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The impact of intensified staging and combined therapies in locally advanced pancreatic cancer: a secondary analysis of prospective studies

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Aim: The aim was to investigate the use of comprehensive pretreatment staging with multiple diagnostic modalities, including functional imaging and minimally invasive surgical procedures, in locally advanced pancreatic cancer (LAPC) patients. The primary objective was to detect occult metastatic disease using staging laparoscopy and 18F-FDG-positron emission tomography (PET)/computed tomography (CT) scan. The study also evaluated treatment efficacy and outcomes in LAPC patients treated with combined therapies.

Materials and methods: This study was a secondary analysis of three prospective studies of chemoradiotherapy (CRT) with or without induction chemotherapy (IC). The inclusion period was from December 2009 until February 2023. An intensified pretreatment staging was conducted for all LAPC patients. Patients without distant disease at initial staging, with borderline resectable or unresectable LAPC, were enrolled in CRT combination protocols (CRT with or without IC). IC regimens included GemOx or FOLFIRINOX for four cycles, followed by concurrent CRT with gemcitabine. The primary endpoint was the detection of occult metastatic disease, and secondary objectives included resection rate, treatment toxicity, overall survival (OS), progression-free survival (PFS), local control, and metastasis-free survival.

Results: Out of the 134 LAPC patients, 33.5% were identified with metastatic disease. Of these, 23.1% had a positive exploratory laparoscopy. Additionally, 13.4% were identified as having distant metastases by 18-FDG PET/CT. The median PFS for all patients who completed CRT was 14.3 months, and the median OS was 17.2 months. Resected patients after the combined therapies demonstrated significantly improved outcomes compared to tonon-resected patients (median PFS, 22.5 months vs. 9.5 months, $P < 0.001$; median OS, 38.2 months vs. 13 months, $P < 0.001$). Moreover, patients treated with IC followed by CRT showed significantly better outcomes compared to the upfront CRT group (median PFS, 19 months vs. 9.9 months, $P < 0.001$; median OS, 19.3 months vs. 14.6 months, $P < 0.001$). At univariate logistic regression analysis, the adding of IC was the only predictor for resection rate (95% CI: 0.12–1.02, $P = 0.05$), and this data was confirmed at multivariate analysis (95% CI: 0.09–0.98, $P = 0.04$). Hematological and gastrointestinal toxicities were observed during treatment, with manageable adverse events.

Conclusions: The use of comprehensive pretreatment staging, including laparoscopy and 18F-FDG-PET/CT scan, is an effective approach in identifying occult metastatic disease in LAPC patients. Our findings offer valuable insights into accurate staging and treatment efficacy, providing evidence-based support for optimal management strategies in LAPC patients.

Keywords: Pancreatic cancer, PET/CT, staging laparoscopy

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) poses a significant global threat as one of the most fatal malignancies due to challenges in diagnosis, early metastasis, and resistance to current therapies. The incidence of PDAC continues to rise in both men and women. In the United States alone, it is estimated that there will be 64 050 new cases and 50 550 deaths from pancreatic cancer in 2023. Pancreatic cancer accounts for 8% of all cancer-related deaths and ranks fourth among both sexes[1]. Projections indicate that by 2030, pancreatic cancer will become the second leading cause of cancer-related death in the United States, surpassing breast cancer and trailing only lung cancer[2]. The survival outcome of PDAC patients relies heavily on the stage at diagnosis. Only 20% of patients are eligible for surgical resection at the time of diagnosis, with an estimated 5-year overall survival (OS) rate of 27%. Unfortunately, patients with metastatic disease, who comprise the majority (53%) of pancreatic cancer cases upon diagnosis, have a poor 5-year survival rate of 3%. In a substantial number of cases, surgical intervention is not feasible even in the absence of metastasis due to vascular involvement[3]. For patients with locally advanced pancreatic cancer (LAPC), neoadjuvant therapy is justified as it increases the likelihood of achieving radical surgery with negative resection margins (R0) in borderline resectable tumors. In the case of unresectable pancreatic cancer, the primary goal of neoadjuvant treatment is to make the patients eligible for surgery and improve OS. Additionally, neoadjuvant treatment aids in the selection of patients who are suitable for surgical resection while excluding those with more biologically aggressive disease that progresses during treatment[4]. Presently, a combination of chemotherapy and radiotherapy is considered the preferred strategy for achieving radical intent in patients with unresectable LAPC or as a neoadjuvant approach for borderline resectable disease[5]. Accurate and comprehensive staging plays a pivotal role in determining the most suitable therapeutic approach for pancreatic cancer patients. In a previous paper, we provided an overview of the latest advances in pretreatment evaluation methods for pancreatic cancer and, based on current literature, proposed an evidence-based algorithm to assist clinicians in decision-making[6]. In particular, we explored whether integrating traditional imaging, functional imaging, and minimally invasive surgical procedures prior to treatment could facilitate complete staging for patients with pancreatic cancer, thereby identifying the most appropriate treatment pathway for each individual[6].

In this study, we present a secondary analysis of prospective studies, including patients with LAPC who underwent an accurate staging, as previously proposed, and were treated by different frontline induction approaches. The primary endpoint of this study was to detect occult metastatic disease at staging laparoscopy and 18F-FDG-positron emission tomography (PET)/computed tomography (CT) scan in LAPC patients.

Materials and methods

This study is a secondary analysis of three prospectively managed databases of chemoradiotherapy (CRT) with or without induction chemotherapy (IC)[4,7,8]. The inclusion period was from December 2009 until February 2023. All patients were discussed in a local multidisciplinary meeting. The study enrolled patients who had histologically confirmed pancreatic cancer, with either borderline resectable or locally advanced disease. The definitions of borderline and unresectable disease adhered to the guidelines set by the National Comprehensive Cancer Network (NCCN). Borderline resectable tumors were characterized by involvement of the superior mesenteric vein or portal vein, encasement of the gastroduodenal artery, or abutment of the superior mesenteric artery up to 180°. Unresectable disease was defined as superior mesenteric artery involvement exceeding 180°, superior mesenteric vein/portal vein occlusion that could not be reconstructed, or invasion or encasement of the aorta or inferior vena cava. Eligible patients did not have a history of metastatic cancer, prior abdominal radiotherapy, or were under 18 years old. Only patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and satisfactory hematologic parameters indicating adequate bone marrow, renal, and hepatic function, were included. Comprehensive pretreatment staging was conducted for all cases, involving physical examination, complete blood tests and tumor markers, endoscopic ultrasonography with fine needle aspiration biopsy, contrast-enhanced multilayer CT scan of the chest, abdomen, and pelvis, PET/CT with 18F-2-fluoro-2-deoxy-D-glucose (FDG), and laparoscopy with peritoneal washing. Patients with jaundice before or during treatment received endoscopic biliary stenting. During the staging laparoscopy, a routine inspection was conducted, covering the liver, diaphragm, bowel, and peritoneum. Figure 1 shows the comprehensive pretreatment assessment process for pancreatic cancer staging, which involves multiple diagnostic modalities, and the workflow of how patients were treated. Patients who had no distant disease at initial staging, and were classified with borderline resectable or locally advanced unresectable disease, were enrolled within chemoradiotherapy combination protocols (CRT with or without IC). The studies we conducted were three consecutive phase II prospective trials. Unlike the first protocol, where IC was not implemented, the second and third studies incorporated IC before CRT in their design: in the second study, patients undergoing IC received the GemOx regimen (gemcitabine 1000 mg/mq and oxaliplatin 100 mg/mq every 14 days), in the third FOLFIRINOX protocol (oxaliplatin 85 mg/mq and irinotecan 180 mg/mq plus leucovorin 400 mg/mq followed by bolus fluorouracil 400 mg/mq on day 1, then fluorouracil 2.400 mg/mq as a 46 h continuous infusion, every 14 day), both for four cycles. In the combined phase with radiation therapy, concurrent chemotherapy consisted of weekly gemcitabine at the dose of 600 mg/mq. Radiotherapy volumes were defined by CT scan and PET/CT scan. The clinical target

HIGHLIGHTS

- By 2030, pancreatic cancer is projected to become the second leading cause of cancer-related death.
- Accurate and comprehensive staging, involving the integration of traditional imaging, functional imaging, and minimally invasive surgical procedures prior to treatment, plays a crucial role in determining the most appropriate therapeutic approach for patients with pancreatic cancer.
- The combination of chemotherapy and radiotherapy is the preferred approach to achieve radical intent in patients with unresectable locally advanced pancreatic cancer or as a neoadjuvant strategy for borderline resectable disease.

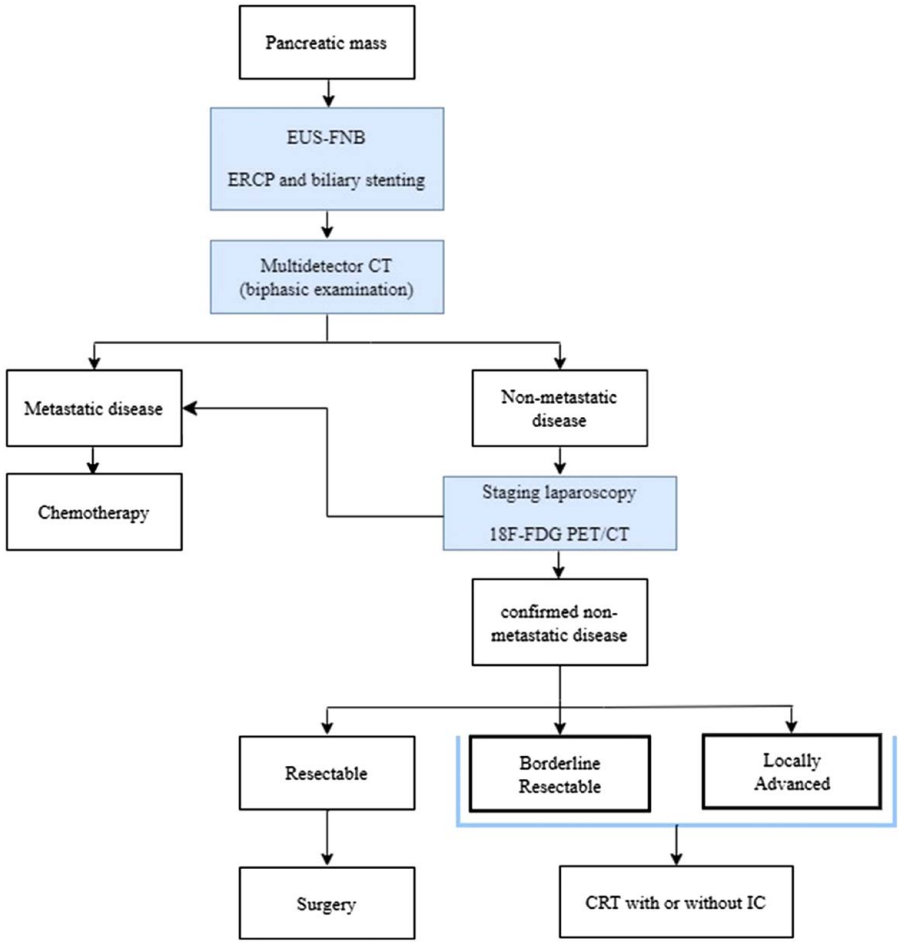


Figure 1. Multimodal pretreatment workup for pancreatic cancer staging. A EUS-FNB is mandatory in presence of a pancreatic mass before treatment. ERCP can be considered in patients with non resectable pancreatic cancer, who is a candidate for first-line chemotherapy, or in those patients with a malignant biliary duct obstruction who need to be treated with a neoadjuvant therapy before surgery. Multidetector CT with a biphasic examination is the first-line imaging for diagnosis and tumor staging. In nonmetastatic pancreatic cancer, after initial CT assessment both laparoscopy and 18F-FDG PET/CT can potentially add information to the staging workup. CT, computed tomography; CRT, chemoradiation; EUS-FNB, endoscopic ultrasonography-fine needle biopsy; ERCP, endoscopic retrograde cholangiopancreatography; 18F-FDG, 18F-Fluorodeoxyglucose; PET, positron emission tomography; IC, induction chemotherapy.

volume for patients diagnosed with borderline pancreatic cancer encompassed the tumor, as well as the affected lymph nodes, which were identified as being larger than 1 cm on CT scan and PET positive. External beam radiation was administered with a total dose of 54 Gy with a fractionation of 1.8 Gy daily for 5 days a week. In the case of patients with unresectable LAPC, the clinical target volume comprised the tumor and the involved lymph nodes for a total dose of 59.4 Gy, targeting also frequently involved peripancreatic lymph nodes at risk for the dose of 45 Gy, with a fractionated dose of 1.8 Gy per day, over 5 days a week. According to the National Cancer Institute Common Toxicity Criteria (version 4.0) scale, all adverse events that arose were documented, noting their frequency and characteristics. After the completion of CRT, a restaging evaluation was conducted 4 weeks later. This included clinical examination, laboratory tests, tumor marker analysis, a CT scan, and a PET/CT scan. The tumor response was determined using the WHO definition, based on the findings from CT scan and PET/CT scan. For patients with technically resectable tumors, surgery was considered as an option. Following surgical resection, patients underwent regular evaluations every 3 months as part of a standard surveillance protocol. This included a thorough medical history, physical examination, cross-sectional imaging, and measurement of serum markers. After 2 years, the evaluation intervals were extended to 6 months. Patients who were not eligible for resection were monitored based on their individual clinical progression. Descriptive statistics were used to summarize the characteristics of the study sample. The primary endpoint of this study was to detect occult metastatic disease at staging laparoscopy and 18F-FDG-PET/CT scan in treatment naïve patients with a diagnosis of LAPC based on a CT scan. Secondary objectives included the resection rate, the analysis of the toxicity of patients who completed the treatment protocol, and therefore the OS, the progression-free survival (PFS), the local control (LC) and the metastasis-free survival (MFS). In this retrospective study, the sampling approach involved retrieving and analyzing data from a predefined pool of cases or participants who met the inclusion criteria of three prospectively managed databases, ensuring representation of patients with histologically confirmed pancreatic cancer, including those with borderline resectable or

unresectable locally advanced disease. OS was determined from the day of the histological diagnosis. PFS was measured from the start of treatment until the observation of disease progression or recurrence, or until the last follow-up if no such event occurred. The Kaplan–Meier method was used to calculate the survival curves for OS and PFS. Univariate and multivariate logistic regression analyses were used to model the resection rate probability using clinically relevant variables. The selection of variables for the multivariate analysis was based on their significance observed during the univariate analysis. A two-sided *P*-value of 0.05 was considered significant. The statistical analysis was conducted using the Statistical Package for the Social Sciences, version 27 (SPSS Inc.). The study underwent review, approval, and monitoring by the independent Ethics Committee of our institution. Prior to participation, all patients provided informed consent specific to the study.

Results

Patient characteristics

One hundred and thirty-four patients were included in this analysis. Patients' characteristics are shown in Table 1. The median age was 64 years (range, 36–75). All patients showed a good performance status (ECOG Score 0–1) and none received prior chemotherapy or radiotherapy treatments. The majority of tumors (81.3%) were located in the pancreatic head, while 18.7% were found in the body of the pancreas. The mean serum CA 19-9 value among all patients was 346.7 U/ml (range, 2–12 000 U/ml). At the time of diagnosis, 47 patients (35.0%) were identified as having severe obstructive jaundice. These jaundiced patients underwent biliary drainage before treatment. Out of the total patient population, 81 (60.5%) had locally advanced unresectable tumors, while 53 patients (39.5%) presented with borderline resectable disease. With regard to pretreatment 18F-FDG-PET/CT, the mean interval time between PET/CT and the beginning of treatment was 16 days, ranging from 2 to 30 days. In all cases, staging laparoscopy was performed in the same week as the PET/CT scan, following this exam.

Table 1

Patient characteristics.

Characteristics	Number of patients (*N* = 134) (%)
Age (years)	
Median	64
Range	36–75
Sex	
Male	71 (53)
Female	63 (47)
ECOG performance status	
0	75 (56)
1	59 (44)
Ca 19-9 at diagnosis, U/ml	
Median	346.7
Range	0–12 000
Tumor localization	
Head	109 (81.3)
Body/Tail	25 (18.7)
Resectability status	
Borderline resectable	53 (39.5)
Locally advanced unresectable	81 (60.5)

Patient selection

A total of 134 patients were enrolled. After conducting endoscopic ultrasonography with a fine needle aspiration biopsy and a contrast-enhanced multilayer CT scan of the chest, abdomen, and pelvis, all patients underwent a diagnostic laparoscopy to confirm the absence of occult peritoneal and/or hepatic metastases and to perform peritoneal washing. Thirty-one patients (23.1%) had a positive laparoscopy. Specifically, 26 patients had peritoneal carcinomatosis, 4 had histologically confirmed hepatic metastases and one patient had peritoneal carcinomatosis and hepatic metastases that were not detected by the CT scan. Additionally, all patients underwent 18F-FDG-PET/CT, which revealed distant disease in 18 patients (13.4%): three with pulmonary metastases, seven with liver metastasis, two with extraregional nodal metastases, four with peritoneal nodules, and two with bone metastases. Four patients, already included in the two previous groups, presented abdominal nodules both on laparoscopy and a PET/CT scan (Table 2). Based on the findings from this pretreatment evaluation, 45 patients (33.5%) were identified as having metastatic disease and were consequently excluded from the protocols for locally advanced disease (Fig. 2). This was the intended objective of the study. Eighty-nine patients (66.4%) had LAPC. Of these, 22 patients (24.7%) performed CRT without IC, while 67 patients (75.3%) underwent IC. The patients who underwent IC were re-evaluated with CT scan and PET/CT scan after four cycles of treatment. Ten patients experienced disease progression: one patient with local progression and liver metastases, six patients with local progression and peritoneal carcinomatosis, two patients with liver metastases, and one patient with peritoneal carcinomatosis and liver metastases. One of these 10 patients underwent palliative surgery. The other 57 patients had no local and metastatic progression and maintained a satisfactory overall condition; two patients declined to continue the protocol. Fifty-five patients underwent concomitant CRT. Thus, adding the 22 patients who underwent CRT alone to the 55 patients who performed CRT after IC, a total of 77 patients completed CRT treatment. At restaging examinations, 18.2% of patients (14/77) were found to have metastases and were therefore excluded from surgery. Three of these patients underwent palliative surgery. The remaining 81.8% of patients (63/77) completed CRT without disease progression. Out of the 77

Table 2

Details of occult metastases by staging laparoscopy and 18F-FDG PET/CT scan.

Initial Staging	*N* = 45/134 patients (33.5%)
Occult metastases by PET/CT	*n* = 14
	Liver: 6
	Bone: 2
	Extraregional lymph nodes: 2
	Lungs: 3
	Peritoneal carcinosis: 1
Occult metastases by laparoscopy	*n* = 27
	Peritoneal carcinosis: 23
	Liver: 3
	Peritoneal carcinosis + liver: 1
Occult metastases by PET/CT and laparoscopy	*n* = 4
	Peritoneal carcinosis: 3
	Liver: 1

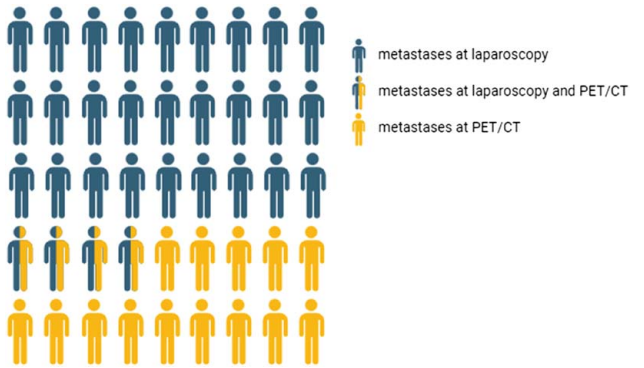


Figure 2. Patient population with occult metastases detected by staging laparoscopy and 18F-FDG-PET/CT scan.

patients, 39 (50.6%) underwent radical surgery, eight (10.4%) underwent palliative resection, and 16 (20.8%) did not undergo surgery. Out of the patients who underwent radical surgery, the distribution of different procedures was as follows: 11 patients (28.2%) had a pancreaticoduodenectomy using the Traverso-Longmire technique, 10 patients (25.4%) had a pancreaticoduodenectomy with the Whipple procedure, 13 patients (33.3%) had a total pancreatectomy, and five patients (12.8%) had a distal pancreatectomy. Figure 3 illustrates these findings.

Treatment efficacy and outcomes

The median follow-up of the entire population was 13 months (range, 2–141.7 months). At the time of evaluation, 23 patients were alive with a median follow-up of 26.5 months, and eight out of 39 patients were free from disease after surgery.

At univariate analysis for resection rate probability, only IC was significantly correlated with resection rate (95% CI: 0.12–1.02, $P = 0.05$), and this data was confirmed at multivariate analysis (95% CI: 0.09–0.98, $P = 0.04$) (Table 3).

All patients who completed CRT were included in the survival analysis. The median PFS was 14.3 months (95% CI: 8.25–20.74). The 1-year, 2-year, and 3-year PFS were 57, 35, and 23%, respectively (Fig. 4A). The initial site of progression was distant in 43 patients, local in 5 patients and both local and distant in 14 patients. The median PFS for borderline resectable patients was 12.2 months compared with 14.5 months for unresectable patients ($P = 0.3$). The 1-year, 2-year, and 3-year LC were 84, 69, and 64%, respectively (Fig. 4B). The 1-year, 2-year, and 3-year MFS was 66, 43, and 33%, respectively, with a median of 19 months (95% CI: 14.21–24.58) (Fig. 4C). Median

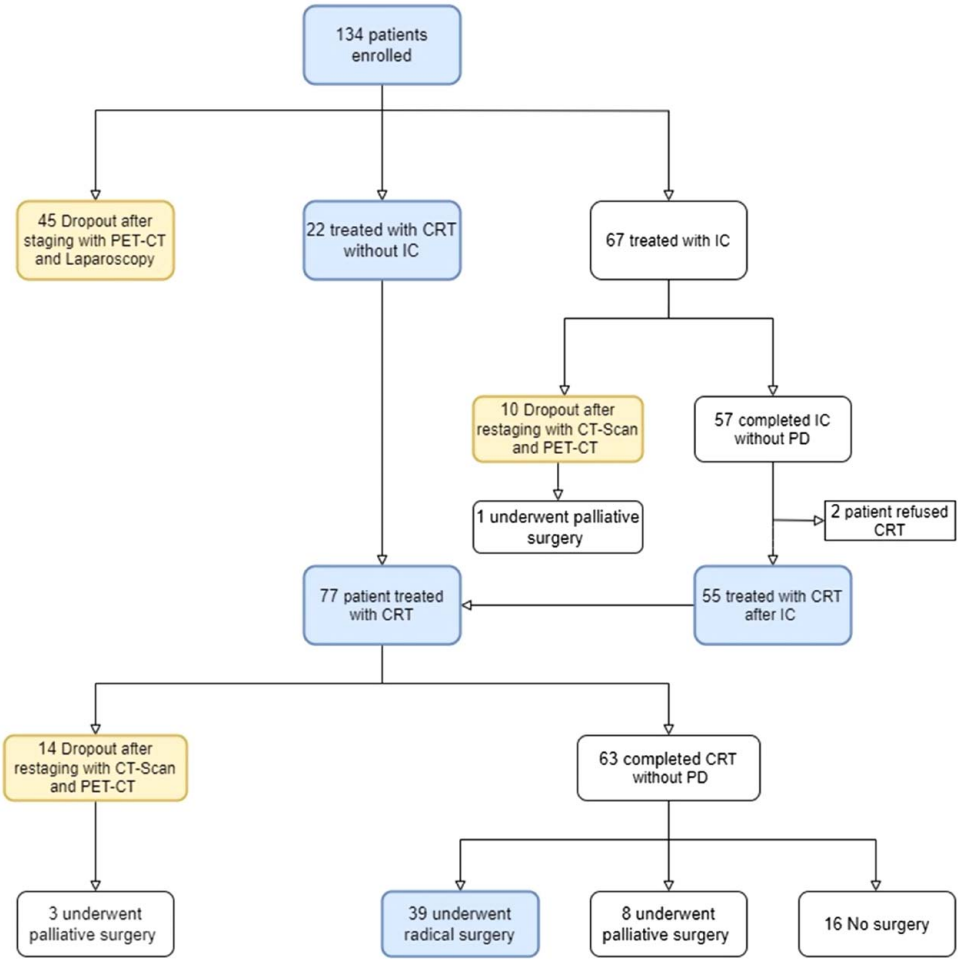


Figure 3. Flow chart of patients' selection for the treatments.

Table 3

Results of univariate and multivariate analysis for resection rate.

	Analysis for resection rate			
	Univariate		Multivariate	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Sex				
Male	0.95 (0.38–2.32)	0.91	—	—
Female				
Age (years)				
≤65	1.61 (0.65–3.98)	0.30	—	—
>65				
Tumor Site				
Head	0.68 (0.21–2.19)	0.52	—	—
Body/Tail				
CA 19-9 value				
≤500 U/ml	1.07 (0.42–2.69)	0.88	—	—
>500 U/ml				
Resectability Status				
Borderline	1.59 (0.64–3.93)	0.30	—	—
Unresectable				
Induction Chemotherapy				
Yes	0.36 (0.12–1.02)	0.05	0.30 (0.09–0.98)	0.04
No				

OS was 17.2 months (95% CI: 11.22–23.84). The 1-year, 2-year, and 3-year OS were 76.6, 38, and 30%, respectively (Fig. 4D). No significant difference in OS was observed between borderline resectable patients compared to unresectable patients (median OS 17 vs. 17.5 months, respectively; $P = 0.5$). Patients who underwent resection had a significantly longer median OS compared to non-resected patients (38.2 months vs. 13 months, $P < 0.001$) (Fig. 5A). The median PFS for resected patients was 22.5 months compared to 9.5 months for non-resected patients ($P < 0.001$) (Fig. 5B). LC and MFS were also significantly higher in resected compared to non-resected patients. Specifically, median values were not reached for LC with a *P*-value of 0.04. Similarly, the median MFS was 26 months for resected patients, significantly surpassing the median of 11.2 months observed in non-resected patients ($P = 0.001$).

Patients treated with upfront CRT had median OS and PFS of 14.6 and 9.9 months, respectively, compared to 19.3 and 19 months for patients treated with IC followed by CRT ($P < 0.001$) (Fig. 6A–B). Furthermore, LC and MFS were also found to be significantly higher in patients who received IC followed by CRT compared to those who underwent upfront CRT. Specifically, the median LC was 20.3 months in the upfront CRT group, while it was not reached in the IC followed by CRT group ($P = 0.02$). Similarly, the MFS was 12.4 months and 19.4 months, respectively ($P = 0.02$).

Treatment-related toxicity

During IC and CRT, hematologic and gastrointestinal toxicities were reported. Specifically, during CRT without IC, the most common toxicity was hematological. Leukopenia of all grades was found in 17 patients (77.2%). Neutropenia was found in 17 patients, of which five cases (22.7%) being greater than grade 3. Thrombocytopenia was observed in 15 patients

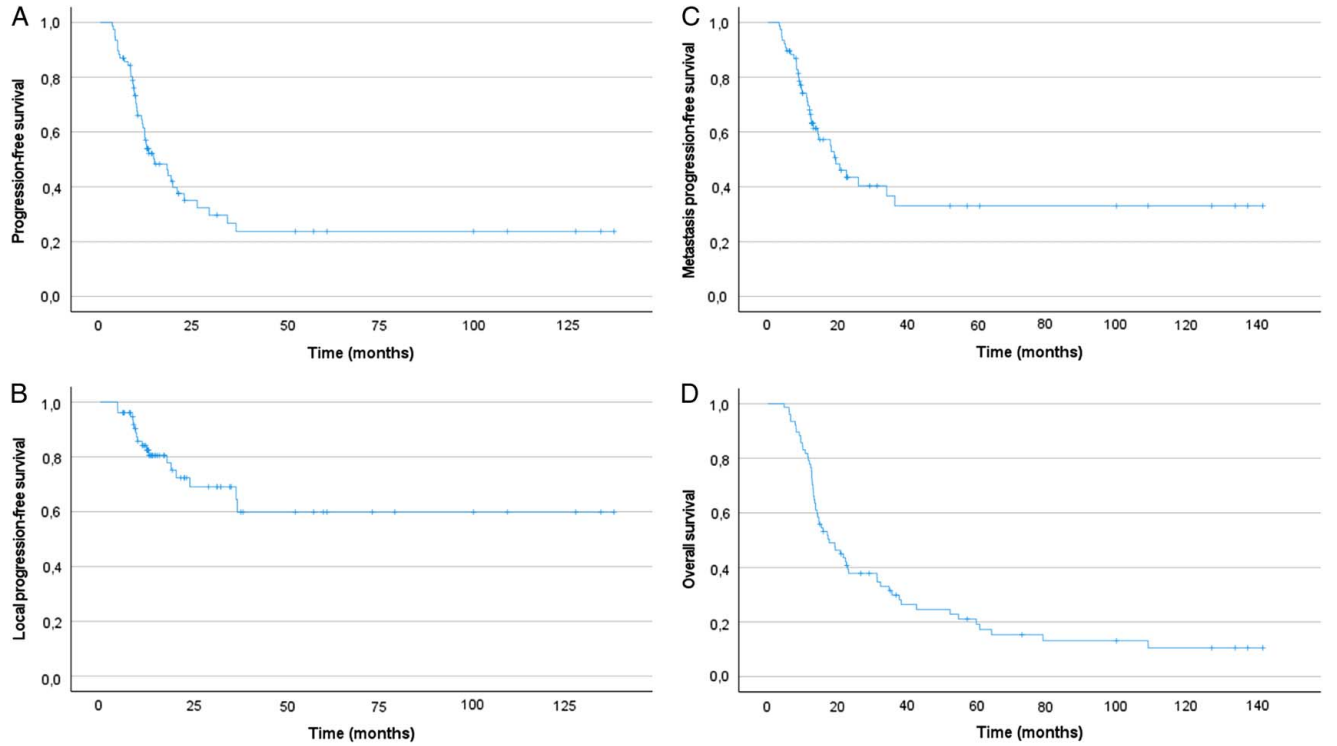


Figure 4. A: Kaplan–Meier method for Progression-free survival. B: Kaplan–Meier method for local progression-free survival. C: Kaplan–Meier method for metastasis-free survival. D: Kaplan–Meier method for overall survival.

(68.1%), with most cases being grade 1 (12 patients, 54.4%). An elevated grade of hypertransaminasemia was observed in nine patients, but never above grade 3. Diarrhea was observed in only one patient (4.5%) who had grade 1 side effects, while nausea was more frequent and was observed in 10 patients, never higher than grade 3. Sixty-seven patients received IC. The predominantly reported all-grade toxicities were hematologic: leukopenia (16.4%), neutropenia (20.9%), thrombocytopenia (29.8%), anemia (31.3%), hyperbilirubinemia (13.4%), hypertransaminasemia (35.8%). We observed grade 3 neutropenia in three cases (4.4%), and grade 4 in two cases (3%). Thrombocytopenia was observed in two cases above grade 3 (3%). Gastrointestinal toxicity was reported as follows: nausea was mainly grade 1 (19.4%) and only in three patients of grade 3 (4.4%). Grade greater than 3 diarrhea was observed in only one case (Table 4). Fifty-five patients completed CRT. Also during this phase, the most common toxicities were hematological and gastrointestinal. Hematologic toxicity consisted of leukopenia (10.9% for grade 1, 3.6% for grade 2, 2% for grade 4), neutropenia (10.9% for grade 1, 5.4% for grade 2, 1.8% for grade 3), thrombocytopenia (18.2% for grade 1, 9% for grade 2, 5.4% for grade 3). No cases of anemia of grade above 3 were observed. An elevated grade of hypertransaminasemia was observed in 21 patients (38.1%), with only one case of toxicity greater than grade 3. Gastrointestinal toxicity consisted of nausea (18.2% for grade 1, 5.4% for grade 2, 1.8% for grade 3) and diarrhea (5.4% for grade 1, 3.6% for grade 2 and 1.8% for grade 3) (Table 5).

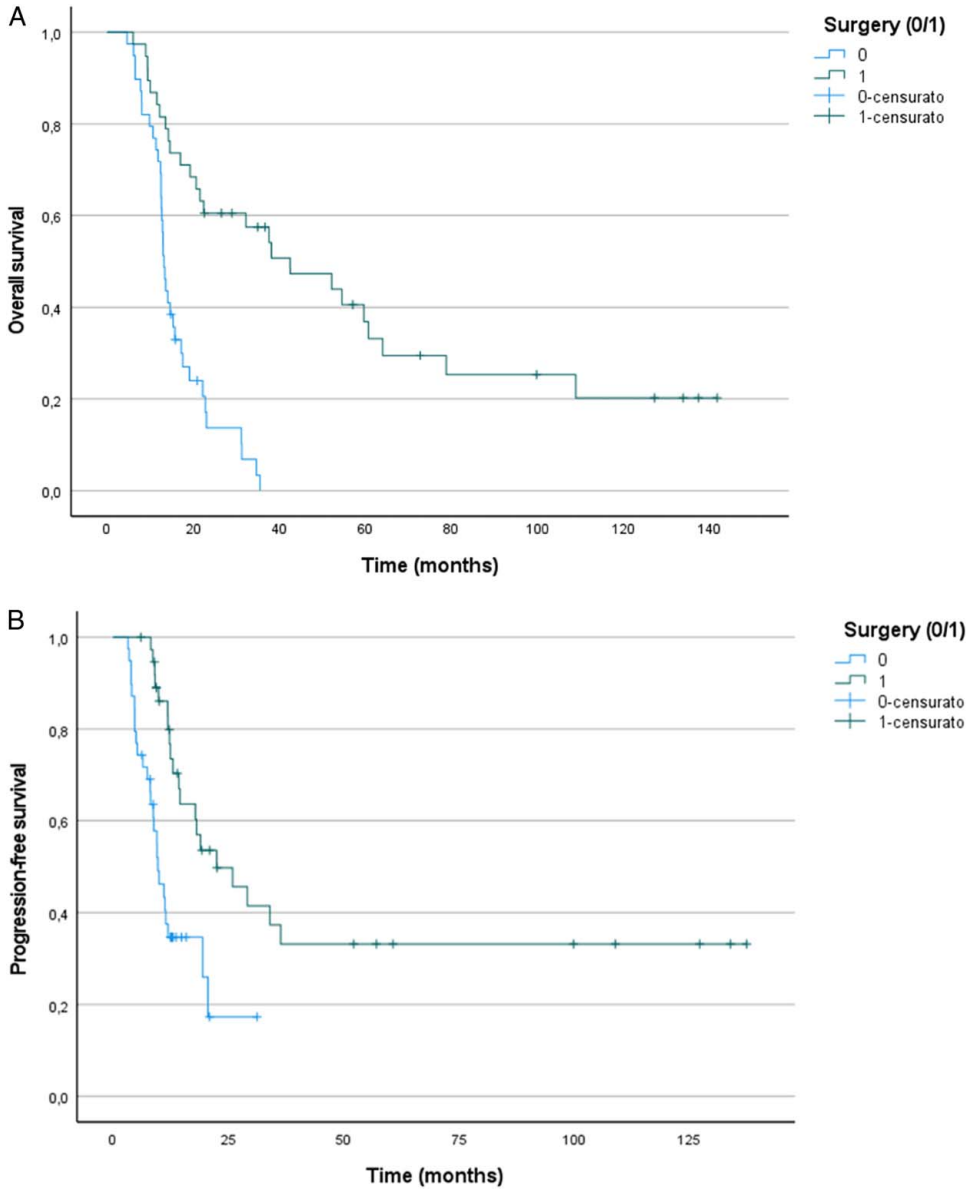


Figure 5. A: Kaplan–Meier method for overall survival comparing the group of resected patients (green line) and the group who did not receive surgery (blue line) following combined therapy. B: Kaplan–Meier method for progression-free survival comparing the group of resected patients (green line) and the group who did not receive surgery (blue line) following combined therapy.

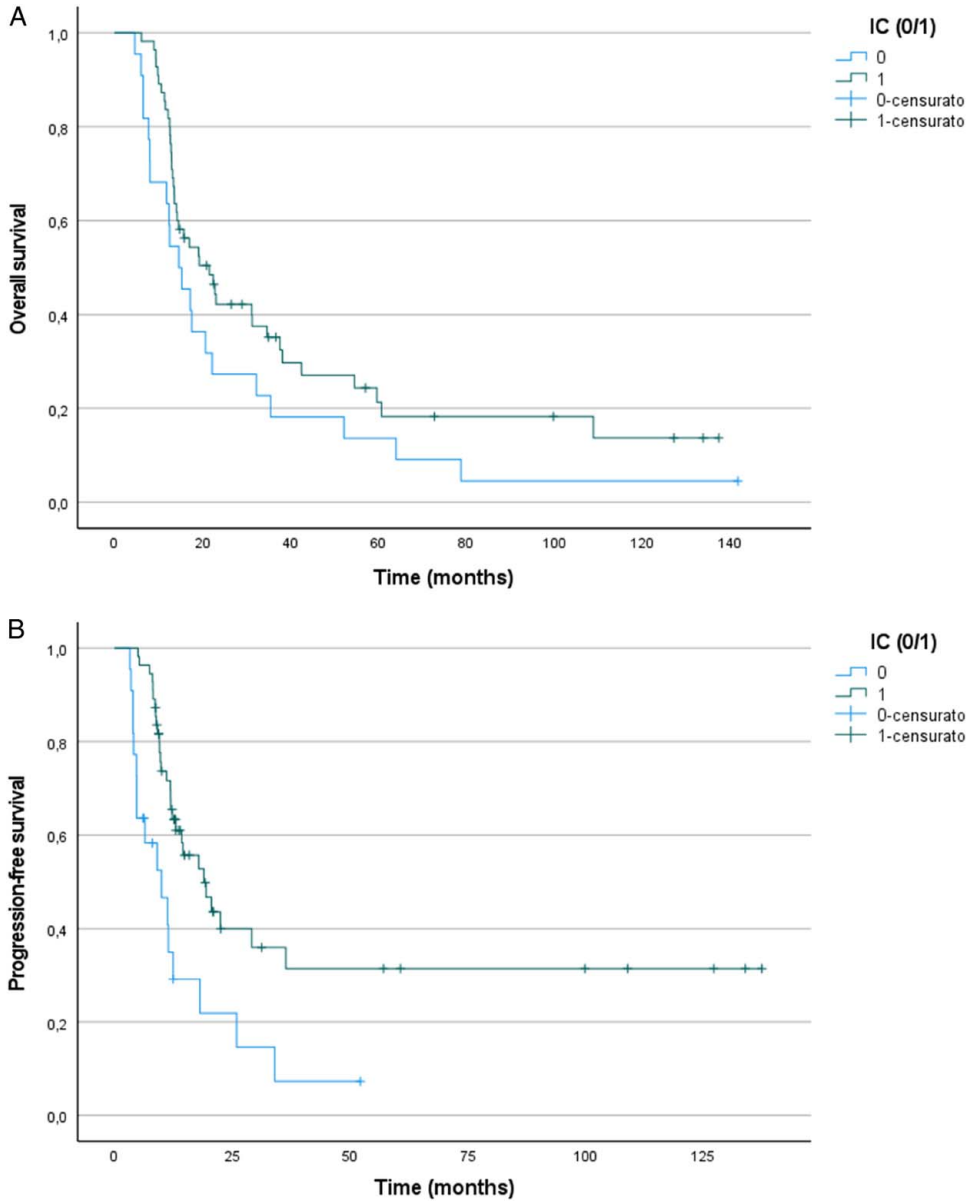


Figure 6. A: Kaplan–Meier method for overall survival comparing the group of patients who received IC (green line) and the group who did not (blue line). B: Kaplan–Meier method for progression-free survival comparing the group of patients who received IC (green line) and the group who did not (blue line).

Table 4

Toxicity profile of induction chemotherapy (*N* = 67 patients).

	G1	G2	G3	G4	≥ G3
Toxicity	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Hematological					
Leukopenia	7 (10.4)	2 (3)	0 (0)	2 (3)	2 (3)
Neutropenia	7 (10.4)	2 (3)	3 (4.4)	2 (3)	5 (7.5)
Thrombocytopenia	11 (16.4)	7 (10.4)	1 (1.5)	1 (1.5)	2 (3)
Anemia	15 (22.4)	6 (8.9)	0 (0)	0 (0)	0 (0)
Hyperbilirubinemia	6 (8.9)	3 (4.4)	0 (0)	0 (0)	0 (0)
Hypertransaminasemia	16 (2.4)	6 (8.9)	2 (3)	0 (0)	2 (3)
Gastrointestinal					
Nausea	13 (19.4)	2 (3)	3 (4.4)	0 (0)	3 (4.4)
Diarrhea	5 (7.5)	2 (3)	1 (1.5)	0 (0)	1 (1.5)

Discussion

In the present study, the combination of staging laparoscopy and 18F-FDG-PET/CT scan resulted in a detection rate of 33.5% for hidden metastases in borderline resectable and unresectable pancreatic cancer. In a previous review, we investigated the potential benefits of combining CT scan, 18F-FDG-PET/CT scan, and laparoscopy before initiating treatment, and we proposed an evidence-based algorithm[6]. In this study, we applied the flow-chart described in that review to enhance the accuracy of staging in pancreatic cancer patients. Specifically, out of the 134 patients in our study, 31 patients (23.1%) had a positive exploratory laparoscopy, with 26 having peritoneal carcinomatosis, four with hepatic metastases, and one with both. Additionally, 18 patients (13.4%) were identified to have distant metastases by 18-FDG

Table 5

Toxicity profile of chemoradiation after induction chemotherapy (*N* = 55 patients).

	G1	G2	G3	G4	≥ G3
Toxicity	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Hematological					
Leukopenia	6 (10.9)	2 (3.6)	0 (0)	2 (3.6)	2 (3.6)
Neutropenia	6 (10.9)	3 (5.4)	1 (1.8)	0 (0)	1 (1.8)
Thrombocytopenia	10 (18.2)	5 (9.0)	3 (5.4)	0 (0)	3 (5.4)
Anemia	12 (21.8)	5 (9.0)	0 (0)	0 (0)	0 (0)
Hyperbilirubinemia	6 (10.9)	0 (0)	0 (0)	0 (0)	0 (0)
Hypertransaminasemia	14 (25.4)	6 (10.9)	1 (1.8)	0 (0)	1 (1.8)
Gastrointestinal					
Nausea	10 (18.2)	3 (5.4	1 (1.8)	0 (0)	1 (1.8)
Diarrhea	3 (5.4)	2 (3.6	1 (1.8)	0 (0)	1 (1.8)

PET/CT, which were undetected by the initial CT scan. In 2019, Ta *et al.* published a meta-analysis that included 12 studies conducted between 1996 and 2009, involving a total of 1756 patients with resectable or borderline resectable pancreatic cancer. This meta-analysis reported a staging laparoscopy yield of 20%[9]. More recently, the PREOPANC trial revealed that staging laparoscopy in resectable or borderline resectable pancreatic cancer had a detection rate of 10%. In this trial, the patients were randomly assigned to receive either preoperative CRT or immediate surgery[10]. A staging laparoscopy before preoperative CRT was mandatory to prevent administering CRT to patients with occult metastasis. It discovered occult metastases in the liver and peritoneum that were not identified by the multiphase CT scan of the abdomen. Among patients who had exploratory laparotomy without prior laparoscopy, 8.5% were found to have occult metastases. This comparable detection rate suggests that staging laparoscopy effectively detects hidden metastasis[11]. It is worth noting that the studies included in Ta's meta-analysis demonstrated a higher yield of staging laparoscopy compared to PREOPANC trial findings. This disparity could be attributed to advances in imaging modalities over the years, as the meta-analysis encompassed several older studies. In patients with locally advanced pancreatic disease, a higher rate of occult metastases is expected in comparison with resectable or borderline resectable pancreatic cancer. Almost a decade ago, two studies, one involving 74 LAPC patients and the other 68 LAPC patients, also investigated the efficacy of staging laparoscopy in this population[12,13]. They observed a yield of 34 and 35%, respectively, for occult metastatic disease detected through staging laparoscopy. In Karabicak *et al.*[14], this percentage reached 52%, likely due to a higher number of body-tail neoplasms, which exhibit later symptom onset compared to head neoplasms, leading to delayed diagnosis and an increased likelihood of developing distant metastases. In a recent study on 91 LAPC patients the yield of staging laparoscopy was 19%. All patients underwent staging laparoscopy following a tri-phasic CT scan of the chest and abdomen. Data were retrospectively analyzed from a prospectively maintained database[15]. In our study, the percentage of patients with positive exploratory laparoscopy was 23.1%. In recent years, advances in the quality of CT scans and the multidisciplinary approach for LAPC has led to an increase in multidisciplinary board reviews for these patients, potentially impacting the yield of CT scans in detecting occult metastatic disease in the LAPC setting. In our study, all CT scans were thoroughly reviewed by specialized radiologists, and all patients underwent evaluation by a multidisciplinary team. As in the study by Sucker *et al.*[15], these factors may have contributed to a lower yield for staging laparoscopy in LAPC compared to earlier studies.

18-FDG PET/CT, when used in the staging context, has shown better accuracy in detecting distant metastases compared to contrast-enhanced CT. Additionally, it exhibits greater sensitivity and specificity in evaluating lymph node involvement when compared to both contrast-enhanced CT and contrast-enhanced MRI[16]. In a study conducted by Crippa *et al.*, 72 patients with resectable pancreatic cancer underwent 18F-FDG-PET/CT. PET/CT successfully diagnosed the presence of distant metastases in 11% of patients, leading to the avoidance of unnecessary surgery. The sensitivity and specificity of PET/CT in detecting distant metastases were found to be 78 and 100%, respectively[17]. In our study, 13.4% of patients were found to have distant metastases through 18-FDG PET/CT. Apart from its role in staging, PET/CT has demonstrated its significance in accurately identifying radiation target volumes, allowing for greater sparing of organs at risk by identifying areas for dose boosting[18]. In our experience, re-evaluation using both total body CT with contrast and 18-FDG PET/CT, performed 4 weeks after the completion of IC and CRT, facilitated the identification of metastatic patients who would otherwise have received inappropriate treatment. Specifically, 10 patients were identified after IC, and 14 patients after CRT.

Currently, the use of integrated therapeutic strategies for LAPC patients is the recommended approach to achieve better clinical outcomes. These integrated treatments should include chemotherapy, radiotherapy, and surgery, but they require careful patient selection. Radiotherapy, along with surgery, is the only treatment that has shown an impact on local disease control[19]. Therefore, the integration of radiotherapy and surgery in local disease control improves outcomes by increasing negative-margin resections and improving PFS, as evidenced by the Dutch PREOPANC study[10]. In this trial, the resection rate was 61% in patients who received preoperative CRT and 72% in patients assigned to immediate surgery ($P = 0.05$). The R0 resection rate was 71 and 40%, respectively ($P < 0.001$). The disease-free survival (HR, 0.73; 95% CI: 0.55–0.96; $P = 0.03$) and the locoregional failure–free interval (HR, 0.56; 95% CI: 0.38–0.83; $P = 0.003$) were significantly better in the preoperative CRT group. With a median follow-up of 59 months, the neoadjuvant CRT group showed improved OS compared to the upfront surgery group (HR, 0.73; 95% CI: 0.56–0.96; $P = 0.02$). In our study, the 1-year, 2-year, and 3-year LC were 84, 69, and 64%, respectively. The resection rate was 50.6%. In all cases, R0 resection was achieved. Resected patients demonstrated a significantly longer median OS compared to the nonresected patients (38.2 months vs. 13 months, $P < 0.001$). Furthermore, the median PFS for resected patients was 22.5 months, whereas it was 9.5 months for non-resected patients ($P < 0.001$). Resected patients also exhibited significantly higher LC and MFS compared to non-resected patients group. Our findings illustrate the potential impact of incorporating neoadjuvant treatments to enhance R0 resection rates. Although the use of neoadjuvant therapy results in a higher R0 resection rate compared to surgery alone in borderline resectable disease, and provides treatment for subclinical metastases, no standardized regimen is available at this time[20,21]. Currently, the chemotherapy such as FOLFIRINOX and gemcitabine combined regimens are widely

used due to the relatively high response rate. The rationale behind introducing IC before CRT lies in the chemotherapy's ability to provide initial systemic disease control and the need to select patients with biologically more aggressive disease. FOLFIRINOX has shown excellent results in the neoadjuvant setting, allowing for surgical intervention with negative margins in both monotherapy[22] and after integration with CRT[23], demonstrating good tolerability and safety in selected patients. In our cohort of patients, hematological and gastrointestinal toxicities were observed during treatment with manageable adverse events. By providing insight into the potential side effects associated with the therapeutic approaches discussed, we aimed to provide a more comprehensive understanding of the impact of these treatments on patients. In our study, univariate logistic regression analysis showed that IC was the only predictor for resection ($P = 0.05$). In a multivariable logistic regression analysis again only IC was an independent predictor for resection rate ($P = 0.04$). Patients treated with IC followed by CRT showed longer median OS and PFS of 19.3 and 19 months, respectively ($P < 0.001$), compared to patients who received upfront CRT (14.6 and 9.9 months, respectively). Additionally, patients who underwent IC followed by CRT also exhibited significantly higher rates of LC and MFS compared to those who received upfront CRT. There are several potential reasons for improved survival in this treatment group, including the administration of early systemic treatment to address undetected micrometastases, an increase in the rate of R0 resection, and the careful selection of patients for the combined approach, ensuring optimal outcomes. The current study's strengths stem from the meticulous implementation of the trial design applied prospectively in the three study protocols, including the same selection criteria for enrollment in therapeutic protocols, and the extended median follow-up, which enhances clinical results. The study's limitations include the long inclusion period and the use of different IC regimens among the protocols, although the CRT regimens were the same. Additionally, even though it is a single-center study, this factor ensured data homogeneity. Given the substantial impact of IC on survival and prognosis, we duly recognize the pivotal role of the IC indication. Notably, there was no randomization in this study; instead, the three consecutive trials were individually designed, resulting in different approaches to IC administration prior to CRT.

In conclusion, the combination of staging laparoscopy and an 18F-FDG-PET/CT scan enhances the detection rate of hidden metastases in borderline resectable and unresectable pancreatic cancer patients. Based on our knowledge, this study represents the first instance of utilizing an intensified staging approach. The integration of treatments, particularly IC before CRT, demonstrates improved survival outcomes, increased resection rates, and better local disease control. A multidisciplinary approach and advanced imaging modalities are crucial in accurately staging pancreatic cancer and guiding treatment decisions. Further research is needed to optimize treatment strategies for LAPC patients.

Ethical approval

The studies were approved by the ethics committee of the Campus Bio-Medico University of Rome (25/08 PAR ComEt CBM; 20/13 PAR ComEt CBM; 2016-000696-25).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.F., S.R., and G.M.P.: conception of the work; M.F., G.M.P., P.T., G.D'.E.A.C., V.L.V., S.T., and P.C.: data collections; M.F., G.M.P., D.C., E.I., C.G., B.B.Z., M.L.C., and R.C.: data analysis and interpretation of the manuscript; S.R. and R.M.D'.A.: supervision; M.F., G.M.P., P.T., G.D'.E., D.C., V.L.V., M.L.C., P.C., C.G., E.I., S.T., B.B.Z., A.C., R.C., R.M.D'.A., S.R.: wrote the paper; S.R. and R.M.D'.A.: revised the paper.

Research registration unique identifying number (UIN)

The protocols were registered at ClinicalTrials.gov with Identifiers NCT02984501 and NCT05399394.

Guarantor

Michele Fiore and Gian Marco Petrianni.

Data availability statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

References

[1] Siegel RL, Miller KD, Wagle NS, *et al*. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.
[2] Rahib L, Wehner MR, Matrisian LM, *et al*. Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open 2021;1: e214708; 4.
[3] National Cancer Institute. Cancer Stat Facts: Pancreatic Cancer. Surveillance, Epidemiology and End Results Program. 2019. Accessed 03 July 2023. https://seer.cancer.gov/statfacts/html/pancreas.html
[4] Fiore M, Ramella S, Valeri S, *et al*. Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer. Sci Rep 2017;7:45845.
[5] Silvestris N, Brunetti O, Bittoni A, *et al*. Clinical practice guidelines for diagnosis, treatment and follow-up of exocrine pancreatic ductal adenocarcinoma: evidence evaluation and recommendations by the Italian Association of Medical Oncology (AIOM). Cancers (Basel) 2020;12: 1681.
[6] Fiore M, Coppola A, Petrianni GM, *et al*. Advances in pre-treatment evaluation of pancreatic ductal adenocarcinoma: a narrative review. J Gastrointest Oncol 2023;14:1114–30.
[7] Fiore M, Trodella L, Valeri S, *et al*. Prospective study of cetuximab and gemcitabine in combination with radiation therapy: feasibility and efficacy in locally advanced pancreatic head cancer. Radiat Oncol 2015;10: 255.

[8] Induction FOLFIRINOX Followed by Chemoradiation in Locally Advanced Pancreatic Cancer (FOLRT). ClinicalTrials.gov ID NCT05399394. https://clinicaltrials.gov/study/NCT05399394
[9] Ta R, O'Connor DB, Sulistijo A, *et al*. The role of staging laparoscopy in resectable and borderline resectable pancreatic cancer: a systematic review and meta-analysis. Dig Surg 2019;36:251–60.
[10] Versteijne E, van Dam JL, Suker M, *et al*. Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the dutch randomized PREOPANC trial. J Clin Oncol 2022;40:1220–30.
[11] van Dongen JC, Versteijne E, Bonsing BA, *et al*. The yield of staging laparoscopy for resectable and borderline resectable pancreatic cancer in the PREOPANC randomized controlled trial. Eur J Surg Oncol 2023;49:811–7.
[12] Liu RC, Traverso LW. Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by Computed Tomography. Surg Endosc 2005;19:638–42.
[13] Morak MJ, Hermans JJ, Smeenk HG, *et al*. Staging for locally advanced pancreatic cancer. Eur J Surg Oncol 2009;35:963–8.
[14] Karabicak I, Satoi S, Yanagimoto H, *et al*. Risk factors for latent distant organ metastasis detected by staging laparoscopy in patients with radiologically defined locally advanced pancreatic ductal adenocarcinoma. J Hepatobiliary Pancreat Sci 2016;23:750–5.
[15] Suker M, Koerkamp BG, Coene PP, *et al*. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. Eur J Surg Oncol 2019;45:1906–11.
[16] Kauhanen SP, Komar G, Seppänen MP, *et al*. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg 2009;250:957–63.
[17] Crippa S, Salgarello M, Laiti S, *et al*. The role of (18)fluoro-deoxyglucose positron emission tomography/computed tomography in resectable pancreatic cancer. Dig Liver Dis 2014;46:744–9.
[18] Fiorentino A, Laudicella R, Ciurlia E, *et al*. Positron emission tomography with computed tomography imaging (PET/CT) for the radiotherapy planning definition of the biological target volume: PART 2. Crit Rev Oncol Hematol 2019;139:117–24.
[19] Bouchart C, Navez J, Closset J, *et al*. Novel strategies using modern radiotherapy to improve pancreatic cancer outcomes: toward a new standard. Ther Adv Med Oncol 2020;12:1758835920936093.
[20] van Dam JL, Janssen QP, Besselink MG, *et al*. Neoadjuvant therapy or upfront surgery for resectable and borderline resectable pancreatic cancer: A meta-analysis of randomised controlled trials. Eur J Cancer 2022;160:140–9.
[21] Hajibandeh S, Hajibandeh S, Intrator C, *et al*. Neoadjuvant chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Meta-analysis and trial sequential analysis of randomized controlled trials. Ann Hepatobiliary Pancreat Surg 2023;27:28–39.
[22] Hosein PJ, Macintyre J, Kawamura C, *et al*. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 2012;12:199.
[23] Suker M, Beumer BR, Sadot E, *et al*. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17:801–10.