CLINICAL CASE

A prolonged follow-up provides new insights into locally advanced pancreatic cancer treatment

Un suivi prolongé permet un regard nouveau sur le traitement du cancer pancréatique localement avancé

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Summary
We report the case of a 64-year-old woman treated for a locally advanced pancreatic adenocarcinoma, which could not undergo radical resection due to encasement of the superior mesenteric artery. After chemoradiotherapy (six weeks), normalization of plasma CA19.9 levels was documented and CT showed shrinkage of the pancreatic mass but persistent encasement of the SMA. Surgical exploration followed by radical resection was performed 18 months later. Resection of the pancreatic head was then performed and the final pathological analysis showed a complete response. This case is unique in terms of the duration of follow-up between chemoradiotherapy and radical resection and raises two main concerns regarding the current standard of care of locally advanced pancreatic tumors; first, the difficulty of assessing the tumor response to chemoradiotherapy, second, the unfeasibility of establishing the timing of surgery, its indications and the survival benefits for patients with an objective response to therapy.

Résumé
Le cas d’une patiente âgée de 64 ans atteinte d’un adénocarcinome de la tête du pancréas localement avancé, non résécable en raison d’un engainement de l’artère mésentérique supérieure est rapporté. Une radiochimiothérapie (six semaines) permettait d’obtenir une normalisation du CA 19-9 et une diminution de la taille de la lésion avec persistance d’un engainement artériel. Une duodénopancréatectomie céphalique n’était réalisée que 18 mois plus tard. L’examen histologique définitif confirmait l’absence de reliquat tumoral. Ce cas est

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original du fait du délai écoulé entre la fin de la radiothérapie et la résection chirurgicale. Il permet ainsi de discuter des difficultés d’évaluation de la réponse tumorale à la radiochimiothérapie, et de l’impossibilité, actuellement, d’évaluer le bénéfice en terme de survie, obtenu après résection d’un adénocarcinome localement évolué ayant répondu de façon objective à la radiochimiothérapie.

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Case

In July 2004, the case of a 64 year-old woman was discussed during the Gastrointestinal Oncology Committee meeting in our institution. The patient had sustained weight loss (4 kilos in three months) associated with elevated plasma CA19.9 (168 U/ml). Abdominal computed tomography (CT) scan revealed a 3 cm hypodense mass in the uncinate process spreading into the pancreatic head and completely encasing the superior mesenteric artery (SMA) (type E in the Loyer classification [1], grade 4 in the Lu classification [2]). There were no distant or nodal metastases (Fig. 1).

Endoscopic ultrasonography confirmed the presence of a hypoechogenic mass in the head of the pancreas encasing the SMA and the superior mesenteric vein (SMV). Fine-needle aspiration cytology was performed. A well-differentiated ductal adenocarcinoma was diagnosed at cytological examination.

According to the above-mentioned classifications, the definitive diagnosis was locally advanced pancreatic adenocarcinoma, making radical resection impossible due to encasement of the SMA. The patient was enrolled in a randomized phase II study (Accord 09 — FFCD-FNCLCC) of primary chemoradiotherapy including systemic chemotherapy with Docetaxel 20 mg/m² per week and Cisplatin 20 mg/m² per week for six weeks combined with a 54 Gy dose of radiotherapy delivered in 1.8 Gy daily fractions to the celiac area over six weeks. The patient received treatment from August 2004 to October 2004 which she tolerated well. Five weeks later, at physical examination, a good general condition (WHO performance status 0) and normalization of plasma CA19.9 levels (5 U/ml) was documented. Post-chemoradiotherapy CT showed shrinkage of the pancreatic mass but persistent encasement of the SMA (Fig. 1). The patient was then followed up by clinical examination, plasma CA 19.9 determination, CT and/or MRI every four months which showed stabilization of the pancreatic mass whose tissue continued to surround the SMA.

After 18 months, as there was no disease progression, the case was again discussed during the in-house Gastrointestinal Oncology Committee meeting. In keeping with current practice [3], surgical exploration followed by radical resection was recommended after completion of the preoperative work-up involving endoscopic ultrasonography, PET and CT scan. Endoscopic ultrasonography confirmed the presence of a hypoechogenic area around the SMA where the tumour was first described and both CT and PET scan were negative for local or distant disease. The patient underwent a laparotomy in September 2006. During surgery, multiple samples of tissue surrounding the SMA were removed for immediate histological examination whose results were negative for tumour. Resection of the pancreatic head was then performed and the final pathological analysis showed a complete response. In March 2007, the patient was disease free at the final follow-up, 29 months after completion of chemoradiotherapy.

Current multimodality treatment of locally advanced pancreatic cancer

Current treatment of unresectable locally advanced pancreatic adenocarcinomas without distant metastases is based on chemoradiotherapy. This combined treatment, compared to chemotherapy and radiation alone, has been shown to improve overall and median survival [3,4]. Moreover, chemoradiotherapy can induce downstaging of the tumour...
allowing radical resection in approximately 20% of patients \[5—10\]. In this group of patients, survival is reported to be at least the same as that of patients undergoing primary resection for a localized resectable tumour with a median survival of approximately 20 months \[7,10,11\]. In addition, 3—18% of lesions have no neoplastic foci at pathological examination \[5,9—12\]. This evidence and the case reported here, which is unique in terms of the duration of follow-up between chemoradiotherapy and radical resection, raise two main concerns regarding the current standard of care of locally advanced pancreatic tumours.

First, to date the assessment of tumour response to chemoradiotherapy is based on clinical examination, CA 19-9 level, and multidetector CT scanning which is considered the best imaging technique for determining pancreatic tumour resectability \[12—14\]. A pancreatic tumour is defined as unresectable on CT scan when one or more of these conditions are present: encasement of the peripancreatic arteries (celiac axis, SMA, or both), thrombosis of the SMV, portal vein (PV) or SMV-PV confluence \[2,3,11\]. Unfortunately, CT scan, as well as endoscopic ultrasonography, cannot distinguish remnant tumour tissue from a chemoradiotherapy-induced fibrous reaction surrounding or directly touching the adjacent arteries, even in case of a complete tumour response \[12\].

Therefore, in the absence of distant metastases, surgical resection is decided exclusively based on performance status, CA 19-9 plasma level and a decrease in the size of the pancreatic mass with the consequent risk of performing a pancreatic resection with positive margins \[6,7,9,11,12,14,15\]. In our opinion, multiple intraoperative sampling of the area surrounding the initially encased artery is essential to determine the pathological response to chemoradiotherapy of locally advanced tumours amenable to radical surgery. If frozen sections are negative, surgical resection can be safely performed, while positive pathological findings should be considered an absolute contraindication to resection.

Second, surgical resection is generally indicated four to six weeks after the end of chemoradiotherapy \[5,7,11\]. An important drawback to this is the difficulty of establishing the timing of surgery, its indications and the survival benefits in patients with an objective response to therapy because of the brief interval between the end of chemoradiotherapy and surgery. The long disease-free survival after chemoradiotherapy experienced by our patient raises the question of the usefulness of surgical resection. Although cases with such long disease-free survival are purely anecdotal \[16\], it is noteworthy that postoperative mortality in the group of patients with a negative pathological examination at surgery is mainly related to distant metastases (25—42%) rather than to local recurrences which develop in patients who undergo primary resection for a localized tumour \[5,6,9,10,12,18,19\]. Although we cannot know whether our patient benefited from this delayed pancreatic resection, this case report and all previous observations suggest that there is a small sub-
group of pancreatic tumours that could strongly benefit from chemoradiotherapy alone but, to date, imaging techniques and tumour markers cannot identify them [12,17].

A larger series is warranted to confirm this hypothesis and studies to identify more efficient imaging techniques and molecular markers of diverse responses of pancreatic tumour to chemoradiotherapy are needed.

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References