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Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer

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Abstract Neoadjuvant chemotherapy has become common practice in the management of patients with non-metastatic pancreatic adenocarcinoma. This strategy helps better select patients who would benefit from surgical resection and also increase the number of patients amenable to surgical resection whose tumor seemed too locally advanced on initial imaging. However, several studies have shown that the radiological evaluation of the response after neoadjuvant therapy is difficult for pancreatic carcinoma. This article reviews the scientific basis of neoadjuvant therapy for non-metastatic pancreatic cancer and provides an update on tumor response evaluation with imaging after neoadjuvant treatment.

Pancreatic cancer (PC) is a major issue in public health. Indeed, although its incidence is relatively low (7th or 8th depending on the studies), it currently represents the fourth leading cause of death from cancer in Europe and the United States [\textsuperscript{1,2}]. PC is even considered the most lethal solid tumor, with a five-year survival rate for all stages combined between 5 and 7\%. Moreover, the incidence of PC is rising sharply in some countries, which remains unexplained yet. In France, the incidence of PC has increased about 3\% each year since 1980 \textsuperscript{3}, whereas in the United States it is believed that the total number of deaths due to PC will rise dramatically in the coming years, and become the second cause of death by cancer by 2030 \textsuperscript{4}.

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Surgical resection is currently the only potentially curative treatment for PC that may provide a five-year survival rate between 15 and 25% [5–7]. One of the most important prognostic factors for survival is the quality of the resection. Indeed, the survival rate associated with complete resection (R0) is significantly greater than with R1 (residual tumor cells on resection margins) or R2 (macroscopic residual tumor cells) resection. If surgical resection is incomplete (R1 or R2), survival rate is lower and similar to the survival rate after radio-chemotherapy without surgery [8–10]. But, PC is generally aggressive and evolves rapidly. Hence, surgical resection at the time of diagnosis may not be possible in more than 80% of the patients because the cancer is too locally advanced (LA) or already metastatic [11]. Indeed, surgery is performed only in patients with locally confined tumors, without locoregional vascular invasion nor distance metastases. In tumors with possible peri-pancreatic arterial or venous involvement, it has been demonstrated that adjuvant radiochemotherapy of chemotherapy allows tumor downsizing and downstaging in about 30% of the patients [12]. In these patients, the rates of complete resection R0 and of survival are close to those observed in patients who undergo surgery without neoadjuvant treatment [13,14].

To allow patients to benefit from the best possible therapeutic strategy, initial staging of pancreatic adenocarcinomas has been optimized in recent years. Multiphase computed tomography (CT) is essential for staging pancreatic cancers and is the best modality to assess resectability. Many studies have shown its performance to predict tumor invasion of peri-pancreatic vessels, especially the retroperitoneal margin that includes the superior mesenteric artery (SMA) and the superior mesenteric vein-portal vein confluence (SMV/PV) [15–18]. However, what about the performance of CT after neoadjuvant radio-chemotherapy? How is the treatment response evaluated using cross-sectional imaging?

This article reviews the scientific basis of neoadjuvant therapy for non-metastatic pancreatic cancer and provides an update on tumor response evaluation with imaging after neoadjuvant treatment.

**Determination of resectability**

Multi-phase CT is essential to stage PC, and to determine the resectability or unresectability of tumors (Fig. 1). CT is very useful to predict unresectability of PC tumors (positive predictive value above 90%) and slightly less well to predict resectable tumors (negative predictive value = 70–90%) [15–18]. This difference may be partly explained by the difficulty to detect very small hepatic metastases or the onset of peritoneal carcinomatosis with CT. For a patient with a PC considered resectable, magnetic resonance imaging (MRI) examination of the liver should be performed to exclude possible subcentimeter hepatic metastases.

In the absence of metastases, pancreatic CT is useful to define resectability and discriminate between patients with resectable PC who benefit from surgical resection and those with unresectable PC for whom systemic treatment is preferred. In 2001, an intermediate class of tumors was defined for the first time. These tumors were considered “borderline” (i.e., potentially resectable), but with a high probability of incomplete R1 or R2 resection [19]. In 2006, the guidelines of the American National Comprehensive Cancer Network (NCCN) defined this group of tumors at the border between resectable and unresectable tumors as being “borderline resectable’’ (BR). Subsequently, several definitions have been proposed to describe accurately the three groups. Most of the criteria were based on the excellent capability of CT to predict vascular invasion by the tumor. Several criteria were used such as the degree of contact between the tumor and the surrounding vessels, the teardrop deformity of the vein, and even vein occlusion [20–22].

But differences remained between the various classifications, mainly because of the exact definition of “borderline” tumors [23–25]. Indeed, there have been improvements not only in the area of imaging techniques and semiology, but also in surgery techniques and in pancreatic resection. Hence, when CT shows tumor invasion of the SMV or PV, surgeons can now obtain complete resection (R0) by resection and reconstruction of the vessel. This approach is usually avoided when the vessel is an artery (celiac artery (CA); superior mesenteric artery (SMA) or hepatic artery (HA)) because resection/reconstruction is less likely to succeed and increases morbidity [26].

Recently, a group of experts proposed a new definition of pancreatic cancer resectability that has been more widely accepted [27] and recommended in the 2015 NCCN guidelines [10]. This classification is based solely on the degree of contact between the tumor and the vessel rather than
signs of deformity subjectively perceived. This classification defines the three following groups:

- resectable tumor:
  - degree of contact tumor-artery (SMA, HA, or celiac artery [CA]): none,
  - degree of contact tumor-vein (SMV-PV): none or less than 180° of vessel wall circumference;
- “borderline” tumor:
  - degree of contact tumor-artery (SMA or CA): less than 180°,
  - degree of contact tumor-artery (HA): reconstructable short segment, interface of any degree,
  - degree of contact tumor-vein (SMV-PV) ≥ 180° of vessel wall circumference, or reconstructable occlusion;
- unresectable tumors (locally advanced): higher values.

It is now well-established that patients must be selected for surgery based on the probability to achieve complete (R0) resection. In case of doubt or high risk of achieving incomplete (R1) resection, neoadjuvant (radio) chemotherapy is now recommended [28]. The objective is to increase the probability of R0 resection and to select patients whose cancer is evolving rapidly to avoid unnecessary surgery and morbidity. The use of the classification should of course be considered individually, but also according to the local expertise of pancreatic surgeons, because the management of PC has become increasingly specialized. The benefit of hospitals with high volume (number of pancreatic surgeries) on the rate of complete resection and survival rate has been demonstrated [29].

Neoadjuvant treatment and resectable PC

The standard treatment for resectable PC combines surgery and adjuvant chemotherapy. This is based on the ESPAC1 and CONKO 001 studies that have shown significant improvement in overall survival without recurrence in the group receiving an adjuvant chemotherapy, whatever the status, NO/N+ or R0/R1 [30,31]. However, the results of this standard treatment remain poor, with an overall 5-year survival rate of about 20%. Furthermore, in the first year, one-quarter of the patients die and almost half have recurrent disease. It should be noted that even in these patients with initially diagnosed resectable PC, surgery is usually R1 [32–34] and also that 30% of the patients do not receive adjuvant therapy because of the morbidity associated with pancreatic surgery. All this provides a strong rationale for neoadjuvant treatments.

However this strategy has still not been assessed in a phase III study; it remains therefore impossible to use neoadjuvant treatments in patients with resectable PC outside a therapeutic trial. It is likely that the results obtained with new therapeutic associations (FOLFIRINOX or gemcitabine-NAB-paclitaxel) that show an increase in overall survival rate and especially about 30% response rates compared to gemcitabine alone [35,36], will justify trials to evaluate this strategy.

In France, a randomized phase 2 study (PANACHE) funded by the hospital clinical research program (PHRC) is about to start. It is a 3-arm study; one arm will receive FOLFIRINOX as neoadjuvant treatment, one arm will receive FOLFOX as neoadjuvant treatment, and one arm will receive the standard treatment (surgery and adjuvant chemotherapy). The primary endpoint is a composite endpoint that combines feasibility and overall survival at 1 year.

Neoadjuvant treatment and locally advanced PC

The primary objective of systemic treatment in patients with locally advanced PC is palliative, like for patients with metastatic cancer. The aim is to lengthen survival time with an acceptable general condition. Chemotherapy is selected based on patient general condition. Gemcitabine is recommended if the general condition is impaired or if the patient is considered too old, while a more intensive treatment such as FOLFIRINOX [35] or gemcitabine combined to NAB-paclitaxel [36] is given to patients in good general condition [10]. If the disease seems well controlled after the first cycles of chemotherapy, especially if no metastases have appeared, some groups recommend adding radio-chemotherapy.

It has been shown that induction chemotherapy ± radio-chemotherapy may be more than simply palliative. A significant response or downsizing has been observed, creating an opportunity for curative surgical resection. The accurate rate of secondary resectability obtained after (radio)-chemotherapy is difficult to evaluate, because large heterogeneities exist among chemotherapy protocols in the different studies, with supplementary radiotherapy or not, and also in the definition of resectability when the study included only locally advanced PC or combined LA and BR groups. In 2000, a French study showed a secondary resectability rate of 21% in LA patients when only gemcitabine was given to patients for palliative purpose [37]. A literature review revealed that 80% of patients with unresectable PC responded or stabilized after neoadjuvant treatment [38]. Secondary resection was possible in 33.2% of the patients (95% CI: 25.8–41.1%) with R0 rates of 79.2% (72.4–85.2%) [38].

Since 2010 and the French multicenter study published by Conroy et al. [35], other studies have investigated the rate of secondary resectability after FOLFIRINOX. A French multicenter study that included 77 patients with LA pancreatic adenocarcinoma showed good tolerance to FOLFIRINOX, and also tumor control and an objective response of 84 and 28%, respectively. Altogether, 36% of the patients had curative surgery [39]. Another French multicenter study analyzed the results obtained in 80 patients operated after neoadjuvant treatment by FOLFIRINOX for a BR (n = 47) or LA PC (n = 33) [40]. This study confirmed the absence of excess morbidity following secondary surgery, and in particular a very low rate of pancreatic fistula. Twenty six percent of the patients had major histological response (ypT0 or T1N0) and 15% had complete histological response. After a median follow-up of 38.2 months, the median survival time from diagnosis, from surgery and the disease-free survival time were 59.2 months, 43.5 months and 17.4 months, respectively [40].

All these data suggest that in patients with BR or LA PC, it is possible to obtain a response that allows satisfactory secondary resection (R0) with acceptable morbidity.
and a survival time at least comparable to the survival time obtained in patients whose tumors had been immediately resected [14,41].

**Response evaluation after neoadjuvant treatment**

The evaluation of a PC response after neoadjuvant treatment is particularly difficult, as evidenced by the small number of scientific papers on the subject and the lack of consensus and recommendations. However as early as 2001, White et al. suggested that after neoadjuvant treatment, CT would overestimate resectability [42]. In other words, (i) the diagnostic performance of CT to predict resectability or unresectability seems to be reduced after neoadjuvant treatment; and, (ii) the radiological response seems to correlate poorly with the histological response. During the following years, several studies started to question these results, showing no decrease in the diagnostic performance of CT to evaluate resectability and unresectability [43–45]. However, these studies were not very powerful, as they were carried out in a very low number of patients (less than 15 in general). We had to wait until 2012 for the researchers of the MD Anderson Center (Houston, TX) to confirm the results [46]. In a retrospective series of 129 patients with “borderline” PC they showed that, on the one hand, a tumor morphological response at imaging was rare after neoadjuvant therapy, and on the other hand, that the usual RECIST criteria were not suitable to evaluate the response [46]. In 2013, we performed a comparative analysis of preoperative CT scans of 80 patients with pancreatic head adenocarcinomas. 42 patients had been treated with first-line surgery and 38 patients had been treated with surgery after neoadjuvant therapy. The analysis was performed by two radiologists who did not know the clinical history nor if the patient had been administered a neoadjuvant treatment. The results showed that the diagnostic performance of CT to predict R0 resectability was lower after neoadjuvant treatment (58% versus 83%), and that the capacity to predict unresectability was also significantly lower (52% versus 88%), mainly because the degree of contact with vessels and tumor volume were overestimated after neoadjuvant treatment [47]. Finally, another study published in 2015 confirmed these results; in a series of 40 BR or LA patients, 28 were still considered BR or LA on imaging after neoadjuvant treatment, and yet the R0 resection rate was 92% for the entire series [48].

The reasons that explain this poor performance of imaging after neoadjuvant treatment are related to the nature of the PC. PC consists of a more or less great number of tumor cells embedded within a dense, fibrosa stroma. After successful chemo and/or radiation therapy, tumor cells tend to disappear, but fibrosis persists, although it is not possible to determine whether the tumor fibrosis was pre-existing or developed in response to the treatment. If we add to this a possible locoregional edema induced by radiotherapy, or potential inflammatory changes secondary to biliary drainage, we understand better why the response to treatment for this type of cancer is a serious challenge.

**Some clues to better evaluate response to treatment**

In the absence of reliable criteria to evaluate response, the following strategy is routinely followed:

- continuation of palliative chemotherapy in case of progressive disease (based on CT findings or tumoral marker values);
- in patients with stable, or regressing disease, treatment is based on clinical evaluation and evolution of CA 19-9:
  - patients with clinical improvement, decreased CA 19-9 serum level (<200) and if disease looks stable or regressing on CT: surgical exploration is performed to see if resection is possible,
  - in the other cases: continuation of medical treatment.

This strategy has limitations. First, many patients are operated although the disease remains advanced, with vascular invasion still present. Second, some patients will not undergo exploration ± resection because of important vascular contact that makes the physicians unsure about a possible significant histological response.

It is therefore essential to establish reliable criteria to evaluate response accurately. As stated above, tumor volume and therefore RECIST or WHO criteria are not reliable for PC. Furthermore, in 2013, a study carried out in 16 patients concluded that the evolution of the tumor density on CT, as well as the evolution of tumor vascular contacts, did not provide additional information [49]. We partially confirmed these results in a study that included 47 patients with BR or LA tumors, by showing that the tumor density variations, whether during the arterial or portal phase, were not correlated with response to neoadjuvant therapy [50]. In contrast, a reduction, even partial, of the contact between the tumor and the peri-pancreatic vessels was associated with a high probability of R0 resection. Moreover, a decrease in tumor size, even slight, was also correlated with an R0 resection. And finally, the persistence of LA disease, including the persistence of stenosis or occlusion of the SMV/PV was only slightly predictive of an R1 resection (Figs. 2 and 3). Based on this study, we may draw the following conclusions:

- if the disease is stable after neoadjuvant treatment, the usual radiological criteria cannot help determine the histological response, therefore surgical exploration should be recommended;
- the histological response is underestimated on imaging. A decrease in tumor size or vascular contacts, even partial or moderate, is possibly associated with an underestimated tumor response, and must therefore prompt surgical exploration even in case of initially locally advanced disease.

The results of this study are helpful, but remain insufficient. It is very likely that functional imaging will provide new solutions in the future. A 2010 study that focused on about 20 locally advanced PC showed that a decrease >50% of standardized uptake value (SUV) on PET-CT examination scan was strongly predictive of R0 resection [51]. But ultimately, there is very little literature about the use of PET-CT scan for this indication. Perfusion imaging has also shown encouraging results. In 2008, Park et al. showed in about
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Figure 2. 52-year-old woman with pancreatic cancer diagnosed in May 2013. Computed tomography (CT) images obtained during the portal venous phase following intravenous administration of iodinated contrast material in the transverse (a) and coronal (b) planes show a large pancreatic mass encasing the celiac trunk on its whole circumference (white arrow), the portal vein (black arrow), and in contact with the left adrenal gland (arrowhead). On the coronal plane, the mass is clearly in contact with the portal vein and close to the superior mesenteric artery but with persistence of a fatty border around its entire circumference. After neoadjuvant chemotherapy CT images in the transverse (c) and coronal planes (d) show that the tumor has clearly shrunken, but there remains infiltration surrounding the celiac trunk and close to the portal vein. The patient was operated in July 2014. Resection was complete (R0) and the tumor was staged pT3N1Mo. The patient died from bowel obstruction in April 2015 as a consequence of surgery despite the absence of tumor recurrence. (Courtesy of Dr Benoit Gallix, Mc Gill University).

30 patients with PC that an initial high value of \( K^{\text{trans}} \) was associated with a good tumor response on CT [52]. And on MRI, a study that included 11 patients confirmed that an initial high value of \( K^{\text{trans}} \) was associated with satisfactory response [53]. Unfortunately, perfusion imaging techniques in digestive imaging are not yet sufficiently developed and these promising results must be confirmed by larger scale studies.
**Figure 3.** 65-year-old woman with pancreatic cancer. (a) Computed tomography (CT) image obtained during the portal venous phase following intravenous administration of iodinated contrast material in the transverse plane shows large soft tissue mass centered on the pancreatic neck surrounding and stenosing the mesenteric-portal vein confluence (black arrow), and invading the retroperitoneal margin with discrete contact with the superior mesenteric artery (white arrow). (b) after neoadjuvant treatment, CT shows that the tumor shrank, as well as the contacts with the mesenteric vein and portal vein which are now evaluated less than 180° on multiplanar reconstructions. The patient was operated 10 months later. Resection was complete (R0) and the tumor was staged pT2N0M0. The patient is still alive without recurrence.

**Conclusion**

The radiological evaluation of treatment response in non-metastatic PC is a challenging field of research where much progress is still needed. PC is one of the few cancers for which the usual morphological criteria do not perform well in the evaluation of tumor response after chemotherapy. The histological response is generally underestimated with imaging and the strategy of recommending surgical exploration in case of stable disease remains relevant so far. In case of tumor response observed on imaging, even partial or moderate, that involves either the tumor size or the contacts between the tumor and the peri-pancreatic vessels, surgical exploration is recommended regardless of the extent of residual disease, because it is likely that the histological response is underestimated by imaging. Finally, functional imaging will have a major role to play in the future, but this must be demonstrated.

**Take-home messages**

- With borderline or locally advanced pancreatic cancers, neoadjuvant therapy with (radio) chemotherapy makes it possible to downsize and downstage a tumor in about 30% of patients.
- Patients must be selected for surgery based on the probability of obtaining a complete R0 histological resection. In case of high risk of achieving an incomplete resection (R1 or R2), neoadjuvant treatment is now recommended.
- The diagnostic performance of CT to predict resectability or unresectability decreases after neoadjuvant treatment.
- After neoadjuvant therapy, CT or MRI tends to underestimate the histological response.
- All decrease in tumor size or tumor vascular contacts, even mild or moderate, potentially underestimates the histological response and should therefore prompt surgical exploration even if the disease was and remains locally advanced.
- Functional imaging will certainly have a major role to play in this indication, but more progress is needed to evaluate accurately the response after neoadjuvant therapy of nonmetastatic pancreatic cancers.

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