Radical Surgery of Synchronous Oligometastatic Liver Lesions of the Ductal Adenocarcinoma of the Pancreas Results in Prolonged Survival

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Abstract

Background

The ductal adenocarcinoma of the pancreas (PDAC) remains one of the most lethal malignancies. The role of surgery for circumscribed synchronous hepatic lesions of PDAC remains controversial. Thus, the aim of our study was to compare survival outcome (OS) after surgery of patients with hepatic metastases (M1surg) to patients with only localized disease.

Methods

Correlation analysis of clinicopathological data and OS after resection of M1surg patients and patients with localized PDACs (M0) was performed. Patients were included for survival analysis only if a complete staging including perineural, venous and lymphatic invasion was available.

Results

Out of the study collective, 35 patients received extended surgery (M1surg), whereas 202 patients received standardized surgery for localized disease (M0). Clinicopathological variables were homogenously distributed between M1surg and M0. The length of hospitalization and morbidity was similar in both groups. FOLFIRNOX as an adjuvant treatment regime was administered in ~ 23% and ~ 8% of M1surg and M0 patients, respectively. In a multivariate analysis, there was no difference in overall survival between both groups. Only the resection status (R1 vs R0) and venous invasion (V1) were identified as independent prognostic factors.

Conclusion

This is the first study demonstrating a survival benefit after extended surgery for synchronously hepatic-metastasized PDACs. We found no difference in survival outcome of metastasized patients when compared to patients with localized disease. FOLFIRINOX as an adjuvant treatment regime for resected M1surg presumably is worthwhile. Larger multicenter studies are still needed to validate our results.

Background

The ductal adenocarcinoma of the pancreas (PDAC) has a poor prognosis with a median overall survival of ~ 6 months and is estimated to become the second leading cause of cancer-related death in the United States and also in Germany by 2030 (1, 2). To date, the only curative therapy remains the margin-negative oncological resection with an adjuvant treatment regime starting within 6 weeks of the operation (3, 4). Because oncological advances for PDAC have been slow and poor, the 5-year overall survival rate did not change over the past decade and remains under 10% (5).

The PDAC metastasizes primarily the peritoneum, the liver and to the lungs (6). At diagnosis of PDAC, 50% of patients have already metastasized synchronously and further 30% presented with locally advanced disease, which is not suitable for surgery. Thus, only 20% of the patients with a PDAC received curative-intended surgery. Therefore, it is still regarded as one of the most lethal cancers indicated by a very high mortality-to-incidence ratio (5, 7).

Palliative intended therapy or chemotherapy is the standard of care for patients with metastasized or locally advanced PDACs (8, 9). To date, however, no standardized surgical treatment exists for patients with synchronous or metachronous oligometastatic disease. Therefore, in current clinical practice, unlike in other malignancies, synchronous metastasectomy of PDAC has rarely been performed. In these patients, neoadjuvant chemotherapy with subsequent resection and ablative technologies are possible treatment options for metastasized PDAC. Hence, therapeutic regimes, such as FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) or gemcitabine and nab-paclitaxel, have very recently been established as neoadjuvant or primary treatment options (9, 10). To date, it is unclear which patient group might benefit from such an individual approach of neoadjuvant therapy followed by radical tumor resection. Moreover, it is unclear whether chemotherapy-naive patients with small tumor burdens, patients with a stable disease, or patients with tumor regression after neoadjuvant therapy would benefit from a multimodal approach.

The aim of our study was to analyze patients who received extended surgery in our department for synchronously hepatic-metastasized ductal adenocarcinomas of the pancreas (M1surg) and to compare those to two control groups: patients after multimodal therapy for localized disease (M0) and patients who received palliative intended therapy for metastasized disease (M1pall).

Methods

Patient selection and clinicopathological data

Patients with ductal adenocarcinoma of the pancreas who consecutively received surgery or palliative therapy between September 2003 and December 2019 at the Heinrich Heine University Hospital of Duesseldorf were included in the study. Exclusion criteria were patients with (1) malignancies of the pancreas other than ductal adenocarcinoma, (2) in whom the TNM staging did not include information about lymphatic, perineural and venous invasion (Lx, Pnx, Vx), (3) in patients who were lost to follow-up, (4) in patients who received palliative intended therapy other than for isolated resectable hepatic metastases, and (5) in patients who succumbed within the 30-day of surgery. Cut off point during follow-up was 60 months. Clinical data of these consecutively treated patients collected from patient's medical records were compiled into an Excel®-file database and analyzed retrospectively.

Patients who received palliative intended therapy were included only if information about the number, size and location of the hepatic metastases were available. This data was compared to patients with extended surgery for metastasized disease. Information of the TNM staging system (size of tumor /

involvement of adjacent arteries, lymph node status, and status on distant metastasis), along with grading, perineural invasion, lymphatic and venous invasion was retrospectively collected from the original histopathological reports for each patient. The TNM staging system, if applicable, was updated to the 8th Edition of the UICC TNM classification of malignant tumors [17]. Size by greatest diameter measured pathologically, and the location and number of hepatic metastases were re-assessed from the pathological reports and radiographic imaging. Clinico-pathological data (gender, age at the time of surgery, overall survival (OS) and results of follow-up examinations including time of diagnosis of metastases and sight of metastases) were retrieved.

The analysis was performed in conformity to the Declaration of Helsinki and to good clinical practice. Furthermore, the study war approved by the Institutional Review Board (IRB) of the Ethics Committee, Heinrich Heine University Duesseldorf (IRB-no. 2019-473-2).

Statistical analysis

The Wilcoxon test was used to analyze differences in clinicopathological data between the three subgroups. The Mann-Whitney U test was used to examine numerical data and to correlate between clinic-pathological variables. For categorical data, the chi-square test was applied. The overall survival (OS) was determined as the period from the date of surgery until the date of death of any cause, or the last follow-up. Disease-free survival described the period from the date of surgery until the date of diagnosed metachronous metastases or local recurrence. Kaplan–Meier curves were generated and analyzed by using the log-rank (Mantel Cox) test, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. For multivariate survival analysis, all variables were included into a logistic regression analysis. Analyses were performed using SPSS® statistics for Windows (version 25.0; SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

From a total cohort of 346 patients who received surgery for PDAC with curative intend, regardless of tumor stage, 251 patients met our pre-defined inclusion criteria for the analysis of synchronous-metastasized PDAC and received surgery in our hospital (Table 1). Thirty-five patients met the inclusion criteria of oligometastatic disease to the liver (group: M1surg). In the same period, 202 consecutive patients received surgery for localized disease (group: M0) and 14 patients with oligometastatic disease to the liver (group: M1pall) were treated with a palliative intended chemotherapy according to national guidelines (11). Both groups served as controls for matched pair analysis

The median age of all 251 patients at the time of surgery was 69 years (range 41–95 years). Our collective consisted of 144 males (57.4%) and 107 females (42.6%) and did not show any differences within the three groups. In 229 patients, the PDAC was located in the pancreatic head. In further 22 patients, the tumor originated from the pancreatic tail (Table 1). In our total cohort of patients, the mean follow-up period was 17.4 months (range: 0.72-59 months).

Correlation analyses of clinicopathological variables

Of all analyzed clinicopathological variables, only T-stage and R-status were heterogeneously distributed between patients who received curative-intended surgery for localized and metastasized disease respectively (M0 vs M1surg) (Tables 1 and 2). Thus, a larger tumor size correlated with synchronous hepatic metastases. The median hospital stay for surgically resected patients with localized disease (M0) and for patients who received extended surgery for metastasized disease (M1surg) was 22 days (range: 9-262 days) and 21 days (range: 10–88 days) respectively, with no significant difference in hospital stay and rate of morbidity between both surgically treated groups (*p = 0.503*) (Table 2). However, in group M1pall, the median hospital stay was significantly shorter compared to both other groups (median days: 11 days; range: 5–15 days) (Table 2).

A correlation analysis of pathological data in the group with palliative intended therapy was not performed due to incomplete pathological staging for the primary tumor (Tables 1 and 2). As evident in computed tomography and histopathological reports, the size and number of hepatic metastases were homogeneously distributed between M1pall and M1surg patients (Table 3). In the median, one metastasis (range: 1–4) was resected in patients with synchronously metastasized PDAC, and diagnosed via surgical exploration in group M1pall (range: 1–2). In 27 (51.9%) surgically treated patients and in nine (64.5%) patients with palliative intended treatment, the metastases were located in the left hepatic lobe. In correlation analysis, there was no significant difference in number, size and site of metastases between each group (Table 3).

Survival analysis

Two-hundred patients (74%) died during the follow-up period. The median OS of all 270 patients was 20.8 months (95%CI: 18.7–23.1 months). The follow-up cut off was set to 60 months. Out of the total study collective, 82.9% of the patients received an adjuvant therapy. In group M0, 158 patients (71.5%) were given gemcitabine as monotherapy, whereas 48 patients (21.7%) received a combination therapy with paclitaxel. Only 18 patients (8.1%) were given FOLFIRINOX as a standardized adjuvant treatment regime. In the M1surg group, 15 patients received an adjuvant gemcitabine therapy (42.8%), while eight patients received FOLFIRINOX (22.8%) (Four perioperative and four postoperative) and two patients received an adjuvant gemcitabine multidrug regime with either erlotinib or paclitaxel (5.7%). Further five patients entered the HEAT study and received adjuvant radiochemotherapy (14.2%). No patient after extended resection or palliation (M1surg and M1pall) for oligometastatic disease to the liver was still alive five years after diagnosis.

Overall survival

Univariate survival analysis was performed for the total cohort and for all three subgroups separately (M0, M1surg, and M1pall; Table 4). In the univariate analysis of all 270 studied patients, patients with higher median age, PDACs of the pancreas tail, surgically resected synchronous hepatic metastases, higher tumor grading, positive venous infiltration, and positive resection margins had a significantly worse overall survival (Table 5, Fig. 1A). Thus, patients who received resection of the primary PDAC with synchronous liver metastases had a median OS of 10.3 months (95%CI: 7.2–13.4 months) (M1surg), which was shorter than in patients with localized disease (median: 17.9 months, 95%CI: 14.9–20.8

months) (M0) (*p = 0.006*). In group M1surg, higher median age, T-stage and tumor grading as well as positive resection margins were associated with worse overall survival (Table 4). Due to a deficiency in the available clinicopathological variables for patients with palliative intended therapy, only univariate analysis was performed for gender and tumor grading in this group (*p = 0.738* and *p = 0.637*) (Table 4). The median OS of the 14 M1pall patients was 8.15 months (range: 0.46-14 months).

Univariate subgroup analysis for overall survival

Subgroup analysis was performed for R0 resected patients independent of the M-stage (M0 vs. M1surg). In univariate analysis, there was no significant difference in overall survival between both surgically treated subgroups (M1surg vs. M0) (*p = 0.440*). Thus, the median OS with 17.6 months (95CI: 8.8–26.5 months) in patients who received histopathologically proven tumor-free extended resection (M1surg; n = 17) was not statistically different compared to the median OS with 19.4 months (95%CI: 16.9–22.0 months) in patients who received histopathological proven tumor-free resection for localized disease (M0; n = 171) (Fig. 1A).

Further subgroup survival analysis was performed between R0 resected M1surg patients and M0 patients who received FOLFIRINOX as an adjuvant treatment regime. When all patients were included for analysis independent of resection status, patients with localized disease (M0, n = 18) showed a clear survival benefit (*p = 0.013*). However, when only R0 resected patients in group M1surg were considered for analysis (M0 n = 18; M1surg n = 17), no significant survival difference was detected (*p = 0.432*) (Fig. 1B).

Furthermore, survival analysis between M1surg and M1pall patients was performed. In univariate analysis, patients who received extended surgery for metastasized PDACs had a similar survival outcome when compared to M1pall cohort (*p = 0.051*). By considering only margin-negative resected patients for the survival analysis (n = 17), patients treated with palliative intent showed a worse survival outcome compared to the M1surg group (*p = 0.005*, Fig. 1C).

Multivariate survival analysis

Multivariate survival analysis was performed in 154 patients of the total cohort of 237 patients, followed by subgroup analysis (M0 and M1surg) (Table 5). Only patients with a complete staging system incorporating also perineural, venous and lymphatic invasion were included for analysis (Table 1). In multivariate analysis of all 154 studied patients, only higher median age, positive venous invasion and positive resection margins were independent prognostic factors for overall survival (Table 5). In patients with surgically resected metastasized disease (M1surg), higher T-stage and higher tumor grading were left as independent prognostic factors. In patients with surgically resected localized disease (M0), the distribution of independent prognostic factors was equivalent to the total cohort (Table 5).

Furthermore, in multivariate subgroup analysis of only margin-negative resected patients, distant hepatic metastases were not independent prognostic factors for survival (*p = 0.10*; HR = 1.4; 95%CI (0.94–1.9). Only higher median age and positive venous invasion were shown to be prognostic relevant (HR = 2.3; 95%CI (1.4–3.7) and HR = 2.1; 95%CI (1.2–3.6), respectively.

Discussion

To date, little is known about the feasibility and survival outcome of patients who undergo surgery for synchronously hepatic metastasized PDACs. To the best of our knowledge, this is the first study to compare survival of patients after extended surgery for synchronous hepatic metastases (M1surg) to patients with localized disease (M0).

Taking the revised 8th edition TNM staging system into account with inclusion of lymphatic, perineural, and venous infiltration, our data demonstrated that patients with isolated synchronous hepatic metastases showed a similar overall survival in multivariate analysis compared to patients with localized disease (Group M1surg vs. M0). Length of hospitalization, morbidity and mortality rates did not show any statistical difference between the two groups.

Improved survival outcome by curative surgery, especially in regard to long-term outcome, has never been adequately studied in patients with limited and isolated synchronous hepatic metastases of PDAC. To date, surgery in these cases is not recommended in any current guideline. Therefore, this treatment strategy is only applied in highly selected patients (11, 12). However, for colorectal liver metastases, surgery remains the gold standard of care. Moreover, it has been proven to be oncologically beneficial, to prolong survival, and to improve the quality of life (13, 14). Furthermore, surgical therapy is also widely accepted for hepatic metastases of pancreatic neuroendocrine tumors (15). In PDAC with oligometastatic disease, however, only limited evidence is available.

It is clear that the decision for a surgical approach is made after subjective reflection of the surgeon. To date, pancreatic resections with synchronous metastasectomies of the liver are rarely performed only in high-volume centers with adequate experience (16). Thus, to date, only case reports and a limited number of larger case series exist. In previous literature, patients with surgically resected synchronously metastasized PDACs were mostly correlated to patients who were treated in palliative intent (16–20).

In two recent studies, a larger number of patients with synchronously hepatic metastasized PDACs were analyzed (16, 18). Six European pancreatic centers retrospectively reported on 69 patients diagnosed with synchronously hepatic metastasized PDACs, who received simultaneous pancreatic and liver resections (18). Patients treated in palliative intent served as a control group. A significant benefit for survival was achieved for patients undergoing this extensive surgical approach with tolerable rates of morbidity and mortality compared to patients who only received an exploration (14.5 vs. 7.5 months respectively; $p < 0.001$). In a large single-center study from Heidelberg, analogous

results were reported (16). No study compared the survival outcome after synchronously oligometastatic resection to patients with localized PDACs (M0). Our results clearly showed for the first time a survival benefit after surgery for M1 PDACs, as survival outcome was similar in patients with localized disease (M0).

However, our study has several limitations including different applied adjuvant treatment regimes. FOLFIRNOX for a multimodal treatment setting was applied in 22.8% of all M1surg and only 8.1% of all M0 patients. An intensified gemcitabine/cisplatin based adjuvant radiochemotherapy was again only administered in M1surg patients. Presumably, this might have influenced the benefit in survival outcome in M1surg patients. Considering the limited number of patients in group M1surg with FOLFIRINOX as a multimodal treatment concept, further studies are warranted to analyze the oncological benefit of this interdisciplinary therapeutic approach and foremost the setting of multimodality (9, 21).

Conclusion

In summary, selected patients with synchronously hepatic metastasized PDAC may benefit from extended surgery. Simultaneous pancreatic and liver resections are feasible and well justified by similar morbidity and mortality rates compared to patients with isolated pancreatic surgery. Despite the advanced stage of PDAC, survival outcome after extended surgery was prolonged and thus similar when compared to patients who received surgery for localized PDACs. To validate our results, future studies are warranted to determine which patients may benefit from simultaneous resections (22–24).

Abbreviations

Chem chemotherapy

CI confidence interval

CTX chemotherapy

DFS disease free survival

FOLFIRINOX folinic acid, fluororuracil, irinotecan, oxaliplatin,

Hep Hepatic

HR hazard ratio

Meta metachronous/metachronously

OS overall survival

Pall palliative

PDAC pancreatic ductal adenocarcinoma

Pul pulmonary

RSS relapse specific survival

Surg surgical

syn synchronous/synchronously

UICC Union for international cancer control

Declarations

Ethics approval and consent to participate

This study was approved by the local institutional review board (Heinrich Heine University, Duesseldorf, Germany; study-no.: 2019-473-2). All procedures performed in this study were in accordance to the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Informed consent was waived because no data regarding the cases were disclosed.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Study conception, design and overall analysis and interpretation of data and drafting of the manuscript (S-A.S, N.L.), revising the manuscript (N.L., V.K., L.H.), data acquisition (S.A.S), analysis (S.A.S) and interpretation (S.A.S; N.L.), manuscript preparation (S.A.S, N.L.), conceptual contributions and manuscript revision (A.R., L. H., G.F., A.K., W.T.K.).

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Tables

Table 1: Demographic table of all 251 studied patients divided into three groups: M0, M1surg and M1pall. p-value≤ 0.05 indicates significance. M1surg correlated with higher T-stage and higher rate of margin positive resections compared to M0.

	M0 n=202		M1surg n=35		M1pall n=14		*p-value*
Age in years Median (range)	70 (17-95)		67 (45-80)		71.5 (51-87)		*0.875*
Gender	**n**	**%**	**n**	**%**	**n**	**%**	*0.840*
Male	117	57.9	20	42.9	7	50	
Female	85	42.1	15	57.1	7	50	
Tumor location							***0.001***
Head	189	93.6	27	77.1	13	92.9	
Tail	13	6.4	8	22.9	1	7.1	
T-stage							***0.028***
T1	18	8.9	4	11.4	-	-	
T2	117	57.9	11	31.4	-	-	
T3	63	31.2	18	51.4	-	-	
T4	4	2.0	2	5.7	-	-	
N-stage							*0.976*
N0	44	21.8	7	20.0	-	-	
N1	153	75.7	27	77.1	-	-	
N2	5	2.3	1	2.9	-	-	
Grading							*0.656*
G1/G2	113	56.0	17	48.6	12	85.7	
G3	88	43.6	17	48.6	2	14.3	
missing	1	0.5	1	2.9	-	-	
Pn							*0.377*
Pn0	27	13.4	11	31.4	-	-	
Pn1	96	47.5	24	68.6	-	-	
missing	79	39.1	-	-	-	-	
L							*0.996*
L0	84	41.6	18	51.4	-	-	
L1	73	36.1	17	48.6	-	-	
missing	45	22.3	-	-	-	-	
V							*0.198*
V0	118	58.4	23	65.7	-	-	
V1	39	19.3	12	34.3	-	-	
missing	45	22.3	-	-	-	-	
R-status							***0.000***
R0	171	84.7	17	48.6	-	-	
R1	31	15.3	18	51.4	-	-	

surg: surgical; pall: palliative; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table 2: Correlation analysis of subgroups (M0, M1surg and M1pall) and clinicopathological variables in PDAC. Pearson test was used to test for statistical significance. p-value≤ 0.05 indicates significance. Hospitality length was significantly shorter in M1pall patients.

	M1surg vs. M0	M1surg vs. M1pall	M0 vs. M1pall
	p-value	*p-value*	*p-value*
Tumor location	***0.000***	*0.563*	*0.347*
Age	*0.145*	***0.031***	*0.173*
Gender	*0.909*	*0.703*	*0.833*
T-stage	***0.028***	-	-
N-stage	*0.976*	-	-
Grading	*0.735*	*0.087*	***0.040***
Pn	*0.377*	-	-
L	*0.996*	-	-
V	*0.198*	-	-
R-status	***0.000***	-	-
Morbidity	*0.665*	***0.003***	***0.001***
Hospital stay (days)	*0.503*	***0.001***	***0.002***

surg: surgical; pall: palliative; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table 3: Correlation analysis of metastatic configuration of the two subgroups (M1surg and M1pall). p-value$\leq$*0.05* indicates significance. Amount, size and location of metastases were homogenously distributed between group M1surg and M1pall.

	M1surg n=35 n	M1pall n=14 n	Fisher-exact test *p-value*
Number of metastases			*0.111*
Single lesion	21	12	
2 lesions	8	2	
3 lesions	3	0	
4 lesions	3		
Size of metastases			*0.246*
<2cm	26	13	
≥2cm	9	1	
Location of metastases			*0.426*
left lobe	19	9	
right lobe	16	5	

surg: surgical; pall: palliative

Table 4: Univariate survival analysis and subgroup analysis for overall survival (total cohort, groups M0, M1surg, M1pall). Analysis was performed by log-Rank test. p-value≤ 0.05 indicates significance.

	M1surg and M0 n=237	M1surg n=35	M0 n=202	M1pall n=14
		Log-rank test		
	p-value	***p-value***	***p-value***	***p-value***
Tumor Location	***0.006***	*0.343*	***0.001***	-
Age	***0.002***	***0.474***	***0.001***	-
Gender	*0.631*	*0.649*	*0.661*	*0.738*
T-stage	*0.887*	***0.004***	*0.929*	-
N-stage	*0.385*	*0.209*	*0.386*	-
M-stage	***0.000***	-	-	-
Grading	***0.009***	***0.045***	***0.025***	*0.637*
Pn	*0.559*	*0.175*	*0.282*	-
L	*0.599*	*0.094*	*0.748*	-
V	***0.001***	*0.172*	***0.003***	-
R-status	***0.001***	***0.020***	***0.043***	-

surg: surgical; pall: palliative; LN: lymphnode; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table 5: Multivariate analyses for overall survival of total cohort and groups M0 and M1surg. Multivariate analyses were performed by forward logistic regression.

	All patients n=154		
	p-value	HR	95%CI
Age	*0.000*	2.3	1.5 - 3.5
V	*0.002*	2.4	1.6 - 3.8
R-status	*0.004*	2.8	1.8 - 4.3
	M1surg n=34		
	p-value	HR	95%CI
T-stage	*0.017*	2.2	1.1 - 4.1
Grading	*0.042*	2.7	1.0 - 7.0
	M0 n=120		
	p-value	HR	95%CI
Age	*0.000*	2.8	1.6 - 4.5
V	*0.001*	2.7	1.6 - 4.5
R-status	*0.002*	2.4	1.3 - 4.3

Surg=surgical; HR= Hazard ratio; CI= confidence interval; NS: not significant; V: venous invasion

Figures

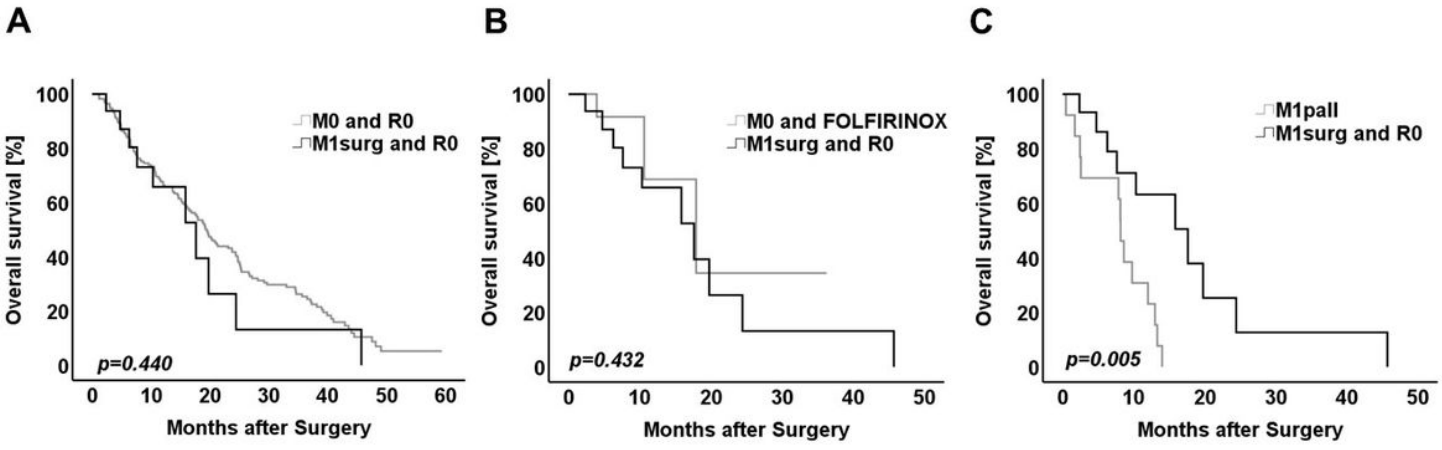

Figure 1

Kaplan Meier survival curves for (A) Overall survival of R0 resected patients without synchronous metastases (M0 and R0; n=171) in correlation to R0 resected patients with extended surgery (M1surg and R0; n=17) (B) Overall survival of R0 extended resected patients (M1surg; n=17) and patients after surgery with localized disease and FOLFIRINOX as adjuvant treatment regime (n=15) (C) Overall survival of patients after margin negative extended surgery (M1surg and R0; n=17) in correlation to patients treated in palliative intend (M1pall; n=14). Log rank test was used to test for significance. p-value≤0.05 indicates significance.