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Detection, Treatment, and Survival of Pancreatic Cancer Recurrence in the Netherlands

A Nationwide Analysis

Lois A. Daamen, MD,[*†✉] *Vincent P. Groot, MD, PhD,*[*] *Marc G. Besselink, MD, PhD,*[‡] *Koop Bosscha, MD, PhD,*[§] *Olivier R. Busch, MD, PhD,*[‡] *Geert A. Cirkel, MD, PhD,*[¶||] *Ronald M. van Dam, MD, PhD,*[**] *Sebastiaan Festen, MD, PhD,*[††] *Bas Groot Koerkamp, MD, PhD,*[‡‡] *Nadia Haj Mohammad, MD, PhD,*[¶] *Erwin van der Harst, MD, PhD,*[§§] *Ignace H. J. T. de Hingh, MD, PhD,*[¶¶] *Martijn P. W. Intven, MD, PhD,*[†] *Geert Kazemier, MD, PhD,*[||||] *Maartje Los, MD, PhD,*[¶] *Gert J. Meijer, PhD,*[†] *Vincent E. de Meijer, MD, PhD,*[***] *Vincent B. Nieuwenhuijs, MD, PhD,*[†††] *Bobby K. Pranger, BSc,*[***] *Mihaela G. Raicu, MD, PhD,*[‡‡‡] *Jennifer M. J. Schreinemakers, MD, PhD,*[§§§] *Martijn W. J. Stommel, MD, PhD,*[¶¶¶] *Robert C. Verdonk, MD, PhD,*[||||||] *Helena M. Verkooijen, MD, PhD,*[****] *Izaak Quintus Molenaar, MD, PhD,*[††††] *and Hjalmar C. van Santvoort, MD, PhD*[††††✉], *for the Dutch Pancreatic Cancer Group*

Objective: To evaluate whether detection of recurrent pancreatic ductal adenocarcinoma (PDAC) in an early, asymptomatic stage increases the number of patients receiving additional treatment, subsequently improving survival.

Summary of Background data: International guidelines disagree on the value of standardized postoperative surveillance for early detection and treatment of PDAC recurrence.

Methods: A nationwide, observational cohort study was performed including all patients who underwent PDAC resection (2014–2016). Prospective baseline and perioperative data were retrieved from the Dutch Pancreatic Cancer Audit. Data on follow-up, treatment, and survival were collected retrospectively. Overall survival (OS) was evaluated using multivariable Cox regression analysis, before and after propensity-score matching, stratified for patients with symptomatic and asymptomatic recurrence.

Results: Eight hundred thirty-six patients with a median follow-up of 37 months (interquartile range 30-48) were analyzed. Of those, 670 patients (80%) developed PDAC recurrence after a median follow-up of 10 months (interquartile range 5–17). Additional treatment was performed in 159/511 patients (31%) with symptomatic recurrence versus 77/159 (48%) asymptomatic patients ($P < 0.001$). After propensity-score matching on lymph node ratio, adjuvant therapy, disease-free survival, and recurrence site, additional treatment was independently associated with improved OS for both symptomatic patients [hazard ratio 0.53 (95% confidence interval 0.42–0.67); $P < 0.001$] and asymptomatic patients [hazard ratio 0.45 (95% confidence interval 0.29–0.70); $P < 0.001$].

Conclusions: Additional treatment of PDAC recurrence was independently associated with improved OS, with asymptomatic patients having a higher probability to receive recurrence treatment. Therefore, standardized postoperative surveillance aiming to detect PDAC recurrence before the onset of symptoms has the potential to improve survival. This provides a rationale for prospective studies on standardized surveillance after PDAC resection.

From the [*]Department of Surgery, UMC Utrecht Cancer Center, Utrecht University, Utrecht, the Netherlands; †Department of Radiation Oncology, UMC Utrecht Cancer Center, Utrecht University, Utrecht, the Netherlands; ‡Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands; §Department of Surgery, Jeroen Bosch Hospital, Den Bosch, the Netherlands; ¶Department of Medical Oncology, Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, Utrecht University, the Netherlands; ||Department of Medical Oncology, Meander Medical Center, Amersfoort, the Netherlands; [**]Department of Surgery, Maastricht UMC+, Maastricht, the Netherlands; ††Department of Surgery, OLVG, Amsterdam, the Netherlands; ‡‡Department of Surgery, Erasmus MC, Rotterdam, the Netherlands; §§Department of Surgery, Maasstad Hospital, Rotterdam, the Netherlands; ¶¶Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands; ||||Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands; [***]Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; †††Department of Surgery, Isala, Zwolle, the Netherlands; ‡‡‡Department of Pathology, Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, the Netherlands; §§§Department of Surgery, Amphia Hospital, Breda, the Netherlands; ¶¶¶Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands; ||||||Department of Gastroenterology, Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, the Netherlands; [****]Imaging Division, University Medical Centre Utrecht; Utrecht University, Utrecht, the Netherlands; and ††††Department of Surgery, Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, Utrecht University, the Netherlands.

✉H.C.vanSantvoort@umcutrecht.nl, L.A.Daamen-3@umcutrecht.nl.

I. Quintus Molenaar and Hjalmar C. van Santvoort share senior authorship.

Authors' contributions: Study conception and design: Daamen, Groot, Besselink, Bosscha, Busch, Cirkel, van Dam, Festen, Groot Koerkamp, Haj Mohammad, van der Harst, de Hingh, Intven, Kazemier, Los, Meijer, de Meijer, Nieuwenhuijs, Pranger, Raicu, Schreinemakers, Stommel, Verdonk, Verkooijen, Molenaar, van Santvoort.

Acquisition of data: Daamen, Groot, Besselink, Bosscha, van Dam, Festen, Groot Koerkamp, van der Harst, de Hingh, Kazemier, de Meijer, Nieuwenhuijs, Pranger, Schreinemakers, Stommel, Molenaar, van Santvoort

Analysis and interpretation of data: Daamen, Groot, Besselink, Groot Koerkamp, Haj Mohammad, de Hingh, Intven, Meijer, Verkooijen, Molenaar, van Santvoort

Drafting of manuscript: Daamen, Groot, Molenaar, van Santvoort

Critical manuscript revision: Daamen, Groot, Besselink, Bosscha, Busch, Cirkel, van Dam, Festen, Groot Koerkamp, Haj Mohammad, van der Harst, de Hingh, Intven, Kazemier, Los, Meijer, de Meijer, Nieuwenhuijs, Pranger, Raicu, Schreinemakers, Stommel, Verdonk, Verkooijen, Molenaar, van Santvoort

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Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival of only 12%–17% after resection.[1–3] Despite the introduction of (neo)adjuvant systemic therapy, almost all patients develop disease recurrence.[4–8] Recent advancements in treatment of PDAC have resulted in more potent systemic and local treatment options, such as fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) chemotherapy and stereotactic body radiation therapy.[8–12] Prospective studies evaluating the efficacy, timing, and impact on quality of life of these therapies in patients with PDAC recurrence are, however, lacking. Hence, the true benefit of standardized postoperative surveillance for the early detection and treatment of PDAC recurrence remains unclear.[13]

The few, small retrospective studies on this subject suggest that treatment of PDAC recurrence prolongs survival including survival with good quality of life.[14–17] This benefit mainly seems to apply to patients with asymptomatic PDAC recurrence, detected during routine imaging surveillance.[15,16] Postoperative surveillance using cross-sectional imaging at regular intervals hypothetically leads to earlier detection of PDAC recurrence, possibly improving eligibility for recurrence-oriented treatment. Consequently, standardized surveillance with routine imaging is increasingly being considered by pancreatic cancer clinicians worldwide.[18–20]

However, standardized surveillance has several drawbacks. Routine diagnostic testing may increase the patient's fear of cancer recurrence and worsen quality of life.[21,22] Furthermore, when disease progression is diagnosed in an asymptomatic patient, it is yet unclear whether immediate treatment improves survival. Quality of life may only worsen when chemotherapy is started in asymptomatic patients. Moreover, dubious findings on imaging, not necessarily indicative of disease recurrence, could also negatively impact quality of life. Current European PDAC guidelines therefore do not recommend standardized postoperative surveillance, whereas US and Asian guidelines support a standardized follow-up program.[18–20,23–27] This has led to widely varying surveillance and treatment strategies in daily clinical practice.

The aim of this nationwide, multicenter observational cohort study was to evaluate whether detection of PDAC recurrence in an early, asymptomatic stage increases the number of patients receiving additional treatment, subsequently improving survival rates.

METHODS

Study Design

A nationwide, multicenter observational cohort study was performed in all 16 Dutch centers for pancreatic cancer surgery. Institutional review board approval of each participating center was obtained. All patients registered within the prospective, mandatory Dutch Pancreatic Cancer Audit who underwent resection of histologically proven PDAC between 2014 and 2016 were included.[28] Exclusion criteria were a macroscopically positive resection margin (R2 resection) and death within 90 days after resection. Outcomes of interest were incidence of PDAC recurrence, timing, and location of recurrence, symptoms at time of recurrence diagnosis, type of treatment for recurrence versus best-supportive-care, overall survival (OS), and disease-free survival (DFS). Within the Netherlands, follow-up after PDAC resection commonly consists of a periodic, symptomatic follow-up without routine serum tumor marker testing or imaging. Patients are informed and instructed to report to the center for cross-sectional imaging in case of symptoms suggestive of disease recurrence. However, based on shared-decision making, or as part of a study-specific follow-up or local protocols, a proportion of patients receives standardized serum carbohydrate antigen (CA) 19-9 testing and cross-sectional imaging during postoperative surveillance.[24,29]

Data Collection

Prospective baseline and perioperative data were retrieved from the clinical audit database. Additionally, data on follow-up, detection, and treatment of PDAC recurrence, and survival were collected retrospectively from the patients' records within each participating hospital. Information on height and weight was used to calculate the body mass index (BMI) for each patient; the Charlson age-comorbidity index (CACI) was calculated using the MDCalc CACI calculator.[30] Serum CA 19-9 levels of $\geq$37 U/mL were deemed elevated. The TNM-status was assessed according to the seventh American Joint Committee on Cancer guidelines.[31] Resection margin status was considered positive (R1) if tumor cells were present within 1 mm of the resection margin at pathological examination. R0 resection was defined as a margin clearance of $\geq$1 mm. Major postoperative complications were defined as complications requiring a surgical or radiological intervention, intensive care unit admittance, single- or multi-organ failure, or patient demise. Diagnostic testing focused on the detection of PDAC recurrence was counted during the follow-up period from the date of primary resection until the date of recurrence diagnosis. Follow-up CA 19-9 measurements and/or imaging procedures were considered standardized if they were performed with a certain frequency, for instance every 3 or 6 months.

Outcomes

OS was defined as the time from the date of operation to death from any cause or last follow-up. DFS was defined as the time from the date of resection to the date of diagnosis of PDAC recurrence. PDAC recurrence was either pathologically proven, or suspected through cross-sectional imaging, preferably confirmed by consensus during a multidisciplinary meeting. Symptomatic recurrence was defined as the presence of symptoms suggestive for PDAC recurrence at recurrence diagnosis. This group included patients with and without standardized follow-up imaging in whom PDAC recurrence was discovered due to a patient-reported symptom which prompted or expedited further diagnostic testing. Symptoms considered suggestive for disease recurrence were abdominal pain, back pain, weight loss, jaundice, dyspnea, nausea or vomiting, abdominal distension, change of stool, loss of appetite, malaise, and fatigue or weakness. If PDAC recurrence was detected in absence of suspected symptoms, disease recurrence was defined as asymptomatic.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Missing baseline and follow-up data were considered to be missing at random and handled using multiple imputation with the iterative Markov chain Monte Carlo method (5 imputations; 10 iterations).[32] In case of missing information on vital status, participants were censored from the date of their last follow-up appointment. Kaplan-Meier survival curves were used to assess OS, and the log-rank test was used to compare groups. To assess the association between routine follow-up imaging and OS, compared to no routine follow-up imaging, multivariable Cox proportional hazard analysis was performed, adjusting for potential confounders. The association between treatment for recurrence and OS, as compared to best-supportive-care, was evaluated using multivariable Cox proportional hazard analysis in a propensity-score-matched sample. Propensity-score matching was performed using the ''nearest neighbor'' method to create pairs of patients who received either additional treatment for

recurrence or best-supportive-care (1:1) with comparable individual patient and tumor characteristics. The propensity-score model included variables that were found to be related to the outcome (i.e., OS) in Cox-proportional hazard analysis.[33,34] The standardized mean difference (SMD) in propensity-scores was diminished, with an SMD of <0.100 representing adequate balance.[35] Consequently, patients outside the joint range of propensity-scores were excluded. Remaining potential confounders were included in the multivariable Cox regression model. Survival analyses were stratified for symptomatic and asymptomatic patients. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R language environment (version 1.1.463, ''mice,'' ''MatchIt,'' ''cobalt,'' and ''survival'' packages; http://www.R-project.org). A *P*-value <0.05 was considered statistically significant.

RESULTS

Study Population and Follow-up

A total of 836 patients who underwent resection of PDAC were included, with a median follow-up of 37 months [interquartile range (IQR) 30–48 months] (Supplementary Data File – Appendix I, http://links.lww.com/SLA/C248). In total, 670 patients (80%) developed PDAC recurrence after a median of 10 months (IQR 5–17 months) (Supplementary Data File – Table 1, http://links.lww.com/SLA/C250). CA 19-9 was measured during postoperative follow-up in 489 patients (73%), of whom 77 patients (16%) had routine CA 19-9 testing with a certain frequency. A total of 649 patients (97%) underwent imaging with computed tomography, magnetic resonance imaging or positron emission tomography-computed tomography for the detection of PDAC recurrence during follow-up, with a median number of 1 scan (IQR 1–3 scans) per patient. In 88 of these patients (14%), imaging was performed routinely.

Detection of Recurrence

A total of 136 patients (20%) were diagnosed with isolated local recurrence after a median interval of 12 months (IQR 8–21 months) (Supplementary Data File – Table 1, http://links.lww.com/SLA/C250). Liver- and lung-only metastases occurred in 112 patients (17%) and 35 patients (5%) after a median interval of 5 months (IQR 2–9 months) and 19 months (IQR 10–33 months), respectively. In about half of the patients [n = 354 (53%)], PDAC recurrence occurred at multiple sites after a median interval of 9 months (IQR 6–16 months). The remaining 32 patients (5%) had other isolated distant metastases after a median interval of 10 months (IQR 3–20 months).

The first sign suggestive for PDAC recurrence was new onset of symptoms in 474 patients (71%), suspected findings on imaging in 153 patients (23%), and elevation of CA 19-9 in 43 patients (6%). At the time of recurrence diagnosis, 511 patients (76%) experienced symptoms suggestive for PDAC recurrence, whilst 159 patients (24%) were asymptomatic (Supplementary Data File – Fig. 1, http://links.lww.com/SLA/C249).

Treatment for Recurrence

In total, 236 patients (35%) underwent some form of treatment for PDAC recurrence, as compared with 434 patients (65%) who received best-supportive-care (Supplementary Data File – Table 1, http://links.lww.com/SLA/C250). Additional treatment was administered in 159 patients (31%) with symptomatic recurrence and in 77 patients (48%) with asymptomatic recurrence ($P < 0.001$). Reasons for best-supportive-care were patient's wish (40%), poor overall performance status (30%), and other reasons (30%). PDAC recurrence was pathologically proven in 115 patients (49%) who underwent additional treatment. Of 136 patients with isolated local PDAC recurrence, 50 patients (37%) received chemotherapy; 10 patients (7%) radiotherapy; and 3 patients (1%) other therapies. Three patients with isolated local recurrence received local ablative therapy with stereotactic body radiation therapy (n = 1) or irreversible electroporation (n = 2) in addition to chemotherapy. Out of 534 patients with distant metastases, respectively 139 patients (26%), 16 patients (3%), and 17 patients (3%) received chemotherapy, radiotherapy, and other therapies. The most frequently administered chemotherapy regimen was FOLFIRINOX (68%); 7% of patients received gemcitabine monotherapy; 18% gemcitabine with nab-paclitaxel; and 7% of patients received other regimens. Of patients receiving additional treatment, 36% finished treatment per protocol and 21% experienced progression during treatment. In respectively 13%, 16%, and 5% of patients, treatment was terminated early due to toxicity, a poor overall performance status, and the patients' wish.

Survival Analysis

Median OS in 836 patients within the original cohort was 19 months [95% confidence interval (CI) 17–21 months]. In 670 patients with disease recurrence after primary resection, median OS from the date of primary resection was 15 months (95% CI 14–17 months). Median OS was 25 months (95% CI 21–31 months) in 88 patients receiving routine follow-up imaging, as compared with 15 months (95% CI 13–16 months; $P < 0.001$) in 582 patients undergoing a symptomatic follow-up, during which imaging was only performed when considered indicated based on symptoms associated with recurrence (Fig. 1). After adjustment for potential confounders, routine follow-up imaging was found to be independently associated with improved survival [hazard ratio (HR) 0.52 (95% CI 0.37–0.73); $P < 0.001$] (Table 1).

Variables selected for propensity-score matching were lymph node ratio, administration of adjuvant therapy, DFS, and recurrence site (Table 1). All 236 patients who underwent additional treatment for recurrence were matched with 236 patients who received best-supportive-care (Supplementary Data File – Table 3, http://links.lww.com/SLA/C251). As a result, differences in patient and tumor characteristics were balanced between the 2 groups and the SMD in propensity-scores was diminished (SMD 0.084). Within the matched sample, median OS in patients who underwent additional treatment for recurrence was 26 months (95% CI 23–29 months), as compared with 15 months (95% CI 13–17 months) for patients who received best-supportive-care ($P < 0.001$) (Fig. 2). Subsequently, multivariable Cox regression analysis showed that treatment for recurrence was independently associated with longer survival, as compared with best-supportive-care [HR 0.54 (95% CI 0.44–0.66); $P < 0.001$]. This applied to both patients with symptomatic PDAC recurrence [HR 0.53 (95% CI 0.42–0.67); $P < 0.001$] and asymptomatic recurrences [HR 0.45 (95% CI 0.29–0.70); $P < 0.001$] (Table 2). Eventually, this resulted in a median OS from the date of primary resection of 15 months (95% CI 13–16 months) for all 511 patients with symptomatic PDAC recurrence and 20 months (IQR 16–25 months) for all 159 asymptomatic patients ($P < 0.001$).

DISCUSSION

This study shows that treatment of both symptomatic and asymptomatic PDAC recurrence is independently associated with improved OS in an unselected, nationwide cohort of patients reflecting daily clinical practice in the Netherlands. Moreover, patients with asymptomatic disease recurrence were more likely to receive additional treatment, and routine follow-up imaging was significantly associated with improved survival. These findings suggest that standardized postoperative surveillance, intended to detect PDAC recurrence in an early, asymptomatic stage, increases the number of

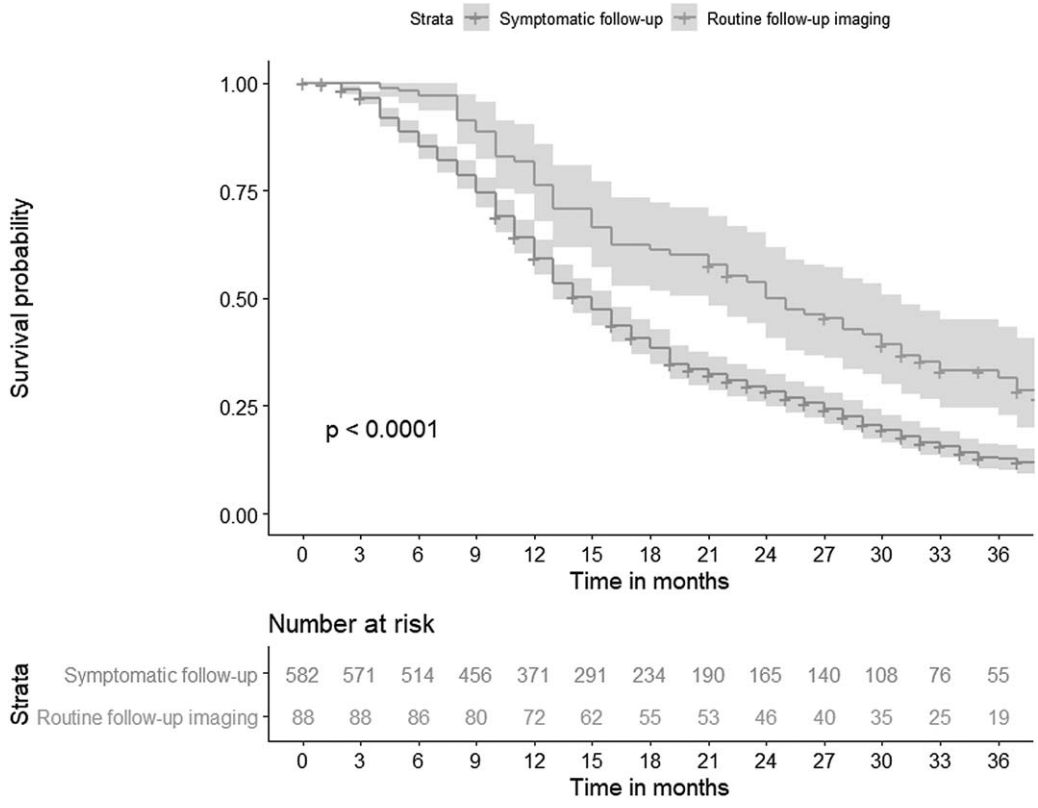

FIGURE 1. Kaplan-Meier curve comparing overall survival in patients who received routine follow-up imaging versus a non-standardized, symptomatic follow-up.

TABLE 1. Pooled Cox-proportional Hazard Analysis After Multiple Imputation to Select Variables for Propensity-score Matching That are Related to Overall Survival in Patients With Recurrence of PDAC

	HR	95% CI	*P*-value
Sex (male vs female)	1.08	0.92–1.27	0.353
CACI (≥4 vs <4)	1.08	0.91–1.28	0.360
Neoadjuvant therapy			
FOLFIRINOX chemotherapy versus none	0.90	0.54–1.48	0.667
Gemcitabine chemo (radio)therapy versus none	1.59	0.94–2.71	0.086
Preoperative serum CA 19-9 (continuous)	1.00	0.99–1.01	0.276
Location tumor (body/tail vs head)	1.08	0.85–1.38	0.527
Vascular resection (yes vs no)	1.16	0.95–1.43	0.141
Tumor size in cm (continuous)	0.99	0.94–1.06	0.923
Tumor differentiation (poor vs well/moderate)	1.17	0.95–1.44	0.140
Microscopic lymphovascular invasion (yes vs no)	1.15	0.89–1.49	0.295
Microscopic perineural invasion (yes vs no)	1.21	0.78–1.87	0.405
Lymph node ratio (>0.2 vs ≤0.2)	**1.27**	**1.05–1.54**	**0.018**
Resection margin status (R1 vs R0)	1.12	0.94–1.35	0.207
Major postoperative complications (yes vs no)	1.02	0.82–1.26	0.863
Adjuvant chemotherapy (yes vs no)	**0.77**	**0.62–0.95**	**0.021**
Disease-free survival* **(≥12 months vs <12 months)**	**0.11**	**0.09–0.14**	**<0.001**
Recurrence location			
Liver-only vs local-only	1.24	0.83–1.84	0.303
Lung-only vs local-only	0.59	0.35–1.00	0.055
Multiple-site vs local-only	**1.61**	**1.17–2.20**	**0.009**
Other isolated distal site vs local-only	1.72	0.91–3.24	0.121
Routine follow-up imaging (yes vs no)	**0.52**	**0.37–0.73**	**<0.001**

*Disease-free survival was measured from the date of primary resection until the date of recurrence diagnosis.

CA 19-9 indicates carbohydrate antigen 19-9; CACI, Charlson age-comorbidity index; CI, confidence interval; HR, hazard ratio; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, oxaliplatin; PDAC, pancreatic ductal adenocarcinoma.

Bold indicates statistical significance.

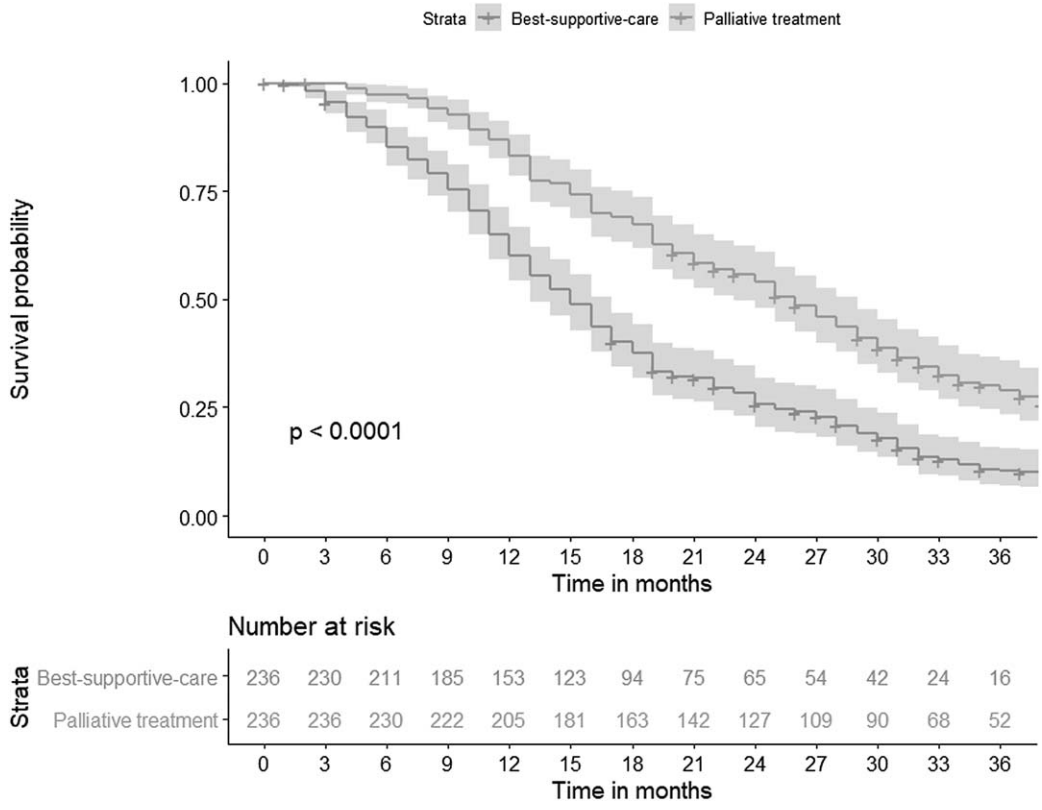

FIGURE 2. Kaplan-Meier curve after propensity-score matching comparing overall survival in patients who received additional treatment versus best-supportive-care.

patients receiving additional treatment, potentially improving survival outcomes.

Our study provides the best available evidence with regard to the impact of different surveillance and treatment strategies, using propensity-score matching and multivariable regression analysis to adjust for potential confounders. Similar to our study, Tzeng et al found that patients with asymptomatic PDAC recurrence were treated more often, and that additional chemotherapy and radiation therapy were associated with a longer post-recurrence survival.[16] Nordby et al and Tjaden et al also reported on the importance of the detection of asymptomatic PDAC recurrence, which might facilitate patients' eligibility for additional treatment potentially improving prognosis.[14,15] In these small, single-center studies, however, all patients received standardized follow-up imaging at a 3–6 monthly interval. Consequently, the additional value of routine follow-up imaging for the detection of asymptomatic recurrence could not be evaluated. A single-center study of Groot et al showed that with a follow-up waiting for clinical symptoms, without routine imaging, PDAC recurrence was mostly diagnosed at a late stage.[36] This potentially limits patients to undergo additional treatment for

TABLE 2. Stratified Survival Analyses for Patients With Symptomatic and Asymptomatic PDAC Recurrence

	Symptomatic Recurrence			Asymptomatic Recurrence		
	Total	**Additional Treatment**	**BSC**	**Total**	**Additional Treatment**	**BSC**
Number of patients (%)	511 (76)	159 (31)*	352 (69)	159 (24)	77 (48)*	82 (52)
Disease-free survival in months, median (95% CI)	10 (9–11)†	12 (11–14)	8 (8–9)	10 (8–11)†	10 (8–14)	9 (7–11)
Overall survival in months, median (95% CI)	15 (13–16)‡	25 (21–29)	12 (11–13)	20 (16–25)‡	26 (22–32)	14 (13–18)
Hazard ratio (95% CI); *P*-value§	0.530 (0.420–0.670); <0.001			0.446 (0.285–0.698); <0.001		

*Chi-square: $P < 0.001$.
†Kaplan-Meier: $P = 0.810$.
‡Kaplan-Meier: $P < 0.001$.
§Cox-proportional hazard analysis after propensity-score matching comparing overall survival between patients who underwent additional treatment and patients who received best-supportive-care, adjusted for sex, neoadjuvant therapy, preoperative serum CA 19-9, tumor size, tumor differentiation, resection margin status, microscopic perineural invasion, and microscopic lymphovascular invasion.
BSC indicates best supportive care; CI, confidence interval; PDAC, pancreatic ductal adenocarcinoma.

recurrence. Just one small, retrospective study investigated the direct impact of imaging surveillance after PDAC resection on survival. In line with our findings, this study found that routine imaging surveillance was associated with prolonged OS in a multivariable model.[17]

A cost-effectiveness analysis of surveillance strategies, however, found that limited surveillance every 6 months was the most cost-effective.[37] This proposed strategy consisted of clinical evaluation and serum CA 19-9 testing every 6 months and imaging in case of symptoms, clinical findings or CA 19-9 elevation. Nevertheless, this study was performed before the introduction of more effective and individualized therapies, such as FOLFIRINOX and gemcitabine with nab-paclitaxel. Therefore, novel analyses of the cost-effectiveness or, more importantly, cost-utility of an increased frequency and intensity of postoperative surveillance for patients after PDAC resection are warranted. Furthermore, two previous studies that focused on the impact of standardized imaging surveillance on quality of life suggested indirect quality of life benefits of standardized surveillance. These studies showed that standardized surveillance contributes to the induction or modification of oncological and symptom-directed treatment, including relevant burdens as exocrine and endocrine pancreas insufficiency.[14,21]

Several studies suggest that PDAC recurrence has a highly heterogeneous biological behavior and that recurrence location and timing can reflect tumor aggressiveness.[5,38,39] Hence, it might be possible that the prolonged survival in asymptomatic patients, as found in our study, is a result of a more favorable tumor biology. However, stratification of survival analyses showed no significant difference in DFS between patients with asymptomatic and symptomatic PDAC recurrence. Therefore, it seems unlikely that in patients with symptomatic recurrence, aggressive tumor biology alone accounts for decreased survival. More likely, patients with asymptomatic PDAC recurrence have a more favorable Eastern Cooperative Oncology Group (ECOG) performance state at time of recurrence diagnosis, which is known to be one of the most important predictors for survival.[40] In our cohort, asymptomatic patients had a mean ECOG performance score of 1.9 ± 0.7 at recurrence diagnosis as compared with a mean ECOG score of 2.3 ± 0.9 in symptomatic patients ($P < 0.001$). This could increase the eligibility for treatment in asymptomatic recurrence, thereby improving survival in these patients.

Survival benefits in patients with asymptomatic PDAC recurrence, however, do not necessarily reflect survival benefits of recurrence-focused surveillance. Patients receiving standardized imaging surveillance may still develop symptomatic PDAC recurrence between surveillance intervals. Of the 88 patients in our cohort who received standardized follow-up imaging, 43 patients (49%) had symptomatic PDAC recurrence and 45 patients (51%) had asymptomatic recurrences. Therefore, the true value of recurrence-focused follow-up has yet to be established. Moreover, patients who are willing to receive standardized surveillance and additional treatment in case of disease recurrence might reflect a different patient group with a more favorable prognosis. In our cohort, 64/88 patients (73%) receiving routine follow-up imaging were included in clinical studies with a study-specific follow-up. This might have affected the prognosis of patients in the routine follow-up imaging group. Of these 64 patients, only 24 patients received protocol-related treatment. Survival analysis after excluding these patients still showed a significant survival benefit for patients that received imaging surveillance. Consequently, study-related treatment was not expected to be responsible for the assessed survival benefit of routine imaging.

This study has several limitations. First, although a prospective database was used for baseline and perioperative data, data on follow-up and recurrence treatment were collected retrospectively. This might have led to different types of bias, such as confounding by indication. In this context, it might be possible that patients who received follow-up imaging and additional treatment for recurrence had a better *a priori* prognosis. Moreover, not all patients received standardized follow-up imaging, and the intervals and frequency of standardized follow-up imaging varied between patients. Consequently, only selected patients had the potential to be diagnosed with PDAC recurrence in an asymptomatic stage. This was mainly the case for patients participating in specific clinical trials, who accordingly received a study-specific, standardized follow-up. Survival benefits of additional treatment for recurrence as shown in this study could be subjected to guarantee-time bias. To adjust for these potential biases, we performed propensity-score matching. As a result, the probability to receive additional treatment for recurrence was comparable in both the treatment and best-supportive-care groups. Unfortunately, we were not able to include the ECOG performance score at time of recurrence diagnosis for propensity-score matching, due to the considerable number of missing data (48%). To avoid potential lead-time bias when reporting on post-recurrence survival, the main outcome of the study was OS, calculated from the date of primary resection. As shown in our results, however, DFS was comparable between symptomatic and asymptomatic patients and lead-time bias seems unlikely. Second, not all patients in whom PDAC recurrence was detected through abdominal imaging received additional imaging of the thorax to screen for pulmonary metastases. This should be taken into account when interpreting the distribution of the specific recurrence-sites within the study population.

In conclusion, the results of this nationwide, multicenter observational cohort study show that treatment of PDAC recurrence is associated with improved survival, with asymptomatic patients having a higher probability to receive recurrence treatment. This suggests that recurrence-focused surveillance, aiming to detect disease recurrence before the onset of symptoms, might increase the number of patients receiving additional treatment, with potential survival benefits. The optimal timing for treatment of recurrence, however, remains unclear. To guide future surveillance recommendations and to enable selection of patients who might benefit of recurrence-focused follow-up the most, a prospective intervention study is needed.

REFERENCES

1. Latenstein AEJ, van der Geest LGM, Bonsing BA, et al., Dutch Pancreatic Cancer Group. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. *Eur J Cancer*. 2020;125:83–93.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7–30.
3. Paniccia A, Hosokawa P, Henderson W, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. *JAMA Surg*. 2015;150:701–710.
4. Jones RP, Psarelli EE, Jackson R, et al., European Study Group for Pancreatic Cancer. Patterns of Recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. *JAMA Surg*. 2019;154:1038–1048.
5. Groot VP, Rezaee N, Wu W, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. *Ann Surg*. 2018;267:936–945.
6. Tanaka M, Mihaljevic AL, Probst P, et al. Meta-analysis of recurrence pattern after resection for pancreatic cancer. *Br J Surg*. 2019;106:1590–1601.
7. Groot VP, Blair AB, Gemenetzis G, et al. Recurrence after neoadjuvant therapy and resection of borderline resectable and locally advanced pancreatic cancer. *Eur J Surg Oncol*. 2019;45:1674–1683.
8. Conroy T, Hammel P, Hebbar M, et al., Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379:2395–2406.
9. Ryan JF, Groot VP, Rosati LM, et al. Stereotactic body radiation therapy for isolated local recurrence after surgical resection of pancreatic ductal adenocarcinoma appears to be safe and effective. *Ann Surg Oncol*. 2018;25:280–289.

10. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. *HPB (Oxford)*. 2017;19:83–92.
11. Conroy T, Desseigne F, Ychou M, et al., Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–1825.
12. Sperti C, Moletta L, Merigliano S. Multimodality treatment of recurrent pancreatic cancer: mith or reality? *World J Gastrointest Oncol*. 2015; 7:375–382.
13. Daamen LA, Groot VP, Intven MPW, et al. Postoperative surveillance of pancreatic cancer patients. *Eur J Surg Oncol*. 2019;45:1770–1777.
14. Tjaden C, Michalski CW, Strobel O, et al. Clinical impact of structured follow-up after pancreatic surgery. *Pancreas*. 2016;45:895–899.
15. Nordby T, Hugenschmidt H, Fagerland MW, et al. Follow-up after curative surgery for pancreatic ductal adenocarcinoma: asymptomatic recurrence is associated with improved survival. *Eur J Surg Oncol*. 2013;39:559–566.
16. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. *HPB (Oxford)*. 2012;14:365–372.
17. Elmi A, Murphy J, Hedgire S, et al. Post-Whipple imaging in patients with pancreatic ductal adenocarcinoma: association with overall survival: a multivariate analysis. *Abdom Radiol*. 2017;42:2101–2107.
18. Neuzillet C, Gaujoux S, Williet N, et al. Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC). *Dig Liver Dis*. 2018;50:1257–1271.
19. National Comprehensive Cancer Network. Pancreatic Adenocarcinoma (Version 2. 2018–July 10, 2018). Available at: https://www2.tri-kobe.org/nccn/guideline/pancreas/english/pancreatic.pdf#page=16. Accessed March 11, 2019.
20. Yamaguchi K, Okusaka T, Shimizu K, et al. EBM-based clinical guidelines for pancreatic cancer (2013) issued by the Japan Pancreas Society: a synopsis. *Jpn J Clin Oncol*. 2014;44:883–888.
21. Deimling GT, Bowman KF, Sterns S, et al. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psychooncology*. 2006;15:306–320.
22. Deobald RG, Cheng ES, Ko YJ, et al. A qualitative study of patient and clinician attitudes regarding surveillance after a resection of pancreatic and peri-ampullary cancer. *HPB (Oxford)*. 2015;17:409–415.
23. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology Clinical Practice guideline update. *J Clin Oncol*. 2017;35:2324–2328.
24. Nederlandse Vereniging voor Heelkunde. Landelijke richtlijn pancreascarcinoom. Available at: http://www.dpcg.nl/images/Richtlijn_Pancreascarcinoom_2019.pdf. Accessed June 4, 2019.
25. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v56–v68.
26. Takaori K, Bassi C, Biankin A, et al. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. *Pancreatology*. 2016;16:14–27.
27. O'Reilly D, Fou L, Hasler E, et al. Diagnosis and management of pancreatic cancer in adults: a summary of guidelines from the UK National Institute for Health and Care Excellence. *Pancreatology*. 2018;18:962–970.
28. Dutch Pancreatic Cancer Audit (DPCA). Available via: http://www.dica.nl/dpca. Accessed June 4, 2019.
29. Groot VP, Daamen LA, Hagendoorn J, et al. Current strategies for detection and treatment of recurrence of pancreatic ductal adenocarcinoma after resection: a nationwide survey. *Pancreas*. 2017;46:e73–e75.
30. Walker G. Charlson Comorbidity Index (CCI) Calculator. MdCALC. Available at: https://www.mdcalc.com/charlson-comorbidity-index-cci. Accessed July 11, 2019.
31. Edge S, Byrd DR, Compton CC, et al., eds. *American Joint Committee on Cancer Staging Manual*. 7th ed., New York: Springer; 2010.
32. Donders AR, van der Heijden GJ, Stijnen T, et al. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59:1087–1091.
33. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163:1149–1156.
34. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. *Biometrics*. 1996;52:249–264.
35. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
36. Groot VP, Daamen LA, Hagendoorn J, et al. Use of imaging during symptomatic follow-up after resection of pancreatic ductal adenocarcinoma. *J Surg Res*. 2018;221:152–160.
37. Tzeng CW, Abbott DE, Cantor SB, et al. Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis. *Ann Surg Oncol*. 2013;20:2197–2203.
38. Groot VP, Gemenetzis G, Blair AB, et al. Defining and predicting early recurrence in 957 patients with resected pancreatic ductal adenocarcinoma. *Ann Surg*. 2019;269:1154–1162.
39. Groot VP, Gemenetzis G, Blair AB, et al. Implications of the pattern of disease recurrence on survival following pancreatectomy for pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2018;25:2475–2483.
40. Maltoni M, Caraceni A, Brunelli C, et al., S; Steering Committee of the European Association for Palliative Care. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations–a study by the Steering Committee of the European Association for Palliative Care. *J Clin Oncol*. 2005;23:6240–6248.