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Pancreatic ductal adenocarcinoma complete regression after preoperative chemotherapy: Surgical results in a small series

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) becomes a systemic disease from an early stage. Complete surgical resection remains the only validated and potentially curative treatment; disappointingly only 20% of patients present with a resectable tumour. Although a complete pathological regression (pCR) after the preoperative chemotherapy could intuitively lead to better outcomes and prolonged survival some reports highlighted significant rates of recurrence.

Cases Presentation: We describe three cases of pCR following preoperative chemotherapy for PDAC. The first two cases received neoadjuvant mFOLFIRINOX and PAX-G scheme for borderline resectable PDAC. Recurrence appeared 9 and 12 months after surgery. Although both patients started adjuvant therapy straight after the diagnosis of recurrence, the disease rapidly progressed and led them to death 12 and 15 months after surgery. The third case was characterized by germline BRCA2 mutation. The patient presented with PDAC of the body, intrapancreatic biliary stenosis and suspected peritoneal metastasis. One year later, after first and second-line chemotherapy, she underwent explorative laparoscopy and total spleno-pancreatectomy without evidence of viable tumour cells in the surgical specimen. At six months she is recurrence-free.

Conclusions: Very few reports describe a complete pathological response following preoperative chemotherapy in pancreatic cancer. We observed three cases in the last three years with disappointing oncological results. Further investigations are needed to predict PDAC prognosis in pCR after chemotherapy.

Background

Pancreatic ductal adenocarcinoma (PDAC) is associated with a very poor prognosis with a 5-year overall survival rate lower than 10 % [1,2].

PDAC remains one of the few tumours that is not treated with new-generation therapies, as chemotherapy still represents the only effective therapeutic strategy in advanced-stage disease [3–5].

Surgery remains the only potentially curative option in localized disease, although only 15 % to 20 % of patients are eligible for surgery at the time of diagnosis [6].

Computed tomography (CT) scan tumour extension together with biological markers of malignancy levels define different clinical scenarios with different therapeutic and prognostic implications: upfront resectable, borderline resectable, locally advanced, and metastatic

Abbreviations: pCR, pathological complete response; PDAC, pancreatic ductal adenocarcinoma; mFOLFIRINOX, modified FOLFIRINOX; CT, computed tomography; TRG, tumours regression grade; AJCC, American Joint Committee on Cancer; EUS, endoscopic ultrasound; CAP, College of American Pathologist; SMPV, spleno-mesenteric-portal vein; GCSF, Granulocyte Colony-Stimulating Factor; FDG-PET, Fluorodeoxyglucose-Positron Emission Tomography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration biopsy; ERCP, endoscopic retrograde cholangio-pancreatography; CHT, chemotherapy; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19.9; SBRT, stereotactic body radiation therapy; DFS, disease free survival.

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PDAC [6,7].

In the present oncological era, neoadjuvant chemotherapy treatment has gained popularity and support mainly in borderline and locally advanced PDAC, since it could increase the chance of complete tumour resectability [7]. In consequence, NCCN guidelines recommend radiological and biochemical re-evaluation after neoadjuvant or first-line chemotherapy in borderline resectable and locally advanced patients [7]. Moreover, randomized controlled trials have suggested a positive prognostic trend of neoadjuvant treatments also in upfront resectable PDAC settings [8,9].

Other theoretical benefits of neoadjuvant therapy include early treatment of local (operative field) and/or distant micro-metastatic disease, selection of patients affected by rapidly progressive disease ('trial of biology"), reduced toxicity compared with adjuvant therapy and cost-effectiveness. Possible disadvantages include a higher risk of complications in case of multiple invasive procedures, low rate of complete or relevant pathological response, systemic toxicity and tumour progression during treatment [8].

Various drug associations with or without radiation therapy were successfully administered in a neoadjuvant setting. A combination of Fluorouracil, Leucovorin, Oxaliplatin and Irinotecan scheme (mFOLFIRINOX), or a combination of Gemcitabine, Nab-paclitaxel, Capecitabine, Cisplatin scheme (PAXG) are the two most frequently used in Italy [10].

Accurate determination of tumour regression grade (TRG) is of paramount importance because it could predict a patient's prognosis by reflecting the therapeutic response. Fibrosis and the amount of residual cancer cells on the resected specimen indicate the tumoral regression and a favourable response to neoadjuvant chemotherapy.

The challenge is that some histological features proposed to assess the treatment effect (cytological atypia, necrosis, and fibrosis) overlap with features seen in untreated tumours. Several TRG systems, originally developed for different tumour types or organs, have been proposed to evaluate the regression in PDAC specimens following neoadjuvant therapy [11]. However, there is no international agreement on which system represents best practice and is not yet standardized the extent of tissue sampling that is required to ensure adequate assessment of the residual cancer burden, considering the heterogeneity of tumour response [12]. We adopted the 2010 American Joint Committee on Cancer (AJCC) system [13], a modification of the Rayan system [14], supported by the College of American Pathologists (CAP) [15]. The CAP scoring system is considered the most adequate scoring system to date because it is based on the presence and amount of residual cancer cells instead of tumour regression [12].

Intuitively, patients with a complete pathological regression (pCR) after preoperative chemotherapy (AJCC Grade 0) should present higher recurrence-free and overall survival rates [16,17], however, some reports highlighted unexpected significant rates of recurrence [1,2,13]. Moreover, pCR after preoperative treatment represents an extremely rare condition that, nevertheless, could help in a better understanding of PDAC natural history and therapy [3].

Here we present the only three cases of PDAC with pCR after preoperative chemotherapy observed in an Italian tertiary referral centre from 2019 to 2023.

Case 1 (Table 1)

He is a 70-year-old man who was accidentally diagnosed with a malignant tumour of the pancreatic body (Fig. 1). At the time of diagnosis, the CT scan revealed a 26 mm nodule causing a complete occlusion of the splenic vein, close to the spleno-mesenteric portal vein (SMPV) confluence, and encasement of the splenic artery (Fig. 2A). Centimetric regional lymphadenopathies at the celiac trunk were present. A percutaneous biopsy confirmed the presence of PDAC. The carbohydrate antigen CA 19-9 was elevated (710 U/mL; reference range < 37 U/ml). The patient had no major comorbidities and showed a good performance status (Eastern Cooperative Oncology Group 0).

The patient was enrolled in the neoadjuvant chemotherapy protocol consisting of mFOLFIRINOX (modified FOLFIRINOX: Oxaliplatin 85/m^2, Irinotecan 150 mg/m^2 with Levofolinic acid 200 mg/m^2 given by Y-site injection, followed by a continuous intravenous infusion of 2400 mg/m^2 over a 46-hour period every 2 weeks).

He was started on mFOLFIRINOX at 75 % of the standard dose and biosimilar Granulocyte Colony-Stimulating Factor (GCSF) (filgrastim 300 μg), one a day subcutaneous injection for 4 days. The treatment was well tolerated, and 5 cycles with the 25 % dose reduction were completed until re-evaluation for surgery. As side effects the patient reported only diarrhoea Grade 1.

At the restaging, three months after the diagnosis, a lowering level of CA 19-9 to 104 U/mL was observed while the CT scan imaging showed extent, vascular involvement and regional lymph nodes involvement stability (Fig. 2B).

The patient underwent a distal spleno-pancreatectomy with resection of part of the SMPV confluence. The surgical procedure was straightforward, and no complications were observed.

The histological examination of the specimen surprisingly showed a

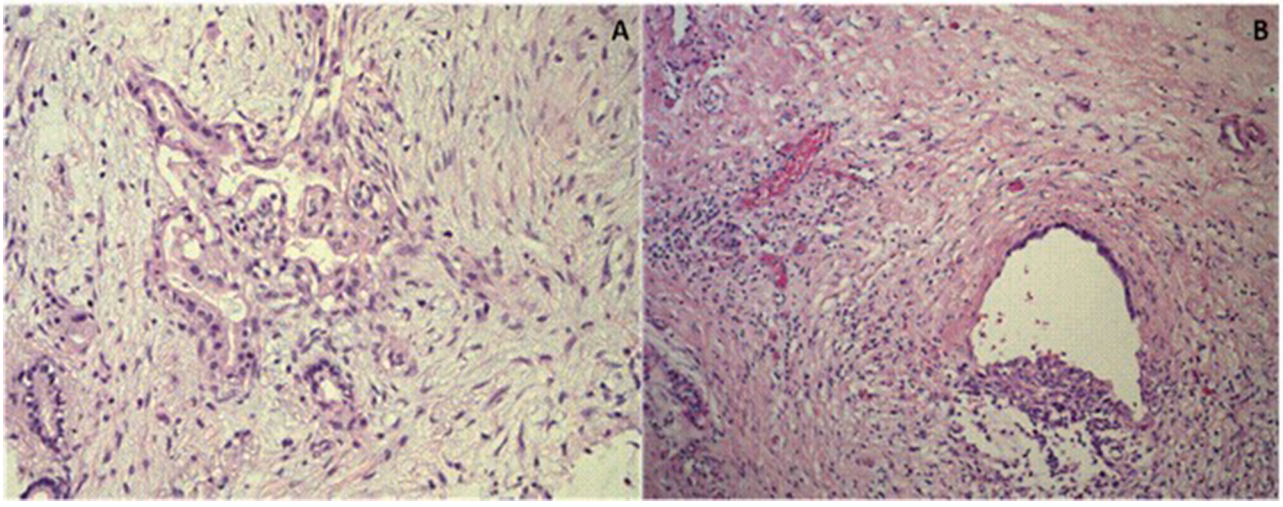

Fig. 1. [Case 1 – Histological Examination] A. Needle US-guided biopsy sample of pancreatic mass demonstrating neoplastic glands with fibrous tissue (H&E, 100X). B. Post-chemotherapy pancreatic surgical specimen showing a complete replacement of previous neoplastic mass by fibrous tissue infiltrated by inflammatory cells; note a central duct massively infiltrated by neutrophils (H&E, 100X).

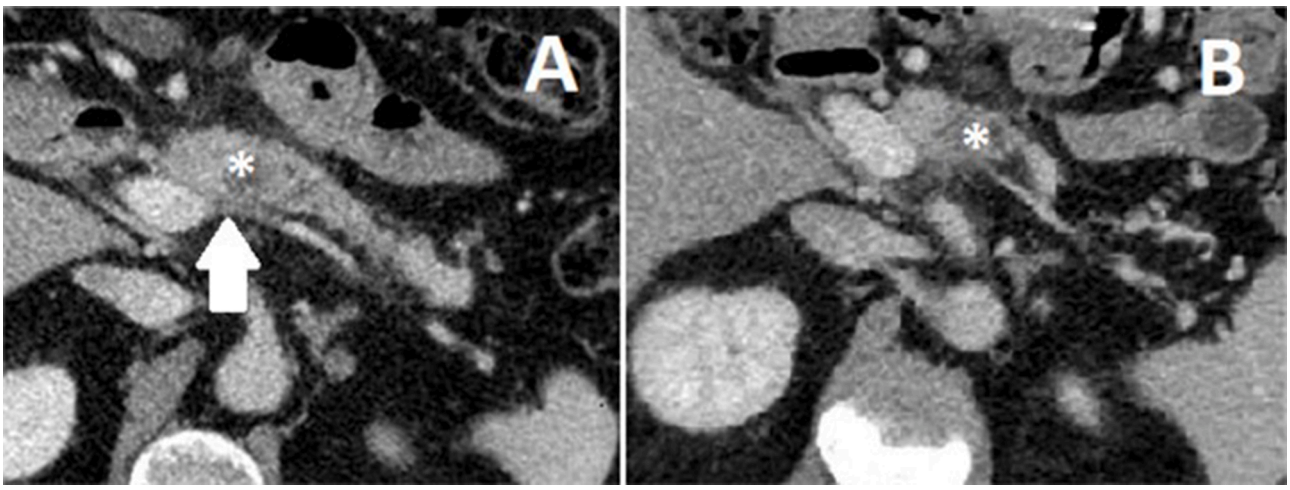

Fig. 2. [Case 1 – CT Abdomen] A. Portal phase CT scan showing the nodule of the pancreatic body (*) with occlusion of the splenic vein (arrow). B. Restaging after neoadjuvant FOLFIRINOX, showing a stable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

complete replacement of previous neoplastic mass by fibro-sclerotic tissue associated with complete atrophy of the exocrine component; nodal metastases were absent (TRG 0 Ryan modified version AJCC; ypT0-N0/6-R0-M0) (Fig. 3).

Based on this response no adjuvant chemotherapy was administered.

Five months after surgery, a routine follow-up CT scan revealed the presence of suspected neoplastic tissue around the celiac trunk and superior mesenteric artery which showed hyper-fixation at the FDG-PET scan. The CA 19-9, decreased to 40 after surgery and raised again to 725 U/mL. The tumour recurrence was therefore proven by an endoscopic ultrasound (EUS)-guided biopsy.

Chemotherapy with Nab-Paclitaxel + Gemcitabine was administered for 4 cycles at 80 % of the standard dose. The patient died from recurrence 15 months after surgery.

Case 2 (Table 1)

A 74-year-old woman presented to the hospital with a four-week history of abdominal pain, recent onset of jaundice and significant body weight loss. Her past medical history included fibromyalgia syndrome, rheumatic polymyalgia and osteoporosis, no family history of cancer.

The CT scan showed a 29 mm cephalopancreatic mass coherent with malignancy and two 5 mm lesions at the hepatic dome which were not further typeable as well as a small nodule in the left adrenal gland; no lung metastases (Fig. 3). The CA 19-9 level was 250 U/mL and the total bilirubin was 6 mg/dL. The patient underwent an endoscopic positioning of biliary stent and fine needle aspiration which confirmed the presence of adenocarcinoma.

Since the imaging revealed a borderline resectable pancreas tumour for the involvement of the spleno-portal confluence, the patient started systemic chemotherapy with six cycles of nab-Paclitaxel 125 mg/m^2 and Gemcitabine 1000 mg/m^2. After the first 3 months of treatment, the CT scan revealed the reduction of the pancreatic lesion (24 × 19 mm), a mild increase of the adrenal nodule (18 mm vs 15), and absence of new-onset lesions; the serological response was satisfactory (CA 19-9 = 5 U/mL).

After 3 further cycles of nab-Paclitaxel and Gemcitabine, the CT scan revealed further regression of the pancreatic mass to 19 × 10 mm, with no other modifications. The case was then investigated with MRI: the pancreatic lesion was not clearly distinguishable, nor clear hepatic metastases were found, and the left adrenal gland was considered

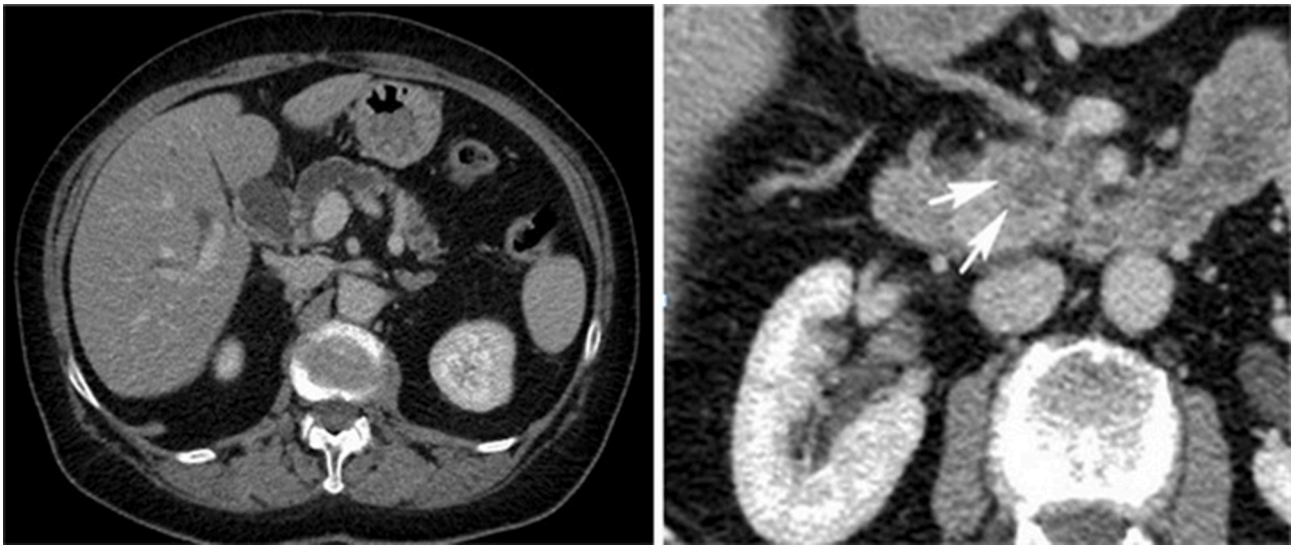

Fig. 3. [Case 2 – CT Abdomen] Portal phase CT-scan showing a parenchymal alteration in the head and uncinate process of the pancreas of 26mm (arrows); fine needle aspiration confirmed the presence of adenocarcinoma.

hyperplastic. Surgical treatment was therefore offered to the patient, as a potentially curative treatment.

The surgical procedure was performed eleven weeks after the discontinuation of the chemotherapy and thirty-seven weeks from the date of diagnosis. No major technical difficulties were encountered in the procedure, although there was considerable fibrotic tissue surrounding the superior mesenteric vein (Fig. 4). No vascular resection or reconstruction was required. The postoperative course was unremarkable. She was discharged home on day 10 and readmitted 4 days later with a wound infection, successfully managed by negative pressure wound healing therapy.

Histological examination of the surgical specimen revealed no evidence of residual adenocarcinoma (Fig. 4), consistent with a complete response to treatment (TRG 0 Ryan modified version AJCC). Chronic pancreatitis and areas of fibrosis were noted, together with scattered foci of low-grade pancreatic intraepithelial neoplasia. All 21 resected lymph nodes were negative for malignancy (ypT0-N0/21-R0-M0).

Following surgery, adjuvant therapy was not given. Her CT scans at 3 and 6 months postoperatively showed no evidence of recurrence with CA 19–9 at 45,7 U/mL.

She remained disease-free 10 months after surgery, and 19 months after diagnosis. A follow-up CT scan on the 10th month after surgery, in the absence of symptoms, showed recurrence with 15 hepatic metastases in addition to central abdominal and hepatic hilum nodal metastasis.

Chemotherapy with nab-Paclitaxel 125 mg/m^2 and Gemcitabine 1000 mg/m^2 was started as soon as possible but disease recurrence proved to be very aggressive. The patient died 12 months after surgery.

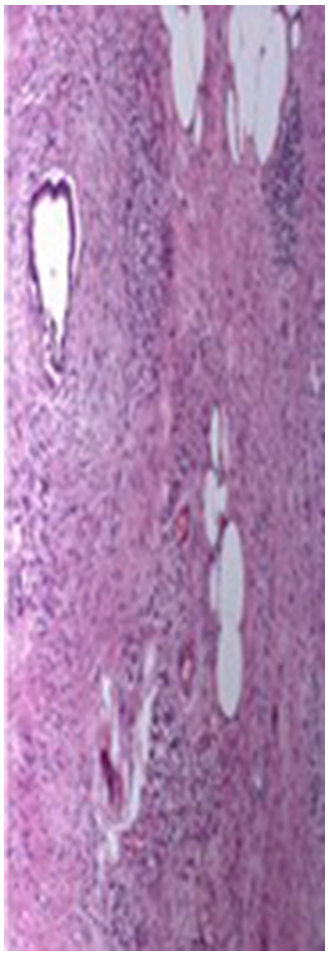

Fig. 4. [Case 2 – Histological Examination] Histological examination of the surgical specimen revealed no evidence of residual adenocarcinoma, consistent with a complete response to treatment (2010 AJCC Grade 0).

Case 3 (Table 1)

The third patient was a 66-year-old woman with a previous history of infiltrating ductal breast carcinoma (pT2G2N3 -18/21) with vascular invasion dated 19 years earlier. She had undergone a left-sided mastectomy, subsequent chemo- (Adriamycin+Taxane), radiotherapy, and maintenance oral therapy with Tamoxifen. Three years later she underwent a prophylactic video-laparoscopic oophorectomy considering both a family history of breast cancer and the presence of a BRCA2 mutation. After almost two decades of well-being and negative follow-up, she presented to the hospital with jaundice.

The CT scan of the abdomen revealed a 27 × 24 mm parenchymal alteration of the body of the pancreas in contact with the splenic artery and infiltrating the spleno-portal confluence; the scan also showed intrahepatic biliary dilatation associated with the presence of enhancement in the distal common bile duct, peritoneal effusion and suspected pelvic peritoneal metastasis (Fig. 5A, B).

The patient underwent an endoscopic ultrasound showing a 39 × 22 mm hypoechoic mass with a cystic component in the body of the pancreas and a lesion in the distal biliary tract causing stenosis; the FNA pancreatic biopsy confirmed the presence of ductal adenocarcinoma. An ERCP was performed to place a biliary fully-covered metallic stent and obtain the brushing of the biliary stenosis which resulted positive for cell atypia with suspicion of malignity. The CA 19-9 serum level at the time of diagnosis was 5310 U/mL (CEA 8,9 ng/mL).

The patient started systemic chemotherapy with nab-Paclitaxel 150 mg/m^2, Gemcitabine 800 mg/m^2, Capecitabine 1250 mg/m^2, and Cisplatin 30 mg/m^2.

The re-staging after six cycles of CHT showed a stable body-located disease, with a good serological response (CA 19-9 26 U/mL). She received 4 further CHT cycles with the same regimen before showing G3 gastrointestinal toxicity. After a collegial discussion, she stopped the ongoing chemotherapy and began maintenance with Olaparib (300 mg twice a day).

The patient underwent surgery twenty-one weeks after the beginning of the Olaparib therapy in the presence of stable disease. The pelvic exploration did not confirm the suspected peritoneal findings. A total spleno-pancreatectomy was performed; no vascular reconstructions were required. The postoperative course was regular, except for wound infection, managed by negative pressure therapy, and difficult glycaemic control. The Patient was discharged home on day 20.

The pathological report revealed atrophic pancreatic parenchyma with fibrous tissue of 3 cm in the pancreas body incorporating the common bile duct with no evidence of residual adenocarcinoma. All 18 resected lymph nodes were negative for malignancy. Following surgery, the patient continued with Olaparib therapy. CT scans at 3, 6 and 12 postoperative months did not show recurrence. At that time CA 19-9 and CEA were within the normal range. She is now under strict follow-up with imaging and blood tests.

Discussion

pCR has been defined as the presence of an area of scarring and chronic inflammation, with or without acellular mucin pools and histiocytic infiltrates in the pancreatectomy specimen [1]. It is estimated that about 2-10 % of the patients with PDAC have a pCR after preoperative chemotherapy although it is yet to demonstrate whether this result means a better patient outcome in terms of recurrence rate and disease-specific survival [18].

In some anatomical sites, such as the rectum or oesophagus, stronger evidence confirms that patients achieving pCR after preoperative chemoradiotherapy have a better prognosis.

Existing literature on pCR in the PDAC field consists mainly of small case series and individual case reports. One recent systematic review selected 34 studies with adequate clinical information in the last twenty years. Only one multicentric and one monocentric study reporting more

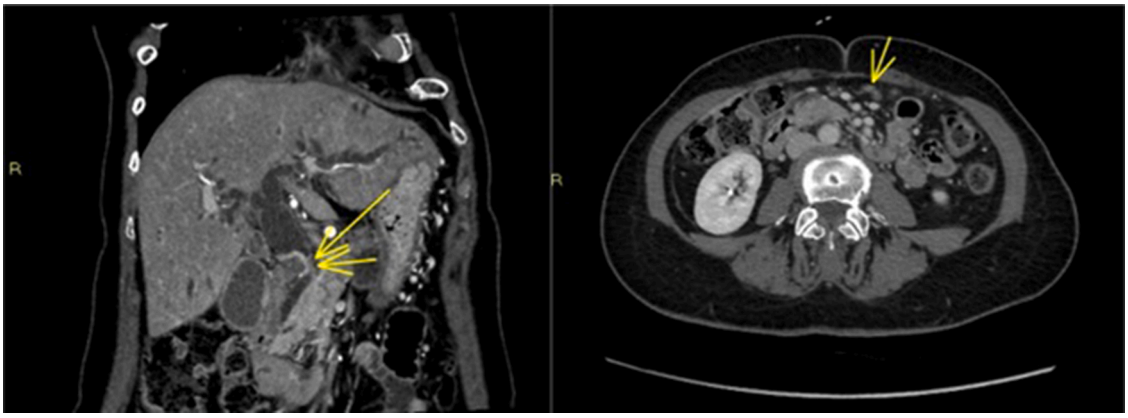

Fig. 5. [Case 3 - CT Abdomen] Imaging at the time of diagnosis showing pathologic enhancement in the distal common bile duct and suspected pelvic peritoneal metastasis.

than 10 patients were suitable. The 87 patients with pCR showed a more favourable prognosis (1, 3, 5-year survival respectively 97.6 %, 70.3 %, 70.3 %) but also noticed a significant risk of recurrence (33.3 %) during a median follow-up period of 22.4 months [19].

A recent retrospective cohort study from Johns Hopkins Hospital, including 30 patients with pCR out of 331 receiving neoadjuvant therapy for PDAC between 2009 and 2017 [20,21], reported 48 % of recurrences with 29 months median DFS. Both of these are superior to those obtained in the up-front resectable PDAC cohort in the same institution (82 % recurrences and 8 months DFS), confirming a better prognosis of these exceptional responders.

Of note, nearly half of the patients received adjuvant therapy before any documented recurrence despite having a pCR on the final pathology report.

In the last three years, we have progressively enlarged the indications to neoadjuvant treatments in PDAC aiming to improve prognosis. In cases 1 and 2 the chemotherapeutic regimen adopted was FOLFIRINOX and PAX-G respectively. We did not administer any adjuvant treatment after surgery, reserving chemotherapy in case of recurrence (Table 1).

Unexpected recurrence appeared 6 and 9 months after surgery respectively. Patterns of recurrence (liver metastases and local recurrence) were similar in the two patients. Although chemotherapy was started immediately after the diagnosis of recurrence in both cases, the disease quickly progressed and rapidly took the patients to death; they died 12 and 15 months respectively after surgery.

Tumour recurrence could be explained by two mechanisms [22]. Firstly, residual cancer cells in the pancreatic specimen could not be easily detected by routine pathological examination due to therapy-induced diffuse fibrosis and chronic pancreatitis. Alternatively, metastatic foci might still exist in the systemic circulation, which may cause subsequent recurrence. Pancreatic cancer may present as a systemic disease from the beginning. The disease recurrence occurs in up to 80–90 % of patients after resection of PDAC and is the main cause of disease-specific mortality. As 75 % of recurrences occur at distant sites, most patients with pancreatic cancer should be considered affected by a

Table. 1
Cases comparison.

Parameters	Case 1	Case 2	Case 3
Age, years	70	74	62
Sex	Male	Female	Female
Medical history	ND	Fibromyalgia	BRCA 2 mutation
Clinical presentation	Asymptomatic Patient (Incidental US Diagnosis)	Jaundice Abdominal pain	Jaundice
Site of pancreas lesion	Body/Tail	Head/Uncinate	Body/Tail
Tumour size at diagnosis	27 × 23 mm	36 × 20 mm	39 × 22 mm
Preoperative PDAC Histology	Yes (percutaneous FNA)	Yes (EUS-FNA)	Yes (EUS-FNA) + suspicion malignancy (Brushing ERCP)
CA 19-9 at diagnosis	710 U/ml	250 U/ml	5319 U/ml
Radiographic stage	Borderline resectable	Borderline resectable	Potentially Resectable; Pelvic Peritoneal Mets (°)
Preoperative Chemotherapy	Neoadjuvant Regimen: FOLFIRINOX	Neoadjuvant Regimen PAX-G	1st line - PAX-G 2nd line - Olaparib
CHT Cycles number	4	6	10
CHT Duration (*)	61 days	233 days	200 days + 150 days
CA 19-9 at surgery	104 U/ml	5 U/ml	26 U/ml
Surgical procedure	Distal pancreatectomy	Pancreaticoduodenectomy	Explorative laparoscopy Total Spleno-Pancreatectomy
Vascular resection	Yes	No	No
Morbidity (Clavien-Dindo)	Nd	Wound infection (grade II)	Wound Infection (grade II)
Final Pathological Report	ypT0,N0 (0/6),R0, M0	ypT0, N0 (0/21), R0, M0	ypT0, N0 (0/18),R0, M0
Adjuvant therapy	No	No	Olaparib (maintenance)
Recurrence	Yes	Yes	No
Recurrence pattern	Local, Liver	Local, Liver	-
Recurrence timing	6 months	9 months	-
CHT after recurrence	Nab.Placliaxel,Gem	Abraxane, Gem	-
Follow-up from surgery	Death (15 months)	Death (12 months)	Alive (12 months)

(*) CHT Duration: start of neoadjuvant therapy to time of surgery; (°) Radiologically suspected

systemic disease at the time of the surgical resection [23].

Current standards of clinical care fail to define whether patients with a pCR should receive adjuvant therapy. The disappointing rate of recurrence we observed suggests a more aggressive post-operative oncological approach. Adjuvant treatment could be advocated although the usual factors associated with increased risk of recurrence (margin infiltration, nodal metastases, neural and vascular invasion) are lacking. Ongoing studies show that the monitoring of peripheral circulating tumour cells or circulating tumour DNA are promising tool for estimating the recurrence risk in this cohort [24].

Nevertheless, due to the current lack of data, this decision can be made at the discretion of the treating medical oncologist. Moreover, unlike in rectal cancer, imaging cannot distinguish between treatment-related fibrosis and viable cancer [25].

Theoretically, we believe that all PDAC patients who have no evidence of disease progression on radiological imaging after chemotherapy should be considered for exploratory laparotomy. The third case described is an example: a good serological response and stable disease encouraged the multidisciplinary team to offer the patient a surgical option. The patient underwent explorative laparoscopy that excluded pelvic peritoneal seeding and the final histological report showed pCR.

By reviewing this case, we can gain valuable insights. Firstly, the exploratory laparoscopy performed during the initial presentation could have the potential to reclassify this PDAC from metastatic to resectable, which would have resulted in significant changes in the treatment strategy and prognosis.

Although this study outlines a very small series of pCR patients, we think it must be described considering the paucity of these cases. This cohort will increase rapidly in next future [26] due to the more extensive use of chemotherapeutics treatment upfront and the exponential rise in the incidence of PDAC.

It is of paramount importance to improve and standardize a prognostic stratification and define objective and standardized pathological criteria to evaluate the extent of viable tumours. Our experience seems to confirm previous findings suggesting that PDAC arises and probably remains a systemic disease, hence the importance of carrying on with the pharmacological treatment instead of waiting for recurrence in selected patients. Said that, we still believe in the role of a surgical resection following a radiological response.

Further investigations are needed to predict the real prognosis in these cohorts of exceptional responders and to select who will benefit from subsequent therapy. Radiotherapy and immunotherapy, which at present find a role only in clinical trials, might become part of a standardized course of treatment.

Conclusions

Very few reports describe a complete pathological response following preoperative chemotherapy in pancreatic cancer. We observed three cases in the last three years with disappointing oncological results. Further investigations are needed to predict PDAC prognosis in pCR after chemotherapy.

Ethical statement

This case series has been prepared in accordance with ethical standards and guidelines. The informed consent of patients for the collection and publication of their anonymized data has been obtained prior to the publication of this report. All identifying information has been removed or anonymized to protect the patient's privacy. The publication of the report has not been subjected to ethical committee approval due to its retrospective and descriptive nature. We have followed the principles outlined in the Declaration of Helsinki throughout the conduct of this study. The authors affirm that they have no conflicts of interest to disclose. We are committed to upholding the highest ethical standards in medical research and patient care.

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CRediT authorship contribution statement

Domenico Pinelli: Project administration, Supervision. **Andrea Micalef:** Visualization, Writing – original draft, Investigation. **Barbara Merelli:** Writing – review & editing. **Rosangela Trezzi:** Resources, Writing – review & editing. **Annalisa Amaduzzi:** Writing – review & editing. **Stefano Agnesi:** Writing – original draft. **Michela Guizzetti:** Writing – review & editing. **Stefania Camagni:** Writing – review & editing. **Veronica Fedele:** Writing – original draft, Investigation. **Michele Colledan:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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