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CT response of primary tumor and CA19-9 predict resectability of metastasized pancreatic cancer after FOLFIRINOX

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ABSTRACT

Background: Effective chemotherapy protocols are currently changing the treatment options for metastasized pancreatic cancer. Survival benefits after synchronous metastasectomy have been reported for selected patients. We set out to assess predictive factors of resectability for synchronous metastases after FOLFIRINOX.

Methods: Consecutive patients with metastatic pancreatic cancer undergoing surgery after FOLFIRINOX between 2011 and 2017 were identified from a prospectively collected database. Surgery following chemotherapy was indicated in patients with no more than six metastatic lesions, no progression detected on CT, and technically resectable disease. Patients who received synchronous metastasectomy were compared with patients who received explorative laparotomy or palliative surgery in terms of predictors of resectability and overall survival. In patients undergoing resection, prognostic factors were examined.

Results: Of 101 patients scheduled for surgery after FOLFIRINOX, synchronous metastasectomy was performed in 43 cases (43%) and non-resection surgery in 58 cases (57%). The shrinkage rate of the primary tumor on CT ($P = 0.04$) and the postchemotherapy serum CA19-9 concentration ($P = 0.02$) were associated with resectability. The median overall survival of the patients undergoing metastasectomy was longer than that of the patients without resection (21.9 months vs 16.4 months, $P = 0.006$). Post-chemotherapy serum CA19-9 value ($P = 0.04$) and lymph node ratio ($P = 0.01$) were prognostic factors in the patients undergoing metastasectomy.

Conclusions: In selected patients who satisfied our surgical criteria, shrinkage rate of primary tumor and postchemotherapy serum CA19-9 level, which predict resectability of metastasized pancreatic cancer, should be considered in decision making to avoid unnecessary surgery.

Background

With a 5-year survival rate of 8% [1], the prognosis of pancreatic ductal adenocarcinoma (PDAC) is still dismal [2]. Complete surgical resection is the only curative treatment option for pancreatic cancer patients, but only 10%–20% of tumors are resectable at primary diagnosis [3]. A further 10% of patients become candidates for curative surgery following induction treatment [4]. The large majority of patients present with locally advanced unresectable or metastatic disease, where treatment is generally considered palliative rather than curative [5].

In the setting of palliative treatment for metastatic pancreatic cancer, the median overall survival was 11.1 months with FOLFIRINOX as first-line therapy (ACCORD trial) [6]. Although metastatic disease is generally regarded as a contraindication to resection [7], survival benefits after metastasectomy with/without preoperative chemotherapy have been reported in selected patients with oligometastatic pancreatic cancer [8–11]. Decisions regarding

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Abbreviations

AUC	area under the curve
CT	computed tomography region of interest
PDAC	pancreatic ductal adenocarcinoma
ROC	receiver operating characteristic
ROI	region of interest

resection in the setting of metastasized pancreatic cancer have been made on a highly individual basis. To date, no objective criteria identifying the patients most likely to benefit from surgery have been clearly described or assessed.

Therefore, the aims of this study were (1) to assess radiological and clinical factors predicting resectability, (2) to evaluate the survival of patients undergoing pancreatic resection with synchronous metastasectomy after preoperative FOLFIRINOX treatment, and (3) to investigate prognostic factors for survival in patients undergoing metastasectomy.

Methods

Study design and population

Consecutive patients undergoing induction chemotherapy with FOLFIRINOX as first-line treatment followed by surgery for metastatic pancreatic cancer at primary diagnosis between February 2011 and June 2017 at the Department of Surgery, University of Heidelberg, were identified from a prospectively collected database and included in this study. The data on included patients were collected and handled in compliance with the guidelines of the Institutional Ethics Committee after approval (Ethics Committee Approval No. S-011/2015).

Based on previous results, FOLFIRINOX was selected as first-line chemotherapy for the majority of patients with metastasized pancreatic cancer in our institute [6,12]. Although at least six cycles of FOLFIRINOX (as either an original or a modified regimen) were planned for patients with metastatic pancreatic cancer at primary diagnosis, patients with fewer than six cycles by reason of adverse events or poor performance status were included in this study. Patients with other protocols as second-line chemotherapy were excluded.

Patient surveillance during chemotherapy and imaging investigation

From the time of first diagnosis and commencement of induction chemotherapy with FOLFIRINOX, patients were re-evaluated every 3 months during chemotherapy by computed tomography (CT), measurement of CA19-9 serum levels, and clinical examination.

The details of CT acquisition were described previously [13]. Briefly, four phase images (nonenhanced, arterial, venous, delayed phase) were acquired. At baseline and follow-up examinations, the largest tumor area was measured in the portal venous phase on axial CT slices by manually tracing the tumor outline with a region of interest (ROI) [14]. The ROIs were drawn 3 times in the same CT slice, and the mean value data was regarded as the patient's representative value. The tumor size response during chemotherapy was calculated as (postchemotherapy tumor size)/(prechemotherapy tumor size).

Patients with Lewis antigen negative (CA19-9 < 5.0 U/mL [15]) at primary diagnosis were excluded from the analyses of CA19-9. The parameter delta CA 19-9 was calculated as (postchemotherapy CA19-9) − (prechemotherapy CA19-9).

Indication for surgery and surgical approach

Surgery was scheduled for those patients who satisfied all of the imaging criteria for synchronous metastasectomy after FOLFIRINOX: a maximum of six metastatic lesions, no tumor progression, and technically resectable disease. Aside from metastatic lesion, the indication for the primary tumor resection was based on the criteria of resectable and borderline resectable pancreatic cancer, as defined by the National Comprehensive Cancer Network (NCCN) guidelines and the ISGPS consensus [16,17].

Metastatic burden was evaluated intraoperatively via surgical exploration and ultrasonography of the liver. If progressive disease and/or technically unresectable tumor were detected, explorative or palliative surgery was performed. Patients with six or fewer metastases and resectable tumor underwent combined resection of the primary pancreatic tumor and the metastases.

Outcomes

The primary endpoint of this study was to determine predictors for resectability of the primary tumor and its metastases. Relevant patient characteristics and surgical outcomes were extracted from the institution's pancreatic database, and analyzed to compare patients undergoing resection with patients undergoing explorative or palliative surgery. Each continuous variable was divided by an individual cutoff value to be a categorical variable. The postoperative surgical complications were evaluated according to the Clavien-Dindo classification [18,19].

As subgroup analyses, overall survival was analyzed in the two groups and prognostic factors were evaluated in the patients undergoing resection.

Statistical analysis

Categorical variables were compared using either the chi-square test or Fisher's exact test, while continuous variables were compared using the Mann-Whitney *U* test. Multivariable modeling was done using the logistic regression model to evaluate predictors for resectability. Optimal cutoff values for resectability in receiver operating characteristic (ROC) curves were determined by means of the Youden index [20]. A median of lymph node ratio (LNR; (number of positive lymph node)/(number of harvest lymph node)) was regarded as cutoff value of LNR for overall survival in patients undergoing resection. Sensitivity and specificity of resectability or overall survival at the point of the cutoff values were calculated. Overall survival from the date of initial chemotherapy was compared using Kaplan-Meier survival analysis. Data were censored if the patients were alive at the time of the analysis or had been lost to follow-up. The multivariate Cox regression model was utilized to determine significant predictors of prognosis. All statistical analyses were performed using R version 3.2.3 (R Project for Statistical Computing, Vienna, Austria), and a P value < 0.05 was considered to show a statistically significant difference.

Results

Demographics of the study cohorts and surgical outcomes

A total of 101 patients with metastatic pancreatic cancer who underwent laparotomy with or without oncologic resection after FOLFIRINOX as initial treatment were included. Forty-three patients (43%) underwent resection and 58 patients (57%) received explorative or palliative surgery (Table 1). Among the 43 patients

Table 1
Patient demographics. ASA, American Society of Anesthesiologists.

Parameter	Metastasectomy	Exploration or palliation	*P*
	N = 43	N = 58	
Age, years; median (range)	60 (33–76)	61 (35–80)	0.53
Male gender, n (%)	23 (54%)	39 (67%)	0.22
Duration of preoperative FOLFIRINOX, months; median (range)	4 (1–23)	4 (1–16)	0.48
ASA score, n (%)			0.17
1	3 (7%)	1 (2%)	
2	25 (58%)	28 (48%)	
3	15 (35%)	29 (50%)	
Prechemotherapy CA19-9, U/mL; median (range)	914 (7–23000)	525 (12–42518)	0.91
Postchemotherapy CA19-9, U/mL; median (range)	47 (4–13743)	215 (6–17510)	0.01
Delta CA19-9, U/mL; median (range)	−622 (-22979–12673)	−152(-40593–12839)	0.13

with synchronous metastasectomy, 16 (37%) underwent pancreaticoduodenectomy, 19 (44%) distal pancreatectomy, and 8 (19%) total pancreatectomy for their primary tumor (Table 2). In addition to the pancreatic resection, six metastatic lesions (the maximum for inclusion) were resected in 2 patients (5%) and one single lesion was removed in 19 patients (44%). In 5 patients (11%), no viable cancer cells were detected in the resected metastatic lesions. The two sites from which most metastases were resected were liver (30 patients, 70%) and peritoneum (7 patients, 16%). Major morbidity (Clavien-Dindo grade lll–V) occurred in 12 patients (28%). The remaining 58 patients did not undergo resection, due to the intraoperative findings of disease progression (46 patients, 79%) or technically unresectable disease (12 patients, 21%) (Supplementary Table 1). Forty-six of these patients (79%) underwent only exploratory surgery and 12 patients (21%) received palliative surgery.

Table 2
Procedure and findings of metastasectomy.

Parameter	Metastasectomy
	N = 43
Type of pancreatectomy, n (%)	
Pancreaticoduodenectomy	16 (37%)
Distal pancreatectomy	19 (44%)
Total pancreatectomy	8 (18%)
Vascular resection, n (%)	
Portal vein	15 (35%)
Artery (hepatic artery)	1 (2%)
Number of resected metastases[a], n (%)	
None (disappeared)	5 (11%)
1	19 (44%)
2	11 (26%)
3	4 (9%)
4	0 (0%)
5	2 (5%)
6	2 (5%)
Site of resected metastases, n (%)	
Liver	30 (70%)
Peritoneum	7 (16%)
Lymph nodes	3 (7%)
Lung	1 (2%)
Adrenal glands	1 (2%)
Peritoneum + adrenal glands	1 (2%)
Tumor characteristics	
T stage, n (%)	
ypT0	3 (7%)
ypT1	7 (16%)
ypT2	5 (11%)
ypT3	28 (65%)
ypT4	0 (0%)
N stage, n (%)	
ypN0	24 (56%)
ypN1	9 (21%)
ypN2	10 (23%)
R0 margin[b], n (%)	22 (51%)
LNR; median (range)	0.08 (0.00–0.58)
Hospital stay, days; median (range)	13 (5–56)
Morbidity (Clavien–Dindo grade 3+), n (%)	12 (28%)
30-day mortality, n (%)	1 (2%)
Adjuvant chemotherapy, n (%)	
Yes	4 (9%)
No	30 (70%)
Unknown	9 (21%)
Disease free survival, months; median (range)	6.9 (2.0–36.3)

LNR, lymph node ratio.
[a] Number of resected metastases examined by pathologist.
[b] Defined as a minimum 1-mm margin.

Cut-off value analysis

The best cut-off value of duration of preoperative FOLFIRINOX (AUC = 0.54) for resectability was 8.1 months, with sensitivity of 16% and specificity of 97% (Fig. 1A). Pre- and postchemotherapy CT scans were available for 70 out of 101 patients (69%). The best cut-off value of the shrinkage rate of the primary tumor for resectability (AUC = 0.83) was 0.47, with sensitivity of 62% and specificity of 90% (Fig. 1B).

Three patients (3%) were deemed Lewis antigen negative at primary diagnosis and excluded from the analyses of CA19-9. Prechemotherapy CA19-9 values were available from 72 out of 101 patients (71%; median 641 U/mL, range 7–42,518), and postchemotherapy CA19-9 values from 96 patients (95%; median 146 U/mL, range 4–17,510). For prechemotherapy CA19-9, the area under the curve (AUC) was 0.49 and the optimal cut-off for resectability was 914 U/mL, with sensitivity of 52% and specificity of 63% (Fig. 1C). In similar fashion, the best cut-off value for postchemotherapy CA19-9 (AUC = 0.67) was 147 U/mL, with sensitivity of 73% and specificity of 65% (Fig. 1D), and the best cut-off value for delta CA19-9 (AUC = 0.61) was −870 U/mL, with sensitivity of 48% and specificity of 81% (Fig. 1E).

Accordingly, the cut-off values based on these results were set as follows: 8 months for period of preoperative FOLFIRINOX, 0.5 for shrinkage rate of primary tumor, 900 U/mL for prechemotherapy CA19-9, 150 U/mL for postchemotherapy CA19-9, −850 U/mL for delta CA19-9, and 0.1 for LNR.

Predictors for resectability

Univariate and multivariate analysis revealed that both the shrinkage rate of the primary tumor as defined by CT and the postchemotherapy CA19-9 serum levels were significantly related to resectability of the primary tumor and its metastases (univariate analysis: $P < 0.01$ and $P < 0.01$; multivariate analysis: $P = 0.04$ and $P = 0.02$, respectively) (Table 3). Imaging response in terms of size and number of metastases after chemotherapy did not predict resectability ($P = 0.80$).

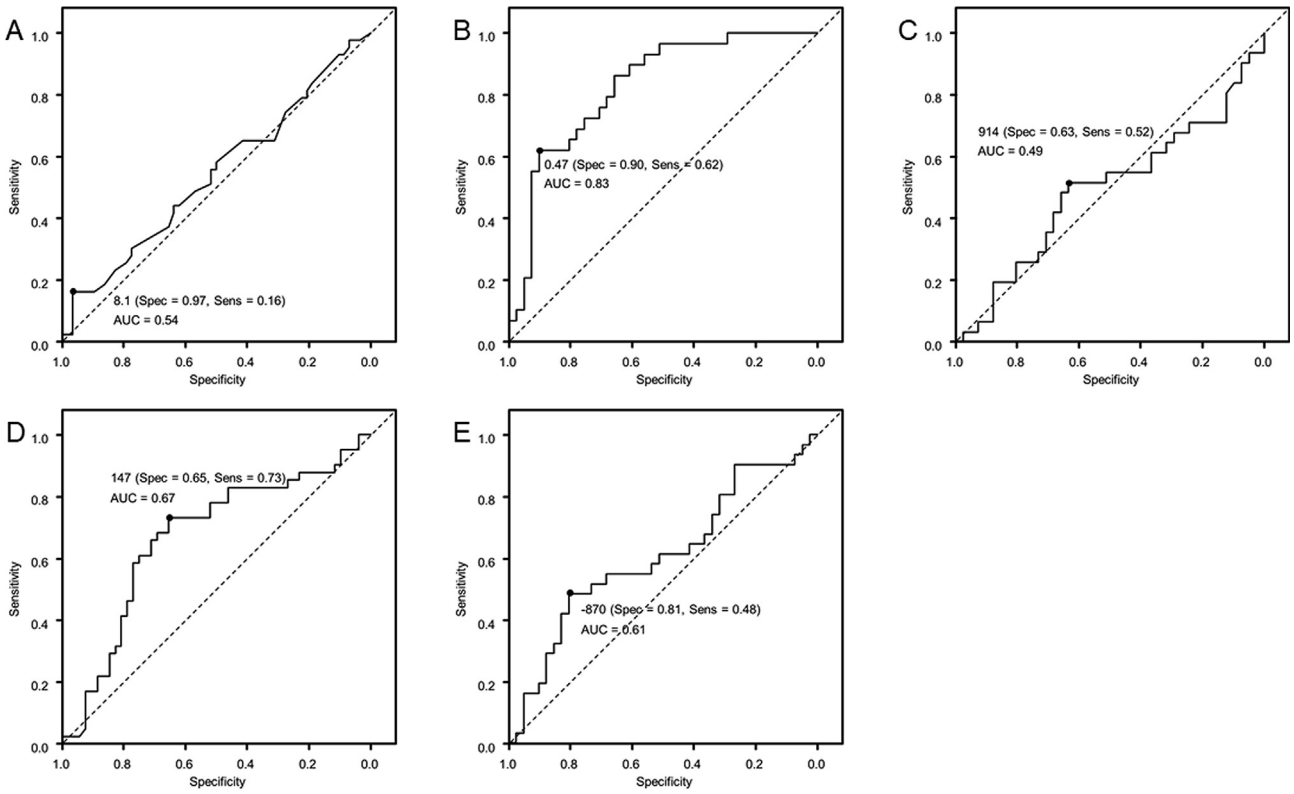

Fig. 1. Predictors for resectability in patients with metastatic pancreatic cancer.
The receiver operating characteristics (ROC) curves constructed based on each predictor for resectability are demonstrated. The optimal cut-off value is determined by the maximum of Youden index (sensitivity + specificity - 1), which is the maximum vertical distance between the curve and the diagonal chance line (broken line).
(A) Duration of preoperative chemotherapy; (B) Shrinkage rate of primary tumor; (C) Prechemotherapy CA19-9; (D) Postchemotherapy CA19-9; (E) Delta CA19-9;
Spec, Specificity; Sens, sensitivity; AUC, area under curve.

Survival

Of the entire cohort of 101 patients, survival information was available for 89 patients (88%) while the remaining 12 patients were lost to follow-up. A median duration of follow-up was 17 months (range, 3–55 months). There was a significant difference in overall survival between the patients who underwent oncological resection including metastasectomy and those who received explorative or palliative surgery ($P = 0.006$). The median survival time was 21.9 and 16.4 months, respectively (Fig. 2).

Predictors for survival in patients undergoing pancreatic resection and synchronous metastasectomy

Univariate and multivariate analysis showed that post-chemotherapy serum CA19-9 values and LNR below the cut-off were significantly associated with longer overall survival in patients undergoing pancreatectomy with synchronous metastasectomy (univariate analysis: $P < 0.01$ and $P < 0.01$; multivariate analysis: $P = 0.04$ and $P = 0.01$, respectively) (Table 4).

Discussion

In this study, the shrinkage rate of the primary tumor and postchemotherapy CA19-9 levels were independent predictors for resectability of the primary tumor and its metastases after FOLFIRINOX for PDAC. The patients treated with synchronous resection had a better prognosis than patients who underwent explorative or palliative surgery without oncological resection, and postchemotherapy CA19-9 levels and LNR were prognostic factors after metastasectomy.

According to the international guidelines for the treatment of pancreatic cancer and widespread clinical practice, resection of pancreatic cancer metastases is not recommended and therefore not routinely performed in clinical practice [7,21]. However, recent developments in chemotherapy may provide more opportunities for potentially curative resection in carefully selected patients with metastatic pancreatic cancer [9,22]. The evidence on selection of patients eligible for this aggressive approach is based primarily on small case series [9,22]. Our study has confirmed the predictors for resectability of metastasectomy in combination with primary tumor resection following induction chemotherapy with FOLFIRINOX in a large cohort of patients selected based on our standardized criteria.

In our institute, surgery was scheduled for those patients who fulfilled the surgical criteria for synchronous metastasectomy after preoperative FOLFIRINOX (i.e. no more than six metastatic lesions after induction chemotherapy, no progression on CT, technically resectable disease). If the disease was found to exceed these limits at operation, explorative or palliative surgery was carried out instead. On the other hand, unnecessary surgery should be avoided whenever possible. The established diagnostic criteria failed to predict resectability accurately in our cohort. However, shrinkage rate of primary tumor and serum CA19-9 levels after FOLFIRINOX were associated with resectability and could therefore be incorporated into the decision-making algorithm for resection of metastasized pancreatic cancer in the future. In contrast, imaging findings in terms of the size and number of metastatic lesions did

Table 3
Univariate and multivariate analysis of predictors for resectability.

Variables	Metastasectomy	Exploration or palliation	Univariate analysis	Multivariate analysis		
	N = 43	N = 58	*P*	Odds ratio	95% CI	*P*
Duration of preoperative FOLFIRINOX, months			0.09	1.0	0.4–26.3	0.99
<8	36 (84)	55 (95)				
≥8	7 (16)	3 (5)				
Shrinkage rate of primary tumor size after chemotherapy			<0.01	13.0	1.0–162.0	0.04
<0.5	18 (62)	6 (15)				
≥0.5	11 (38)	35 (85)				
Unknown	14	17				
Prechemotherapy CA19-9, U/mL			0.24			
<900	16 (52)	15 (37)				
≥900	15 (48)	26 (63)				
Unknown or excluded	12	17				
Postchemotherapy CA19-9, U/mL			<0.01	10.3	1.4–76.3	0.02
<150	31 (74)	20 (37)				
≥150	11 (26)	34 (63)				
Unknown or excluded	1	4				
Delta CA19-9, U/mL			0.01	5.4	0.63–46.5	0.12
<-850	15 (48)	8 (20)				
≥-850	16 (52)	33 (80)				
Unknown or excluded	12	17				
Site of metastases[a]			0.09	1.4	0.1–15.2	0.79
Liver only	30 (81)	27 (63)				
Peritoneum only	7 (19)	16 (37)				
Others	6	15				
Imaging response in terms of size and number of metastases after chemotherapy[b]			0.80			
Yes	11 (38)	14 (34)				
No	18 (62)	27 (66)				
Unknown	14	17				

[a] Site of metastases as evaluated by CT and intraoperative findings.
[b] Any effective response of size and number on CT was categorized as Yes.

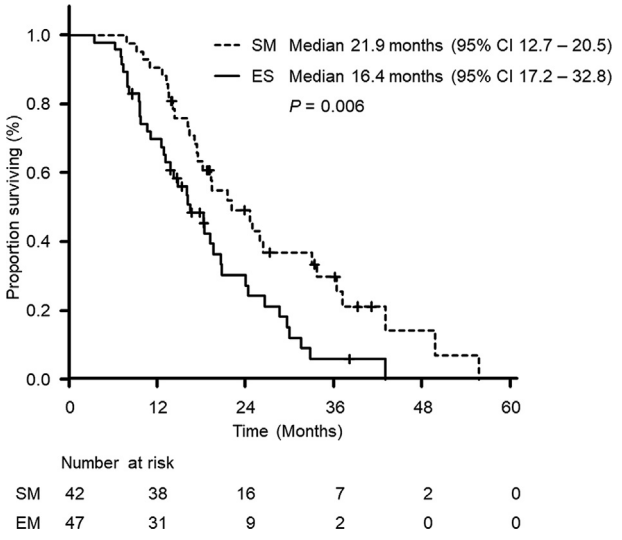

Fig. 2. Overall survival in patients with metastatic pancreatic cancer undergoing treatment with FOLFIRINOX followed by surgery with/without resection.
SM, Patients undergoing synchronous metastasectomy; ES, patients undergoing explorative or palliative surgery.

not predict resectability and therefore should not be considered in the decision-making process. This finding might be partially explained by the low sensitivity of current CT protocols in detecting small hepatic and peritoneal metastases of pancreatic cancer [23,24]. The common issue in evaluation of primary tumor and metastatic lesions is that chemotherapy induces fibrosis and necrosis and consequently hampers accurate determination of the actual tumor burden [24,25]. To avoid the heterogeneity of morphologic response by various agents, we focused exclusively on FOLFIRINOX. Predictors for resectability after induction chemotherapy with other agents than FOLFIRINOX may be different and should therefore be evaluated in future studies.

Focusing on long-term outcomes, the median overall survival of the patients with explorative or palliative surgery (16.4 months) was considerably higher than that of the patients with metastatic pancreatic cancer (11.1 months) in the ACCORD trial, where FOLFIRINOX was selected as first-line therapy in patients with unresectable metastatic pancreatic cancer [6]. This difference may be explained by preoperative selection of patients with less advanced disease, as defined by the above-mentioned criteria. In addition, the better prognosis in the patients undergoing synchronous metastasectomy compared with those undergoing the explorative or palliative surgery may reflect appropriate intraoperative re-evaluation of resectability and favorable decision-making.

Even after potentially successful metastasectomy, there is no standard treatment following induction chemotherapy and resection [26,27]. We found that the postchemotherapy serum CA19-9 concentration and LNR had an impact on the overall survival after resection of the primary tumor and its metastases. These two factors may guide optimal follow-up and postoperative treatment and help to identify patients at risk of early relapse.

Various limitations need to be addressed. First, due to the retrospective design of this study, it was not possible to include patients satisfying our surgical criteria for synchronous metastasectomy but then not undergoing surgery. The better prognosis observed in the patients undergoing resection is likely from patient selection. The true impact of metastasectomy on overall survival requires re-evaluation in a more controlled analysis, preferably a multicenter randomized controlled trial. Second, missing data including CT and survival information may have contributed to the risk of bias. In some patients, tumor status after chemotherapy was re-evaluated only by MRI rather than CT, so these patients had to be

Table 4
Univariate and multivariate analysis of predictors for survival of patients with metastasectomy.

Variables		Univariate analysis	Multivariate analysis		
		P	Hazard ratio	95% CI	*P*
Duration of preoperative FOLFIRINOX, months	≥8 vs < 8	0.16			
Shrinkage rate of primary tumor size after chemotherapy	≥0.5 vs < 0.5	0.10	1.54	0.47–5.08	0.48
Prechemotherapy CA19-9, U/mL	≥900 vs < 900	0.63			
Postchemotherapy CA19-9, U/mL	≥150 vs < 150	<0.01	4.64	1.08–19.88	0.04
Delta CA19-9, U/mL	≥-850 vs < -850	0.45			
Site of metastases	Liver vs peritoneum	0.91			
Imaging findings: effective response of size and number of metastases after chemotherapy[a]	Yes vs no	0.16			
Vascular resection[b]	Yes vs no	0.139			
R1 margin[c]	Yes vs no	<0.01	1.31	0.39–4.42	0.67
LNR	≥0.1 vs < 0.1	<0.01	4.93	1.43–16.96	0.01

LNR, lymph node ratio.
[a] Any effective response of size and number on CT was categorized as Yes.
[b] Resection of portal vein or hepatic artery.
[c] R1 margin was defined as less than 1 mm of tumor clearance.

excluded from analyses of CT data. Third, dose modification of FOLFIRINOX and timing of prechemotherapy CA19-9 test (e.g. before or after biliary drainage) also may have contributed to the risk of bias. Most of patients underwent preoperative treatment at non-affiliated institutions, some of which did not provide sufficient information of their clinical course.

In summary, in the framework of patients eligible for our surgical indication, the shrinkage rate of the primary tumor and the postchemotherapy CA19-9 level predict the resectability of the primary tumor and the synchronous metastases of pancreatic cancer after FOLFIRINOX. These factors should be considered in decision making to avoid unnecessary surgery.

Disclosure information

None of the authors has any actual or potential conflict of interest in relation to the submission of this article. This paper is not based on a previous communication to a society or meeting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.039.

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