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Survival Benefit Associated With Resection of Locally Advanced Pancreatic Cancer After Upfront FOLFIRINOX Versus FOLFIRINOX Only

Multicenter Propensity Score-matched Analysis

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Objective: This study compared median OS after resection of LAPC after upfront FOLFIRINOX versus a propensity-score matched cohort of LAPC patients treated with FOLFIRINOX-only (ie, without resection).

Background: Because the introduction of FOLFIRINOX chemotherapy, increased resection rates in LAPC patients have been reported, with improved OS. Some studies have also reported promising OS with FOLFIRINOX-only treatment in LAPC. Multicenter studies assessing the survival benefit associated with resection of LAPC versus patients treated with FOLFIRINOX-only are lacking.

Methods: Patients with non-progressive LAPC after 4 cycles of FOLFIRINOX treatment, both with and without resection, were included from a prospective multicenter cohort in 16 centers (April 2015–December 2019). Cox regression analysis identified predictors for OS. One-to-one propensity score matching (PSM) was used to obtain a matched cohort of patients with and without resection. These patients were compared for OS.

Results: Overall, 293 patients with LAPC were included, of whom 89 underwent a resection. Resection was associated with improved OS (24 vs 15 months, $P < 0.01$), as compared to patients without resection. Before PSM, resection, Charlson Comorbidity Index, and Response Evaluation Criteria in Solid Tumors (RECIST) response were predictors for OS. After PSM, resection remained associated with improved OS [Hazard Ratio (HR) 0.344, 95% confidence interval (0.222–0.534), $P < 0.01$], with an OS of 24 versus 15 months, as compared to patients without resection. Resection of LAPC was associated with improved 3-year OS (31% vs 11%, $P < 0.01$).

Conclusions: Resection of LAPC after FOLFIRINOX was associated with increased OS and 3-year survival, as compared to propensity-score matched patients treated with FOLFIRINOX-only.

Keywords: FOLFIRINOX, locally advanced pancreatic cancer, resection

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Currently, resection of pancreatic cancer combined with systemic chemo(radio)therapy is the only treatment option that may provide long-term survival.[1] Patients with locally advanced pancreatic cancer (LAPC) are increasingly treated with a combination of leucovorin, 5-fluorouracil, plus irinotecan, and oxaliplatin (FOLFIRINOX).[2,3] After treatment with FOLFIRINOX chemotherapy about 20% of these patients may undergo a resection.[4–6] Several studies have reported improved overall survival (OS) after resection of LAPC, with a median OS ranging from 20 to over 40 months.[7] However, resection of LAPC may also result in increased morbidity and mortality rates, although others have reported that morbidity and mortality are comparable to upfront resected patients.[6,8–11]

Patients with LAPC who undergo resection represent a highly selected population. It is unknown to what extent tumor resection actually contributes to survival, as compared to treatment with FOLFIRINOX only.[12] A pooled analysis in patients with LAPC treated with FOLFIRINOX, in about half of the patients combined

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with additional therapy, demonstrated a remarkable median OS of 24 months.[4] Up to date, no randomized trial or large comparative study has investigated the survival benefit associated with resection of LAPC after upfront FOLFIRINOX.

This study aims to compare OS in propensity score matched patients with LAPC who underwent at least 4 cycles of FOLFIRINOX with and without resection.

METHODS

Patient Selection

This is a post-hoc analysis of a prospective, multicenter registry of patients with LAPC in the Netherlands. Consecutive patients diagnosed with LAPC before start of chemotherapy were included in 16 centers affiliated with the Dutch Pancreatic Cancer Group (DPCG) between April 2015 and December 2019.[13] Included were patients aged ≥18 years, diagnosed with LAPC according to the DPCG criteria[14] (ie, >90° involvement of the superior mesenteric artery), common hepatic artery or celiac axis (CA), or >270° involvement of the superior mesenteric vein or portal vein (Supplemental Table 1, http://links.lww.com/SLA/D318), who had RECIST non-progressive (ie, regression or stable) disease after ≥4 cycles FOLFIRINOX and underwent a resection. Additional data on all patients who started chemotherapy was available for the first half of the study period (April 2015–December 2017), providing us with a control group to match the resected patients. Data for patients without a resection in the period January 2018 to December 2019 is not yet available. All patients gave informed consent for the registry and the Institutional Review Boards approved the registry within all participating centers.

Data Collection

We selected potential factors influencing survival and resection based on the literature and experience from clinical practice. The following parameters were extracted from the database: patient demographics at diagnosis (age, sex, Charlson Comorbidity Index score, World Health Organization performance score), tumor characteristics [tumor size, tumor location, TNM stage (eighth AJCC edition[15]), serum carbohydrate antigen 19.9 (CA 19.9) (at baseline and follow-up), and vascular involvement of the tumor], treatment characteristics (number of cycles FOLFIRINOX, additional treatment, postoperative outcomes), and survival (OS). After induction chemotherapy (ie, chemotherapy given with the intention to downsize the tumor to a resectable/borderline resectable situation. In this study this was mostly 4 cycles of FOLFIRINOX), most baseline Computed Tomography (CT)-scans and evaluation CT-scans were prospectively evaluated by a national expert panel. The panel consists of experienced abdominal radiologists and pancreatic surgeons. For all CT-scans vascular involvement and response according to RECIST 1.1[16] were scored. Surgeons reviewed all evaluation CT-scans according to the National Comprehensive Cancer Network (NCCN) criteria[17] [ie, >180° involvement of superior mesenteric artery or CA, or unreconstructable superior mesenteric vein/portal vein due to tumor involvement or occlusion (Supplemental Table 1, http://links.lww.com/SLA/D318)], to assess whether a resection was possible. Primary outcome was OS, which was measured from date of LAPC diagnosis until date of death. In case patients were still alive at final follow-up or lost to follow up they were censored.

Statistical Analysis

Continuous data were presented as median with interquartile range or mean with standard deviation when applicable. Categorical data were presented as counts with percentage. OS was estimated using the Kaplan Meier method, and differences between groups were analyzed using the log-rank test. Missing data was handled by multiple imputation, to which 5 datasets were created. The analyses were performed in 5 imputed datasets, pooled estimates, and statistics were reported.

Propensity score matching (PSM) was used to minimize selection bias and create balance between variables. A Cox regression with backward selection according to Akaike information criterion, with an elimination criterion of $P > 0.05$, was performed to select variables influencing OS, which were used for the PSM.[18] A one-to-one nearest neighbor matching was performed to match patients undergoing tumor resection after induction therapy with patients not undergoing tumor resection. Equal distribution of baseline characteristics was tested using standard mean difference, with an overall standard mean difference of <0.10 representing good balance. After PSM, a multivariate Cox regression was performed with variables not used in the PSM to assess the influence of resection on OS.

A sensitivity analysis was performed excluding patients who did not meet the LAPC definition according to the most recent NCCN guidelines[17] (ie, the DPCG criteria for LAPC are different from the NCCN guidelines). Cox regression with backward selection according to Akaike information criterion was performed in these patients to select the variables for PSM. PSM was repeated in all patients with LAPC according to NCCN guidelines before start of chemotherapy.

Analyses were performed using R version 4.0.2 (The R Project for Statistical Computing, Vienna, Austria; cran.r-project.org). A 2-sided P value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The study flowchart is shown in Figure 1. In total, 461 patients were treated with ≥4 cycles FOLFIRINOX (April 2015–December 2019), of which 204 patients were treated between April 2015 and December 2017. Eighty-nine patients (19%) with LAPC underwent a resection between April 2015 and December 2019. Baseline characteristics of patients undergoing a resection and patients treated with FOLFIRINOX only are shown in Table 1 (before and after PSM). In both groups the median age was 62 years, about half of the patients was female. The majority of tumors were located in the pancreatic head, with a median tumor size of 42 mm in non-resected and 37 mm in resected LAPC ($P < 0.01$). Postoperative outcomes of the resected patients are presented in Supplemental Table 2, http://links.lww.com/SLA/D318. R0 resection was seen in 48 patients (55%) and 90-day mortality after resection was 2%. In total, 55 patients (63%) received adjuvant therapy, mostly FOLFIRINOX (50 patients, 91%). Of the non-resected patients, 142 (70%) received second-line therapy; radiotherapy in 72 patients (51%), chemotherapy in 35 patients (25%) [FOLFIRINOX in 10 patients (7%), nab-paclitaxel plus gemcitabine in 9 patients (6%), gemcitabine in 7 patients (5%), and chemotherapeutic treatment in a study in 9 patients (6%)], and local ablative therapy (Radiofrequency ablation or Irreversible electroporation) in 35 patients (25%). In 154 of the non-resected patients (76%) progression occurred; distant metastasis in 97 patients (63%) and local progression in 56 patients (37%).

Overall Survival

Median OS in patients who underwent resection was 24 months [95% confidence interval (CI) 19–38 months] versus 15 months (95% CI 15–17 months) in patients without resection ($P < 0.01$). The survival curve is shown in Figure 2A. Three-year OS was 31% (95% CI 18%–51%) after resection and 8% (95% CI 4%–13%) without resection.

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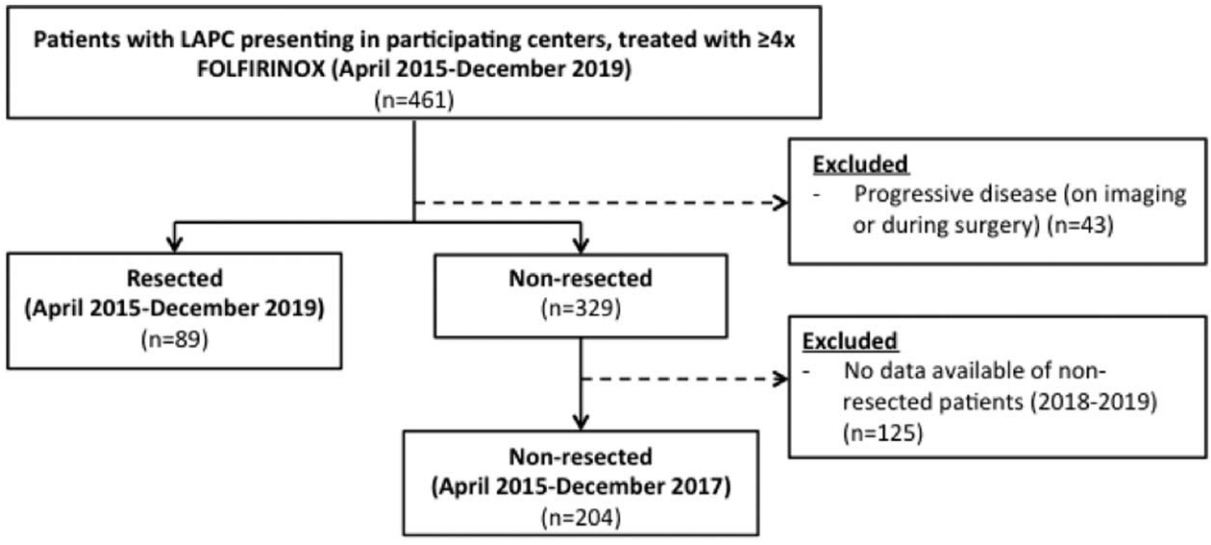

FIGURE 1. Flowchart patient selection. LAPC indicating locally advanced pancreatic cancer.

The results from the multivariate Cox regression analysis are shown in Table 2. Resection, Charlson Comorbidity Index score, and RECIST response after induction FOLFIRINOX were significant predictors for OS. PSM was performed with these predictors, excluding resection.

Outcomes After PSM

All 89 patients with LAPC who underwent resection were matched with 89 patients with LAPC without resection. Baseline characteristics of both patient groups after PSM are shown in Table 1, with the corresponding standard mean difference. The overall standard mean difference is <0.01. In the matched sample, median OS after resection was 24 months (95% CI 19–38 months) versus 15 months (95% CI 13–18 months) without resection. The survival curve is shown in Figure 2B. Three-year OS was 31% (95% CI 18%–51%) after resection and 11% (95% CI 6%–23%) without resection ($P < 0.01$). Multivariable Cox regression showed that resection remained independently associated with OS (HR 0.344, 95% CI [0.222–0.534], $P < 0.01$).

Sensitivity Analyses

Among 191 patients with LAPC according to the most recent NCCN criteria at diagnosis, 31 underwent resection after induction FOLFIRINOX, with a median OS of 26 months (95% CI 16 months-not reached) versus 17 months (95% CI 15–19 months) in patients without resection. After PSM, based on the multivariate Cox regression analysis (Supplemental Table 1, http://links.lww.com/SLA/D318), resection remained an independent predictor for improved OS [HR 0.359, (95% CI 0.172–0.749), $P < 0.01$]. Median OS after PSM was 26 months (95% CI 16 months-not reached) in the resected group versus 17 months (95% CI 13–25 months) in patients without resection.

DISCUSSION

In this multicenter propensity score matched cohort study, patients with non-progressive LAPC after 4 cycles of FOLFIRINOX who underwent a resection had a 9 months improved OS, as compared to patients with non-progressive LAPC treated with FOLFIRINOX only (24 vs 15 months). Furthermore, patients who underwent a resection had a 20% increased 3-year survival rate (31% vs 11%), as compared to patients treated with FOLFIRINOX only.

This is the first propensity-score matched multicenter study, which compared patients with LAPC who did or did not undergo resection after upfront treatment with FOLFIRINOX chemotherapy. The prospective, observational population-based cohort used for this study reflects current daily clinical practice. In the last decade, several studies reported an improved OS in patients with LAPC undergoing a resection, with median survival ranging from 20 to 64 months.[2,5,6,19–21] Moreover, a recent systematic review of 26 studies reported an OS ranging from 25 to 40 months. None of these studies, however, compared patients with LAPC with and without resection after FOLFIRINOX.[7] Furthermore, most previous studies are single center studies representing a highly selected and possibly favorable patient group. It is unknown whether these patients would have had the same survival if treated with FOLFIRINOX only. Some selected studies show comparable median OS of 25 to 46 months in patients with LAPC treated with FOLFIRINOX only.[4,22]

Because current CT imaging cannot reliably asses tumor response after induction FOLFIRINOX, several factors need to be taken into account when considering the decision to proceed to surgery after induction chemotherapy.[23,24] RECIST response on imaging is a commonly used factor in deciding to proceed to surgery. Tumor fibrosis and active tumor tissue, however, are difficult to distinguish on imaging, therefore patients with at least stable disease on imaging are often given the option for exploration.[10,23–25] Furthermore, international consensus is lacking about the acceptable tumor involvement of vital vessels before deciding on surgical exploration.[12,26] A recent survey showed that there is still a substantial variation worldwide in management preferences for LAPC.[27] As discussed in several studies, serum CA 19.9 response may predict response on induction chemotherapy and patients prognosis.[28–30] The present studies shows that patients who underwent resection had improved serum CA 19.9 response rates, as compared to patients not undergoing resection. Currently, there is no consensus about the optimal numbers of cycles of induction FOLFIRINOX before deciding to proceed to surgery. In the present study, and in others, no

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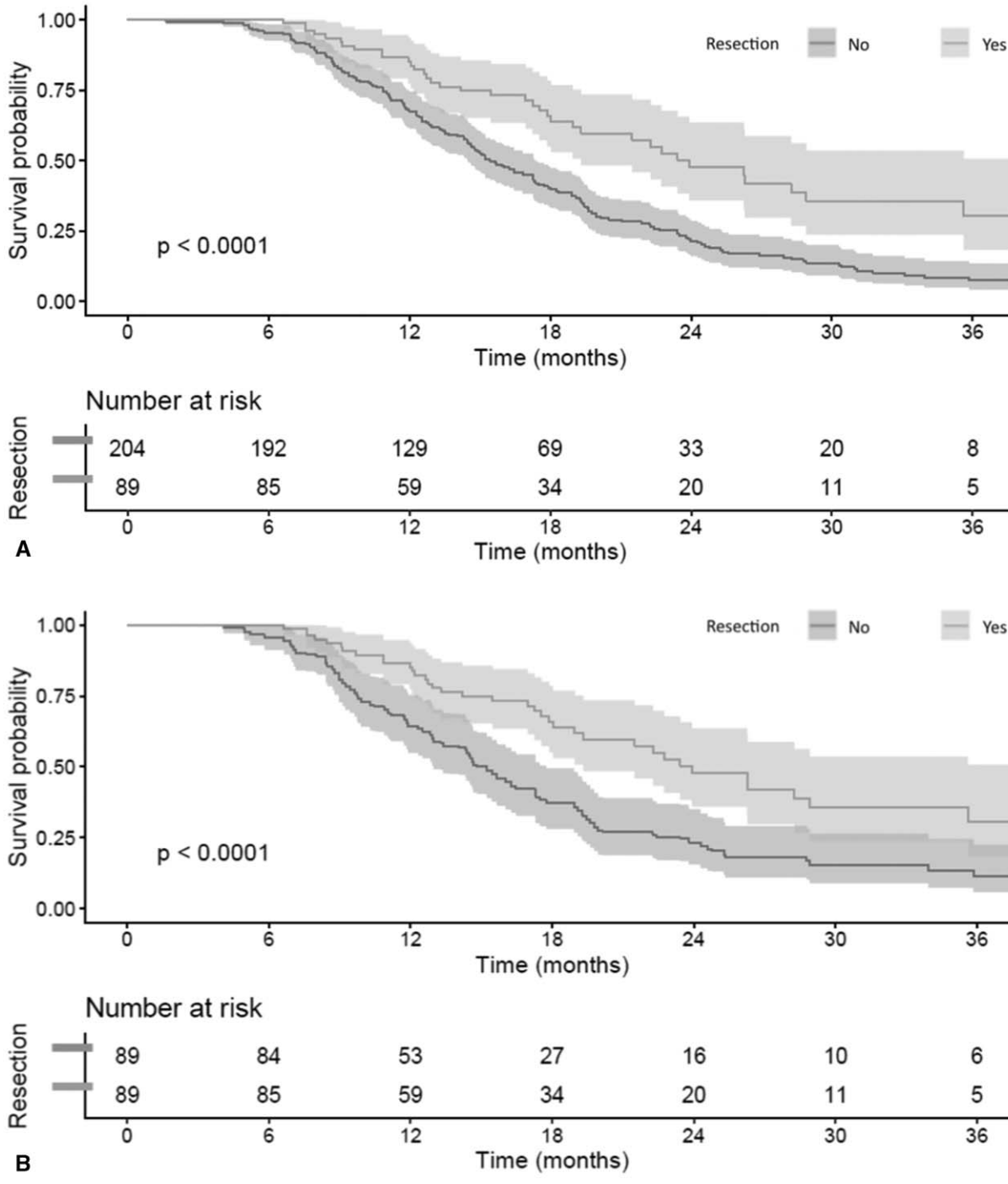

FIGURE 2. Overall survival from initial diagnosis in patients with locally advanced pancreatic cancer with and without resection after upfront FOLFIRINOX chemotherapy. Before (A) and after (B) propensity score matching.

correlation has been found between the numbers of cycles and median OS.[4,31,32] We cannot exclude the possibility that more patients could have undergone a resection if patients had undergone exploration after 8 cycles of FOLFIRINOX, rather than after 4 as mostly seen in this study.

Although this study suggests improved survival after resection of LAPC as compared to chemotherapy only, data on quality of life in these patients are lacking. To date, no study has reported on quality of life in patients after resection of LAPC. It is, however, to be expected that most patients would prefer resection. In patients not eligible for a resection, FOLFIRINOX chemotherapy provides a treatment option for improved or preserved quality of life.[33–35] It is known that pancreatic resection decreases quality of life in the first 3 months after surgery.[36,37] However, full recovery of quality of life to baseline

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TABLE 1. Baseline Characteristics of Patients With Locally Advanced Pancreatic Cancer Treated With Upfront FOLFIRINOX With and Without Resection, Before and After Propensity Score Matching

	Before PSM			After PSM		
	Resection $n = 89$	No Resection $n = 204$	SMD	Resection $n = 89$	No Resection $n = 89$	SMD
Age, mean ±SD	62 ±9	62 ±9	0.005	62 ±9	62 ±8	0.004
Female	48 (54%)	103 (51%)	0.069	48 (54%)	48 (54%)	0.009
Year of diagnosis	2015–2019	2015–2017				
WHO ps			0.293			0.151
0–1	78 (96%)	159 (89%)		83 (93%)	79 (89%)	
>1	3 (4%)	20 (11%)		6 (7%)	10 (11%)	
Charlson Comorbidity Index		0.153			0.048	
0–1	74 (84%)	160 (79%)		75 (84%)	73 (82%)	
>1	14 (16%)	43 (21%)		14 (16%)	16 (18%)	
Tumor location			0.263			0.070
Head	65 (73%)	124 (61%)		65 (73%)	62 (70%)	
Body/tail	24 (27%)	80 (39%)		24 (27%)	27 (30%)	
Tumor size			0.614			0.179
<20mm	3 (4%)	8 (4%)		3 (3%)	4 (5%)	
20–30mm	22 (26%)	37 (18%)		24 (27%)	23 (26%)	
30–40mm	38 (46%)	61 (30%)		40 (45%)	34 (38%)	
40–50mm	10 (12%)	56 (28%)		11 (13%)	15 (17%)	
50–60mm	5 (6%)	20 (10%)		6 (7%)	6 (7%)	
60–70mm	2 (2%)	12 (6%)		2 (2%)	3 (3%)	
>70mm	3 (4%)	8 (4%)		3 (3%)	4 (4%)	
Serum CA 19.9 response		0.691			0.214	
Increase	7 (11%)	45 (38%)		20 (23%)	27 (30%)	
<30% decrease	12 (19%)	15 (13%)		8 (9%)	9 (10%)	
30%-50% decrease	2 (3%)	7 (6%)		3 (3%)	4 (5%)	
50%-75% decrease	13 (21%)	29 (24%)		18 (20%)	16 (18%)	
>75% decrease	29 (46%)	23 (19%)		40 (45%)	33 (37%)	
Cycles, mean ±SD	7 ±3	8 ±3	0.228	7 ±3	8 ±4	0.263
RECIST response after 4 cycles		0.336			0.214	
Partial response	16 (22%)	21 (15%)		25 (28%)	21 (23%)	
Stable disease	56 (78%)	118 (85%)		64 (72%)	68 (77%)	
Vascular involvement						
Superior mesenteric artery			0.824			0.142
<90°	62 (71%)	80 (40%)		63 (71%)	59 (66%)	
90°-180°	19 (22%)	49 (24%)		19 (22%)	21 (24%)	
>180°	6 (7%)	73 (36%)		6 (7%)	9 (10%)	
Celiac trunc			0.724			0.208
<90°	72 (85%)	112 (56%)		76 (85%)	69 (77%)	
90°-180°	7 (8%)	26 (13%)		7 (8%)	11 (13%)	
>180°	6 (7%)	63 (31%)		6 (7%)	9 (10%)	
Common hepatic artery			0.451			0.152
<90°	50 (57%)	84 (41%)		51 (57%)	47 (53%)	
90°-180°	19 (21%)	34 (17%)		19 (21%)	17 (19%)	
>180°	19 (21%)	85 (42%)		19 (21%)	25 (28%)	
Portal vein >270°	7 (8%)	66 (33%)	0.697	7 (8%)	9 (11%)	0.077
Superior mesenteric vein >270°	10 (12%)	89 (44%)	0.787	10 (12%)	16 (18%)	0.191

PSM indicates propensity score matching; SMD, standard mean difference; SD, standard deviation; WHO ps, World Health Organization performance score; CA 19.9, carbohydrate antigen 19.9.

values can take up to 6 months after surgery.[38–40] Therefore, the influence on quality of life should be taken in account when informing patients about the possibility to proceed to surgery after induction FOLFIRINOX.

The findings of this study should be interpreted in light of several limitations. First, because only patients treated with at least 4 cycles of FOLFIRINOX or undergoing a resection after neo-adjuvant treatment with FOLFIRINOX were included, this study is prone to selection bias. Although essentially all studies describing patients who underwent treatment after FOLFIRINOX report on a selected population, the current nationwide, multicenter prospective observational design closely resembles current daily clinical practice in the Netherlands. Second, in the Netherlands LAPC is diagnosed according to the DPCG criteria,[14] which are more conservative than the NCCN criteria used for LAPC. The NCCN criteria require arterial involvement beyond 180°, or unreconstructable venous involvement.[17] These subtle differences in definition may explain differences in outcomes between studies reporting on survival in LAPC. A conservative definition for LAPC will, however, lead to more patients receiving neoadjuvant chemotherapy [ie, chemotherapy given before surgery in upfront (borderline) resectable tumors]. Neoadjuvant therapy is increasingly given to patients with borderline resectable tumors as well, which seems to improve survival over upfront resection.[14,41–43] Because all patients in our cohort are still

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TABLE 2. Multivariable Cox Regression Analysis With Factors Influencing Overall Survival in Patients With LAPC Treated With FOLFIRINOX

	HR	95% CI	*P* value
Resection (Yes)	0.416	[0.288–0.602]	<0.01
Charlson Comorbidity Index (>1)	2.164	[1.533–3.053]	<0.01
RECIST response			
Partial response	Ref	–	–
Stable disease	1.471	[1.073–2.018]	0.02

reviewed according to the NCCN criteria after induction chemotherapy, this will not deprive patients from their option of resection. To overcome the differences in criteria, the present study performed a sensitivity analysis in patients with LAPC according to the most recent NCCN criteria at baseline. This analysis confirmed that patients undergoing resection still have an improved OS over treatment with FOLFIRINOX only. Third, patients were mostly matched based on their characteristics at diagnosis. After induction chemotherapy the clinical performance status of patients might have changed, with some patients having a worse performance score due to their chemotherapeutic treatment. This and other factors might lead to residual confounding. Ideally, a randomized trial comparing patients after upfront FOLFIRINOX with and without resection might report the real survival benefit of resection. It is however unclear if such a trial is feasible. Nonetheless, future research is necessary and should focus on the benefit of resection in LAPC patients and improving the resectability criteria after systemic therapy. In the Netherlands, a nationwide implementation program (PREOPANC-4) has started to improve the extent and quality of surgery in patients with non-progressive LAPC after systemic therapy.

In conclusion, this multicenter cohort study suggests that resection in patients with LAPC after FOLFIRINOX is associated with a 9 months improved median OS and a 20% increase in 3-year OS as compared to propensity-score matched patients treated with FOLFIRINOX without resection.

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DISCUSSANTS

Jean-Marc Regimbeau (Amiens, France)

I would like to thank the ESA for the privilege of being the first discussant of this paper, and the authors for this really interesting study questioning the impact of tumor resection on survival in patients with LAPC, who remain stable after intensive chemotherapy, which is still a hot topic in multidisciplinary oncological team meetings.

A few questions arise during the evaluation of the study. The first point which needs clarification concerns the definition of ''irresectable''? The unresected patients were apparently stable after 4 courses of chemotherapy, yet some are still referred to as being irresectable? What does this correspond to, locally or metastatic progression?

The second point is as follows: could the authors please explain how both populations before PSM (resection vs no resection) were similar in terms of the resectability criteria?

The third point, is more a question than a comment: could the authors please tell us whether they currently offer surgical exploration in patients with LAPC, who have had chemotherapy reassessment, +/− radiochemotherapy reassessment, and have a clinical, biological response at best and without metastasis?

Response From Lilly Brada (Amsterdam, The Netherlands)

With regard to the definition of ''irresectable'' in the study, we evaluated all patients after 4 cycles of FOLFIRINOX according to the NCCN criteria. This is done in a multidisciplinary panel, in which all of the parameters are taken into account. Surgeons will look at the degree of vascular involvement, tumor response and plasma tumor marker (CA19–9, CEA) response. The patients, who are not resected in the study, also have RECIST stable disease after 4 cycles of FOLFIRINOX, yet, they have, for example, too much vascular involvements for us to offer the possibility of a resection. In short, there is no local or metastatic progression; they are all stable patients. But, as I mentioned in the presentation, we are considering expanding the resectability criteria in the Netherlands, to offer surgical exploration and resection after FOLFIRINOX to more patients with locally advanced pancreatic cancer.

Robin McLeod (Toronto, Canada)

First, I think that it is great that you are going to measure the quality of life. How are you going to do that and what are you looking for? Second, I must say that I think that is very important because when we give chemotherapy to patients, who we know are not going to live, the question arises as to which is better: for them to live longer but have chemotherapy, which has negative side effects, or shorter but their quality of life is better. This study begins to measure things like this. I think it is really important to assess whether they are willing to live longer, even though they may not be as happy.

Response From Lilly Brada (Amsterdam, The Netherlands)

We have not yet measured the quality of life in all of these patients. However, in the Netherlands, the PACAP nationwide study, in which all patients with pancreatic cancer are sent quality of life questionnaires at several time periods during the course of their treatment, is ongoing. We will see whether we have sufficient data and questionnaires to assess the quality of life. Second, I do agree with you. I think that quality of life is really important and it is increasing in importance with time. So, it is good to take this into account as well.

Conor Delaney (Weston, FL, USA)

Could you please provide some more information about how you tried to standardize the imaging of the resection criteria because that is obviously significant when you have so many centers involved? Can you also comment on whether you were surprised by the lack of difference in survival between the resected and non-resected patients?

Response From Lilly Brada (Amsterdam, The Netherlands)

In answer to your first question, we did standardize imaging. All patients had a CT-scan with portal venous and arterial phase, and all imaging was sent to a single imaging coordinator. We have an online panel of 4 surgeons and 4 interventional radiologists, who review all of this imaging. They are very experienced, and it is like giving these patients a second opinion to see what the possibilities are. In this way, we do not yet standardize the resectability criteria, but that is also why we have this study, to improve the resectability rate in the Netherlands.

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