THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Comparison of radiological and pathological tools to assess response to neoadjuvant treatment in resected pancreatic ductal adenocarcinoma patients

Ther Adv Med Oncol

2025, Vol. 17: 1–12

DOI: 10.1177/17588359251403909

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Abstract

Background: In non-metastatic pancreatic adenocarcinoma (PDAC), the appropriate evaluation of tumor response to neoadjuvant treatment (NAT) has a substantial prognostic impact, but the tools used to assess it are imperfect and sometimes discordant.

Objectives: We aimed to explore the prognostic impact of morphological and pathological evaluations of tumor response to NAT.

Design: Single-center retrospective observational study.

Methods: We retrospectively studied all patients with borderline or locally advanced PDAC who underwent surgery after neoadjuvant chemotherapy (NAC) with FOLFIRINOX, ±additional chemoradiation (NACR) between 2016 and 2022 in a tertiary center. Morphological response was evaluated according to RECIST 1.1, and pathological response was assessed according to the CAP score and proportion of viable tumor cells (VTC). The primary endpoint was recurrence-free survival (RFS), and the secondary endpoint was overall survival (OS). Factors associated with the risk of recurrence were analyzed using ROC curves and multivariable Cox proportional hazard models.

Results: We included 91 patients (52% male, median age 66, 83% with borderline PDAC) who underwent surgery following NAC with additional NACR in 85% of patients. Overall, 38% of patients had an objective morphological response according to RECIST 1.1, which was not associated with prolonged RFS HR 1.16, 95% CI (0.62–2.10), $p = 0.64$). Conversely, poor pathological response was associated with shorter RFS on multivariable analysis, notably VTC $\geqslant$ 30% (HR 2.28, 95% CI [1.08–5.13], $p = 0.037$). Median OS was 62.2 months with VTC $\geqslant$ 30% versus 45.1 months with VTC $<$ 30% ($p = 0.025$). Identifying PDAC with VTC $<$ or $\geqslant$30% had a strong reproducibility (kappa 0.86).

Conclusion: Morphological response per RECIST should not be the aim of NAT in patients with PDAC. Conversely, the proportion of VTC could be a reproducible, simple, and effective prognostic tool. Should this marker be further confirmed as valuable, it may help inform the adaptation of adjuvant treatment and follow-up in this setting.

Keywords: morphological response, neoadjuvant therapy, pancreatectomy, pancreatic neoplasms, pathological response

Received: 2 August 2025; revised manuscript accepted: 17 November 2025.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 12th most frequent and 7th most common cause of cancer death worldwide,[1] and its incidence is increasing worldwide.[2] Whenever feasible, surgical resection offers the only opportunity for prolonged survival. However, at the time of diagnosis, only 10%–15% of patients have resectable disease.[3] According to the criteria of the International Association of Pancreatology (IAP), the definition of resectability is based on anatomic factors (tumor contact with vessels), serum carbohydrate antigen (CA) 19–9 level, and performance status.[4] In patients with borderline resectable or locally advanced but potentially resectable PDAC, neoadjuvant treatment (NAT), which relies on neoadjuvant chemotherapy (NAC) with or without additional neoadjuvant chemoradiation (NACR), aims at obtaining tumor response or control to consider secondary resectability. Nevertheless, the 5-year overall survival (OS) rate hardly exceeds 30% after surgical resection despite NAT,[5] which can be explained in part by the presence of occult metastatic disease and circulating tumor cells.[6]

Factors associated with favorable outcomes in patients undergoing resection after NAT include extended duration of chemotherapy (⩾6 cycles), decrease in the CA19-9 level following NAC, major pathological response (based on the College of American Pathologist [CAP] tumor regression grading (TRG)) and complete surgical resection (R0).[7–10] Of note, the relevance of the CAP score has been questioned. The assessment of response to antineoplastic agents in solid tumors relies on the morphological RECIST 1.1 criteria,[11] as it is usually associated with positive outcomes. However, in patients with PDAC receiving NAT, the ability of morphological response to predict OS has been contradictory in the literature and is highly debated.[9,12] Notably, several studies have reported that morphological downstaging after NAT is not associated with R0 resection, histological response, or prolonged survival in patients with resected PDAC.[7,12,13]

This study aimed to assess the association of morphological and pathological response to NAT on recurrence-free survival (RFS) in patients operated on for a non-metastatic PDAC.

Methods

Patients

We conducted a retrospective study in one high-volume expert center in France (Beaujon Hospital, Clichy, France). We studied the medical records of all consecutive patients with pathologically proven PDAC who were operated on by pancreaticoduodenectomy (PD) following NAT between 01/01/2016 and 01/01/2022. NAT consisted of NAC using FOLFIRINOX, followed or not by NACR. We only included patients with borderline resectable or locally advanced but potentially secondarily resectable PDAC. Patients who received another type of NAC other than FOLFIRINOX and those with other concomitant active malignancies were not included. We excluded patients with early (<1 month) postoperative death, unavailable postoperative data, non-measurable tumor at baseline, and/or who performed baseline CT scan more than 1 month before the first cycle of NAC.

Treatment procedures

All therapeutic indications were decided during dedicated weekly multidisciplinary tumor boards, following national guidelines.[14] The clinical tumor stage, that is, borderline resectable or locally advanced but potentially secondarily resectable, was determined on contrast-enhanced CT scan done at initial diagnosis. The absence of liver metastases was assessed on systematic liver MRI, including diffusion-weighted sequences.

One cycle of FOLFIRINOX consisted of a 2-h infusion of oxaliplatin (85 mg/m^2) followed by a 2-h infusion of leucovorin (400 mg/m^2) concomitantly with a 90-min infusion of irinotecan (150 mg/m^2), followed by a 46-h continuous infusion of 5-fluorouracil (2400 mg/m^2), every 2 weeks. The decision to administer additional NACR was made during a multidisciplinary team meeting (involving oncologists, surgeons, and radiation oncologists), when imaging following NAC showed persistent vein encasement or deformation, or arterial contact, suggesting that an R0 resection would only be achievable following further treatment. When done, NACR consisted of 54 Gy delivered in 30 daily fractions over 6 weeks with concurrent capecitabine at 800 mg/m^2 twice

daily on days of radiation therapy. The planned target volume was determined on a dedicated simulation contrast-enhanced CT as previously described.[15] A CT scan was performed within 1 month before NAC initiation and after every six cycles, and 4–6 weeks after NACR if performed. Patients underwent standardized clinical and biological evaluation before every chemotherapy cycle and weekly during NACR.

Surgical resection was decided in a tumor board meeting in patients with clinical (no pain and weight gain) and biological (normalization or CA 19-9 $<$ 200) response, and without radiological progression. All patients had a CT scan, MRI, and, if needed, a PET scan within 1 month before surgery. Venous resection was frequently planned except in patients who had invasion of superior mesenteric vein collaterals and/or complete stenosis of the venous axis with cavernous circulation. In patients with superior mesenteric artery invasion, surgery was considered only in patients with a short segment ($<$2 cm), lateral invasion ($<$180), without arterial stenosis, and in whom liberation of the SMA can be done without resection. No case of SMA resection was done. Surgery was done 4–8 weeks after the end of radiotherapy, and laparoscopic exploration was considered in some patients with doubtful extra-pancreatic disease despite complete preoperative exploration. Surgical resection was planned preoperatively, and a few patients had arterial sheath biopsies to rule out tumoral invasion. Some selected cases were operated on by the laparoscopic approach.

Postoperative follow-up consisted of clinical, biological, and CT examinations at least every 3 months for the first 2 years and every 6 months thereafter. All patients with compatible clinical conditions received adjuvant chemotherapy for 3–6 months, as decided during multidisciplinary tumor boards in accordance with national guidelines, starting within 12 weeks after the date of surgery.[14]

Data collection

We collected all relevant epidemiological, tumor, treatment, and follow-up de-identified data on a predefined standardized electronic chart. Postoperative complications (within 3 months) were scored according to the Clavien-Dindo classification.[16]

Morphological data (PDAC size, initial stage, response, and recurrence) were reassessed centrally on CT scans by two experienced radiologists who were blinded from the other data. Tumor response after NAT (i.e., after NAC and after NACR) was measured according to RECIST 1.1 (as a complete response (CR), partial response [PR], or stable disease [SD]).[11] Objective response refers to either CR or PR. Pathological features (ypTNM stage, R status, response) were assessed centrally by an experienced pathologist, blind to the other data. The pathological response was assessed according to CAP score, as CAP0 (complete response), CAP1 (near complete response: single/rare group(s) of cancer cells), CAP2 (partial response, residual cancer with regression), or CAP3 (poor response, no tumor regression).[17] The proportion of viable tumor cells (VTC) was measured on the whole specimen by two experienced pathologists.

The study protocol conformed to the ethical guidelines outlined in the Declaration of Helsinki. As a retrospective, monocentric observational study, and in accordance with French legislation, it was exempt from institutional review board approval.

Statistical analyses

Continuous variables were described as medians with their 25th–75th interquartile range (IQR) and compared using the Mann–Whitney test. Categorical variables were expressed as frequencies and percentages and compared using the Chi^2 or Fisher's test.

The primary endpoint was RFS, which was measured from the time of surgery to the date of recurrence. The secondary endpoint was OS, measured from the time of surgery to the date of death. Patients alive without event at their last follow-up were censored at that date. Median RFS and OS were estimated using the Kaplan–Meier method and were compared using the log-rank test.

The association between the proportion of VTC and the 2-year RFS rate was explored using the area under the receiver-operating curve (AUROC) and its 95% confidence interval. The best threshold was determined using the Youden method. The interobserver reproducibility of this threshold (i.e., classification of VTC $<$ 30% or $\geqslant$30%) was determined by computing Cohen's kappa coefficient on a random sample of 15 patients. Variables associated with RFS, and then those associated with OS, were explored using Cox proportional hazards backward stepwise multivariable regression models, which included non-collinear,

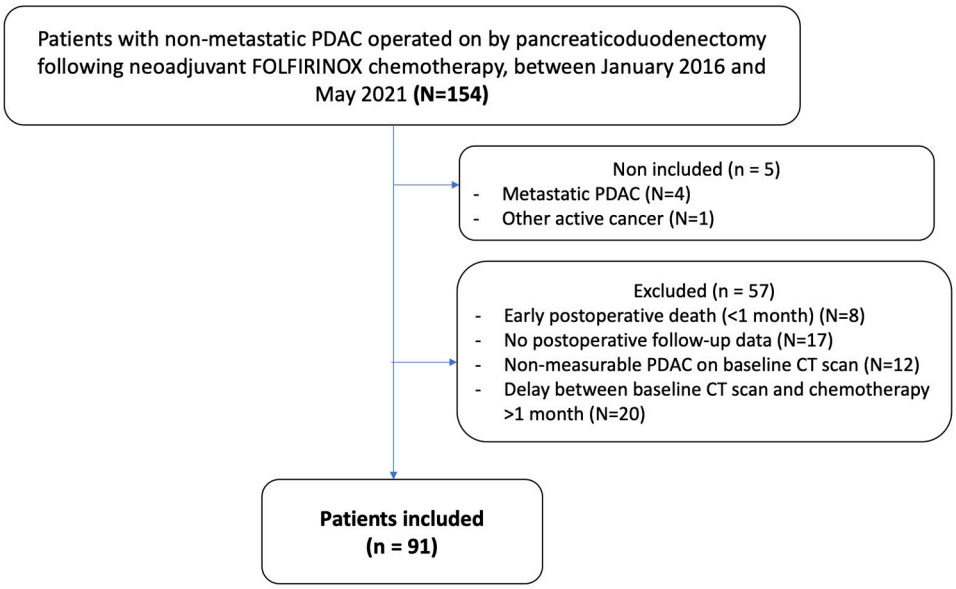


Figure 1. Flowchart of the study.

clinically relevant variables. Values of $p < 0.05$ were considered statistically significant. All statistical tests were bilateral. Statistical analyses were performed with the Prism software (version 10, Graphpad).

The reporting of this study conforms to the STROBE guidelines[18] (Supplemental File: STROBE checklist).

Results

Characteristics of patients

During the study period, 154 patients were operated on by PD for a borderline resectable or locally advanced PDAC after receiving FOLFIRINOX NAC in our institution. Among them, 63 patients were excluded because of inappropriate pre-therapeutic CT scan (non-measurable lesion or too long delay before NAC initiation), absence of postoperative follow-up data, or early postoperative death (Figure 1).

The characteristics at the time of surgery of the 91 patients included are summarized in Table 1. Briefly, the median age was 65.5 years, and the sex ratio was balanced. As expected, most patients were in good general condition with low performance status (PS) and ASA score. Most patients (78%) needed endoscopic biliary stenting to treat obstructive jaundice. At initial staging, most patients (87%) had borderline resectable PDAC, whereas 13% of patients had locally advanced PDAC due to arterial involvement.

Neoadjuvant treatment and morphological response

Before surgery, all 91 patients had received FOLFIRINOX NAC, consisting of an average of 6 cycles (range 4–13; Table 2). Half of them did not receive 5-fluorouracil bolus (mFOLFIRINOX regimen), and the dose of oxaliplatin and/or irinotecan was reduced in 45% and 35% of patients, respectively. In comparison with the initial CT scan, the post-NAC CT scan identified morphological response (CR+PR) in 21 patients (23.1%) and SD in the 70 others (Figure 2).

Then, 77 patients (85%) received additional NACR as decided during tumor board, to improve resection margins[10] (Table 2). NACR yielded a further decrease in tumor size in 37 patients (48%, green plots in Figure 2) and an increase in tumor size in 4 patients (5%, red plots in Figure 2). In comparison with the initial CT scan, the post-NACR CT scan identified objective response in 30/77 patients (39%), including 14 patients (18%) who had not achieved

objective response after NAC. Overall, NAT (NAC ± NACR) yielded objective morphological response in 35/91 patients (38%).

Surgery and postoperative evolution

Surgery was performed a median of 62 days (IQR, 48–73) after the end of NAT. PD was associated with porto-mesenteric vein reconstruction in 60% of cases (Table 2). Severe (Clavien-Dindo grade III/IV) postoperative complications occurred in 13 patients. At the histopathological examination of the resected specimens, most PDAC were classified as well (56%) or moderately (37%) differentiated. Tumor stage mostly consisted of ypT1 or ypT2 (84%), and 29% were associated with lymph-node metastases (median lymph-node ratio 0.11, IQR [0.05–0.16]). Overall, 22 patients (24%) had a pathological complete (CAP0) or nearly complete (CAP1) response. The median proportion of VTC was 30% (IQR, 18–60).

Following surgery, 79 patients (87%) received adjuvant chemotherapy, which was initiated a median of 61 days (IQR, 49–73) after surgery (Table 2). Adjuvant chemotherapy mostly consisted of LV5FU2 (53%) or mFOLFIRINOX (23%). 13% of patients did not receive adjuvant chemotherapy due to a general health status incompatible with the administration of adjuvant treatment within the required timeframe (12 weeks).

Recurrence-free survival and associated factors

The median postoperative follow-up was 32.1 months (95% CI (28.6–35.5)). During this follow-up, 51 patients (56%) had recurrence. The first site of recurrence was the liver, lungs, the peritoneum, local, and cutaneous in 20, 16, 11, 3, and 1 patients, respectively. Median RFS was 26.2 months (IC 95% (22.3–30.1)).

There was no statistically significant association between the percent of tumor size evolution after NAT (as depicted in Figure 2) and the risk of recurrence at 2 years (AUROC 0.565, 95% CI (0.44–0.69), $p = 0.31$). Accordingly, RFS was similar in patients with or without morphological response (partial or complete) after NAT ($p = 0.62$; Figure 3(a)).

There was no statistically significant association between the CAP score and the risk of recurrence (Figure 3(b)). However, the CAP score was prognostic for RFS when used as a binary variable (CAP0-1 vs CAP2-3, median not reached vs 18.9 months, respectively, $p = 0.038$) (Supplemental Figure 1(A)).

Conversely, there was a significant association between the proportion of VTC and the risk of recurrence at 2 years (AUROC 0.671, 95% CI (0.56–0.79), $p = 0.007$), with the best threshold identified for VTC $\geqslant 30$, corresponding to a sensitivity of 83.7% (95% CI (70%–91.9%)) and a specificity of 47.6% (95% CI (33.4–62.3)). The determination of this threshold had excellent

Table 1. Baseline characteristics of the 91 patients.

Age (years), median (IQR)	65.5 (58.4–70.5)
Male sex, *n* (%)	47 (52)
Body mass index (kg/m^2), median (IQR)	23.6 (21.9–27.1)
Smoking, *n* (%)	20 (22)
Diabetes mellitus, *n* (%)	27 (30)
Biliary stent, *n* (%)	71 (78)
Performance status, *n* (%)	
PS0	31 (34)
PS1	49 (54)
PS2	3 (3)
Unknown	8 (9)
ASA score, *n* (%)	
I	9 (10)
II	70 (77)
III	12 (13)
Anatomic location of PDAC, *n* (%)	
Head	77 (85)
Neck	9 (10)
Uncinate process	5 (5)
Initial staging, *n* (%)	
Borderline	79 (87)
Locally advanced	12 (13)
Tumor size (mm) before treatment, median (IQR)	27 (24–33.5)

ASA, American Society of Anesthesiologists; IQR, interquartile range.

Table 2. Description of treatments received and their results on tumor response.

Neoadjuvant FOLFIRINOX chemotherapy	91 (100)
Number of cycles, median (IQR)	6 (5–7)
No 5-fluorouracile bolus, *n* (%)	45 (49)
Irinotecan dose reduction, *n* (%)	32 (35)
Oxaliplatin dose reduction, *n* (%)	41 (45)
Neoadjuvant chemo-radiotherapy, *n* (%)	77 (85)
Dose (Gy), median (IQR)	54 (50.4–54)
Morphological response after neoadjuvant treatment, *n* (%)	
Complete response (CR)	13 (14)
Partial response (PR)	22 (24)
Stable disease (SD)	56 (62)
Pancreatic surgery	
Vein reconstruction, *n* (%)	55 (60)
Clavien grade III/IV complications, *n* (%)	13 (14)
Length of hospitalization (days), median (IQR)	16 (12–20)
Pathological morphology of the resected specimen, *n* (%)	
Well-differentiated carcinoma	51 (56)
Moderately differentiated carcinoma	34 (37)
Poorly differentiated carcinoma	6 (7)
Primary tumor pathological stage, *n* (%)	
ypT0	3 (3)
ypT1	37 (41)
ypT2	39 (43)
ypT3	11 (12)
ypT4	1 (1)
Lymph-node metastasis pathological stage, *n* (%)	
ypN0	65 (71)
ypN1	20 (22)
ypN2	6 (7)
Incomplete resection (R1), *n* (%)	15 (16)
Pathological response (CAP score), *n* (%)	
CAP0	3 (2)
CAP1	19 (21)
CAP2	54 (59)
CAP3	15 (16)
Percent viable cells (%), median (IQR)	30 (18–60)
Adjuvant chemotherapy, *n* (%)	
None	12 (13)
LV5FU2	48 (53)
mFOLFIRINOX	21 (23)
FOLFIRI	4 (4)
Gemcitabine + capecitabine	4 (4)
Gemcitabine	3 (3)
Number of cycles of adjuvant chemotherapy, median (IQR)	6 (6–6)

CAP, College of American Pathologist.

interobserver reproducibility, with a kappa coefficient of 0.86 ± 0.14. Accordingly, RFS was longer in patients with VTC $< 30\%$ than in those with VTC $\geqslant 30\%$ (median not reached vs 17.2 months, respectively, $p = 0.003$; Figure 3(c)).

Of note, although there was a weak but significant correlation between the evolution of tumor size on CT scans and the proportion of VTC ($r = 0.33$, $p = 0.002$; Figure 4(a)), objective morphological response per RECIST was poorly concordant with a proportion of VAT $< 30\%$ (kappa 0.20 ± 0.11; Figure 4(b)).

On univariable analyses, tumor stage > than pT1 (HR 2.10, 95% CI (1.19–3.82), $p = 0.012$), lymph-node metastases (HR 2.41, 95% CI (1.33–4.27), $p = 0.003$), CAP2/3 score (HR 2.11, 95% CI (1.08–4.63), $p = 0.043$), and VTC $\geqslant 30\%$ (HR 2.44, 95% CI (1.29–5.01) $p = 0.009$) were significantly associated with an increased risk of recurrence (Supplemental Table 1). Of note, morphological response after NAT (HR 0.87, 95% CI (0.48–1.52), $p = 0.62$) did not significantly influence the risk of recurrence.

On multivariable analysis adjusted for the presence of a biliary stent, NACR, lymph-node metastases, and adjuvant chemotherapy, VTC $\geqslant 30\%$ was significantly associated with an increased risk of recurrence (HR 2.28, 95% CI (1.08–5.13), $p = 0.037$) while objective response after NAT did not (Table 3).

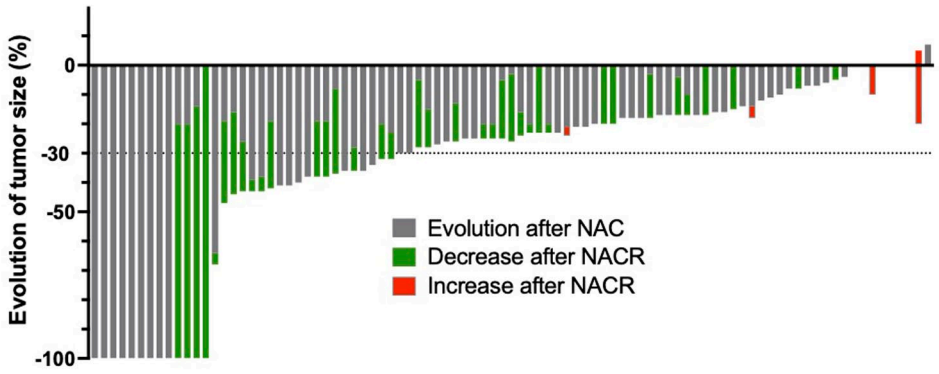


Figure 2. Waterfall plot of the evolution of tumor size after neoadjuvant chemotherapy (NAC) ± additional neoadjuvant chemo-radiotherapy (NACR).

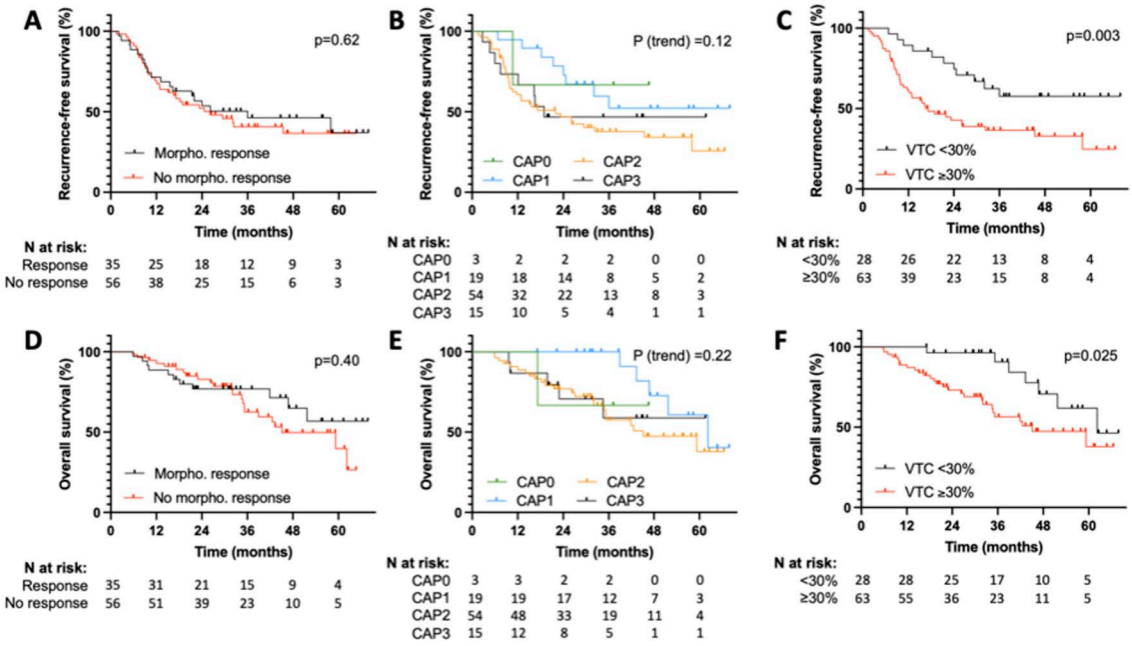


Figure 3. Kaplan–Meier curves of recurrence-free survival (RFS) and overall survival (OS) from the time of surgery. (a–c) RFS depending on (a) morphological response after neoadjuvant treatment or (b) pathological response according to CAP score or (c) the proportion of viable tumor cells (VTC) (D-E-F) OS depending on (d) morphological response after neoadjuvant treatment or (e) pathological response according to CAP score or (f) the proportion of viable tumor cells (VTC).

Overall survival

Thirty-four (37%) patients died during the follow-up. The cause of death was PDAC for 32 patients, one patient died from a postoperative late complication (liver ischemia), and one from liver cirrhosis. Median OS from surgery was 59.3 months (95% CI (55.8–62.8). On univariable analyses, tumor stage > than pT1 (HR 2.13, 95% CI (1.06-4.48), $p = 0.038$), lymph-node metastases (HR 2.42, 95% CI (1.14–4.95), $p = 0.017$), and VTC ⩾ 30% (HR 2.52, 95% CI (1.15–6.33), $p = 0.031$) were significantly associated with shorter OS (Supplemental Table 2).

The risk of death was neither influenced by morphological response after NAT (Figure 3(d)) nor by the CAP score (Figure 3(e)), while OS was numerically longer in patients with CAP0-1 than

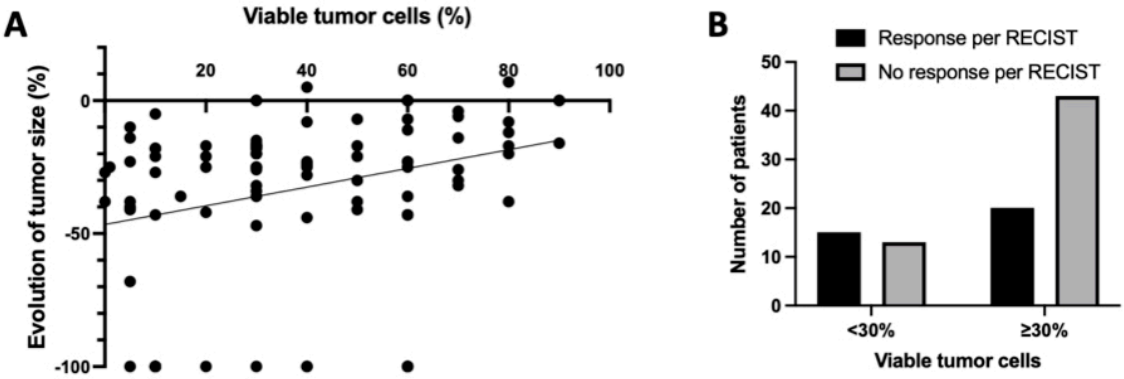


Figure 4. Association between morphological and pathological responses to neoadjuvant treatment: (a) correlation between the evolution of tumor size as measured on CT scan and the proportion of viable tumor cells on the pathological examination of resected specimens ($r = 0.33$, $p = 0.002$). (b) Concordance between morphological response per RECIST and a proportion of viable tumor cells $<$ or $\geqslant 30\%$ (kappa $= 0.20 \pm 0.11$).

in those with CAP 2–3 (median 58.2 vs 48.1 months, respectively, $p = 0.085$) (Supplemental Figure 1(B)). Conversely, OS was significantly longer in patients with VTC $<30\%$ (62.2 months) than in those with VTC $\geqslant 30\%$ (45.1 months, $p = 0.025$; Figure 3(f)).

On multivariable analysis adjusted on male sex, initial stage, and lymph-node metastases, viable tumor cells $> 30\%$ were associated with a 2.45-fold increased risk of death (IC 95%, (1.00–6.62)), although this result was not statistically significant (Supplemental Table 2).

Discussion

To our knowledge, the present study is the first to compare morphological and pathological responses to predict recurrence after PD following NAT for PDAC. It is also the first study to propose VTC $\geqslant 30\%$ as an effective tool for predicting RFS. This pathological marker is reproducible, simpler, and more accurate than the CAP score.

Our study is consistent with several others that have demonstrated the inaccuracy of CT scans to evaluate the response to NAT. In particular, radiological assessment does not predict R0 resection or pathological response, which are associated with better OS.[13,19] In the study of Cassinoto et al.,[20] an overestimation of tumor size was reported with a variability of 10 mm after NAT. In addition, 12/31 patients assessed as being at risk for R1 resection based on CT data were ultimately found to have an R0 resection after NAT. The misinterpretation of CT scan after NAT may be linked to the inflammatory reaction of the peritumoral stroma and the inability to distinguish tumor cells from post-therapeutic fibrous tissue.[19,21] The evolution of tumor size (as used in RECIST criteria) does not appear to be a suitable evaluation criterion and should, therefore, not be a goal of NAT. Hence, while preoperative morphological imaging remains mandatory to ensure the absence of distant metastases or significant local progression, it may not be appropriate to evaluate response to NAT preoperatively.

Among alternatives to evaluate tumor response to NAT preoperatively, the normalization of CA 19-9 could be a better predictor of response.[7,22–24] In addition, a few studies have demonstrated a relationship between metabolic response on [18F]-FDG PET and treatment efficacy.[25,26] In the study of Akita et al., 83 patients underwent [18F]-FDG PET before and after NACR. A regression $> 50\%$ between pre- and post-treatment SUVmax predicted NACR efficacy and was an independent prognostic factor in multivariable analysis.[25] However, the role of [18F]-FDG PET in evaluating the efficacy of NAT should be further explored in larger prospective studies to better define its role in this setting.

In contrast to radiology, major pathological response has been recognized as an independent prognostic factor in many studies.[7,10,27] However, how pathological response should be optimally assessed is still a matter of debate, and no standardized grading system for the pathological

Table 3. Multivariable Cox proportional hazard models of variables associated with the risk of recurrence.

Variable	HR	95% CI	*p* Value
Biliary stent (vs absence)	1.85	0.85–4.49	0.14
NACR (vs NAC only)	0.80	0.38–1.89	0.58
Objective response after NAT (vs stability)	1.16	0.62–2.10	0.64
Lymph-node metastases (vs absence)	1.58	0.80–3.11	0.18
Viable tumor cells ⩾ 30%	2.28	1.08–5.13	0.037
Adjuvant chemotherapy (vs absence)	0.67	0.31–1.66	0.34

evaluation of PDAC response to NAC has been established yet. Different criteria have been proposed, such as the primary tumor and lymph node metastasis stages and tumor regression grade, including the CAP score.[28–30] At our center, we used the CAP score, a four-tiered grading system that evaluates the level of response through the ratio between residual tumor and fibrosis. Indeed, the CAP score may be more closely associated with long-term prognosis than the MD Anderson[28] and Evans[29] scores.[9] Nevertheless, the CAP score also has its limitations. Notably, the categories (CAP0—complete response, CAP1—single/rare group(s) of cancer cells, CAP2—residual cancer with regression, CAP3—no tumor regression) are unbalanced (e.g., CAP0 is very rare, while CAP2 is a very large and heterogeneous category). In addition, these categories lack objective and reproducible thresholds, which, added to the challenge of distinguishing fibrosis from tumor regression, may lead to an insufficient concordance between pathologists (e.g., the coefficient of concordance was 0.64 in the study by Cacciato et al.[31] Our study is the first to investigate a threshold of VTC to predict survival. The use of VTC at a threshold of 30% as a prognostic marker for RFS presents several advantages over the traditional CAP. Unlike the CAP score, the VTC threshold of 30% is a clear and quantitative cutoff, which minimizes subjectivity in interpretation and reduces interobserver variability. The quantitative nature of the VTC threshold makes it particularly amenable to automation and analysis via digital pathology. Thus, this new parameter could provide a more accurate assessment of tumor response while being more reproducible and having a more relevant prognostic impact. By definition, VTC could only be analyzed on a resected specimen. However, future research should focus on assessing whether preoperative imaging, including CT, MRI, or 18FDG PET-CT, could enable measurement of VTC.

The main purpose of accurately assessing pathologic response is to provide the most precise prognostic evaluation. Although all patients currently have similar postoperative follow-up protocols to detect recurrence, it may be suggested that the type and frequency of follow-up exams could be tailored to the pathologic response. In addition, pathologic response may provide valuable information on individual sensitivity to NAT and could be used to tailor the type of adjuvant treatment. In our study, the limited variety of adjuvant chemotherapy regimens prevented us from exploring this hypothesis. However, the ongoing PRODIGE-93/PANACHE-02 trial is expected to evaluate the adaptation of adjuvant chemotherapy for resected PDAC according to tumor stage after neoadjuvant therapy.

The current study had several limitations, particularly due to its retrospective nature, which introduced significant selection bias. Such selection was notably due to missing data; however, the cohort had good external validity, as evidenced by the identification of usual prognostic factors (T-stage, N-stage, and CAP stage). In addition, all patients were treated by the same expert surgical team, following the same preoperative and postoperative procedures. It is also noteworthy to highlight potential heterogeneity, as not all patients received NACR, although the proportion of patients treated with NAC only (15%) may be too limited to influence the results. While adding NACR to NAC may yield limited survival benefits, the impact on pathological

response appears substantial,[32–34] which may potentially influence the results of our study. Finally, the high number of missing CA 19-9 values prevented us from including this variable in our analysis.

Conclusion

In conclusion, imaging-based morphological response to NAT is not associated with improved postoperative outcomes and is poorly correlated with pathological response. Therefore, this should not be the aim of NAT. Conversely, the pathological response to NAT on resected PDAC is a significant predictor of postoperative recurrence in patients with resected PDAC. Beyond its high reproducibility, the proportion of VTC $< 30\%$ could be a more straightforward and more informative marker than the CAP score. Should our results be confirmed, they could lead to the consideration of adapting the type of adjuvant chemotherapy based on pathological response.

Declarations

Ethics approval and consent to participate

The study protocol conformed to the ethical guidelines outlined in the Declaration of Helsinki. As a retrospective, monocentric observational study, and in accordance with French legislation, it was exempted from institutional review board approval. All participants provided informed consent prior to enrollment in the study.

Consent for publication

Not applicable.

Author contributions

Anaïs Jenvrin: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft.

Riccardo Sartoris: Formal analysis; Methodology; Writing – review & editing.

Safi Dokmak: Formal analysis; Methodology; Writing – review & editing.

Anne-Laure Védie: Conceptualization; Writing – review & editing.

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Matthieu Tihy: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

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Vinciane Rebours: Conceptualization; Supervision; Validation; Writing – review & editing.

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Acknowledgements

Not applicable.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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