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ORIGINAL RESEARCH

Prognostic and predictive value of CA 19-9 in locally advanced pancreatic cancer treated with multiagent induction chemotherapy: results from a prospective, multicenter phase II trial (NEOLAP-AIO-PAK-0113)☆

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Background: The prognostic and predictive value of carbohydrate antigen 19-9 (CA 19-9) in locally advanced pancreatic cancer (LAPC) has not yet been defined from prospective randomized controlled trials (RCTs).

Patients and methods: A total of 165 LAPC patients were treated within the NEOLAP RCT for 16 weeks with multiagent induction chemotherapy [ICT; either nab-paclitaxel/gemcitabine alone or nab-paclitaxel/gemcitabine followed by FOLFIRINOX (combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin)] followed by surgical exploration of all patients without evidence of disease progression. CA 19-9 was determined at baseline and after ICT and correlated with overall survival (OS) and secondary R0 resection rate.

Results: From the NEOLAP study population ($N = 165$) 133 patients (81%) were evaluable for CA 19-9 at baseline and 81/88 patients (92%) for post-ICT CA 19-9 response. Median OS (mOS) in the CA 19-9 cohort ($n = 133$) was 16.2 months [95% confidence interval (CI) 13.0-19.4] and R0 resection ($n = 31$; 23%) was associated with a significant survival benefit [40.8 months (95% CI 21.7-59.8)], while R1 resected patients ($n = 14$; 11%) had no survival benefit [14.0 (95% CI 11.7-16.3) months, hazard ratio (HR) 0.27; $P = 0.001$]. After ICT most patients showed a CA 19-9 response (median change from baseline: −82%; relative decrease ≥55%: 83%; absolute decrease to ≤50 U/ml: 43%). Robust CA 19-9 response (decrease to ≤50U/ml) was significantly associated with mOS [27.8 (95% CI 18.4-37.2) versus 16.5 (95% CI 11.7-21.2) months, HR 0.49; $P = 0.013$], whereas CA 19-9 baseline levels were not prognostic for OS. Multivariate analysis demonstrated that a robust CA 19-9 response was an independent predictive factor for R0 resection. Using a CA 19-9 decrease to ≤61 U/ml as optimal cut-off (by receiver operating characteristic analysis) yielded 72% sensitivity and 62% specificity for successful R0 resection, whereas CA 19-9 nonresponders (<20% decrease or increase) had no chance for successful R0 resection.

Conclusions: CA 19-9 response after multiagent ICT provides relevant prognostic and predictive information and is useful in selecting LAPC patients for explorative surgery.

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Key words: CA 19-9, locally advanced pancreatic cancer, multiagent induction chemotherapy, NEOLAP, R0 resection rate

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INTRODUCTION

At diagnosis, ∼30% of patients present with locally advanced pancreatic cancer (LAPC) in which probability of margin-negative primary resection is low due to perivascular tumor infiltration. Induction chemotherapy (ICT) with or without chemoradiation therapy (CRT) improves resection rates and median overall survival (mOS) ranging from 12 to 17 months in recent randomized controlled trials (RCTs).[1-4] The efficacy of modern multiagent ICT regimens such as FOLFIRINOX (combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin) or nab-paclitaxel/gemcitabine seems similar,[1,5,6] but response evaluation in LAPC is difficult as only few patients experience significant tumor shrinkage by RECIST. However, effective multiagent ICT results in significantly increased R0 resection rates associated with markedly improved overall survival (OS).[1,7-10] Multiagent ICT with or without CRT can even induce complete pathological remission with excellent long-term survival.[11,12]

Carbohydrate antigen 19-9 (CA 19-9) is one of the most widely studied tumor markers in patients with pancreatic cancer due to its utility in determining prognosis and response to treatment.[13,14] Despite known limitations in specificity (elevation by other cancers, cholangitis, biliary obstruction) and undetectability in Lewis-antigen-negative patients, biochemical response evaluation by serial CA 19-9 testing is sensitive and objective. By contrast, radiographic imaging for response evaluation has limitations as the presence of dense stroma and treatment-related fibrosis in LAPC may mask tumor shrinkage, and tumors that appear unresectable on radiographic imaging may be surgically resectable.[15-17] As previous studies exploring the prognostic and predictive value of CA 19-9 are heterogeneous in terms of analysis type (mostly retrospective), inclusion criteria/definition of LAPC and intensity of ICT (single agent versus multiagent as well as addition of CRT) results are difficult to compare.

The prospective NEOLAP trial, with systematic surgical exploration after 4 months of multiagent ICT (nab-paclitaxel/gemcitabine followed by FOLFIRINOX versus nab-paclitaxel/gemcitabine alone) and subsequent high secondary resection rates (32% complete macroscopic resections and 22% R0 resections), offers the unique opportunity to clarify the prognostic and predictive value of CA 19-9 in LAPC.[1]

MATERIALS AND METHODS

Study design and patient population

This is a preplanned exploratory analysis on the prognostic and predictive value of CA 19-9 levels (at baseline and after ICT at week 16) for OS and R0 resection rate, conducted on data of the prospective randomized phase II NEOLAP trial. Patient population and trial design of the multicenter NEOLAP study, which prospectively enrolled and treated 165 patients with LAPC with two different 4-month multiagent ICT regimes between 18 November 2014 and 27 April 2018, have been described in detail previously.[1] In brief, the NEOLAP (AIO-PAK-0113) trial was a multicenter, open-label, randomized phase II trial carried out at 28 academic and nonacademic hospitals in Germany. Eligible patients were aged 18-75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Patients were required to have histologically or cytologically confirmed pancreatic adenocarcinoma considered to be locally advanced by a local multidisciplinary team. Criteria for locally advanced status were either borderline resectable tumors with arterial involvement or unresectable tumors based on the National Comprehensive Cancer Network (NCCN) definitions.[18] As primary and secondary efficacy endpoints in the NEOLAP trial did not significantly differ between treatment arms (either nab-paclitaxel/gemcitabine alone or nab-paclitaxel/gemcitabine followed by FOLFIRINOX), this CA 19-9 analysis was performed from pooled treatment arms. Patients with bilirubin concentrations >2 mg/dl were excluded per protocol (see Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2022.100552) ruling out relevant bias in CA 19-9 measurements by obstructive jaundice. Serum CA 19-9 levels were prospectively evaluated at baseline and after completion of multiagent ICT (week 16) per schedule. Patients with missing or non-elevated CA 19-9 levels [≤37 U/ml (upper limit of normal = ULN)] were excluded from the current analysis. All patients without clear evidence of radiological disease progression after 4 months of ICT underwent explorative laparotomy per protocol irrespective of CA 19-9 response. For this analysis missing data (especially pathological resection margin status and CA 19-9 values) and survival status were updated on 12 December 2020 (=database lock). Pathological findings including tumor origin, extension, lymph node metastases, vascular and/or perineural invasion, and resection margins were scored per standard institutional practices according to the 2010 tumor—node—metastasis (TNM) classification, 7th edition.[19] For the current analysis margins were considered microscopically negative (R0) if no vital tumor cells were present at any resection margin. The study was approved by the ethics committee at each participating center and was carried out in accordance with the International Conference on Practice and the Declaration of Helsinki. All patients provided written informed consent before participation.

Statistical analysis

The primary objective of this study was to correlate baseline and post-treatment (after 4 months of ICT) CA 19-9 levels with OS and R0 resection rate based on the final efficacy analysis of the NEOLAP trial from 12 December 2020. As this is a preplanned exploratory analysis of the NEOLAP trial, no formal statistical assumption on the prognostic and predictive value of CA 19-9 with predefined cut-off levels was used. The analysis on CA 19-9 response was performed in all patients (of the CA 19-9 cohort) completing ICT with available post-ICT (week 16) CA 19-9 measurement.

Continuous data are presented as median and interquartile range (IQR = quartile 1—quartile 3), and categorical data as proportions and percentages. CA 19-9 was used as categorized parameter (according to absolute/relative cut-off levels) in Cox regression and other analyses. Median follow-up for survival analysis was determined by the inverse Kaplan—Meier

method. Survival [expressed as median with 95% confidence interval (CI)] was calculated from the start of ICT using the Kaplan–Meier method for different CA 19-9 cut-offs and statistical significance was determined using the long-rank test. Hazard ratio (HR; with 95% CI) was calculated by Cox regression analysis. The R0 resection rate was compared for different levels of reduction ≤specified absolute CA 19-9 levels (in U/ml) or ≥specified relative decreases (in %), using chi-square test or Fisher's exact test for categorical variables and Wilcoxon test for continuous variables. Correlation between CA 19-9 and resectability was analyzed for diagnostic accuracy based on sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The best cut-off value for prediction of R0 resection by CA 19-9 response was determined based on limiting the number of false negatives and optimizing sensitivity, aided by a receiver operating characteristic (ROC) curve and sensitivity analysis. A multivariate logistic regression analysis assessed the relationship between a number of known baseline and response variables and R0 resection rate; the two-sided significance level was set to 0.05. All statistical analyses were carried out using SAS software (version 9.4) and SPSS software (version 26).

RESULTS

Characterization and outcome of study populations

Between 18 November 2014 and 27 April 2018, 165 patients from 28 centers were prospectively enrolled and treated in the NEOLAP trial; 133 of 165 patients (81%) were evaluable for CA 19-9 baseline measurements [4 patients had missing and 28 patients had not elevated (≤ULN) CA 19-9 baseline values] and formed the CA 19-9 population for this study, while 81 of 88 (92%) patients who completed ICT were assessable for week 16 (post-ICT) CA 19-9 response. Overall, 45 of 133 patients (34%) did not complete ICT (20 disease progression, 11 withdrew consent, 8 adverse events, 4 investigator decision, and 2 protocol deviation) and 7 additional patients had missing CA 19-9 measurement after ICT (week 16), thus yielding 81 patients for CA 19-9 response assessment after ICT (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100552).

Baseline characteristics and outcome parameters (i.e. resection rates and OS status) were well balanced between the CA 19-9 population and the NEOLAP population and thus are representative of the total NEOLAP study population (Table 1). Complete survival data were collected until the database lock on 12 December 2020. Median follow-up for survival analysis was 28.1 months (95% CI 25.0-37.3). Based on this final survival update, mOS was 16.2 months (95% CI 13.0-19.4) in the CA 19-9 population as compared with 17.4 months (95% CI 14.1-20.7) in the total NEOLAP population (Table 1). Protocol-specified surgical exploration after multiagent ICT was performed in 50% of both study populations. R0 resections were achieved in 23% (31/133) and 22% (37/165) of all treated patients and in 46% (31/67) and 45% (37/82) of surgically explored patients in both study populations, respectively (Table 1). The subgroup of 32 patients excluded from the CA 19-9 analysis at baseline ($n = 4$ with missing values and $n = 28$ with not elevated CA 19-9 values) neither had a significantly different OS [20.8 months (95% CI 9.5-32.1), $P = 0.56$] nor a different R0 resection rate (6/32, 19%, $P = 0.65$). As already shown for the total NEOLAP study population,[1] only R0 resection was associated with a significant survival benefit in the CA 19-9 study population [R0- versus R1- and nonresected patients: 40.8 (95% CI 21.7-59.8) versus 14.2 (95% CI 12.0-16.5) months, HR 0.23 (95% CI 0.13-0.43), $P < 0.001$; as well as R0 versus R1 subgroup: 40.8 (95% CI 21.7-59.8) versus 14.0 (95% CI 11.7-16.3) months, HR 0.27 (95% CI 0.11-0.64), $P = 0.001$; Figure 1A]. Therefore, the predictive value of CA 19-9 in this study population was limited to patients achieving R0 resection.

Table 1. Baseline characteristics and outcome

	CA 19-9 population ($n = 133$)	Total NEOLAP population ($N = 165$)
Baseline characteristics		
Median age (years)	62.0 (54-69)	62.0 (55-68)
Patients aged >65 years	54 (41)	62 (38)
Sex		
Male	66 (50)	85 (52)
Female	67 (50)	80 (49)
ECOG performance status		
0	91 (68)	117 (71)
1	38 (29)	43 (26)
Tumor site		
Head	98 (74)	119 (72)
Body/Tail	35 (26)	46 (28)
Size of tumor (mm)[a]	40.0 (30-49)	40.0 (30-49)
Biliary stent	56 (42)	65 (39)
CA 19-9, at baseline (U/ml)	364 (147-1825)	276 (70-999)
≥500 U/ml	55 (41)	55 (33)
Normal (≤ULN)	0	28 (17)
NLR	3.1 (2-4)	3.1 (2-4)
>5	17 (13)	24 (15)
Outcome at week 16		
Resection status		
Explored	67 (50)	82 (50)
Resected	45 (34)	52 (32)
R0 resected	**31 (23)**	**37 (22)**
R1 resected	14 (11)	15 (9)
Not resected	22 (17)	30 (18)
Not explored	66 (50)	83 (50)
Survival, mOS, months (95 CI)		
Total cohort	16.2 (13.0-19.4)	17.4 (14.1-20.7)
Explored	22.3 (10.8-33.7)	22.5 (15.7-29.4)
Resected	27.9 (12.9-42.9)	27.9 (16.4-39.4)
R0 resected	**40.8 (21.7-59.8)**	**40.8 (20.7-60.9)**
R1 resected	14.0 (11.7-16.3)	14.6 (12.2-17.1)
Not resected	19.1 (10.9-27.2)	19.1 (11.8-26.4)
Not explored	12 (8.6-15.4)	12.1 (9.2-15.0)

Data are *n* (%) or median (IQR) unless otherwise specified.
CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; mOS, median overall survival; NLR, neutrophil-to-lymphocyte ratio; ULN, upper limit of normal (37 U/ml).
As this analysis is focused on R0 resection rate this subgroup has been kept in bold in terms of patient number and survival time.
[a]Investigator assessed.

Prognostic and predictive value of CA 19-9 levels at baseline

Baseline CA 19-9 levels in the study population ($n = 133$) ranged from 38 to 65 433 U/ml [median 276 U/ml (IQR 70-999 U/ml)]. Patients with CA 19-9 baseline levels above or below

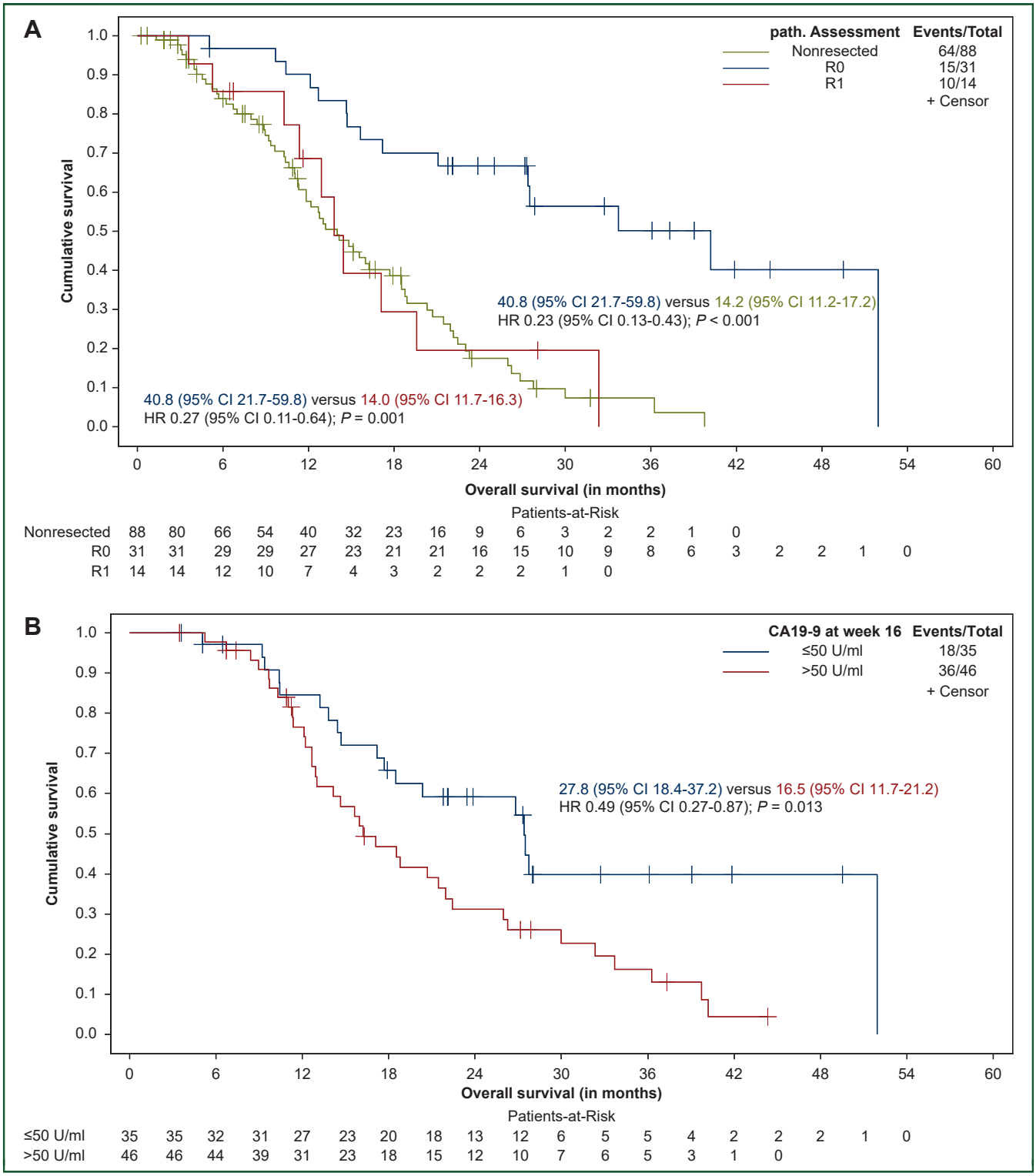

Figure 1. Kaplan–Meier curves. (A) Overall survival by resection status for nonresected (green), R1-resected (red), and R0-resected (blue) patients. (B) Overall survival by CA 19-9 response for patients with CA 19-9 response to ≤50 U/ml (blue) and >50 U/ml (red).
CI, confidence interval; HR, hazard ratio.

500 U/ml (41% versus 59%) were evenly distributed in the study population, while the majority of patients had CA 19-9 baseline levels >100 U/ml (83%). At baseline, CA 19-9 levels were not significantly correlated with OS (Table 2). In addition, baseline CA 19-9 levels of any specified cut-off (≤100 U/ml, ≤ median, ≤500 U/ml, ≤1000 U/ml, ≤5000 U/ml) were not predictive for R0 resection after multiagent ICT (Table 3 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100552).

Prognostic value of CA 19-9 decrease after completion of induction chemotherapy

CA 19-9 levels at week 16 ($n = 81$) ranged from 5 to 14 694 U/ml [median 58 U/ml (IQR 22-219)]. A decrease in CA 19-9

Table 2. Correlation between CA 19-9 baseline levels and survival

CA 19-9 at baseline	133 (100)	Overall survival (months), 95% CI		*P* value*
		Patients below the specified cut-off	Patients above the specified cut-off	
≤100 U/ml	22 (17)	21.8 (16.5-27.0)	15.1 (12.0-18.1)	0.151
≤500 U/ml	78 (59)	18.8 (15.3-22.3)	14.9 (10.8-19.0)	0.283
≤1000 U/ml	94 (71)	18.8 (15.4-22.2)	13.1 (9.8-16.4)	0.269
≤5000 U/ml	118 (89)	17.4 (13.9-20.8)	13.0 (6.7-19.2)	0.517

Data are *n* (%) unless otherwise specified.
CA 19-9, carbohydrate antigen 19-9; CI, confidence interval.
**P* value based on long-rank test.

levels from baseline to week 16 was observed in the majority of patients after multiagent ICT (median change from baseline: −82%; decrease ≥20%: 93%; decrease ≥55%: 83%; decrease ≥90%: 36%; decrease to ≤50 U/ml: 43%; normalization ≤ULN: 40%). Patients who had a robust CA 19-9 response below specified absolute cut-off levels (at least ≤CA 19-9 level of 50 U/ml) had a significant improvement in OS as compared to patients without this specified decrease (Table 4). As shown in Figure 1B, CA 19-9 decrease to ≤50 U/ml was significantly associated with prolonged OS [27.8 (95% CI 18.4-37.2) versus 16.5 (95% CI 11.7-21.2) months; HR 0.49 (95% CI 0.27-0.87); $P = 0.013$]. For relative CA 19-9 decrease (in %) no significant survival difference was observed for any cut-off (Table 4).

Predictive value of CA 19-9 decrease after completion of induction chemotherapy

At week 16, median CA 19-9 levels in R0-resected patients were significantly lower as compared with R1-/nonresected patients [30 (IQR 18-85) versus 99 U/ml (IQR 25-346); $P = 0.01$; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100552]. A similar trend was observed for median CA 19-9 decrease from baseline in R0- versus R1-/nonresected patients [−85% (IQR −72% to −95%) versus −76% (IQR −55% to −94%); $P = 0.087$; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100552]. Most importantly, CA 19-9 nonresponders (decrease <20% from baseline or increase) had no chance for successful R0 resection (NPV 100%; Table 5 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100552). R0 resection rate was significantly higher for patients with a robust CA 19-9 response (at least ≤absolute cut-off level of 100 U/ml or ≥55% relative decrease; Table 5).

However, the best cut-off value for absolute CA 19-9 decrease at week 16 (from baseline to ≤61 U/ml by ROC analysis; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100552 and Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100552) yielded a sensitivity of 72% and specificity of 62% (PPV: 51%, NPV: 80%) for successful R0 resection. Likewise, the best cut-off for relative CA 19-9 decrease (≥55% by ROC analysis) yielded a sensitivity of 97% and specificity of 25% (PPV: 42%, NPV: 93%) for successful R0 resection (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100552). In multivariate analysis, only robust CA 19-9 response at week 16 [with either absolute decrease (to ≤50 U/ml, Table 6) or relative decrease (≥55% decrease, data not shown) and investigator-assessed radiographic response were identified as independent predictive factors for R0 resection (Table 6). Conversely, baseline CA 19-9 levels, age, ECOG performance status, baseline neutrophil-to-lymphocyte ratio, baseline tumor size, and tumor localization did not have an independent predictive relevance for R0 resection.

Table 3. Correlation between CA 19-9 baseline levels and R0 resection rate

CA 19-9 variables	CA 19-9 population	R0 resection rate		*P* value*
		Patients below the specified cut-off	Patients above the specified cut-off	
Patients with baseline measurement	133			
≤100 U/ml	22	6/22 (27)	25/111 (23)	0.630
≤500 U/ml	78	20/78 (26)	11/55 (20)	0.449
≤1000 U/ml	94	23/94 (25)	8/39 (21)	0.623
≤5000 U/ml	118	29/118 (25)	2/15 (13)	0.519[a]

Data are *n* or *n/N* (%) unless otherwise specified.
CA 19-9, carbohydrate antigen 19-9.
[a]Fisher's exact test.
**P* value based on chi-square test, except Fisher's exact test for [a].

DISCUSSION

There are currently no guidelines on how to select patients with LAPC for surgery after multiagent ICT with or without CRT. The predictive value of radiographic imaging has limitations as the presence of dense stroma and treatment-related fibrosis may mask tumor shrinkage. Biochemical response evaluation by assessment of CA 19-9 before and after induction therapy represents a broadly available and sensitive alternative to radiographic imaging. The current prespecified exploratory analysis of the NEOLAP trial is the first study to evaluate the prognostic and predictive value of CA 19-9 after multiagent ICT within a prospective RCT. The unprecedented high surgical exploration rate (50%) in this prospective multicenter LAPC trial can be explained by systematic surgical exploration of all patients without clear evidence of disease progression, irrespective of radiographic response. This offered the unique opportunity to analyze the predictive value of R0 resection rate in this setting. As already shown for the total treated NEOLAP population,[1] achievement of a R0 resection (23% of treated patients) was the strongest predictor for long-term survival in this CA 19-9 study population. Our results demonstrate that a robust CA 19-9 response after multiagent ICT was associated with prolonged survival and is an independent predictor for R0 resection, whereas baseline CA 19-9 levels have no prognostic or predictive value in this setting. Furthermore, CA 19-9 nonresponse (≤20% decrease from baseline) defines a small subgroup of LAPC who will not

Table 4. Correlation between CA 19-9 decrease and survival

CA 19-9 response at week 16	Week 16 cohort	Overall survival (months), 95% CI		*P* value*
		Patients with the specified decrease	Patients without the specified decrease	
Patients with week 16 measurement	81 (100)			
≤ULN	32 (40)	27.9 (19.0-36.8)	17.4 (13.4-21.4)	**0.024**
≤50 U/ml	35 (43)	27.8 (18.4-37.2)	16.5 (11.7-21.2)	**0.013**
≤100 U/ml	49 (60)	21.8 (11.8-31.7)	16.5 (8.8-24.1)	0.140
≤500 U/ml	71 (88)	19.1 (14.4-23.7)	22.8 (5.1-40.4)	0.938
Decrease ≥20%	75 (93)	21.0 (12.8-29.2)	19.1 (8.9-29.2)	0.462
Decrease ≥55% (ROC)	67 (83)	18.8 (14.4-23.2)	26.6 (16.6-36.7)	0.956
Decrease ≥90%	29 (36)	17.4 (15.2-19.6)	22.8 (13.9-31.6)	0.912

Data are *n* (%) unless otherwise specified.
Column 2 shows the patient number of the subgroup achieving the specified cut-off (absolute decrease in U/ml and relative decrease in %); the rest of the 81 patients did not achieve the specified cut-off.
CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; ROC, receiver operating characteristic; ULN, upper limit of normal (37 U/ml).
Bold entries are *P*-values ≤0.05 regarded as statistically significant.
**P* value based on long-rank test.

benefit from attempted tumor resection by explorative laparotomy (NPV 100% for R0 resection).

This prospective analysis confirms that the currently most active multiagent chemotherapy regimens such as nab-paclitaxel/gemcitabine or FOLFIRINOX induce a profound CA 19-9 decrease in the majority of patients with LAPC (median % change from baseline: −82%; decrease ≥55%: 83% of patients; normalization rate: 40% of patients). Similar biochemical response rates for CA 19-9 were reported in the prospective LAPACT trial with nab-paclitaxel/gemcitabine,[7] and in retrospective studies and meta-analyses evaluating multiagent ICT with FOLFIRINOX or nab-paclitaxel/gemcitabine (with or without CRT) in LAPC.[10,20-26]

In contrast to studies performed in resectable pancreatic cancer,[13,14,27-31] baseline CA 19-9 levels (using established cut-off levels such as 500 or 1000 U/ml) were neither prognostic (for OS) nor predictive (for R0 resection) in this prospective LAPC trial after multiagent ICT. The two other prospective randomized trials in LAPC using less intensive ICT with or without CRT reported conflicting results about the prognostic role of baseline CA 19-9,[2,32] while other prospective trials in LAPC using multiagent ICT with nab-paclitaxel/gemcitabine[7] or FOLFIRINOX[8] did not analyze the prognostic and predictive role of baseline CA 19-9. However, most of the larger retrospective studies in LAPC using multiagent ICT confirm that CA 19-9 baseline levels are no longer prognostic for OS.[20,33-36]

Consistent with our analysis, robust CA 19-9 response below a similar absolute cut-off level (44 U/ml at week 17) was also associated with prolonged median OS in the prospective randomized SCALOP trial [16.3 (13.9-19.2) versus 12.6 (10.3-14.0) months; $P < 0.001$].[2] Several other retrospective studies in LAPC using multiagent ICT confirm the prognostic value of CA 19-9 response.[20-24,26,33,36] Thus, we hypothesize that effective multiagent ICT mitigates the impact of tumor burden at baseline (reflected by baseline CA 19-9 levels) on survival, while biochemical response during ICT identifies LAPC patients with chemosensitive disease and improved prognosis. CA 19-9 response to certain absolute levels (i.e. ≤50 U/ml) seems to be a more reliable prognostic biomarker for OS than relative CA 19-9 decrease after ICT because relative CA 19-9 decreases do not mirror the initial

Table 5. Correlation between CA 19-9 decrease and R0 resection rate

CA 19-9 response at week 16	Week 16 cohort	R0 resection rate		*P* value*
		Patients with the specified decrease	Patients without the specified decrease	
Patients with week 16 measurement	81 (100)			
≤ULN	32 (40)	16/32 (50)	13/49 (27)	**0.031**
≤50 U/ml	35 (43)	18/35 (51)	11/46 (24)	**0.011**
≤61 U/ml (ROC)	41 (51)	21/41 (51)	8/40 (20)	**0.003**
≤100 U/ml	49 (60)	23/49 (47)	6/32 (19)	**0.010**
≤500 U/ml	71 (88)	27/71 (38)	2/10 (20)	0.318[a]
Decrease ≥20%	75 (93)	29/75 (39)	0/6 (0)	0.083[a]
Decrease ≥55% (ROC)	67 (83)	28/67 (42)	1/14 (7)	**0.014**
Decrease ≥90%	29 (36)	12/29 (41)	17/52 (33)	0.434

Data are *n* (%) or *n/N* (%) unless otherwise specified.
Column 2 shows the patient number of the subgroup achieving the specified cut-off (absolute decrease in U/ml and relative decrease in %); the rest of the 81 patients did not achieve the specified cut-off. In column 3 and 4, the numerators in each line add up to the 29 R0 resected patients and the denominators add up to the total 81 patients of the week 16 cohort.
CA 19-9, carbohydrate antigen 19-9; ROC, receiver operating characteristic; ULN, upper limit of normal (37 U/ml).
Bold entries are *P*-values ≤0.05 regarded as statistically significant.
[a]Fisher's exact test.
**P* value based on chi-square test, except Fisher's exact test for [a].

Table 6. Multivariate analysis for predictive variables of R0 resection

Variable	R0-Resection/Patients	Univariate			Multivariate[a]		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years		0.66	0.25-1.78	0.414	0.42	0.11-1.61	0.205
≤65	21/54						
>65	8/27						
WHO performance status		1.42	0.52-3.91	0.496	1.88	0.52-6.84	0.337
0	19/58						
1	9/22						
Tumor localization		1.18	0.40-3.50	0.763	1.68	0.38-7.40	0.496
Head	21/60						
Body/tail	7/18						
Baseline NLR		0.41	0.08-2.10	0.287	0.30	0.04-2.25	0.242
≤5	26/69						
>5	2/10						
Baseline tumor size[b]		0.85	0.34-2.13	0.723	0.61	0.18-2.03	0.423
≤Median	16/41						
>Median	13/37						
Baseline CA 19-9, U/ml		0.57	0.22-1.48	0.247	0.57	0.14-2.37	0.435
≤500	20/49						
>500	9/32						
Radiographic response[c]		3.93	1.32-11.73	0.014	11.25	2.47-51.24	**0.002**
No	18/63						
Yes	11/18						
CA 19-9 response[d], U/ml		0.30	0.12-0.77	0.012	0.24	0.06-0.93	**0.039**
≤50	18/35						
>50	11/46						

CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; WHO, World Health Organization.
Bold entries are *P*-values ≤0.05 regarded as statistically significant.
[a]Only for patients with known value for all parameters ($n = 72$).
[b]Median tumor size at baseline: 40 mm (greatest lesion).
[c]Investigator-assessed radiographic response at week 16; Yes = partial remission (RECIST).
[d]CA 19-9 reduction to ≤50 U/ml at week 16.

tumor burden (occult metastatic disease). For example, in our analysis the subgroup of patients with ≥90% CA 19-9 decrease had significantly higher CA 19-9 baseline levels than patients with <90% decrease [674 U/ml (IQR 325-3952) versus 266 U/ml (IQR 106-967), $P = 0.001$].

The predictive value of baseline CA 19-9 for secondary resection in LAPC has not been established from previous RCT so far, because secondary resection (conversion) rates were low (<5%).[2,4] Thus, the NEOLAP trial (surgical exploration rate: 50%) is the first prospective RCT to report about the predictive value of CA 19-9 for R0 resection in patients with LAPC.

In line with previous retrospective studies,[21,33] this preplanned exploratory analysis of the prospective NEOLAP RCT confirms that a robust biochemical CA 19-9 response increases the chance for R0 resection in LAPC and biochemical nonresponse (CA 19-9 increase or <20% decrease from baseline) has an NPV of 100% for R0 resection. In addition, robust CA 19-9 response (to ≤50 U/ml) was independently predictive for R0 resection in multivariate analysis. Investigator-assessed radiographic response was also a significant independent predictor in our multivariate analysis. However, without confirmation by central review, investigator-assessed (subjective) radiographic response is less reliable than biochemical response evaluation. The advantage of the latter is that it is a well-standardized, easily available, and objective parameter comparable between studies. In a recent retrospective analysis of LAPC patients, van Veldhuisen and colleagues[21] reported that 90% of patients were correctly classified as resectable (90% sensitivity, PPV 43%) and 20% as unresectable (20% specificity, NPV 75%) by using ≥30% decrease of CA 19-9 as cut-off. This compares to a sensitivity of 97% (PPV 42%) and a specificity of 25% (NPV 93%) for R0 resection in our study using ≥55% relative CA 19-9 decrease as cut-off (determined by ROC analysis). Adding robust CA 19-9 response to radiographic response assessment of LAPC following ICT seems to improve the diagnostic accuracy for secondary R0 resection, which is strongly associated with long-term survival in LAPC.[1,8,37-39]

Despite the prospective and multicenter design of this analysis, our study has some limitations. Although extensive supportive analyses were performed to define the optimal cut-off value, the finding of the optimal cut-off value for CA 19-9 in this study has limitations due to the limited number of tests and further studies are necessary to confirm this cut-off value. Biochemical response evaluation by CA 19-9 is only feasible in 80%-85% of pancreatic cancer patients because it is not elevated in all patients at diagnosis. Therefore novel/additional biomarkers should be investigated in future studies. The definition of LAPC in the NEOLAP trial differs from previous randomized trials,[2,4] and reflects the absence of uniformity in the definition of LAPC and especially the challenges in investigator-based differentiation of borderline from unresectable pancreatic ductal adenocarcinoma. This is highlighted by recently reported high discordance rates between investigator- and central review-based evaluation of resectability status and radiographic response in localized pancreatic cancer. To address this dilemma a *post hoc* central

radiology review of the NEOLAP trial is ongoing and will be correlated with CA 19-9 response to improve the diagnostic accuracy for predicting R0 resection. In addition, combining CA 19-9 response with other imaging methods of response evaluation (such as positron emission tomography—computed tomography,[26] 3D volumetry, and density computed tomography scan or diffusion-weighted magnetic resonance imaging) might further improve diagnostic accuracy for LAPC patients after ICT. Finally, the high dropout rate during ICT in prospective multicenter LAPC trials (only 66% of this cohort reached restaging at week 16) limits the statistical power for CA-19 response assessment, but reflects the suboptimal treatment efficacy in LAPC despite modern multiagent chemotherapy and should be considered when planning future trials in LAPC.

Conclusions

In summary, our study validates the prognostic and predictive value of robust CA 19-9 decrease (to <50 U/ml) after multiagent ICT in a prospective LAPC population and thus will improve selection of patients for surgical exploration.

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