Impact of multicentre diagnostic workup in patients with pancreatic cancer on repeated diagnostic investigations, time-to-diagnosis and time-to-treatment

European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Impact of multicentre diagnostic workup in patients with pancreatic cancer on repeated diagnostic investigations, time-to-diagnosis and time-to-treatment: A nationwide analysis

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ARTICLE INFO

Article history:
Received 2 March 2022
Received in revised form
4 May 2022
Accepted 28 May 2022
Available online xxx

Keywords:
Pancreatic cancer
Centralization
Cancer networks
Diagnostic investigations
Quality of care

ABSTRACT

Background: Due to the centralization of pancreatic surgery, patients with suspected pancreatic cancer may undergo diagnostic workup in both a non-pancreatic centre and a pancreatic centre, i.e. multicentre workup. This retrospective study assessed whether multicentre diagnostic workup is associated with repeated diagnostics, delayed time-to-diagnosis, delayed time-to-treatment, survival and whether variation existed among pancreatic cancer networks.

Methods: This nationwide study included all patients diagnosed with non-metastatic pancreatic ductal adenocarcinoma (PDAC) in 2015, registered by the Netherlands Cancer Registry. A delayed time-to-diagnosis was defined as ≥3 weeks from initial hospital visit to final diagnosis. A delayed time-to-treatment was defined as ≥6 weeks from the first hospital visit to start of first tumour treatment. Multilevel logistic regression analyses and survival analyses were performed.

Results: In total, 931 patients with non-metastatic PDAC were included. Overall, 175 patients (19%) underwent a multicentre diagnostic workup, which was significantly associated with repeated diagnostic investigations (OR = 6.31, 95% CI 4.13–9.64, P < 0.0001), a delayed time-to-diagnosis (OR = 2.66 95% CI 1.74–4.06, P < 0.001), and a delayed time-to-treatment (OR = 1.93 95% CI 1.12–3.31, P = 0.02), but not with decreased survival (HR = 1.09 95% CI 0.83–1.44; P = 0.532). Variation in outcomes per network was observed, especially for time-to-treatment, though the ICC was not statistically significant (P = 0.065).

Conclusion: Multicentre diagnostic workup for patients with PDAC is associated with repeated diagnostic investigations, a delayed time-to-diagnosis and delayed time-to-treatment compared to patients with monocentre workup. To reduce costs and improve treatment times, efforts should be made to improve network coordination, for example via network care pathways.

1. Introduction

In 2011, volume standards for pancreatic surgery were applied in several parts of Europe, including the Netherlands, the United Kingdom, Norway, Sweden, Finland and Denmark [1–4].

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https://doi.org/10.1016/j.ejso.2022.05.031

Please cite this article as: J.S. Hopstaken, P.A.J. Vissers, R. Quispel *et al.*, Impact of multicentre diagnostic workup in patients with pancreatic cancer on repeated diagnostic investigations, time-to-diagnosis and time-to-treatment: A nationwide analysis, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2022.05.031

Centralization of pancreatic surgery was deemed necessary to lower in-hospital mortality rates and improve long-term survival [5–8]. As a result, health care services for patients with pancreatic ductal adenocarcinoma (pancreatic cancer) are now provided in pancreatic cancer networks composed of a non-pancreatic (i.e. referring, local hospitals) and a pancreatic centre. Pancreatic centres provide a treatment advice, after discussion in a specialized multidisciplinary team (MDT), and perform pancreatic surgery. The non-pancreatic centres provide other elements of care such as adjuvant chemotherapy or best supportive care. Adequate collaboration between pancreatic non-pancreatic centres is required to warrant the most appropriate treatment at the most appropriate time and place. Though pancreatic surgery is centralized, diagnostic workup is not. Therefore, patients may undergo diagnostic workup in both a non-pancreatic centre and a pancreatic centre. On average, three diagnostic investigations are required before diagnosis is finalized [9]. This could well consist of an abdominal ultrasonography, abdominal CT-scan, endoscopy with fine needle aspiration, abdominal MRI, and sometimes a diagnostic laparoscopy [10]. It is currently unclear where these diagnostic investigations are usually performed (i.e. pancreatic and non-pancreatic centres) and whether this affects efficiency, e.g. through repeated diagnostic investigations. Moreover, it is unknown whether a multicentre diagnostic workup affects quality indicators of pancreatic cancer care, such as time-to-diagnosis and time-to-treatment, and patient outcomes, such as survival. It is quite conceivable that patients who undergo diagnostic investigations in more than one hospital, have a prolonged diagnostic process and delay in treatment initiation. Therefore, the aim of this study is to assess the extent of multicentre diagnostic workup in patients diagnosed with pancreatic cancer and its association with repeated diagnostic investigations, a delayed time-to-diagnosis, delayed time-to-treatment and survival. A second aim is to assess the variation in these outcomes per pancreatic cancer network.

2. Methods

2.1. Ethical consideration

This study used data from the Netherlands Cancer Registry (NCR). According to the Dutch Medical Research Involving Human Subjects Act, this type of study does not require approval from an ethics committee. The study protocol was approved by the privacy board of the NCR and the scientific committee of the Dutch Pancreatic Cancer Group [11].

2.2. Study design

This nationwide, population-based, retrospective study used data registered by the NCR. The NCR collects data on all newly diagnosed cancer patients in the Netherlands. These data include patient, cancer-related and treatment-related characteristics. Data are retrieved from medical records and anonymized by trained NCR data managers. Data on vital status was available through annual linkage with the Municipal Personal Records database and follow-up was complete until 1st February 2021. This study is in accordance with the STROBE-guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) [12].

2.3. Study population

Patients diagnosed with non-metastatic pancreatic ductal adenocarcinoma (pancreatic cancer) on imaging between 1 January 2015 and 31 December 2015 were included in this analysis. Data was limited to one year as data on diagnostic investigations were only collected in 2015. Patients younger than 18 years, patients diagnosed abroad, patients diagnosed during autopsy or patients for whom data on diagnostic investigations was missing, were excluded.

2.4. Patient, disease and treatment characteristics

Patient characteristics (age at diagnosis, sex, WHO performance status and comorbidities), tumour characteristics (morphology, differentiation grade, stage according to the cTNM-classification 7th edition), characteristics of diagnostic procedures (number of thoracic X-rays, abdominal ultrasonography's, CT-scans, MRI-scans, endoscopic retrograde cholangiopancreatography's (ERCPs), endoscopic ultrasound (EUS)) were available in the NCR. Additionally, the hospital of the diagnostic procedure, i.e. pancreatic centre or non-pancreatic centre, and timing of the investigation was documented. Treatment-related characteristics such as type of treatment ((neo)adjuvant chemotherapy, pancreatoduodenectomy, minimally invasive procedures), treatment plan, preoperative biliary drainage and surgical margin status were also retrieved. 2.5 Data, context and definitions Multicentre diagnostic workup was defined as diagnostic procedures, regardless of the type of investigation, in a pancreatic centre as well as a non-pancreatic centre. A monocentre workup included patients who had all their diagnostic investigations in one centre only. This centre could be either a pancreatic expert centre or a non-expert centre. A repeated diagnostic investigation was defined as a repetition of the same investigation within 10 weeks (70 days), regardless of whether this took place in the same hospital or in a different hospital, and prior to treatment initiation. Time-to-diagnosis was defined as the interval between the first hospital visit and the last MDT meeting before treatment initiation. A delayed time-to-diagnosis was defined as $\geq$3 weeks. Time-to-treatment was defined as the interval between the first visit in the first hospital and the first tumour-targeted treatment (i.e. (neo)adjuvant chemotherapy, surgical resection, or palliative chemotherapy). A delayed time-to-treatment was defined as $\geq$6 weeks. Because a delayed time-to-treatment could be caused by a delayed time-to-diagnosis, we performed an additional analysis with the definition as a delayed time-to-treatment $\geq$3 weeks from last MDT to first tumour-targeted treatment. These intervals and definitions are based on quality indicators described in the Dutch national guidelines and the SONCOS guidelines for oncological network care [13–15].

2.5. Statistical analyses

Descriptive statistics were presented in mean and standard deviation, median and interquartile range (IQR) or proportion and percentages, where appropriate. Differences between mono- and multicentre diagnostic workup were assessed with Chi-squared tests and Mann-Whitney U tests. Missing data were presented per variable. Missing data concerning the interval “first hospital visit and final MDT” (n = 327, 30%, missing at random) were imputed using multiple imputation by chained equations with 5 copies using the variables age, sex, performance status, comorbidities, morphology, tumour stage, tumour diameter and treatment. Multivariable multilevel logistic regression analyses were used to assess associations between multicentre diagnostic workup and the outcomes of interest, presented as odds ratio (OR) and 95% confidence intervals (CI). Pancreatic cancer networks were included as level with random intercepts. The loglikelihood ratio test was used to check whether random slopes were required. The variation per network was determined by the intraclass correlation coefficient (ICC) [16]. Covariables were selected based on clinical relevance, if they were deemed a confounder, or on statistical

significance in univariable logistic regression analysis. Survival distributions for mono and multicentre diagnostic workup were presented in a Kaplan-Meier curve and compared with a Log Rank test. Survival time was defined as time between first hospital visit and date of death or censoring. Among patients with pancreatic resection, multivariable Cox regression analysis was performed, adjusted for age, sex, pT, radical resection and (neo)adjuvant chemotherapy, to determine the association between multicentre diagnostic workup and survival. Hazard ratios (HR) and 95% CI were presented. Two-sided P-values of <0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS version 25 (IBM, Armonk, New York, USA) and SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics

In total, 1188 patients with non-metastatic pancreatic cancer were identified. After exclusion of 257 patients (Fig. 1), the final cohort consisted of 931 patients. Median age was 72 years (IQR 64–78) and 50.8% was male. The majority of patients underwent a monocentre diagnostic workup (n = 756, 81%), of whom 65% and 35% in a non-pancreatic and pancreatic centre, respectively. Nineteen percent (n = 175) of patients underwent a multicentre diagnostic workup. Patients with multicentre diagnostic workup were significantly younger and had better performance status than patients with monocentre workup (Table 1). There were no significant differences in tumour characteristics.

3.2. Multicentre diagnostic workup and repeated diagnostic investigations

Patients with a multicentre diagnostic workup more often had repeated diagnostic investigations, compared to patients with monocentre workup (47% *vs* 12%, P < 0.001) (Fig. 2). When the monocentre diagnostic workup took place in a non-pancreatic centre, diagnostic investigations were repeated in 11.2%, as compared to 12.7% in an expert centre (P = 0.544). The abdominal CT-scan was most frequently repeated for both groups, with significantly more repeats for patients with multicentre diagnostic workup (33.1% *vs* 14.6%, P < 0.001). Repeats of EUS (12% *vs* 6%, P = 0.099), ERCP (21.3% *vs* 15.5%, P = 0.220), abdominal ultrasound (5.6% *vs* 4.8%, P = 0.740), MRI (4% *vs* 0%, P = 0.122), and thoracic X-ray (6.8% *vs* 3.3%, P = 0.280) did not differ. In multilevel analysis, multicentre diagnostic workup was significantly associated with repeated diagnostic investigations (OR 6.31, 95% CI 4.13–9.64, P < 0.0001) (Table 2).

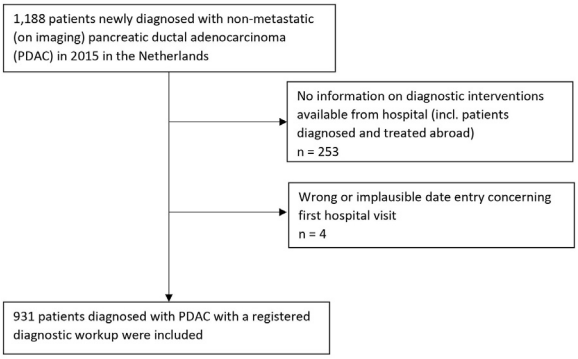

Fig. 1. Selection of study population.

3.3. Multicentre diagnostic workup and quality indicators

3.3.1. Time-to-diagnosis

The proportion of patients with a delayed time-to-diagnosis (≥3 weeks) was significantly higher for patients with multicentre diagnostic workup (70% *vs* 56%, P = 0.001), though in both groups >50% of cases did not meet the standard. In multilevel analysis, multicentre diagnostic workup was associated with delayed diagnostic workup (OR 2.66, 95% CI 1.74–4.06, P < 0.001) (Table 2). Additionally, age (OR 1.03, 95% CI 1.01–1.04) and biliary drainage (OR 0.36, 95% CI 0.24–0.56) were associated with delayed time-to-diagnosis.

3.3.2. Time-to-treatment

In total, 504 patients (54%) received a tumour-targeted treatment. Patients with a multicentre workup more often had a delayed time-to-treatment (≥6 weeks) than those with monocentre diagnostic workup (76% *vs* 63%, P = 0.007). In multilevel analysis, multicentre workup was associated with a delayed time-to-treatment (OR 1.93, 95% CI 1.12–3.31, P = 0.021). Clinical T4-stage was also associated with a delayed time-to-treatment (OR 2.34, 95% 1.02–5.35, P = 0.045) (Table 2). When time-to-treatment was analysed without the diagnostic period, namely as time between last MDT meeting and start first tumour-targeted treatment, median time-to-treatment was 29 days (IQR 19–41) for monocentre and 23 days (IQR 14–37) for patients with multicentre diagnostic workup (P = 0.033). With this definition, multicentre diagnostic workup was associated with a lower likelihood of delay in treatment initiation from MDT onwards (OR 0.55, 95% CI 0.34–0.90, P = 0.020).

3.4. Survival

Median overall survival was 8.6 months (IQR 3.3–16.3), and 12.2 months (IQR 5.4–23.6) for patients with mono- and multicentre diagnostic workup (P = 0.001) (Fig. 3). For patients who underwent pancreatic surgery (n = 339), this was 19.6 (IQR 10.9–36.6) and 20.6 months (IQR 11.3–43) for mono- and multicentre diagnostic workup (P = 0.368), respectively. In multivariable Cox regression analysis for patients who underwent resection, multicentre diagnostics was not associated with decreased survival (HR 1.09, 95% CI 0.83–1.44; P = 0.532) (Supplementary Table 3).

3.5. Variation in outcomes explained by pancreatic cancer networks

There were 17 pancreatic cancer networks identified, with the number of patients varying between 30 and 109 for delayed time-to-diagnosis and 17 and 69 for delayed time-to-treatment. Repeated diagnostic investigations ranged between 9% and 38% across pancreatic centres (P < 0.001) (Fig. 4a). Delayed time-to-diagnosis ranged between 33% and 72% (P < 0.001) (Fig. 4b) and delayed time-to-treatment ranged between 39% and 88% (P < 0.001) (Fig. 4c). For time-to-treatment, 7% of the total variation in time-to-treatment could be attributed to the pancreatic cancer network, though this was not statistically significant (P = 0.065) (ICC Table 2). Variation in networks was present, especially for delayed time-to-treatment, as one network had a significantly higher risk for delayed time-to-treatment (OR 2.34, 95% CI 1.02–5.35, P = 0.045).

4. Discussion

This is the first population-based study that assessed the diagnostic phase of patients with pancreatic cancer in a pancreatic cancer network with centralization of surgery. We demonstrated

Table 1
Baseline characteristics of total cohort (n = 931) of patients with PDAC, divided by monocentre or multicentre diagnostic workup.

	Monocentre	Multicentre[b]	P-value
	n = 756 (81)	n = 175 (19)	
	n (%)[a]	n (%)[a]	
Patient Characteristics			
Age (yrs), median (IQR)	72 (65–80)	68 (61–74)	<0.001
≥65 years	579 (76.6)	112 (64)	<0.001
Sex (male)	389 (51.5)	84 (48)	0.410
Performance status (ECOG)			0.001
0	183 (24.2)	58 (33.1)	
1	134 (17.7)	46 (26.3)	
2	40 (5.3)	10 (5.7)	
3	17 (2.2)	3 (1.7)	
4	4 (0.5)	0 (0)	
Missing	378 (50)	58 (33.1)	
Charlson comorbidity index ≥2	144 (19)	30 (17.1)	0.335
Missing	23 (3)	7 (4)	
cT stage (TNM 7th ed)			0.417
T1	57 (7.5)	13 (7.4)	
T2	162 (21.4)	34 (19.4)	
T3	233 (30.8)	67 (38.3)	
T4	237 (31.3)	49 (28)	
X	67 (8.9)	12 (6.9)	
cN stage (TNM 7th ed)			0.778
0	478 (63.2)	112 (64)	
1	177 (23.4)	43 (24.6)	
X	101 (13.4)	20 (11.4)	
Tumor location, pancreatic head	544 (72)	132 (75.4)	0.237
Tumor differentiation grade			0.405
Well	33 (4.4)	10 (5.7)	
Moderate	130 (17.2)	38 (21.7)	
Poor	103 (13.6)	27 (15.4)	
Undifferentiated	1 (0.1)	0 (0)	
Unknown	489 (64.7)	100 (57.1)	
Care-related characteristics			
Repeated diagnostic investigations			<0.001
No	667 (88.2)	93 (53)	
Yes	89 (11.8)	82 (47)	
Biliary drainage in diagnostic phase			<0.001
No	655 (86.6)	123 (70.3)	
Yes	101 (13.4)	52 (29.7)	
Biliary drainage before treatment initiation			0.125
No	213 (28.2)	59 (33.7)	
Yes	168 (22.2)	64 (36.6)	
Missing, because of no tumor treatment	375 (49.6)	52 (29.7)	
Discussion of patient in MDT			<0.01
No	229 (30.3)	34 (19.4)	
Yes	527 (69.7)	141 (80.6)	
Time to final diagnosis in days[c] median (IQR)	23 (IQR 11–27)	27 (IQR 19–42)	<0.001
Time to treatment in days[d] median (IQR)	49 (IQR 36–67)	57 (IQR 42–83)	<0.01
Treatment characteristics			
Pancreatic surgery	255 (33.7)	84 (48)	<0.001
Neo adjuvant chemotherapy	20 (2.6)	11 (6.3)	<0.01
Adjuvant chemotherapy	139 (18.4)	54 (30.9)	<0.001
Palliative chemotherapy	122 (16.1)	36 (20.6)	0.159
No tumor-related therapy	375 (49.6)	52 (29.7)	<0.001

ECOG = Eastern Cooperative Oncology Group, MDT = multidisciplinary team.
[a] unless indicated otherwise in variable name.
[b] multicentre is defined as diagnostic investigations in both a pancreatic centre as non-pancreatic centre (e.g. local hospital).
[c] Time-to-diagnosis is defined as the period between first hospital visit and last MDT meeting.
[d] Time-to-treatment is defined as the period between first hospital visit and start tumor-related treatment.

that one-fifth of patients undergo a multicentre diagnostic workup and that this was associated with repeated diagnostic investigations, a delayed time-to-diagnosis, and a delayed time-to-treatment, as compared to monocentre diagnostic workup. The delayed time-to-treatment was mainly attributed to the delayed time-to-diagnosis. Between 2 and 7% of the variation in outcomes could be attributed to the pancreatic cancer network. There was no association between multicentre diagnostic workup and overall survival.

No other studies have investigated the association between multicentre diagnostic workup on repeated diagnostic investigations, delayed diagnosis and delayed treatment in centralised pancreatic cancer networks. Repeated diagnostic investigations in a pancreatic centre was previously described in a

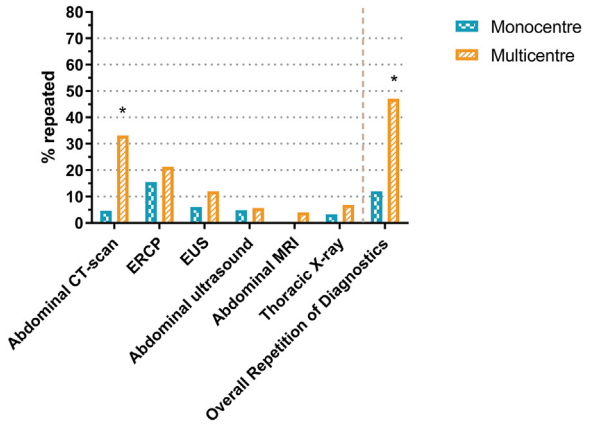

Fig. 2. Bar graphs per diagnostic investigation.

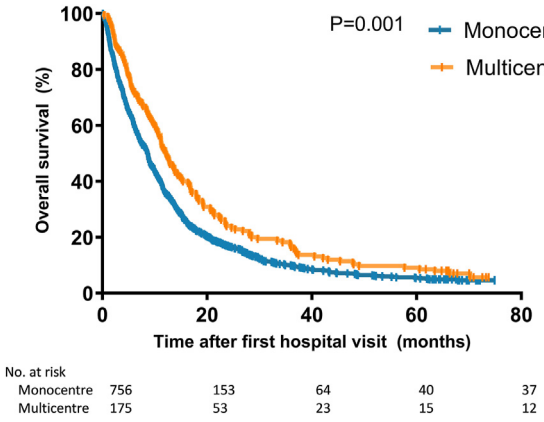

Fig. 3. Kaplan Meier curves with number at risk.

Table 2
Multivariable multilevel analysis for the association between multicentre diagnostic work-up and repeated diagnostic investigations, delayed time-to-diagnosis and delayed time-to-treatment.

	Repetition of diagnostic investigations within 10 weeks		Delayed time − to − diagnosis[a] (≥3 weeks)		Delayed time − to − treatment[b] (≥6 weeks)	
	Multivariable (n = 901)		Multivariable (n = 901)		Multivariable (n = 495)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Fixed effects						
Age	0.99 (0.97–1.01)	0.207	**1.03 (1.01–1.04)**	**<0.001**	1.00 (0.97–1.02)	0.710
Performance status						
WHO 0	Ref		Ref		Ref	
WHO 1	0.81 (0.47–1.39)	0.431	1.03 (0.67–1.59)	0.876	0.97 (0.56–1.67)	0.897
WHO ≥2	1.07 (0.52–2.23)	0.850	0.77 (0.43–1.37)	0.366	1.32 (0.51–3.39)	0.563
Missing	0.96 (0.60–1.53)	0.860	1.26 (0.87–1.82)	0.210	**0.50 (0.30–0.82)**	0.007
cT						
T1	Ref		Ref		Ref	
T2	1.37 (0.58–3.25)	0.470	0.84 (0.46–1.56)	0.581	1.19 (0.53–2.66)	0.664
T3	1.59 (0.70–3.62)	0.263	0.63 (0.35–1.14)	0.124	1.35 (0.62–2.90)	0.444
T4	1.76 (0.77–4.02)	0.180	0.99 (0.54–1.79)	0.966	**2.34 (1.02–5.35)**	**0.045**
X	1.75 (0.66–4.69)	0.258	1.45 (0.69–3.05)	0.328	1.97 (0.74–5.27)	0.172
Biliary drainage[c]						
No	Ref		Ref		Ref	
Yes	1.20 (0.72–1.98)	0.461	**0.36 (0.24–0.56)**	**0.0001**	0.78 (0.50–1.21)	0.216
Multicentre diagnostic workup						
No	Ref		Ref		**Ref**	
Yes	**6.31 (4.13–9.64)**	**<0.0001**	**2.66 (1.74–4.06)**	**<0.001**	**1.96 (1.15–3.36)**	**0.021**
Random effects[d]						
ICC	1.62%	0.203	3.19%	0.069	7.24%	0.065
Range OR of clusters:						
Min	0.85 (0.52–1.37)	0.503	0.58 (0.31–1.09)	0.091	0.54 (0.26–1.13)	0.103
Max	1.32 (0.73–2.38)	0.362	1.43 (0.90–2.27	0.135	**2.34 (1.02–5.35)**	**0.045**

X = reported as unknown tumor stage. Bold ORs and P-values are statistical significant.
ICC = Intraclass correlation coefficient.
[a] Defined as period from first hospital visit to final MDT.
[b] Defined as period from first hospital visit to start first tumor treatment.
[c] Biliary drainage for repetition of diagnostic investigations and time-to-diagnosis was defined as drainage in the period between first hospital visit − MDT; for time-to-treatment biliary drainage was defined drainage in the period between first hospital visit − first tumor treatment.
[d] In the multilevel model only a random intercept was applied because random slopes were not required.

small pilot study [17]. This study described repeated abdominal CTs up to 42%. In our study, with a larger sample size, we observed 33% repeated abdominal CTs. Both studies report a considerably high repetition of diagnostics. In the current study, a repeated diagnostic investigation was defined as a repetition within 10 weeks (70 days), to exclude repeated scans that were performed to evaluate the tumour through time, which is generally performed after 3 months. Exact reasons for repeating the investigations were unknown. However, it seems likely that network care is related to this, as we observed a considerably higher odds of repeated diagnostic investigations among multicentre versus monocentre diagnostic workup. An explanation could be that hospitals may differ in scan protocol or that non-pancreatic centres did not deliver the information required for the pancreatic centre to formulate an appropriate treatment plan in time, resulting in the pancreatic centre repeating the procedure. The latter would be an example of suboptimal network care and should be avoided because it places additional burden on pancreatic cancer patients. Moreover, if indeed a third of all CT-scans are repeated due to suboptimal network care, the associated extra healthcare costs are

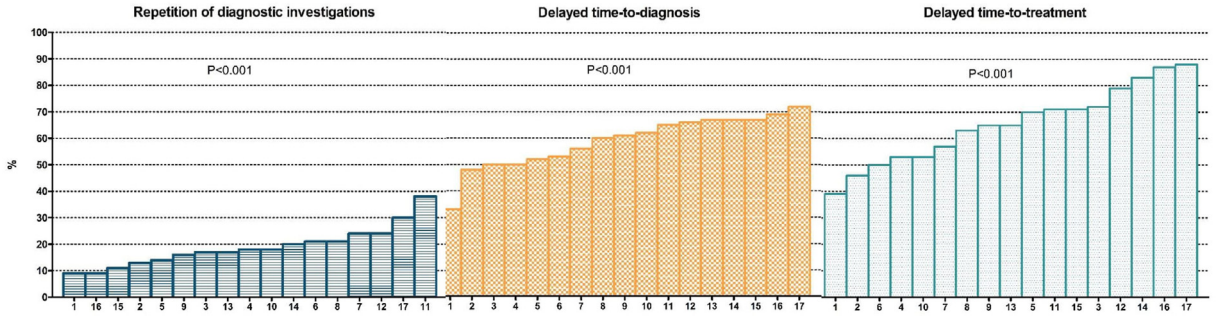

Fig. 4. Bar graphs per pancreatic cancer network (numbered 1 to 17 on x-axis) indicating the percentage of patients with repetition of diagnostic investigations (4a).

considerable. Optimizing network care could therefore lead to resource savings and cost savings.

The overall survival rates in this study and percentage of patients with supportive care only care, are comparable to the rates previously described in the Dutch PDAC population [18,19]. It is worth mentioning here that patients in this cohort study all had non-metastatic PDAC on imaging at initial diagnosis. In some of these patients metastases were then discovered during explorative surgery of diagnostic laparoscopy. This was the case for 87 patients (9.3%) for whom M1-disease was present after initial diagnosis. This could help the interpretation of these survival rates.

Concerning diagnostic delay, we found that for both monocentre and multicentre patients, diagnostic delay was present >50%. However, for multicentre patients this was even higher. Previous studies have mainly focussed on diagnostic delay as a determinant for upfront surgery, not as an outcome measure of multicentre workup. For example, in a retrospective study in a pancreatic centre the relationship between the diagnostic interval and surgical resectability in PDAC patients was studied [20]. A median diagnostic interval of 22 days (8–46 days) was reported, which was comparable to the monocentre group of our study, i.e. 23 days (IQR 11–27). A diagnostic interval of less than two months was associated with increased odds for upfront surgery. Delayed time-to-treatment has also been subject of study as a determinant for resectability and survival [21–24]. However, these studies report conflicting results, with some reporting an increased risk of unresectability [21], and others reporting no impact on resectability and survival [22,23]. Nevertheless, despite the debated relationship between delays and oncological outcomes, it is still worthwhile to critically appraise these delays in the patient journey, as studies indicate that delays are associated with higher cancer-related distress [25,26]. Moreover, a recent Dutch study reported that patients experienced poor coordination between the involved hospitals [27]. Another study indicated that information exchange within care teams is an important determinant for satisfaction with care [28]. The results of these studies, including ours, underline the necessity to critically reflect on the current organization of pancreatic cancer networks and to further improve collaboration between pancreatic and non-pancreatic centres.

The findings of this study should be interpreted in light of some limitations. First, data concerning diagnostic investigations were only registered in the NCR for the year 2015. Although pancreatic cancer networks in the Netherlands have not changed considerably since then, it could be argued that data from this period is not completely representative for patients of today. Second, we were not able to include all patients who were suspected of pancreatic cancer at first presentation as only the final diagnosis was registered in the NCR. Third, we did not have data concerning tumour uncertainty in the diagnostic workup. Patients with tumour uncertainty are probably more often referred to a pancreatic centre and might have a longer time-to-diagnosis. They could require an extra scan or tumour biopsy. Tumour uncertainty could therefore act as a confounder in the relationship we aimed to study and we were not able to adjust for this. A final limitation is that approximately 20% of the total patient population diagnosed with localised PDAC in 2015 was not included in this analysis. This population consisted of patients who were diagnosed or treated abroad or for whom there were no diagnostic investigations registered. For this patient population, we could not determine whether they had a mono- or multicentre diagnostic workup. A strength of this study is that it has elucidated the extent of multicentre pancreatic cancer network care at a national level and investigated possible consequences of such a workup. This provides knowledge to the domain of health services research for pancreatic cancer, which is characterized by a dearth in literature [29], and provides a direction for quality improvement. A second strength is that we used population-based data, of which the results are immediately applicable for the entire Dutch pancreatic cancer population. A final strength is that we performed a multilevel analysis, which is methodologically more robust and provides us with insight on the variance attributed to the pancreatic cancer network.

In the era of centralization, close collaboration between pancreatic and non-pancreatic centres is required in order to prevent unnecessary repetitions and delays in diagnosis and treatment. Improving collaboration within a pancreatic cancer network was also the primary recommendation formulated in the Bratislava Statement (2020) [30]. Pinpointing how these networks should then be organized instead, is cumbersome, as none of the networks in our study significantly outperformed the group average and also because we did not study the agreements within these networks. Future studies should therefore aim to further investigate how pancreatic cancer networks are organized and which type of organization is associated with the best quality of care parameters and patient satisfaction.

In conclusion, multicentre diagnostic workup is present in 20% of patients diagnosed with pancreatic cancer and is associated with a repetition of diagnostic investigations, delayed time-to-diagnosis and delayed time-to-treatment. To improve these outcomes, efforts should be made to improve network coordination, for example via network care pathways.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contributions

Study concept and design: Hopstaken, Vissers, van der Geest, Besselink, Stommel. *Data acquisition and analysis:* Hopstaken,

Vissers, van der Geest, Stommel. *Data interpretation:* All authors. *Manuscript preparation:* Hopstaken, Vissers, Stommel. *Critical revision:* All authors.

CRediT authorship contribution statement

Jana S. Hopstaken: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Pauline A.J. Vissers:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision. **Rutger Quispel:** Conceptualization, Writing – review & editing. **Judith de Vos-Geelen:** Conceptualization, Writing – review & editing. **Lodewijk A.A. Brosens:** Conceptualization, Writing – review & editing. **Ignace H.J.T. de Hingh:** Conceptualization, Writing – review & editing. **Lydia G. van der Geest:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing. **Marc G. Besselink:** Conceptualization, Methodology, Writing – review & editing. **Kees J.H.M. van Laarhoven:** Conceptualization, Writing – review & editing, Supervision. **Martijn W.J. Stommel:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of competing interest

Judith de Vos-Geelen has served as a consultant for Amgen, AstraZeneca, MSD, Pierre Fabre, and Servier, and has received institutional research funding from Servier. All outside the submitted work. Lodewijk Brosens served as a paid consultant for Bristol-Myers Squibb. The other authors have no interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.05.031.

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