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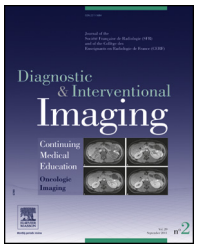

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Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer

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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 [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 [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 [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

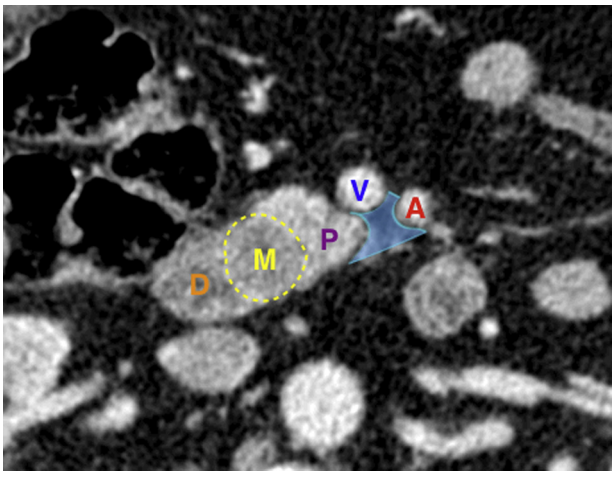

Figure 1. Anatomic representation of the retroperitoneal margin through the pancreatic head and uncinate process on computed tomography image obtained in the transverse plane during the portal venous phase following intravenous administration of iodinated contrast material. Retroperitoneal margin (or retroportal) is determined by the cellular-fatty space between the left border of the uncinate process and the superior mesenteric artery (since its origin), behind the mesenteric-portal veins. Some authors associate also the cellular-fatty space located behind the pancreas head and in front of large retro-peritoneal vessels (inferior vena cava and aorta). (D: duodenum; M: tumor mass of the pancreatic head; P: pancreatic head; V: superior mesenteric vein; A: superior mesenteric artery; Light blue area, retroperitoneal margin).

''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

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