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Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases

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ABSTRACT

Introduction: Locally advanced pancreatic cancer (LAPC) is found in 35% of patients with pancreatic cancer. However, these patients often have occult metastatic disease. Patients with occult metastases are unlikely to benefit from locoregional treatments. This study evaluated the yield of occult metastases during staging laparoscopy in patients with LAPC.
Methods: Between January 2013 and January 2017 all patients with LAPC underwent a staging laparoscopy after a recent tri-phasic CT-scan of the chest and abdomen. Data were retrospectively reviewed from a prospectively maintained database. Univariate and multivariable logistic regression analysis was conducted to predict metastasis found at laparoscopy.
Results: A total of 91 (41% male, median age 64 years) LAPC patients were included. The median time between CT-scan and staging laparoscopy was 21 days. During staging laparoscopy metastases were found in 17 patients (19%, 95% CI: 12%–28%). Seven (8%) patients had liver-only, 9 (10%) patients peritoneal-only, and 1 (1%) patient both liver and peritoneal metastases. Univariate logistic regression analysis showed that CEA (OR 1.056, 95% CI 1.007–1.107, $p = 0.02$) was the only preoperative predictor for occult metastases. In a multivariable logistic regression analysis of the preoperative risk factors again only CEA was an independent predictor for occult metastatic disease ($p = 0.03$). Patients with a CEA above 5 μg/L had a risk of occult metastasis of 91%. FOLFIRINOX was given to 69 (76%) of the patients with a median number of cycles of 8. Subsequent radiotherapy was given to 44 (48%) patients after the FOLFIRINOX treatment. Six (14%) patients underwent a resection after FOLFIRINOX and radiotherapy. The overall 1-year survival was 53% in patients without occult metastasis versus 29% with occult metastasis ($p = 0.11$). The 1-year OS for patients that completed FOLFIRINOX and radiotherapy was 84%.
Conclusion: The yield of staging laparoscopy for occult intrahepatic or peritoneal metastases in patients with locally advanced pancreatic cancer was 19%. Staging laparoscopy is recomended for patients with LAPC for accurate staging to determine optimal treatment.

Introduction

Projections indicate that pancreatic cancer will be the second leading causes of cancer-related death by 2030 [1]. At the time of diagnosis, about 15% of patients has (borderline) resectable disease (stage I or II), 35% locally advanced pancreatic cancer (LAPC, stage III), and 50% metastatic disease (stage IV) [2]. The diagnosis of resectable disease and LAPC is determined by the extent of tumor contact with the superior mesenteric artery, celiac artery, superior mesenteric vein, and portal vein [3]. Several definitions for LAPC vary mainly in the extent of tumor contact.

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Neoadjuvant treatment is becoming the standard treatment in patients with LAPC, where induction chemotherapy followed by locoregional therapy is often used [4]. Patients with dramatic response after neoadjuvant treatment, identified by clinical and radiological response without evidence for metastatic disease, are considered for surgery [5]. Therefore, detection of occult metastatic disease in LAPC patients is particularly relevant in the era of several locoregional treatments for PDAC, including radiofrequent ablation (RFA), irreversible electroporation (IRE), and stereotact body radiotherapy (SBRT) [4,6]. The assumption is that locoregional treatments are not or at least less effective in the presence of occult metastatic disease.

Staging consists of a tri-phasic CT-scan of chest, abdomen, and pelvis to detect metastatic disease [5]. Most guidelines advice that the most recent CT scan should be less than 4–6 weeks old prior to start of treatment. A consensus report by the American Hepato-Pancreato-Biliary Association recommended staging laparoscopy in patients with LAPC [7]. Several studies have estimated the yield of staging laparoscopy in patients with LAPC at about 35%, but imaging has improved considerably in recent years [8,9].

The aim of this study was to assess the yield of staging laparoscopy in patients with LAPC after recent and high-quality tri-phasic computed tomography (CT).

Methods

Between January 2013 and January 2017 all patients with biopsy-proven LAPC and eligible for FOLFIRINOX were included from four hospitals. The diagnostic work-up included a tri-phasic CT scan and EUS with fine needle aspiration (FNA). CT-scan was performed on a 128 slice CT scanner with 3 phases (unenhanced, late arterial (35 s) and portal-venous (70 s) of the upper abdomen after intravenous injection of contrast material. In addition, the lower abdomen and thorax were scanned in the last phase. LAPC was defined according to the Dutch guidelines as tumor contact with the superior mesenteric artery (SMA), coeliac artery, or common hepatic artery exceeding 90° or contact with the superior mesenteric vein or portal vein exceeding 270° (Table 1) [10]. Only patients eligible for protocolled systemic chemotherapy with FOLFIRINOX and subsequent radiotherapy were included [11]. All patients underwent a staging laparoscopy to exclude occult metastases. The institutional review board waived an informed consent.

The staging laparoscopy was standardized in all patients and done under general anesthesia. The procedure started with open introduction of a 10 mm trocar through an infraumbilical incision. The 30° endoscope was inserted and the entire abdominal cavity was inspected. A second (and sometimes third) 5 mm trocar was placed in the right or left upper abdominal quadrant to evaluate the posterior aspect of segments 2, 3, 4, 5, and 6 of the liver, the omentum majus and minus, Douglas, the mesentery of the transverse colon, and Treitz' ligament. Any suspicious lesion was biopsied and submitted for pathological evaluation. If occult metastasis was found during staging laparoscopy only systemic FOLFIRINOX chemotherapy was given, without radiotherapy. For the patients that did not show occult metastasis during staging laparoscopy, patients were re-staged by CT scan after 4 and 8 cycles of FOLFIRINOX chemotherapy. If no metastatic disease was found on imaging, patients received radiotherapy. In the period 2013 to 2015 conventional radiotherapy with 30 fractions of 2 Gray was given, whereas between 2015 and 2017 five fractions of 8 Gray stereotactic body radiotherapy (SBRT) was given. After FOLFIRINOX and radiotherapy patients were considered for exploration and a possible resection based on the local extent of disease and performance status.

Data were collected in a prospectively maintained database, and were retrospectively reviewed. Additional data were collected retrospectively. The following parameters were retrieved: baseline characteristics including serum tumor markers (CEA (μg/L) and CA 19–9 (kU/L), date of CT-scan prior to laparoscopy, date of staging laparoscopy, length of stay, and findings during staging laparoscopy. If an abdominal metastasis was found in the first two months post-laparoscopy on follow-up imaging this was calculated as a false negative rate of the staging laparoscopy.

Univariate and multivariable logistic regression analysis was conducted to predict the presence of occult metastasis found at laparoscopy. Potential preoperative risk factors for occult metastatic disease included gender, age, smoking, tumor size, and serum tumor markers (CEA (μg/L) and CA 19–9 (kU/L)). Conventional cut-off values were used for both tumor markers: serum CA19-9 $\geq$ 35 and CEA value $\geq$ 5. The 1-year overall survival (OS) was calculated from date of histology to date of death. The survival outcomes will be presented using Kaplan-Maier and compared log-rank in SPSS (version 21).

Results

From January 2013 to January 2017, 91 (41% male, median age 64 years) consecutive patients with biopsy-proven LAPC staged on tri-phasic CT-scan underwent a staging laparoscopy to exclude occult metastasis. Symptoms found at presentation were obstructive jaundice in 44 (48%) patients, diabetes in 24 (26%) patients, weight loss in 74 (81%) patients, and pain in 71 (78%) patients. The tumor location was in the pancreatic head in 56 (62%) patients, and pancreatic tail in 36 (38%) patients. Median tumor size was 37 mm [IQR 30–46]. The median time between CT-scan and staging laparoscopy was 21 days [IQR 12–32, 95% range 3–63]. All baseline characteristics of the included patients are shown in Table 2.

During staging laparoscopy, a biopsy was performed in 36 (40%) patients. In 17 (19%) patients the biopsy was consistent with pancreatic adenocarcinoma. In nine (53%) patients the malignant lesions were peritoneal, in seven (41%) patients hepatogenic, and in one (6%) patient both peritoneal and hepatic. A flowchart of staging laparoscopy findings is shown in Fig. 1. Of the 74 patients that did not show occult metastasis during staging laparoscopy, seven (8%) patients showed a new intra-abdominal metastatic lesion on CT-scan within two months from the staging laparoscopy. All these new lesions were found in the liver, with five lesions being superficial and two lesions found deeper in liver parenchyma.

In univariate logistic regression of preoperative parameters, serum CEA (μg/L) was the only statistically significant risk factor (OR 1.06, 95% CI 1.01–1.11, p = 0.02) for occult metastasis found at

Table 1
Definition of resectability according to the Dutch Pancreatic Cancer Group.

	SMA	Celiac axis	CHA	SMV-PV
Resectable (all four required)	no contact	no contact	no contact	≤90° contact
Borderline resectable (minimally one required)	≤90° contact	≤90° contact	≤90° contact	≤90°–270° contact, and no occlusion
Irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion

Table 2
Baseline characteristics.

Baseline characteristics	N = 91 (% or IQR)
Age, median [IQR]	64 [56–69]
Gender	
Male	37 (41)
Female	54 (59)
WHO PS	
0	14 (15)
1	74 (81)
2	3 (3)
Jaundice	44 (48)
Weight loss[a]	74 (81)
Diabetes	24 (26)
Abdominal pain	71 (78)
BMI, median	24 [21–27]
Smoking	
Yes	27 (30)
Never	34 (37)
Former	27 (30)
Missing	3 (3)
Tumor origin	
Head	56 (62)
Distal	35 (38)
Median CA 19.9 (μg/L)	253 [50–1003]
Median CEA (kU/L)	5 [3–11]
Maximum tumor size (mm), median	37 [30–46]
Time between CT-scan and staging laparoscopy (days), median	21 days [12–32]

IRQ: Interquartile range.
WHO PS: World Health Organization Performance Status.
CA 19.9: Cancer antigen 19.9.
CEA: Carcino-embryonaal antigen.
[a] Subjectively assessed by patient.

staging laparoscopy. Whereas, gender, age, smoking, tumor size and CA 19–9 (kU/L) were not statistically significant predictors. In a multivariate logistic regression CEA (μg/L) was the only independent predictor (OR 1.07, 95% CI 1.01–1.14, p = 0.03). A CEA (μg/L) ≥ 5 gave a 91% risk for occult metastatic disease during staging laparoscopy, while CEA <5 gave a 4% risk for occult metastasis (p = 0.04).The serum CA19-9 (kU/L) ≥ 35 gave a 79% risk for occult metastasis, while CA19-9 <35 gave a 19% risk for occult metastasis (p = 1.00). All preoperative parameters are shown in Tables 3 and 4.

FOLFIRINOX was given to 69 (76%) patients, while 19 (21%) patients received best supportive care and three (3%) patients underwent gemcitabine chemotherapy. The reasons for patients to receive best supportive care after staging laparoscopy was due deterioration of condition (n = 9), and patients preference (n = 10). The median number cycles of FOLFIRINOX was 8 [IQR 4–8], with 55% of patients completing the scheduled 8 cycles of FOLFIRINOX. There were 35 (51%) adverse events of grade 3 or 4 during the FOLFIRINOX treatment. Of the patients that received FOLFIRINOX eventually 13 (14%) received conventional radiotherapy, another 31 (34%) patients underwent SBRT. Eventually, six (14%) patients underwent a radical resection after the FOLFIRINOX and radiotherapy treatment (Fig. 2).

The 1-year OS of all 91 patients was 51% (95% CI 40–61) with a median follow-up time of 32 months (95% CI 22–46), as shown in Fig. 3. The 1-year survival for patients without occult metastasis found on staging laparoscopy was 53% (95% CI 41%–64%), while patients with occult metastasis found with occult metastasis on staging laparoscopy was 29% (95% CI 47%–87%) (p = 0.11), as shown in Fig. 4. The 1-year OS for patients that completed both FOLFIRINOX and radiotherapy was 84%(95% CI 69–92).

Discussion

The yield of staging laparoscopy in 91 patients with LAPC was 19%. LAPC patients with occult metastasis had peritoneal and/or liver metastases that were too small for detection by state of the art tri-phasic CT of the chest and abdomen. Our study includes the largest cohort of patients with LAPC that underwent staging laparoscopy.

Two studies (representing 74 and 68 LAPC patients) and published almost a decade ago also evaluated the yield of staging laparoscopy in LAPC patients [8,9]. They found a yield of 34% (95% CI: 24%–45%) and 35% (95% CI: 25%–47%) for occult metastatic disease detected at staging laparoscopy [8,9]. A Cochrane meta-analysis of seven studies (representing 1015 patients) for staging laparoscopy in (borderline) resectable pancreatic cancer showed a yield of 22% [12] The higher yield of about 1 in 3 LAPC patients found in the previous studies versus 19% in the present study could be explained by improvement in the quality of CT scans [8,9]. Furthermore, a specialized radiologist reviewing the CT-scans could also improve the detection of occult metastasis found on CT-scan. In addition, multidisciplinary approach of LAPC in recent years have resulted in more multidisciplinary board review of these patients. This could influence the yield of CT-scan for occult metastatic disease in LAPC setting [13]. In our study, all CT-scans were reviewed by a specialized radiologist, and all patients were reviewed by a multidisciplinary team. This also could have led to a lower yield for staging laparoscopy for LAPC compared to earlier studies.

Systemic chemotherapy with FOLFIRINOX has become the standard initial treatment for LAPC patients with a good performance status. While no randomized controlled trial (RCT) has been published, a patient-level meta-analysis of FOLFIRINOX for LAPC found a median OS of 24 months [14]. In this meta-analysis, 64% received additional radiotherapy, and 62% eventually underwent a curative-intent resection. A systematic review found no RCT to evaluate the benefit of ablative treatments, such as radiofrequency ablation (RFA) and irreversible electroporation (IRE), for LAPC patients [15]. A more recent RCT randomized 269 LAPC patients with progression-free disease after 4 months of systemic treatment to continuation of systemic treatment or chemoradiotherapy. No difference in OS could be demonstrated with a hazard ratio of 1.03 [95% CI: 0.79–1.34; p = 0.83] [16]. All ablative treatments have a small but real risk of mortality [14,15,17]. While an OS benefit of ablative treatment has not been definitively shown for LAPC patients, it is even less likely that LAPC patients with occult metastatic disease benefit from ablative treatments. Staging laparoscopy in patients with LAPC could improve patient selection in clinical trials. A risk of occult metastatic disease of about 20% in LAPC patients seems to justify a staging laparoscopy prior to consideration of ablative treatments. In the Netherlands, several local ablative therapies are studied as subsequent treatment after systemic chemotherapy for LAPC patients. Currently, three ongoing clinical trials examine the safety and potential survival benefit of SBRT (ClinicalTrials.gov Identifier: NCT02292745), IRE (ClinicalTrials.gov Identifier: NCT02791503), and RFA ClinicalTrials.gov Identifier: NCT03690323).

Radiological imaging is advancing fast with more modalities that aim to detect occult metastasis not visible on tri-phasic CT. MRI, 18FDG-PET/CT scan, and contrast-enhanced ultrasonography all have their benefits and pitfalls for detecting occult metastasis in pancreatic cancer. However, superior diagnostic accuracy over CT-scan has not been definitively shown for any of these modalities [18]. Furthermore, if these new modalities raise the suspicion of metastatic disease, a biopsy with pathological confirmation is still required. A biopsy of subcentimeter lesions in the liver or lung can be challenging. The advantage of staging laparoscopy over

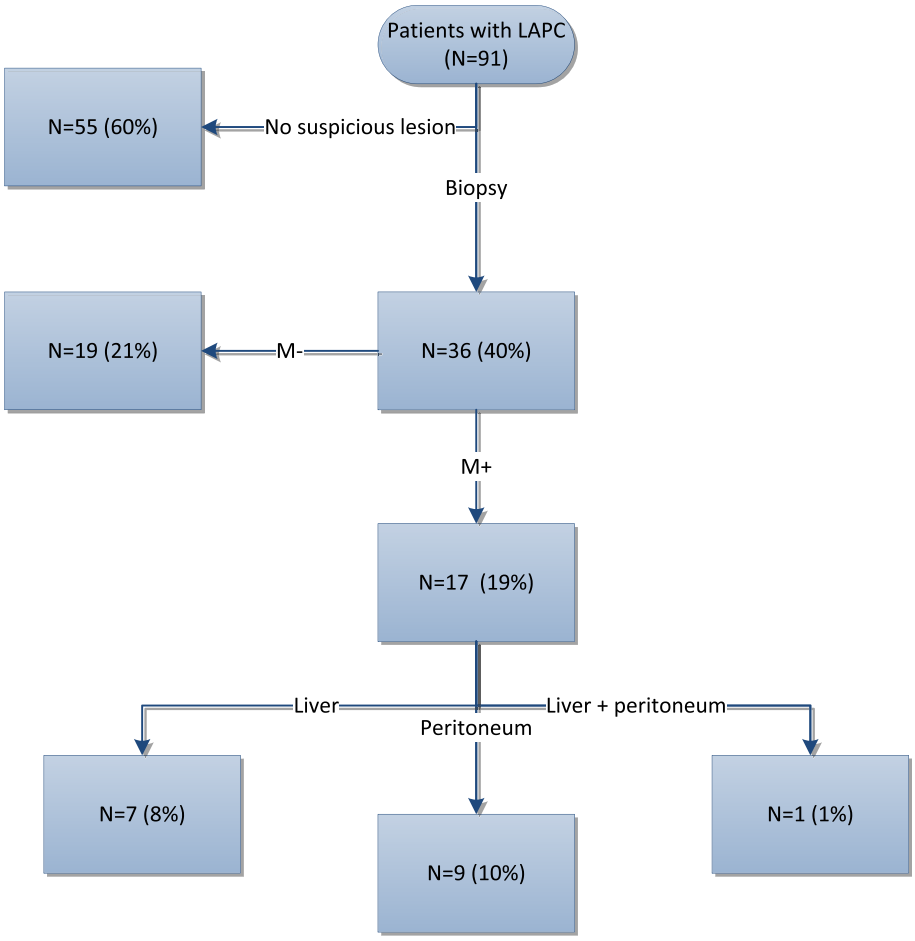

Fig. 1. Flowchart of the staging laparoscopy findings.

Table 3
Univariate and multivariate logistic regression for predictive preoperative parameters.

	Univariate,p-value	OR (95% CI)	Multivariate,p-value	OR (95% CI)
Age	0.35	1.03 (0.97–1.11)	0.83	0.99 (0.84–1.18)
Gender (male)	0.55	0.73 (0.25–2.09)	0.72	0.78 (0.04–14.88)
Smoking	0.96	1.03 (0.03–3.33)	0.34	2.38 (0.22–25.98)
Tumor size	0.75	1.01 (0.96–1.05)	0.65	0.98 (0.87–1.09)
CA 19.9 (μg/L)	0.06	1.00 (1.00–1.00)	0.37	1.00 (0.998–1.001)
CEA (kU/L)	0.02	1.06 (1.01–1.10)	0.03	1.07 (1.01–1.14)

Table 4
The number of patients with occult metastasis found with staging laparoscopy and CEA value higher than 5.

		CEA≥5		
		No	Yes	Total
Occult metastasis	**No**	25	32	**57**
	Yes	1	10	**11**
Total		**26**	**42**	**68**[a]

[a] Preoperative CEA values of 23 patients were unknown before staging laparoscopy.

additional imaging is that pathological confirmation of occult metastatic disease can be obtained. Circulating tumor cells are being examined as a staging parameter in pancreatic cancer [19–21]. However, the results are still not definitive for clinical use.

Serum CEA was the only independent predictive factor for occult metastasis found with staging laparoscopy. Patients with a CEA above 5 μg/L had a risk of occult metastasis of 91%. Although these patients have a particularly high risk of the presence of occult metastases, this risk is still 4% in patients with a CEA below 5. We believe that a staging laparoscopy is justified even in LAPC patients with a somewhat lower risk of occult metastases, as a low CEA level does not exclude the presence of occult metastasis [22,23]. Despite higher CEA levels have been associated with metastatic disease in pancreatic cancer, no definite conclusions on which CEA cutoff level

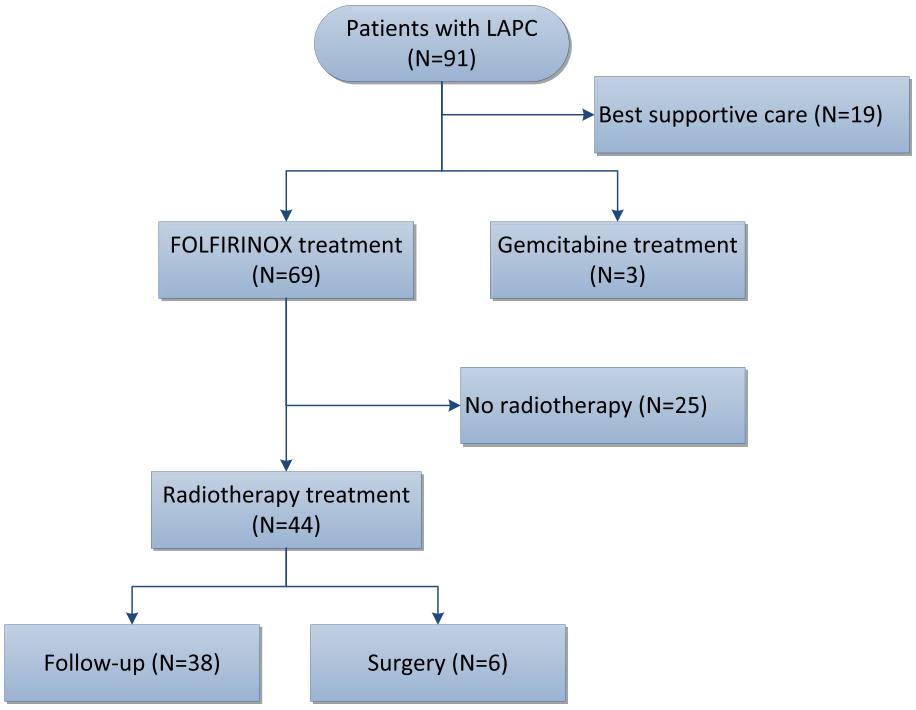

Fig. 2. Flowchart of the treatment modalities given to the patients.

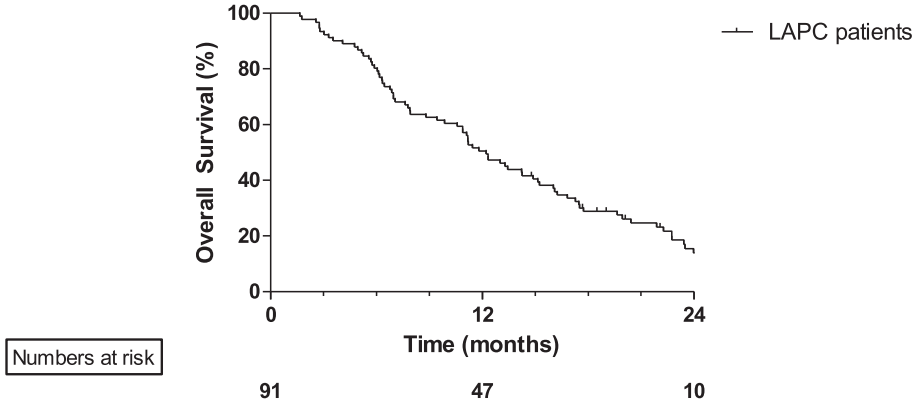

Fig. 3. Overall survival of the included patients in this cohort.

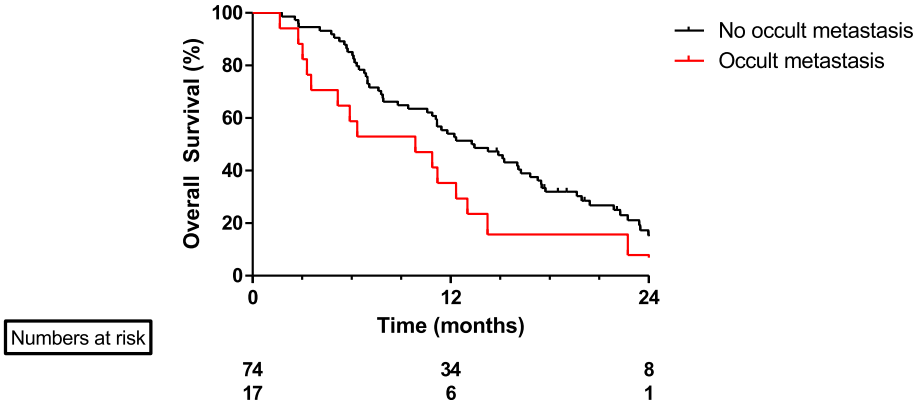

Fig. 4. Overall survival of patients with and without occult metastasis found at staging laparoscopy.

should be used [24].

The 1-year OS in patients without occult metastases was 51%. This was similar to a recent patient-level meta-analysis, in which 1-year OS ranged from 33 to 96% across studies [14]. The 1-year OS for patients that completed FOLFIRINOX and radiotherapy was 84%. Although FOLFIRINOX is currently the most effective treatment for patients with LAPC, better treatments are clearly needed.

The main limitation of our study is that some data (e.g., tumor markers) were collected retrospectively, and therefore sometimes missing. Secondly, we used the Dutch Pancreatic Cancer Group definition for LAPC; some of the included patients would have been classified as borderline resectable when using the NCCN and AHPBA/SSO/SSAT classifications [10,25,26]. This could have led to an underestimation of the yield of staging laparoscopy in LAPC patients. Furthermore, the management for borderline resectable pancreatic cancer in the Netherlands is upfront surgery or in a trial setting neoadjuvant chemoradiotherapy followed by surgery. Therefore, the definitions are of influence on the treatment strategy [10]. In addition, we included only patients with a good performance who were eligible for FOLFIRINOX and subsequent radiotherapy. We performed staging laparoscopy prior to systemic treatment, since we offer all patients without progressive disease SBRT in order to improve the R0 resection rate. Although only 14% of patients in our study underwent a resection, the resection margins were negative in all patients. The drawback of this approach is that initial treatment with systemic chemotherapy remains the same whether or not occult metastases are found. However, about 35% of patients respond to FOLFIRINOX with the risk that small peritoneal and liver lesions disappear and are not found at staging laparoscopy after FOLFIRINOX. These patients would not benefit from SBRT, as in the treatment of metastatic disease there are no studies supporting radiotherapy for metastatic pancreatic cancer [27].

In conclusion, staging laparoscopy upstages 19% of patients with LAPC to metastatic disease. Patients with (occult) metastatic disease are less likely to benefit from local therapy. Therefore, staging laparoscopy should be included in the pretreatment work-up for patients with LAPC if local therapy is considered.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.004.

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