether this concerned cytology or histology (91, 4·5 per cent); clinical diagnostic tests, surgical exploration or autopsy, without pathological confirmation (14, 0·7 per cent). PDAC pancreatic ductal adenocarcinoma; PD, pancreatoduodenectomy. ‡χ^2 or Fisher's exact test, except §Kruskal–Wallis test.

Table 2 Overall survival, resection rate and R0 resection rate of patients with a short, intermediate or long time interval to treatment

	Total cohort ($n = 2027$)	Time interval ≤ 18 days ($n = 677$)	Time interval 19–32 days ($n = 665$)	*P*	Time interval ≥ 33 days ($n = 685$)	*P*
Median OS (months)	16·8 (15·8, 17·8)	17·3 (15·9, 18·8)	16·8 (14·9, 18·9)		16·7 (15·0, 18·4)	
Unadjusted HR		1·00 (reference)	0·95 (0·84, 1·09)	0·471	1·03 (0·91, 1·17)	0·618
Adjusted HR†		1·00 (reference)	0·94 (0·82, 1·07)	0·317	0·99 (0·87, 1·13)	0·929
Resection*	1669 (82·3)	569 (84·0)	551 (82·9)		549 (80·1)	
Unadjusted RR		1·00 (reference)	0·99 (0·94, 1·04)	0·558	0·95 (0·91, 1·00)	0·061
Adjusted RR†		1·00 (reference)	0·99 (0·95, 1·04)	0·791	0·96 (0·91, 1·01)	0·091
R0 resection*	1145 of 1598 (71·7)	398 of 540 (73·7)	357 of 530 (67·4)		390 of 528 (73·9)	
Unadjusted RR		1·00 (reference)	0·91 (0·85, 0·99)	0·023	1·00 (0·93, 1·08)	0·953
Adjusted RR‡		1·00 (reference)	0·92 (0·85, 0·99)	0·032	1·01 (0·94, 1·09)	0·733

Values in parentheses are 95 per cent c.i. unless indicated otherwise; *values in parentheses are percentages. †Adjusted for age and hospital volume; ‡adjusted for hospital volume. OS, overall survival; HR, hazard ratio; RR, relative risk.

applied[16]. Potential confounders were determined based on theory, using a directed acyclic graph approach[17]. Age was considered a potential confounder that may have a causal relationship with the outcome measures of resection rate and overall survival[18]. Hospital volume was considered a potential confounder that may have a causal relationship with all oncological outcome measures[4,18,19]. Analysis of the outcome measures was adjusted for potential confounders. Preoperative biliary drainage was considered an intermediate factor, because it may be a reason for postponing surgery. As it was uncertain whether the last MDT meeting had been before or after biliary drainage, analyses were not adjusted for biliary drainage. Results are presented as both unadjusted and adjusted HRs and RRs. A two-tailed $P < 0{\cdot}050$ was considered statistically significant. A subgroup analysis was performed for patients with PDAC.

Results

In the study period, 2606 patients with a periampullary malignancy were scheduled for surgery (*Fig. 1*). After exclusions, of 2128 patients scheduled for pancreatoduodenectomy, 101 had neoadjuvant chemo(radio)therapy and were also excluded. Thus, 2027 patients were included in the final analysis. A total of 871 patients (43·0 per cent) had surgery within 3 weeks of the MDT meeting. The median interval to surgery was 25 (i.q.r. 14–36) days. The time interval was non-normally distributed (*Fig. 2*).

Patient, tumour and treatment characteristics

Patient, tumour and treatment characteristics are presented in *Table 1*. Patients with an intermediate or long time interval to surgery were older ($P < 0{\cdot}001$) and more often had preoperative biliary drainage ($P < 0{\cdot}001$) compared with patients with a short time interval to surgery.

Overall survival, resection rate and R0 resection rate

Outcomes are presented in *Table 2*. The median follow-up was 15·0 (i.q.r. 7·3–25·5) months. Median overall survival was 16·8 (95 per cent c.i. 15·8 to 17·8) months, the resection rate was 82·3 per cent, and the R0 resection rate 71·7 per cent. There were no statistically significant differences in overall survival or in resection rate between patients with a short *versus* an intermediate or long interval to surgery.

The R0 resection rate was lower in patients with an intermediate interval compared with that in patients with a short time interval to surgery (67·4 *versus* 73·7 per cent respectively; unadjusted RR 0·91, 95 per cent c.i. 0·85 to 0·99, $P = 0{\cdot}023$). After adjustment for hospital volume as a potential confounder, the R0 resection rate was similarly lower (RR 0·92, 0·85 to 0·99, $P = 0{\cdot}032$). In patients with a long time interval to surgery the R0 resection rate was 73·9 per cent, which was not significantly different from that in patients with a short interval to surgery.

Subgroup analysis of patients with pancreatic ductal adenocarcinoma

Data for the subgroup of 1158 patients (57·1 per cent) with PDAC are presented in *Table 3*, and outcomes in *Table 4*. Median follow-up was 13·1 (i.q.r. 5·9–22·0) months. Median overall survival was 13·3 (95 per cent c.i. 12·3 to 14·4) months, the resection rate was 76·5 per cent, and the R0 resection rate 62·4 per cent. There was no statistically significant difference in overall survival between patients with a short *versus* intermediate or long interval to surgery.

Table 3 Characteristics of patients with pancreatic ductal adenocarcinoma† scheduled for pancreatoduodenectomy with a short, intermediate or long time interval to surgery

	Total cohort (n = 1158)	Time interval to surgery (days)			P‡
		≤ 18 (n = 373)	19–32 (n = 385)	≥ 33 (n = 400)	
Patient and tumour characteristics					
Age (years)*	68 (62–74)	67 (60–73)	68 (62–74)	69 (63–75)	0·003§
Male sex	639 (55·2)	214 (57·4)	198 (51·4)	227 (56·8)	0·191
Multidisciplinary team meeting at treating hospital	962 (86·8)	313 (83·9)	324 (84·2)	325 (81·3)	0·137
Missing	50				
pT category					0·775
pT1	28 (3·1)	8 (2·7)	7 (2·3)	13 (4·5)	
pT2	82 (9·2)	31 (10·4)	28 (9·3)	23 (7·9)	
pT3	734 (82·3)	244 (81·6)	248 (82·4)	242 (82·9)	
pT4	35 (3·9)	13 (4·3)	12 (4·0)	10 (3·4)	
pTX	13 (1·5)	3 (1·0)	6 (2·0)	4 (1·4)	
Missing	266				
pN category					0·610
pN0	210 (23·5)	63 (21·1)	72 (23·9)	75 (25·7)	
pN1	676 (75·8)	234 (78·3)	226 (75·1)	216 (74·0)	
pNX	6 (0·7)	2 (0·7)	3 (1·0)	1 (0·3)	
Missing	266				
pM category					0·357
pM0	979 (84·5)	321 (86·1)	328 (85·2)	330 (82·5)	
pM1	179 (15·5)	52 (13·9)	57 (14·8)	70 (17·5)	
Tumour differentiation grade					0·094
Well	86 (10·8)	21 (7·7)	28 (10·4)	37 (14·6)	
Moderate	408 (51·2)	138 (50·4)	147 (54·4)	123 (48·6)	
Poor	302 (37·9)	115 (42·0)	94 (34·8)	93 (36·8)	
Undifferentiated	1 (0·1)	0	1 (0·4)	0	
Missing	361				
Treatment characteristics					
PD volume of treating hospital					0·230
< 20	215 (18·8)	79 (21·6)	68 (17·8)	68 (17·1)	
≥ 20	930 (81·2)	286 (78·4)	315 (82·2)	329 (82·9)	
Missing	13				
Preoperative biliary drainage	525 (45·3)	128 (34·3)	185 (48·1)	212 (53·0)	< 0·001
Postoperative chemotherapy	74 (6·4)	27 (7·2)	22 (5·7)	25 (6·3)	0·685
Postoperative radiotherapy	6 (0·5)	3 (0·8)	1 (0·3)	2 (0·5)	0·579
30-day mortality (n = 1156)	40 (3·5)	15 (4·0)	10 (2·6)	15 (3·8)	0·520
90-day mortality (n = 1156)	127 (11·0)	48 (12·9)	34 (8·9)	45 (11·3)	0·201

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Basis for pathological diagnosis: histological confirmation of primary tumour, including autopsy (959 patients, 82·8 per cent); histological confirmation of distant metastasis only, including autopsy (130; 11·2 per cent); haematological or cytological confirmation, but unclear whether this concerned cytology or histology (69, 6·0 per cent). PD, pancreatoduodenectomy. ‡χ^2 or Fisher's exact test, except §Kruskal–Wallis test.

The resection rate was lower in patients with a long interval compared with that in patients with a short time interval to surgery (72·8 *versus* 79·9 per cent respectively; unadjusted RR 0·91, 95 per cent c.i. 0·84 to 0·98, $P = 0·020$). This difference persisted when adjusted for the potential confounders age and hospital volume (RR 0·92, 0·85 to 0·99, $P = 0·029$).

In addition, the R0 resection rate was lower in patients with an intermediate interval compared with that in those with a short time interval to surgery (56·1 *versus* 65·6 per cent respectively; unadjusted RR 0·85, 95 per cent c.i. 0·75 to 0·98, $P = 0·019$). When adjusted for the potential confounder of hospital volume, the R0 resection rate was lower (RR 0·86, 0·76 to 0·99, $P = 0·033$).

Table 4 Subgroup analysis of overall survival, resection rate and R0 resection rate for patients with a short, intermediate or long time interval to treatment

	Total cohort ($n = 2027$)	Time interval ≤ 18 days ($n = 677$)	Time interval 19–32 days ($n = 665$)	*P*	Time interval ≥ 33 days ($n = 685$)	*P*
Median OS (months)	13·3 (12·3, 14·4)	13·7 (11·5, 15·9)	13·2 (11·7, 14·7)		13·1 (11·3, 14·8)	
Unadjusted HR		1·00 (reference)	0·93 (0·79, 1·10)	0·415	1·03 (0·88, 1·22)	0·680
Adjusted HR†		1·00 (reference)	0·90 (0·76, 1·06)	0·201	0·98 (0·83, 1·15)	0·814
Resection*	886 (76·5)	298 (79·9)	297 (77·1)		291 (72·8)	
Unadjusted RR		1·00 (reference)	0·97 (0·90, 1·04)	0·357	0·91 (0·84, 0·99)	0·020
Adjusted RR†		1·00 (reference)	0·98 (0·90, 1·05)	0·518	0·92 (0·85, 0·99)	0·029
R0 resection*	535 of 858 (62·4)	189 of 288 (65·6)	162 of 289 (56·1)		184 of 281 (65·5)	
Unadjusted RR		1·00 (reference)	0·85 (0·75, 0·98)	0·019	1·00 (0·89, 1·12)	0·971
Adjusted RR‡		1·00 (reference)	0·86 (0·76, 0·99)	0·033	1·02 (0·90, 1·15)	0·754

Values in parentheses are 95 per cent c.i. unless indicated otherwise; *values in parentheses are percentages. †Adjusted for age and hospital volume; ‡adjusted for hospital volume. OS, overall survival; HR, hazard ratio; RR, relative risk.

As in the total cohort, the R0 resection rate of 65·0 per cent in patients with a long interval to surgery was not significantly different from that in patients with a short interval.

Discussion

In this population-based study including over 2000 patients with cancer of the pancreatic head and periampullary region scheduled for pancreatoduodenectomy, no relationships were observed between the time interval from the last MDT meeting to surgery and overall survival and resection rate. In a subgroup analysis of patients with PDAC, resection rates were higher in those with a short interval, with no impact on overall survival. The R0 resection rate was lower for both the total cohort and the subgroup of patients with PDAC with an intermediate interval to surgery, compared with that in patients with a short interval, but this was not found when the time interval was longer.

Time to surgery in relation to the prognosis of patients with pancreatic and periampullary cancer has been investigated in a few other studies. Results from the present study are concordant with those of most other studies[5–8,20,21], which found a longer interval to surgery was not associated with overall survival. One single-centre study[9] of 170 patients found that diagnostic delay (time from onset of signs and symptoms to date of pathological diagnosis) was associated with worse overall survival (HR 1·02, 95 per cent c.i. 1·01 to 1·04; $P < 0·001$). In another study[4] worse overall survival was observed in patients with a time interval longer than 1 month, but only in low-volume centres. One study[10] showed that overall survival was slightly worse when the interval to surgery was short (1–14 days), with a short time interval related to low-volume centres. These authors concluded that delays for medical optimization and referral to high-volume surgeons might be safe.

The effect of time interval to surgery on resection rate has been investigated in a few studies, and also showed conflicting results. One study[11] found a lower resection rate when the interval was longer in patients with pancreatic cancer, whereas three other studies showed that time interval was not associated with resection rate in patients with pancreatic cancer[6], pancreatic head cancer[7] or periampullary adenocarcinoma[20].

From the perspective of patients diagnosed with resectable cancer, their quality of life seemed best when surgery was performed as soon as possible after the indication had been set[22,23]. The lack of effect of time to surgery on overall survival implies that clinicians may reassure patients that the time interval does not affect prognosis. For some patients, postponing surgery to allow for time to improve their physical condition for major surgery may improve quality of care.

The finding that patients with PDAC and a long interval to surgery had a lower resection rate may be explained by the aggressiveness of PDAC. These tumours may rapidly become unresectable owing to local tumour progression and involvement of adjacent structures, or due to distant metastases[24,25].

Survival is the most relevant oncological outcome, and survival was similar regardless of the interval to surgery. Some patients who had an early resection may have developed distant metastases during the early postoperative phase. With a longer time interval, some patients may have been spared unnecessary resection, in the sense that resection would not have improved their overall survival.

Another striking finding in patients with PDAC, also observed in the total cohort, was that the R0 resection rate

was 67·0 per cent with a short time interval, 56·3 per cent with an intermediate interval, and then increased again to 65·0 per cent with a long time interval. Possibly, in the latter group, patients with poorer tumour characteristics may have been filtered out during the longer time interval, resulting in a higher R0 resection rate, although this is speculative. Overall, the interpretation of the relationship between time interval to surgery and the resection rate of patients with PDAC is not unambiguous.

The results of this study should be interpreted in the light of some limitations. Time to treatment can be defined by several starting points, such as onset of symptoms, visit to the general practitioner, visit to the outpatient clinic, the diagnosis established by imaging, the diagnosis established by pathological investigation or the MDT meeting. The authors chose the latter because these data were available in the NCR. Choosing this time point for the definition of time interval may have introduced bias. Prolongation of the interval may already have occurred during the diagnostic process, for example by preoperative biliary drainage or referral to a specialist centre. Although the main strength of this study is its population-based design, one of the limitations of these registries is that detailed information is often lacking. The timing of the MDT meeting may vary between hospitals. Some hospitals discuss their patients in the beginning of the diagnostic process and others at the end, when this process and also the workup for surgery has been completed. In patients who had biliary drainage, it is uncertain whether the last MDT had been before or after the drainage.

Patients who had neoadjuvant therapy were excluded from this study. There is increasing evidence that neoadjuvant treatment improves the prognosis of patients with PDAC. The recently completed PREOPANC trial[15], which compared neoadjuvant chemoradiotherapy followed by surgery and adjuvant therapy with the standard of care, demonstrated improved overall survival. These findings cannot be extrapolated to patients who had neoadjuvant therapy.

Disclosure

The authors declare no conflict of interest.

References

1 Xu JB, Jiang B, Chen Y, Qi FZ, Zhang JH, Yuan H. Optimal adjuvant chemotherapy for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Oncotarget* 2017; **8**: 81419–81429.

2 Liao WC, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP *et al.* Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013; **14**: 1095–1103.

3 van der Geest LGM, Lemmens VEPP, de Hingh IHJT, van Laarhoven CJHM, Bollen TL, Nio CY *et al.*; Dutch Pancreatic Cancer Group. Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. *Br J Surg* 2017; **104**: 1568–1577.

4 Yun YH, Kim YA, Min YH, Park S, Won YJ, Kim DY *et al.* The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol* 2012; **23**: 2731–2737.

5 Jooste V, Dejardin O, Bouvier V, Arveux P, Maynadie M, Launoy G *et al.* Pancreatic cancer: wait times from presentation to treatment and survival in a population-based study. *Int J Cancer* 2016; **139**: 1073–1080.

6 Eshuis WJ, van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, Kuipers EJ *et al.* Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. *Ann Surg* 2010; **252**: 840–849.

7 Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. *Surgeon* 2010; **8**: 239–246.

8 Marchegiani G, Andrianello S, Perri G, Secchettin E, Maggino L, Malleo G *et al.* Does the surgical waiting list affect pathological and survival outcome in resectable pancreatic ductal adenocarcinoma? *HPB (Oxford)* 2018; **20**: 411–417.

9 Gobbi PG, Bergonzi M, Comelli M, Villano L, Pozzoli D, Vanoli A *et al.* The prognostic role of time to diagnosis and presenting symptoms in patients with pancreatic cancer. *Cancer Epidemiol* 2013; **37**: 186–190.

10 Swords DS, Zhang C, Presson AP, Firpo MA, Mulvihill SJ, Scaife CL. Association of time-to-surgery with outcomes in clinical stage I–II pancreatic adenocarcinoma treated with upfront surgery. *Surgery* 2018; **163**: 753–760.

11 Sanjeevi S, Ivanics T, Lundell L, Kartalis N, Andren-Sandberg A, Blomberg J *et al.* Impact of delay between imaging and treatment in patients with potentially curable pancreatic cancer. *Br J Surg* 2016; **103**: 267–275.

12 Oncoline. *Richtlijnen Oncologische Zorg: IKNL*; 2018. http://www.oncoline.nl/pancreascarcinoom [accessed 14 March 2018].

13 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours* (7th edn). Wiley-Blackwell: Hoboken, 2011.

14 Percy C, Fritz A, Jack A, Shanmugarathan S, Sobin L, Parkin DM *et al. International Classification of Diseases for Oncology (ICD-O-3)*. WHO: Geneva, 2000.

15 Tienhoven GV, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA *et al.* Preoperative chemoradiotherapy *versus* immediate surgery for resectable and borderline resectable pancreatic cancer

(PREOPANC-1): a randomized, controlled, multicenter phase III trial. *J Clin Oncol* 2018; **36**: LBA4002.
16 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159**: 702–706.
17 Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008; **8**: 70.
18 van der Geest LGM, Lemmens V, de Hingh I, van Laarhoven C, Bollen TL, Nio CY *et al.* Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. *Br J Surg* 2017; **104**: 1568–1577.
19 Balzano G, Capretti G, Callea G, Cantu E, Carle F, Pezzilli R. Overuse of surgery in patients with pancreatic cancer. A nationwide analysis in Italy. *HPB (Oxford)* 2016; **18**: 470–478.
20 McLean SR, Karsanji D, Wilson J, Dixon E, Sutherland FR, Pasieka J *et al.* The effect of wait times on oncological outcomes from periampullary adenocarcinomas. *J Surg Oncol* 2013; **107**: 853–858.
21 Seo HK, Hwang DW, Park SY, Park Y, Lee SJ, Lee JH *et al.* The survival impact of surgical waiting time in patients with resectable pancreatic head cancer. *Ann Hepatobiliary Pancreat Surg* 2018; **22**: 405–411.
22 Visser MR, van Lanschot JJ, van der Velden J, Kloek JJ, Gouma DJ, Sprangers MA. Quality of life in newly diagnosed cancer patients waiting for surgery is seriously impaired. *J Surg Oncol* 2006; **93**: 571–577.
23 Weisman AD, Worden JW. The existential plight in cancer: significance of the first 100 days. *Int J Psychiatry Med* 1976–1977; **7**: 1–15.
24 Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011; **378**: 607–620.
25 Moss RA, Lee C. Current and emerging therapies for the treatment of pancreatic cancer. *Onco Targets Ther* 2010; **3**: 111–127.