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Real-world evidence of adjuvant gemcitabine plus capecitabine vs gemcitabine monotherapy for pancreatic ductal adenocarcinoma

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Abstract

The added value of capecitabine to adjuvant gemcitabine monotherapy (GEM) in pancreatic ductal adenocarcinoma (PDAC) was shown by the ESPAC-4 trial. Real-world data on the effectiveness of gemcitabine plus capecitabine (GEMCAP), in patients ineligible for mFOLFIRINOX, are lacking. Our study assessed whether adjuvant GEMCAP is superior to GEM in a nationwide cohort. Patients treated with adjuvant GEMCAP or GEM after resection of PDAC without preoperative treatment were identified from The Netherlands Cancer Registry (2015-2019). The primary outcome was overall survival

Abbreviations: CI, confidence interval; GEM, gemcitabine monotherapy; GEMCAP, gemcitabine plus capecitabine; HR, hazard ratio; IQR, interquartile range; mFOLFIRINOX, modified combination of 5-fluorouracil, irinotecan, oxaliplatin and folinic acid; NCR, Netherlands Cancer Registry; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; UICC, Union for International Cancer Control/Union International contre le cancer.

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the design of the study or the collection, analysis and interpretation of data. The authors are solely responsible for the content of the study and do not necessarily represent the viewpoint of the Dutch Cancer Society or ZonMw.

(OS), measured from start of chemotherapy. The treatment effect of GEMCAP vs GEM was adjusted for sex, age, performance status, tumor size, lymph node involvement, resection margin and tumor differentiation in a multivariable Cox regression analysis. Secondary outcome was the percentage of patients who completed the planned six adjuvant treatment cycles. Overall, 778 patients were included, of whom 21.1% received GEMCAP and 78.9% received GEM. The median OS was 31.4 months (95% CI 26.8-40.7) for GEMCAP and 22.1 months (95% CI 20.6-25.0) for GEM (HR: 0.71, 95% CI 0.56-0.90; logrank $P = .004$). After adjustment for prognostic factors, survival remained superior for patients treated with GEMCAP (HR: 0.73, 95% CI 0.57-0.92, logrank $P = .009$). Survival with GEMCAP was superior to GEM in most subgroups of prognostic factors. Adjuvant chemotherapy was completed in 69.5% of the patients treated with GEMCAP and 62.7% with GEM ($P = .11$). In this nationwide cohort of patients with PDAC, adjuvant GEMCAP was associated with superior survival as compared to GEM monotherapy and number of cycles was similar.

KEYWORDS

chemotherapy, pancreatic cancer, survival

What's new?

The benefit of treating pancreatic ductal adenocarcinoma (PDAC) with a combination of gemcitabine plus capecitabine (vs gemcitabine alone) was previously shown in a carefully controlled clinical trial. But does this approach work as well in the real world? In this study, the authors found that the answer is yes—patients had significantly better overall survival (OS) with the combined therapy than with gemcitabine alone. These results may aid in the selection of adjuvant chemotherapy for patients who are not eligible for modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin).

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a common cause of cancer-related mortality among men and women worldwide, with a 5-year overall survival (OS) of only 3%.[1,2] At time of diagnosis, the majority of the patients present with locally advanced or metastatic disease.[3] Only one-fifth of the patients is able to undergo resection.[2,4] However, resection alone does not overcome the risk of local or distant recurrent disease in the majority of patients.[5]

A beneficial effect of adjuvant chemotherapy on the risk of recurrence and OS in PDAC was first shown by Oettle et al in 2007.[6] Ever since, several randomized controlled trials have studied the efficacy of various adjuvant chemotherapeutics in patients with PDAC who underwent resection.[7-11] For many years, gemcitabine monotherapy (GEM) has been the preferred adjuvant treatment in Western countries.[12,13] Based on promising results in the metastatic setting, the use of combination therapies has emerged.[14-17] In 2017, the ESPAC-4 trial compared adjuvant gemcitabine plus capecitabine (GEMCAP) with GEM alone.[10] The median OS for patients treated with GEMCAP was 28.0 months compared to 25.5 months for patients treated with GEM (hazard ratio [HR]: 0.82, 95% confidence interval [CI] 0.68-0.98, $P = .032$) with an acceptable level of treatment-related adverse events. The secondary analysis and long-term results confirmed the survival benefit as well as the decreased risk of developing local recurrence with GEMCAP treatment.[18,19] In 2018, Conroy et al showed the longest estimated survival thus far, with a median OS of 54.4 months in patients receiving adjuvant modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) compared to 35.0 months with GEM (HR: 0.64, 95% CI 0.48-86, $P = .003$).[11] This evident survival advantage came at the cost of increased chemotherapy-related adverse events in patients treated with modified FOLFIRINOX (mFOLFIRINOX). As a consequence, international guidelines recommend adjuvant mFOLFIRINOX only in patients with a good performance status.[12,20-22] In patients with impaired performance status, both adjuvant GEM and GEMCAP can be offered as alternative treatment. In the Netherlands, GEM was approved as adjuvant therapy in 2008 and recommended in the national guideline published in 2011.[23,24] In the 2019 guideline update, the option GEMCAP was added for patients unfit for mFOLFIRINOX.[20,25]

Evidence on the added value of capecitabine to adjuvant GEM monotherapy in PDAC is limited to the ESPAC-4 trial. Since clinical trial results cannot always be reproduced in real-world setting, our study aimed to assess whether adjuvant GEMCAP is associated with superior OS compared to adjuvant GEM in a Dutch nationwide cohort.

2 | METHODS

2.1 | Data collection

This retrospective study used data from the nationwide Netherlands Cancer Registry (NCR). The NCR is a population-based registry including all patients with a newly diagnosed malignancy in the Netherlands since 1989, notified by the nationwide automated pathological archive (PALGA) and supplemented with the National Registry of Hospital Care (DHD-LBZ). Information on patient and tumor characteristics, treatment and clinical outcomes are routinely extracted from the medical records using standardized definitions by trained administrators of the NCR. Patient characteristics included sex, age, performance status and information on comorbidities according to the Charlson Comorbidity Index.[26] Tumor characteristics included the origin and morphology of the tumor classified according to the International Classification of Diseases for Oncology (ICD-O-3, pp. 69-218), tumor size, number of positive lymph nodes, resection margin status (≥1 mm as R0), tumor differentiation grade, TNM classification and corresponding disease stage.[27,28] For our study, the TNM classification was converted to the 8th edition of the American Joint Committee on Cancer for all patients, using pathological tumor size and number of positive lymph nodes.[29] The definitions of pT1 and pT4 were identical between the 7th and 8th edition, and were therefore used for uniform staging. pT2 and pT3 definitions differed between both editions and thus staging of these tumors was based on tumor size according to the 8th edition. Treatment specifications included type and timing of surgery, number of cycles and type of adjuvant treatment. Clinical outcomes included survival data, which was obtained by annual linkage with the nationwide Municipal Personal Records Database including the vital status of all Dutch inhabitants. Follow-up was completed until 1 February 2021.[30]

2.2 | Study population

For the current study, all patients aged ≥18 years with PDAC (ICD-O C25 excluding C25.4, see Table S1 for morphology codes) diagnosed from 2015 to 2019 who underwent a resection were selected from the NCR. Additional inclusion criteria were treatment with adjuvant GEM monotherapy or adjuvant GEMCAP. All patients who received at least one cycle were included. Exclusion criteria were metastatic (stage IV) disease, a resection with macroscopic residual tumor (R2), and neoadjuvant therapy and adjuvant chemotherapy received outside of the Netherlands.

2.3 | Treatment and outcome measures

The primary endpoint was OS, measured from start of chemotherapy until death from any cause. Patients alive at last follow-up were censored. Secondary endpoints included the annual number and proportion of patients receiving GEMCAP or GEM, the number of adjuvant chemotherapy cycles, the number of patients who switched to other adjuvant chemotherapy and the percentage of patients who completed the planned six adjuvant treatment cycles.

2.4 | Statistical analysis

Clinicopathologic characteristics were summarized for all patients and for GEMCAP and GEM separately. Data were presented as frequencies with proportions for categorical variables and median with interquartile range (IQR) for continuous variables. For categorical variables, the χ^2 test was used to compare the treatment groups as appropriate. For continuous variables, the Wilcoxon rank sum test was used.

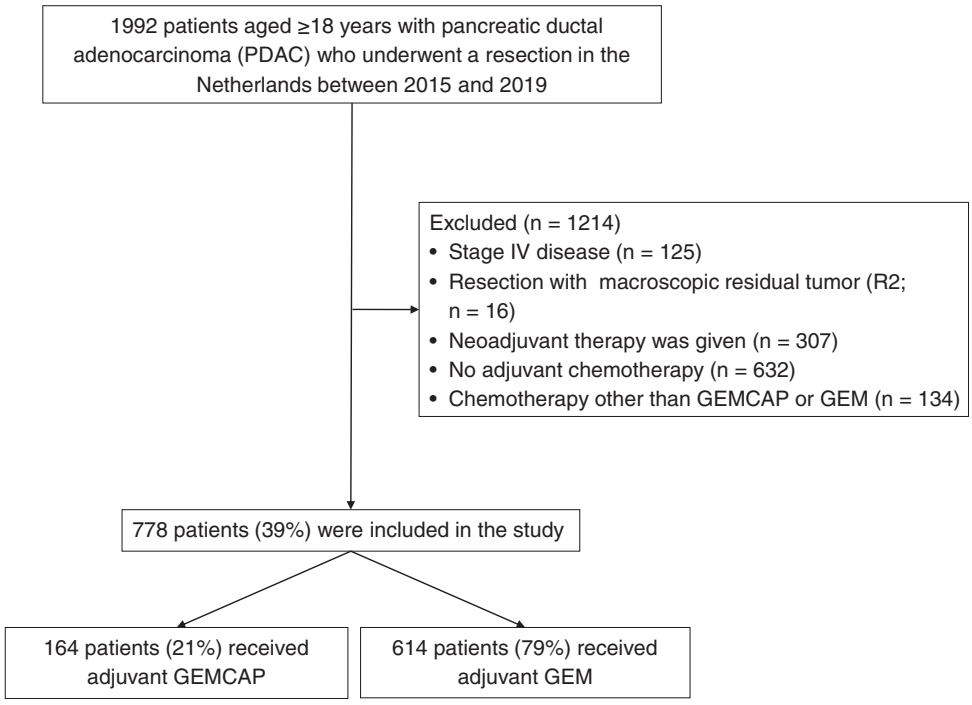

FIGURE 1 Selection of the study population. GEM, gemcitabine monotherapy; GEMCAP, gemcitabine with capecitabine

Median follow-up was calculated with the reverse Kaplan-Meier method. OS was estimated using the Kaplan-Meier method and difference in survival between the two treatment groups was analyzed using the log-rank test. In addition, univariable and multivariable Cox regression analyses were performed to assess the treatment effect expressed as HR with corresponding 95% CI, corrected for known and available prognostic factors (sex, age, WHO performance status, location, pathological tumor size, lymph nodes, resection margin and

TABLE 1 Baseline characteristics

N	Overall 778	GEMCAP 164	GEM 614	*P*-value
Sex, n (%)				.077
Male	420 (54.0)	78 (47.6)	342 (55.7)	
Female	358 (46.0)	86 (52.4)	272 (44.3)	
Age, years (median [IQR])	67.0 [59.0, 72.0]	66.0 [58.0, 71.0]	67.0 [60.0, 72.0]	.118
WHO performance status, n (%)				.455
WHO 0	303 (60.7)	62 (64.7)	241 (59.8)	
WHO 1	161 (32.3)	26 (27.1)	135 (33.5)	
WHO 2-3	35 (7.0)	8 (8.3)	27 (6.7)	
Concurrent conditions, n (%)				.559
None	332 (48.2)	73 (50.7)	259 (47.5)	
Any	357 (51.8)	71 (49.3)	286 (52.5)	
Tumor location, n (%)				.505
Other	148 (19.4)	34 (21.2)	114 (18.9)	
Head	615 (80.6)	126 (78.8)	489 (81.1)	
Type of resection, n (%)				.452
Pancreatectomy	647 (84.6)	127 (83.6)	520 (84.8)	
Body/tail resection	110 (14.4)	22 (14.5)	88 (14.4)	
Total pancreatectomy	8 (1.0)	3 (2.0)	5 (0.8)	
Time to adjuvant chemo (days), (median [IQR])	52.0 [42.0, 64.8]	54.0 [42.0, 71.0]	52.0 [42.2, 64.0]	.332
Pathological tumor stage[a], n (%)				.889
I	134 (22.5)	38 (23.9)	96 (22.0)	
II	244 (41.0)	64 (40.3)	180 (41.3)	
III	217 (36.5)	57 (35.8)	160 (36.7)	
Pathological tumor size, n (%)				.156
<30 mm	245 (42.0)	75 (47.2)	170 (40.1)	
≥30 mm	338 (58.0)	84 (52.8)	254 (59.9)	
Lymph nodes, n (%)				.912
Negative	199 (25.6)	43 (26.2)	156 (25.4)	
Positive	579 (74.4)	121 (73.8)	458 (74.6)	
Resection margin[b], n (%)				.054
R0	424 (55.9)	74 (48.7)	350 (57.8)	
R1	334 (44.1)	78 (51.3)	256 (42.2)	
Tumor differentiation, n (%)				.086
Well	93 (13.9)	24 (16.9)	69 (13.1)	
Moderate	408 (61.0)	92 (64.8)	316 (60.0)	
Poor/undifferentiated	168 (25.1)	26 (18.3)	142 (26.9)	

Note: Percentage of missing data (overall/GEMCAP/GEM): sex (0%/0%/0%), age (0%/0%/0%), WHO performance status (36%/41%/34%), concurrent conditions (11%/24%/11%), location (2%/2%/2%), type of resection (2%/7%/0%), time to adjuvant chemo (0%/0%/0%), pathological tumor stage (24%/3%/29%), pathological tumor size (27%/1%/3%), lymph nodes (0%/0%/0%), resection margin (3%/7%/1%) and tumor differentiation (14%/13%/14%).

Abbreviations: GEM, gemcitabine; GEMCAP, gemcitabine with capecitabine; IQR, interquartile range; WHO, World Health Organization.

[a]Tumor stage according to AJCC 8th edition.

[b]1 mm definition of Royal College of Pathologists.

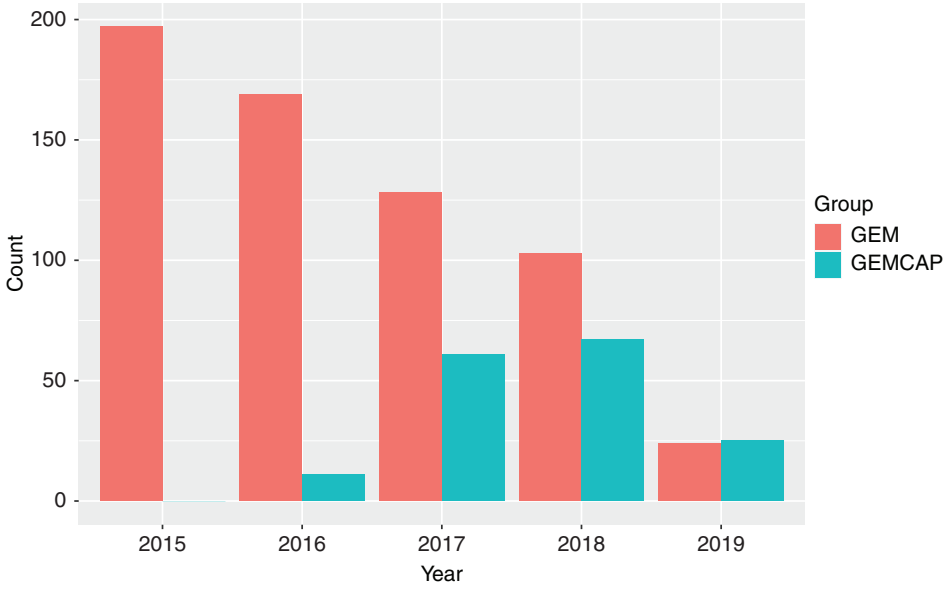

FIGURE 2 Number of patients receiving gemcitabine with capecitabine (GEMCAP) or gemcitabine monotherapy (GEM) over time [Color figure can be viewed at wileyonlinelibrary.com]

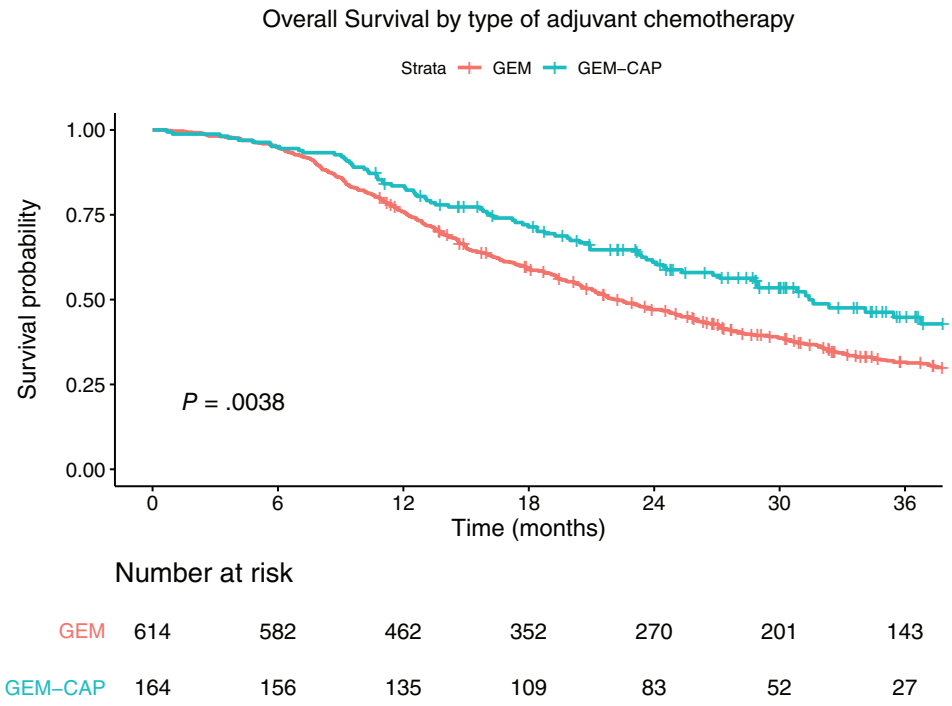

FIGURE 3 Overall survival, by type of adjuvant chemotherapy. Hazard ratio for death: 0.71 (95% CI: 0.56-0.90), log-rank $P = .0038$*. GEM, gemcitabine monotherapy; GEMCAP, gemcitabine with capecitabin [Color figure can be viewed at wileyonlinelibrary.com]

tumor differentiation). Multiple imputation of missing data was performed using 25 imputed datasets with variable estimates obtained with the use of Rubin's rules. Imputation was performed for WHO performance status (n = 279), tumor size (n = 213), resection margin (n = 20) and tumor differentiation (n = 109). The proportional hazards assumption was assessed by visualization of Schoenfeld residuals and the log(−log[survival]) vs log of survival time graph. The proportional hazards assumption was not violated for any of the included variables. Results of the Cox regression analyses were presented as HR with 95% CI. Furthermore, the treatment effect of GEMCAP vs GEM was assessed in prespecified subgroups using a Cox regression model with subgroups based on sex, age, WHO performance status, comorbidities, tumor location, stage, pathological tumor size, lymph nodes, resection margin and tumor differentiation. Interaction was tested by adding the interaction term in the model with the *P*-value of the interaction term as indicator of possible interaction. The χ^2 test was used to compare the proportion of patients who completed at least six cycles of adjuvant chemotherapy and the proportion of patients who received three or less cycles of adjuvant chemotherapy between the two treatment groups. All tests were two-sided and values <.05 were considered statistically significant. All analyses were performed using R software, version 3.4.3.

3 | RESULTS

The NCR database contained data on 1992 patients who underwent resection for PDAC in the period 2015 to 2019. After applying the prespecified eligibility criteria, 778 patients were included, of whom 164 (21.1%) received adjuvant GEMCAP and 614 (78.9%) received adjuvant GEM (Figure 1). Fifty-four percent of the patients were male, the median age was 67 years (IQR 59-72) and 60.7% of the patients had WHO performance status 0 (Table 1). Most patients were diagnosed at stage II (41.0%), followed by stage III (36.5%) and stage I (22.5%). No statistically significant differences in characteristics were seen between treatment groups. Median time (IQR) from resection to start of adjuvant chemotherapy was 54.0 days (42.0-71.0) for patients treated with GEMCAP and 52.0 days (42.2-64.0) for patients treated with GEM ($P = .332$).

The number of patients receiving GEM decreased and the administration of GEMCAP increased from 2015 to 2018, although the absolute number of patients receiving GEMCAP decreased in 2019 (Figure 2).

3.1 | Overall survival

The median follow-up time for patients alive at last follow-up was 33.5 months for patients treated with GEMCAP and 50.8 months for patients treated with GEM. Median OS for patients treated with

TABLE 2 Univariable and multivariable cox regression analysis of overall survival

		Univariable analysis		Multivariable analysis	
Number of patients		**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Treatment					
GEM	614	1 [Reference]	1	1 [Reference]	1
GEMCAP	164	0.71 (0.56-0.90)	.004[a]	0.73 (0.58-0.93)	.010[a]
Sex					
Male	420	1 [Reference]	1	1 [Reference]	1
Female	358	0.97 (0.82-1.16)	.767	0.98 (0.82-1.17)	.810
Age					
<65 years	310	1 [Reference]	1	1 [Reference]	1
≥65 years	468	0.96 (0.79-1.16)	.656	0.94 (0.79-1.13)	.538
Performance status					
WHO 0	303	1 [Reference]	1	1 [Reference]	1
WHO 1	161	1.18 (0.95-1.46)	.179	1.08 (0.87-1.35)	.486
WHO 2-3	35	0.93 (0.58-1.50)	.934	0.93 (0.58-1.49)	.754
Tumor location					
Other	148	1 [Reference]	1	1 [Reference]	1
Head	615	1.29 (1.03-1.62)	.029[a]	1.25 (0.99-1.58)	.062
Pathological tumor size					
<30 mm	245	1 [Reference]	1	1 [Reference]	1
≥30 mm	338	1.70 (1.39-2.09)	<.001[a]	1.54 (1.26-1.89)	<.001[a]
Lymph nodes					
Negative	199	1 [Reference]	1	1 [Reference]	1
Positive	579	1.83 (1.48-2.27)	<.001[a]	1.56 (1.25-1.94)	<.001[a]
Resection margin					
R0	424	1 [Reference]	1	1 [Reference]	1
R1	334	1.44 (1.21-1.71)	<.001[a]	1.38 (1.15-1.65)	<.001[a]
Tumor differentiation					
Well	93	1 [Reference]	1	1 [Reference]	1
Moderate	408	1.57 (1.17-2.10)	.003[a]	1.50 (1.11-2.03)	.008[a]
Poor/undifferentiated	168	2.35 (1.72-3.21)	<.001[a]	2.12 (1.54-2.93)	<.001[a]

Note: Imputation of missing data: sex (0%), age (0%), WHO performance status (36%), location (2%), pathological tumor size (27%), lymph nodes (0%), resection margin (3%) and tumor differentiation (14%).

Abbreviations: CI, confidence interval; GEM, gemcitabine; GEMCAP, gemcitabine with capecitabine; HR, hazard ratio; WHO, World Health Organization.

[a]$P < .05$.

GEMCAP was 31.4 months (95% CI 26.8-40.7) compared to 22.1 months (95% CI 20.6-25.0) for patients treated with GEM (unadjusted HR: 0.71, 95% CI 0.56-0.90, $P = .004$; Figure 3).

Univariable analyses showed that besides treatment, the location of the primary tumor, tumor size, lymph node involvement, resection margin and tumor differentiation were all associated with OS (Table 2). Independent predictors of survival were tumor size, lymph node involvement, resection margin, tumor differentiation and treatment (GEM vs GEMCAP; HR: 0.73, 95% CI 0.58-0.93, $P = .010$).

Subgroup analyses demonstrated comparable or superior survival with adjuvant GEMCAP in almost all subgroups (Figure 4). A significant interaction was found between tumor location and treatment ($P = .02$), with a significant benefit of GEMCAP in patients with a tumor located in the pancreatic head (HR: 0.65, 95% CI 0.50-0.85, $P = .002$), but no significant benefit of GEMCAP in patients with a tumor located outside of the pancreatic head (HR: 1.22, 95% CI 0.74-2.01, $P = .44$). The positive effect of GEMCAP on OS was found in both patients with a positive resection margin (HR: 0.70, 95% CI 0.51-0.97, $P = .034$) and patients with a negative resection margin (HR: 0.67, 95% CI 0.47-0.96, $P = .029$).

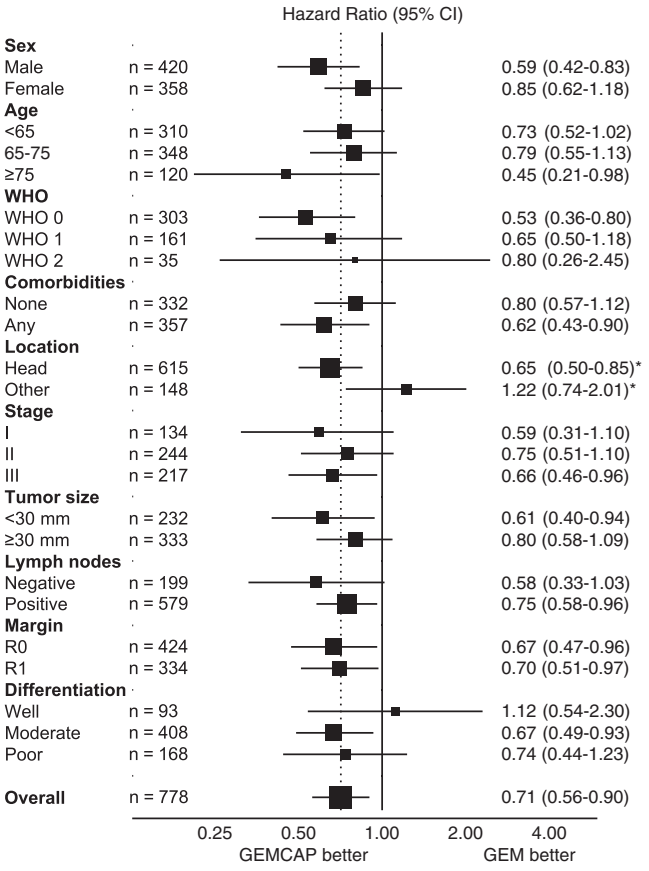

FIGURE 4 Forest plot of the treatment effect on overall survival in prespecified subgroups. *Significant interaction term of tumor location with adjuvant chemotherapy in unadjusted multivariable model including tumor location and adjuvant chemotherapy, $P = .02$

3.2 | Therapy

The proportion of patients completing six cycles of adjuvant chemotherapy was 69.5% in the GEMCAP group and 62.7% in the GEM group ($P = .11$; Table 3). The proportion of patients receiving three or less cycles was 14.7% in the GEMCAP group and 21.4% in the GEM group ($P = .06$).

Of the patients treated with GEMCAP, one patient switched to capecitabine monotherapy and five patients to GEM. Of the patients in the GEM group, one patient switched to GEMCAP, one patient to 5-FU and irinotecan and four patients to capecitabine monotherapy as subsequent adjuvant therapy. One patient received tegafur/gimeracil/oteracil as third therapy after both gemcitabine and capecitabine monotherapy.

4 | DISCUSSION

In this first nationwide study to compare adjuvant GEMCAP with adjuvant GEM in PDAC in daily clinical practice, adjuvant chemotherapy with GEMCAP was associated with a significantly prolonged OS compared to GEM monotherapy (median OS GEMCAP vs GEM: 31.4 vs 22.1 months; HR: 0.71, 95% CI 0.56-0.90, $P = .004$). This survival benefit persisted after adjustment for known prognostic factors in a

TABLE 3 Number of completed chemotherapy cycles in patients treated with gemcitabine with capecitabine (GEMCAP) or gemcitabine (GEM)

Number of cycles (%)[a]	Overall (n = 778)	GEMCAP (n = 164)	GEM (n = 614)
>6	17 (2.2)	3 (1.8)	14 (2.3)
6	482 (62.0)	111 (67.7)	371 (60.4)
5	67 (8.6)	14 (8.5)	53 (8.6)
4	45 (5.8)	6 (3.7)	39 (6.4)
3	63 (8.1)	12 (7.3)	51 (8.3)
2	42 (5.4)	6 (3.7)	36 (5.9)
1	50 (6.4)	6 (3.7)	44 (7.2)
Unknown	12 (1.5)	6 (3.7)	6 (1.0)

[a]The proportion of patients who completed at least six chemotherapy cycles ($P = .11$) and the proportion of patients who received three or less chemotherapy cycles ($P = .06$) did not significantly differ between the two treatment groups.

multivariable Cox regression analysis and was consistent across most subgroups. The number of completed chemotherapy cycles was similar in both treatment groups.

The survival benefit for patients treated with GEMCAP compared to GEM corresponds to the positive effect in the ESPAC-4 trial (median OS 28.0 vs 25.5 months; HR: 0.82, 95% CI 0.68-0.98, $P = .032$).[10] Our study thereby confirms the findings of the ESPAC-4 trial in an unselected nationwide cohort. The superiority of GEMCAP on OS in our study appears to be even greater when compared to the ESPAC-4 study. However, differences in patient characteristics may explain the large difference to some extent. Both the present study and the ESPAC-4 trial excluded patients treated with neoadjuvant therapy and patients who underwent R2 resections. The ESPAC-4 trial also excluded patients with a poor performance status (WHO ≥ 2), while the present study included 7% of patients with WHO 2.[10] Several baseline characteristics in the ESPAC-4 trial were worse than in this nationwide cohort; for example, co-morbidity, R1 resection rate and nodal disease. Nonetheless, these differences existed in both treatment groups, thus this cannot explain the larger treatment effect of GEMCAP found in the current study. A possible explanation for the larger survival benefit of GEMCAP compared to the ESPAC-4 trial is that our patients were not randomized, with subsequent risk of confounding by indication. Although our study showed no difference in baseline characteristics between GEMCAP and GEM and the benefit remained after adjustment for relevant prognostic factors, the possible influence of residual confounding increasing the effect cannot be completely ruled out. Of note, the proportion of patients with pancreatic cancer who are eligible for both surgery and adjuvant therapy is limited. The findings therefore apply to only this subset of patients. However, our patient selection is less restrictive than in clinical trials on adjuvant chemotherapy.

The median OS of patients treated with GEM in our study (22.1 months) and in the ESPAC-4 trial (25.5 months) was lower than the median OS with GEM found in both the PRODIGE 24 trial (35.5 months) and the APACT trial (36.2 months, abstract available only).[11] This might be attributed to the more stringent selection criteria in these randomized studies, including only patients with a good performance status (WHO score 0-1) and with a serum carbohydrate antigen (CA) 19-9 level below 180 U/mL (PRODIGE) or below 100 U/mL (APACT). No criteria on CA 19-9 level was used in either the ESPAC-4 trial and the current study. Another explanation could be a difference in receipt of palliative treatment in case of disease recurrence. This data is unknown for the current study. However, a previous Dutch nationwide study among PDAC patients who underwent resection showed that only 31% of the patients with symptomatic recurrence and 48% of the patients with asymptomatic recurrence received palliative treatment.[31] Due to these inequalities between randomized studies, it is difficult to make a direct comparison between the intervention arms of different randomized studies (eg, GEMCAP, mFOLFIRINOX and nab-paclitaxel plus gemcitabine). Randomized trials with direct comparisons are required to assess which of these contemporary multiagent chemotherapy regimens shows the most favorable results.

We found that treatment with GEMCAP was associated with better OS than GEM alone, for patients with a positive and negative resection margin. This is in contrast with the ESPAC-4 trial, in which the survival benefit of GEMCAP was only demonstrated in patients with a negative resection margin.[10] Both international and national guidelines do not distinguish between patients with positive and patients with negative resection margins.[20,21] Our study confirms that the choice of therapy should not depend on resection margin status. Furthermore, GEMCAP seems to result in a larger survival benefit compared to GEM in patients with a better performance status compared to patients with a poorer performance status. However, only a limited number of patients with a poor performance status (WHO = 2) were included in our study. The interpretation of the impact of performance status on the found survival benefit is therefore hampered.

The addition of capecitabine to gemcitabine does not seem to result in less cycles of gemcitabine. The proportion of patients receiving a minimum of six cycles was similar in the GEMCAP group (69%) compared to the GEM group (62%). Adverse events and dose intensities were not available for our study population, but the ESPAC-4 trial observed no differences in reported adverse events between both treatment groups (26% vs 25%, $P > .05$).[10] In addition, a randomized trial comparing GEMCAP to GEM in patients with locally advanced PDAC showed acceptable levels of toxicity for both treatment groups.[14]

The use of GEMCAP increased after the results of the ESPAC-4 trial were published in 10 March 2017.[10] The use of GEM alone also decreased over time due to the introduction of adjuvant mFOLFIRINOX. Overall, the number of patients who received adjuvant chemotherapy declined due to the increased use of neoadjuvant strategies in more recent years. The Dutch nationwide PREOPANC-2 study comparing two neoadjuvant strategies for patients with resectable or borderline resectable PDAC was initiated in June 2018, with neoadjuvant treatment precluding eligibility for the current study.[32]

This is the first study comparing adjuvant GEMCAP with adjuvant GEM in resectable PDAC in daily clinical practice. However, some limitations of our study should be taken into account. First, the number of patients receiving GEMCAP was only 164 patients, resulting in wide confidence intervals. Second, data on recurrence, palliative treatment, quality of life and adverse events were not available, thereby precluding additional comparisons such as disease-free survival and toxicity. As a result, we cannot conclude what the impact of both adjuvant chemotherapies is on disease-free survival, how palliative treatment might have affected the OS and what the impact of possible side effects has been. Third, inherent to the retrospective study design, some data (eg, tumor size and WHO performance status) were incomplete, which was addressed by multiple imputation in the multivariable Cox regression analysis. Fourth, although we adjusted for many variables, not all possible prognostic variables (eg, CA 19-9 and smoking) were available, with subsequent risk of residual confounding.[33] Fifth, our study population differs from the current patient population as mFOLFIRINOX was introduced in 2019, which is currently considered the preferred adjuvant treatment for most eligible patients.[20,21] Last, patients who received neoadjuvant therapy

were excluded from our study, thereby limiting the generalizability to this specific population.

To conclude, this nationwide study demonstrated that the GEMCAP is associated with better OS as compared to GEM. The proportion of patients receiving the planned number of six chemotherapy cycles were similar in both treatment groups. Therefore, adjuvant GEMCAP should be preferred over GEM in patients who are not eligible for mFOLFIRINOX.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

The study protocol for the present analysis was approved by the scientific committee of the Dutch Pancreatic Cancer Group.[30]

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REFERENCES

1. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. *World J Oncol*. 2019;10:10-27.
2. Latenstein AEJ, van der Geest LGM, Bonsing BA, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. *Eur J Cancer*. 2020;125:83-93.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.
4. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med*. 2014;371:1039-1049.
5. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. *Cancer*. 1993;72:2118-2123.
6. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297:267-277.
7. Shimoda M, Kubota K, Shimizu T, Katoh M. Randomized clinical trial of adjuvant chemotherapy with S-1 versus gemcitabine after pancreatic cancer resection. *Br J Surg*. 2015;102:746-754.
8. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese study Group of Adjuvant Therapy for pancreatic cancer. *Br J Cancer*. 2009;101:908-915.
9. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388:248-257.
10. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011-1024.
11. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379:2395-2406.
12. 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:v56-v68.
13. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34:2541-2556.
14. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27:5513-5518.
15. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the central European cooperative oncology group. *J Clin Oncol*. 2007;25:2212-2217.
16. von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703.
17. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
18. Neoptolemos JP, Palmer DH, Ghaneh P, et al. ESPAC-4: a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma: five year follow-up. *J Clin Oncol*. 2020;38:4516.
19. Jones RP, Psarelli EE, Jackson R, et al. 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.
20. Pancreascarcinoom. Landelijke richtlijn. Nederlandse Vereniging voor Heelkunde; 2019. https://dpcg.nl/wp-content/uploads/2020/04/Richtlijn_Pancreascarcinoom_2019.pdf
21. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 1. *J Natl Compr Canc Netw*. 2020;15(8):1028-1061.
22. Khorana AA, McKernin SE, Berlin J, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37:2082-2088.
23. Tjan-Heijnen VCG, Willemse PHB, Guchelaar HJ, et al. Herbeoordeling: adjuvante therapie met gemcitabine bij curatief geopereerd pancreascarcinoom. *Med Oncol*. 2008;11:54-55.
24. Pancreascarcinoom. *Landelijke richtlijn, Versie 2.0*. Utrecht: Netherlands Comprehensive Cancer Organisation (IKNL); 2011.
25. Adviezen Commissie BOM. Adjuvant gemcitabine in combinatie met capecitabine bij het gereseceerd pancreascarcinoom. *Med Oncol*. 2017;20:41-44.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
27. Percy C, Holten VV, Muir CS. *International Classification of Diseases for Oncology*. Geneva: World Health Organization; 1990.
28. Campbell F, Foulis A, Verbeke C. *Dataset for the Histopathological Reporting of Carcinomas of the Pancreas, Ampulla of Vater and Common Bile Duct*. London: The Royal College of Pathologists; 2010.
29. Amin MB, Edge SB. Melanoma of the skin. In: Amin AB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. New York: Springer; 2017.
30. Strijker M, Mackay TM, Bonsing BA, et al. Establishing and coordinating a Nationwide multidisciplinary study group: lessons learned by the Dutch pancreatic cancer group. *Ann Surg*. 2020;271:e102-e104.
31. Daamen LA, Groot VP, Besselink MG, et al. Detection, treatment, and survival of pancreatic cancer recurrence in The Netherlands: a Nationwide analysis. *Ann Surg*. 2020. Epub ahead of print.
32. Janssen QP, van Dam JL, Bonsing BA, et al. Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial. *BMC Cancer*. 2021;21:300.
33. Poruk KE, Gay DZ, Brown K, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. *Curr Mol Med*. 2013;13:340-351.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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