1 Introduction to Diagnosis and Treatment in Pancreatic Neoplasms

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1.1 The Environment for Nihilism in Pancreatic Cancer

If we adapt the concept of nihilism to our medical field, we could consider it as the approach to knowledge from a fatalistic point of view: in the end, everything is reduced to nothing and, therefore, nothing makes sense. The first World Pancreatic Cancer Day, held in Spain in 2014, had the following headline in the media: "Nihilism is the usual tendency in pancreatic cancer" [1]. It is certainly difficult to find scientific articles that do not begin by describing pancreatic cancer as an intractable malignant tumor with a very poor prognosis. Unfortunately, its incidence is increasing and according to GLOBOCAN 2020 [2], it is the twelfth most common cancer in the world, with 495,773 new cases. However, it is the 7th leading cause of cancer-related deaths, causing 466,003 deceases (4.5% of all cancer deaths). While mortality is declining in other types of cancers, it is increasing in pancreatic cancers. Generally, after diagnosis, only 24% of people survive 1 year and 9% live for 5 years [3]. This situation is not new and, unfortunately, there have not been great advances with enough impact on the results. The keys to this situation that causes nihilism are:

- Pancreatic cancer is mainly diagnosed at an advanced stage. Regrettably, 80–90% of patients present unresectable tumors at the time of diagnosis [4].
- Surgery is the only curative therapeutic option. However, even when resection is performed successfully, the overall survival as well as the disease-free survival rates remain very low due to local recurrence or distant spread [5].

Beyond the epidemiological and screening aspects, this chapter will address the most relevant general aspects of the diagnostic and therapeutic approach and the possible future approaches to improve results.

1.2 Key Points in the Diagnosis of Pancreatic Cancer

1.2.1 Molecular Diagnosis: Toward the Early Diagnosis in Pancreatic Cancer

When the patient presents symptoms of pancreatic cancer, both body and head, the tumor is, in a high percentage of cases, advanced. This makes it necessary to look for other signs that facilitate the diagnosis in earlier stages, for

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instance, germline mutations which are involved in pancreatic cancer development [6, 7]. According to the National Comprehensive Cancer Network guideline, germline testing must be done for any patient with confirmed pancreatic cancer [8].

Ductal intraepithelial neoplasia (PanIN) is considered the most common type of pancreatic adenocarcinoma precursor. There are complex mutational steps from this event until cancer dissemination that include Kras, Ckn2a, Tp53, or Smad4 mutations. From them, Kras gene is mutated in more than 90% of cases [9] and G12D mutation is the most commonly observed [10]. The severity of the cancer evolution is associated with the number of mutant genes. Recently, in a meta-analysis carried out by Zhao et al. [11], it was assessed that the detection of microRNAs was related to not only the prognosis of pancreatic cancer, but also the identification of therapeutic targets [12]. Similarly, promising advances have been developed under the name of "omics". The "omics" concept includes the evaluation of circulating biomarkers, exosomes, or cell-free DNA (cfDNA) through different sequencing techniques, including transcriptomic [13].

An important key is where these markers can be more expressive, either in peripheral blood or in portal blood, where pancreatic cancer drains directly. In theory, the detection of circulating tumor cells (CTCs) in portal blood should be more accurate and it might be associated with a higher probability of liver metastases [14] (Fig. 1.1).

Earl et al. [15] evaluated CTC and DNA circulating in peripheral blood obtaining good results when they were correlated with the existence of pancreatic cancer. However, in a preliminary study carried out by Padillo et al. [16], we detected that CTCs in portal blood correlate better with tumor size and neural infiltration than in peripheral blood.

The fact of discovering a CTC would absolutely not imply the appearance of distant metastases since clusters of cells would be needed for them to occur. It remains to be defined which is the cut-off point for the number of CTCs from which the existence of a high risk of distant disease could be considered. This type of information is relevant to plan the actions to undertake.

In summary, the in-depth study of mutations and their early detection, as well as markers such as microRNA, CTC, cfDNA, or exosomes could allow new therapeutic targets. Due to the fact that a large number of biomarkers are proposed, a platform for the validation of the biomarkers used to detect early stages of pancreatic cancer has been proposed [17].

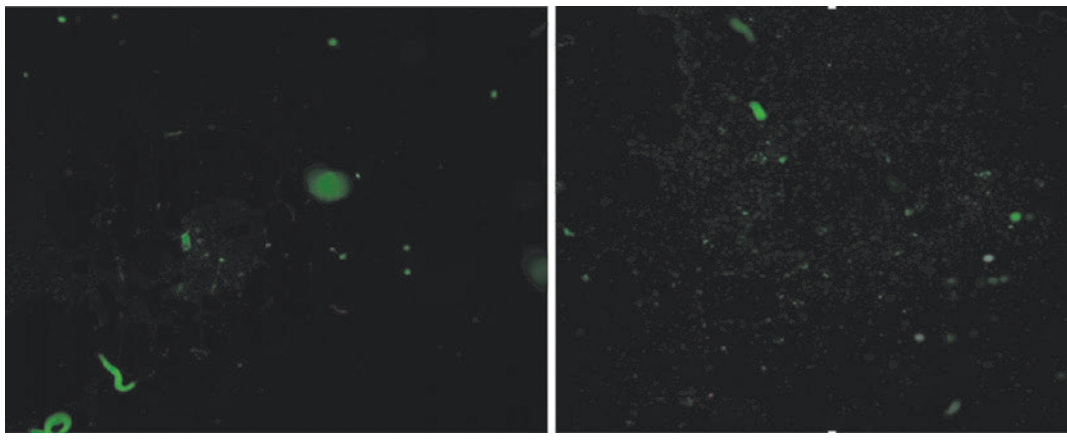

Fig. 1.1 Portal vein vs. peripheral CTCs assessment. Samples from the same patient; Portal blood: 2.170 CTCs and 15 cluster. Peripheral blood: 114 CTCs and 2 cluster

1.2.2 Radiomics: Diagnostic Imaging as a Tool for Pathological Specification and Prognosis in Pancreatic Cancer

When a patient is diagnosed with pancreatic cancer, computerized tomography (CT) scan with vascular contrast is the test of choice to assess the location, size, local extension and possible existence of distant metastases. Today, 3D reconstructions allow to obtain magnificent images that are very useful in diagnosis and treatment planning. However, as mentioned above, it is difficult to reach a diagnosis in the early stages of tumor development. Like other disciplines, radiology is working to image early lesions. Another frequent problem is to obtain a sample significant enough to have a histological diagnosis after biopsy in order to clearly guide the treatment.

Currently, radiology is generating very relevant advancements aimed at providing key preoperative information in relation to both the possible malignancy of the pancreatic lesion and the prediction of results after treatments. In this sense, the "radiomics" described by Lambin et al. [18] uses artificial intelligence and machine learning procedures in the processing of the images that are allowing to make approximations not only to the location and extension but also to the type of tumor and possible vascular or neural infiltration. Radiomics uses artificial intelligence and a machine learning approach to analyze a large amount of radiological images and extracting information from them [18], taking into account the pathology, biomarkers, and tumor phenotypes [19]. Machine learning and artificial intelligence applications allow radiomic findings to be properly correlated with overall survival as well as with the potential response to selected chemotherapy [20–22].

The decision to offer either surgery or neoadjuvant chemotherapy as the first option generates debates within the multidisciplinary committees that evaluate patients with pancreatic cancer. The developments of CT-based radiomic features have proven to be able to provide sufficiently relevant tumor information to establish the prognosis in resectable patients with pancreatic cancer. These features may be really useful to stratify patients for neoadjuvant or alternative therapies [23, 24]. Clinically, there are often doubts about the malignancy of certain types of cystic lesions, especially mucinous ones, and finally, after surgery, there might be up to a 30% of discrepancy between the pre- and postoperative diagnoses. Using multiphase CT radiomics and accepted parameters from international guidelines, Polk and colleagues [25] analyzed mucinous intraductal papillary lesions (IPMNs) to assess the degree of malignancy. The authors compared the nomogram created using only the diagnostic parameters of the International Consensus Guidelines to the one resulted from using both the guidelines and radiomic images. When both tools (radiomics and guidelines) were used, the results in predicting the malignancy of the pathology were far better. Radiomics has also been carried out to assess recurrence and prognosis with other techniques. In fact, in a recent study, a CT radiomic evaluation using clinical data and textural features done in patients with advanced pancreatic cancer, the authors developed a predictive model not only for local recurrence but also for overall survival after Stereotactic Body Radiotherapy application [26, 27]. Another recent study by Tang et al. [28] developed a multiparametric nomogram for the preoperative assessment of local recurrence including clinical stage, and artificial intelligence applied to magnetic resonance imaging (MRI).

In summary, undoubtedly, radiomic tools will allow more precise decisions to be made, generating confidence in both patients and professionals.

1.3 Key Points in the Treatment of Pancreatic Cancer

1.3.1 Medical Treatment: Personalized and Precision Therapy in Pancreatic Cancer

Nowadays, chemotherapy is recommended as a palliative treatment and as an adjuvant therapy in

almost all patients after surgery. As adjuvant therapy, in general, it is recommended not to delay the start of chemotherapy excessively, which is why most protocols start it in the first 3 months after surgery [29, 30]. At present, from the PRODIGE study 24, the treatment of choice in Western countries is the combination of modified FOLFIRINOX (m FOLFIRINOX) [31]. In the study carried out in resected patients, the results showed significant differences in favor of FOLFIRINOX versus Gemcitabine in both pancreatic cancer disease-free survival (21.6 vs. 12.8 months, respectively) and overall patient survival (54.4 vs. 35 months, respectively).

Regarding neoadjuvant chemotherapy, currently there is no doubt about the use of neoadjuvant therapy in locally advanced pancreatic carcinoma. Some meta-analyses performed to evaluate FOLFIRINOX as neoadjuvant chemotherapy, reported a 67.8% resection rate and an 83.9% R0 resection rate [32]. However, since no well-designed studies are included in this meta-analysis, prospective randomized trials are necessary to evaluate properly the role of neoadjuvant therapy. The role of FOLFIRINOX as neoadjuvant therapy in resectable pancreatic cancer is under several studies (NCT02172976, NCT02562716, NCT02243007, NCT02345460). Although current clinical guidelines used routinely in pancreatic adenocarcinoma support the use of neoadjuvant chemotherapy, more prospective trials and meta-analysis including not only chemotherapy but also stereotactic radiotherapy as neoadjuvant therapy are needed to evaluate perioperative strategies in patients with both unresectable and resectable pancreatic cancer. However, as previously shown, despite significantly improving the result over the established standard, the results are still not comparable to those of other tumors. Current guidelines will probably change, mainly those related to the progress in the knowledge of the tumor biology, which could help define the best choice of chemotherapy. According to our research, in pancreatic cancer, better results are obtained when combinations of drugs are used [33, 34].

In the evaluation of medical treatment of pancreatic cancer, the biomarkers that provide relevant diagnostic and prognostic information will have to be taken into account. From the different biomarkers currently being analyzed to assess therapeutics, possibly the most developed one is Circulating Tumor DNA (ctDNA) [29]. Detectable ctDNA before surgery has been associated with a worse prognosis, and when detected after, it has been connected to local recurrence and a significant decrease in survival. The next steps to be evaluated in prospective studies would be whether once this measurement technique is established, the detection of ctDNA could be a systematic indication of the administration of neoadjuvant. One might even wonder whether in patients who continue to present ctDNA after neoadjuvant treatment the surgery is suitable or not. Possibly, the answer is not only in the ctDNA, but in the joint evaluation with other biomarkers such as the measurement of Circulating Tumor Cells (CTCs) as previously mentioned [16], and the measurement of systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) [35]. In these cases, it would be necessary to determine the cut-off points from which its detection is associated with metastases not yet visualized in CT scan images and with the indication of one therapy or another.

But in addition to using biomarkers that help us determine whether a patient would receive surgery or chemotherapy, it is key to personalize cancer therapies including the predictive pathological biomarkers related to the effectiveness of chemotherapy. This line has been specially worked on with Gemcitabine and 2 markers: the equilibrative nucleoside transporter 1 (hENT1) [36] and the phosphorylation by deoxycytidine kinase (dCK) [37]. First is the main transporter that allows the absorption of Gemcitabine into the cell, and the second facilitates the conversion of Gemcitabine into active metabolites. When an increase in the expression of hENT1 or dCK is detected, the permeation to Gemcitabine will be greater and therefore better oncological results could be obtained. These results must be confirmed in long prospective series to be incorporated into the decision algorithms in the clinical guidelines.

On the other hand, pancreatic adenocarcinoma presents different histopathological structures (angiogenesis, stroma, stellate cells, immune cells, etc.) that must be approached individually, since pancreatic adenocarcinoma does not express them equally in all patients. This would lead us to wonder whether the same group of drugs should be applied to all patients or not, when to do it, the doses, etc.

Indeed, at present, transcriptomics and bioinformatics are modifying the approach to these tumors. Based on transcriptomic profiles after bioinformatics analysis, five subtypes of adenocarcinomas have been described: "pure basal-like," "stroma-activated," "desmoplastic," "immune classical," and "pure classical" [38]. As observed in the preliminary results of the COMPASS study in which the effectiveness of FOLFIRINOX was assessed according to the histological subtype of pancreatic adenocarcinoma [39], this classification allowed to determine the best chemotherapy treatment, identifying the specific target in each case. Although more prospective studies that include the different options are needed, work is being done with immunomodulatory, antistromal, and cytotoxic drugs with personalized programming based on the predominant molecular subtypes.

The culmination of all the above is the incorporation of artificial intelligence and radiomic machine learning together with the rest of the biomarkers in order to select the drug which will enable us to obtain the best response to chemotherapy treatment. In a study by Kaississ et al. [40], artificial intelligence and machine learning associated with radiomics made it possible to identify the subtypes of adenocarcinoma of pancreas which were correlated with disease-free survival and overall survival according to the predicted response to Gemcitabine or FOLFIRINOX.

In summary, although the implementation of FOLFIRINOX has improved the results obtained with monotherapy, they are still substantially inferior to other tumors. Hence, the lines of work are focused on personalized therapies to the molecular structure of the tumor through transcriptomic studies, identifying the ideal drug combination for the molecular composition of the tumor. To achieve the greatest therapeutic effectiveness on these molecular structures, it is essential to identify drug effectiveness markers that ensure a high level of permeation in the neoplastic tissue. Finally, in all this algorithm, we will have to take into account biological markers such as ctDNA that will help us define which patients can benefit from one type of therapy or another and their results.

1.3.2 The Surgical Approach as a Guarantor of the Locoregional Eradication of Pancreatic Cancer

As with chemotherapy, the surgical approach does not offer the results that are obtained from oncological surgery in other locations. In pancreatic cancer, the follow-up of the patients has revealed a poor survival rate due to high cancer recurrence. Unfortunately, the rate of surgical margin affected (R1) remains too high, especially in the increasingly frequent cases of locally advanced tumors with prior neoadjuvant treatment [41]. The technique of approaching the superior mesenteric artery initially ("artery-first" approach) has been proposed to try to reduce the rate of R1 [42] (Fig. 1.2). However, in the multicenter randomized study carried out by the pancreas surgery groups in Spain, it has not shown superiority compared to the classical technique of approaching the hilum and portal vein in the first place in duodenopancreatectomy [43]. Regardless of the approach route, to achieve a complete excision of pancreatic cancer, especially in locally advanced tumors, it is necessary to perform a complete vascular approach with dissection of the spleno-porto-meseraic venous axis, mesenteric artery and hepatic artery-celiac trunk (Fig. 1.3). A complete dissection of all these structures is essential to be able to carry out vascular resections when the tumor requires it. These resections may be more localized and be reconstructed with end-to-end venous suture (Fig. 1.4), or more extensive when it affects the confluence of the ileo-ceo-colic and jejunal

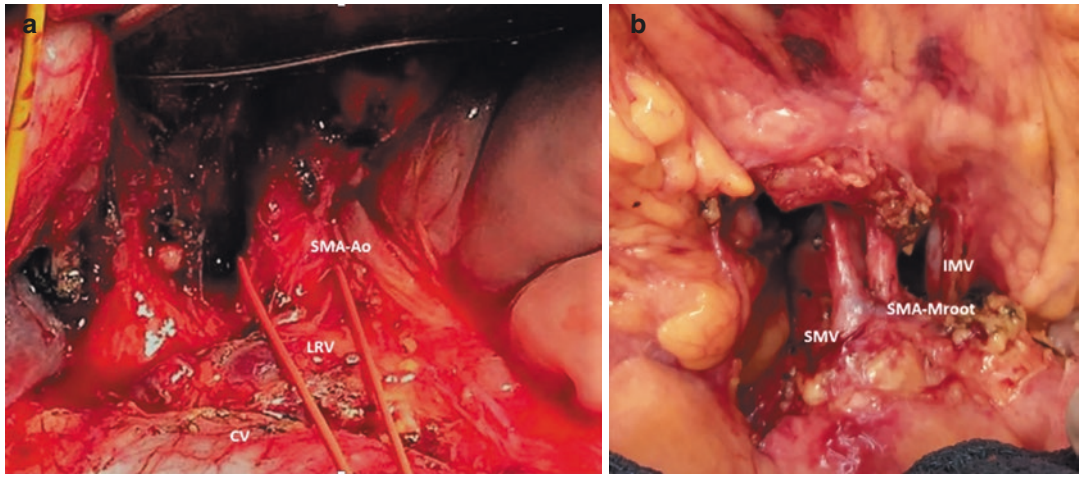

Fig. 1.2 Artery-first approach. (**a**) Proximal approach; *SMA-Ao* superior mesenteric artery at the bifurcation of aorta, *LRV* left renal vein, *CV* cava vein. (**b**) Distal approach; *SMV* superior mesenteric vein, *SMA-Mroot* superior mesenteric artery at mesenteric root, *IMV* inferior mesenteric vein

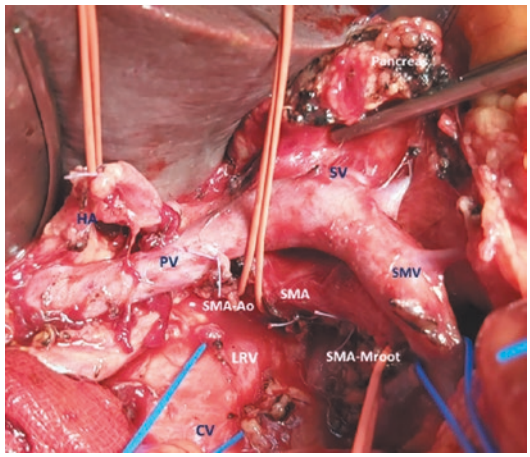

Fig. 1.3 Vascular dissection in duodenopancreatectomy. *HA* hepatic artery, *PV* portal vein, *SV* splenic vein, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery, *SMA-Ao* superior mesenteric artery at the bifurcation of aorta, *SMA-Mroot* superior mesenteric artery at mesenteric root, *LRV* left renal vein, *CV* cava vein

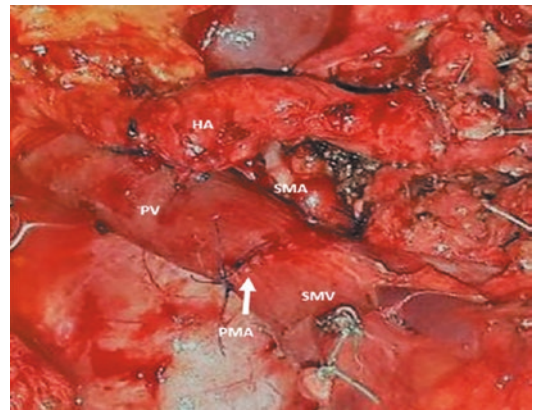

Fig. 1.4 End-to-end venous reconstruction. *HA* hepatic artery, *PV* portal vein, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery, *PMA* porto-mesenteric anastomosis

venous branches in the superior mesenteric vein, requiring a Y prosthesis (Fig. 1.5). The relevance of the experience of the surgeons and the volume of activity of the units for this type of intervention and its impact on surgical and oncological results have been widely discussed. In a study carried out in hospitals in Germany and the Netherlands, they observed that centers with smaller volumes had higher mortality in pancreatic cancer interventions [44]. On the other hand, regarding oncologic approach, less delay in chemotherapy was also found in hospitals with a higher volume of cases [45].

In all this debate on how to optimize oncologic-surgical results, and even without reaching a clear global strategy, the minimally invasive surgery appears. The general benefits of laparoscopic surgery are indisputable, but it is necessary to assess them in each type of intervention. According to the aforementioned, it is obvious that it must ensure an oncological

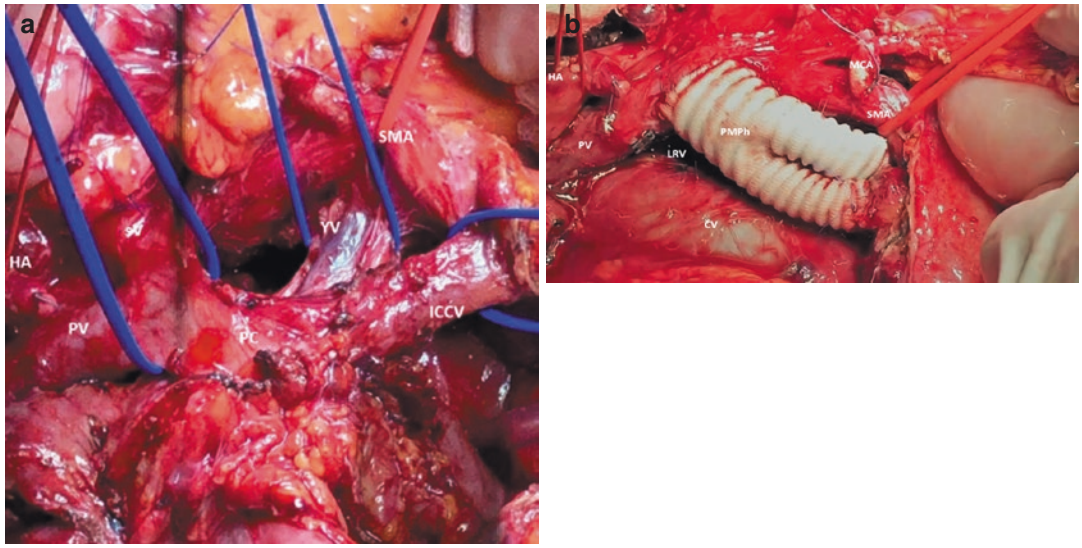

Fig. 1.5 Tumoral invasion of confluence of the ileo-ceo-colic and jejunal venous branches in the superior mesenteric vein, requiring a Y prosthesis. (**a**) *HA* hepatic artery, *PV* portal vein, *SV* splenic vein, *YV* jejunal vein, *ICCV* ileo-ceco-colic vein, *SMA* superior mesenteric artery, *PC* pancreatic cancer. (**b**) *HA* hepatic artery, *PV* portal vein, *SMA* superior mesenteric artery, *MCA* middle colic artery, *LRV* left renal vein, *CV* cava vein, *PMph* porto-mesenteric prosthesis

result at least equal to open surgery and maintain morbidity and mortality standards. Bearing in mind that laparoscopic surgery requires a specific learning curve, one might wonder if it is reasonable to assume even worse results in a pathology with surgical results still to be improved. In body and tail tumors, in which a distal pancreatectomy with lymph node cleansing must be performed, there are different experiences supporting the feasibility and safety of laparoscopic surgery [46]. Nevertheless, because of the reported excess mortality in the randomized LEOPARD-2 trial (10 vs. 2%), currently there is no consensus to recommend a laparoscopy approach for pancreaticoduodenectomy, despite an equivalent quality of exeresis [47]. A recent meta-analysis [48] concluded that, according to the level of evidence, laparoscopic duodenopancreatectomy has no advantage when compared to open surgery. However, nowadays, the quality of evidence is very low regarding the learning curve results in this type of surgery. In this sense, it could be interesting to evaluate the learning curve with a robotic approach to duodenopancreatectomy that, in general, seems to be quite less steep than with the standard laparoscopic approach [49]. As a positive aspect of the laparoscopic approach in patients without severe complications, laparoscopic surgery allows to increase the adjuvant chemotherapy rate as well as to reduce the delay in chemotherapy, due to a prompt recovery [45]. In these cases, in which the same surgical oncological (R0) and morbidity and mortality results can be assured, these considerations may be important.

One aspect that will have to be evaluated is the impact that minimally invasive surgery could have on the intraoperative spread of neoplastic disease. In patients with pancreatic cancer, the pancreas manipulation during open surgery may increase the tumor cell spread via the portal vein and thus increase the risk of liver metastasis. Theoretically, a non-touch isolation technique might reduce the circulating tumor cell (CTC) spread. Thus, we have designed a prospective multicenter randomized study to monitor the CTC level during open pancreaticoduodenectomy in patients with carcinoma of the head of the pancreas [50]. In this study, non-touch and

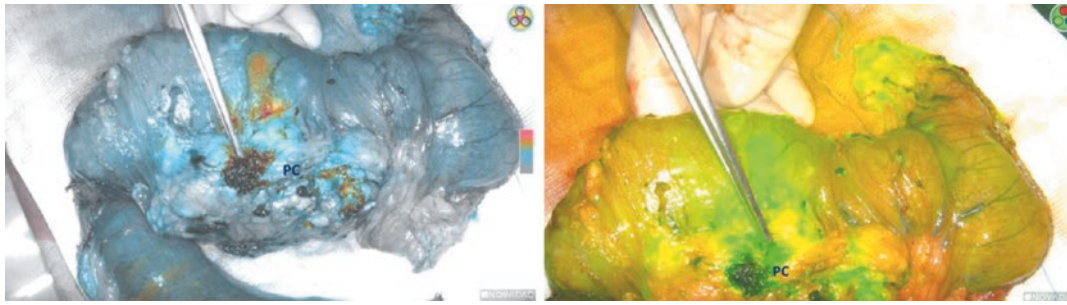

Fig. 1.6 Intraoperative use of indocyanine green. *PC* pancreatic cancer

artery-first approaches are compared and long-term follow-up results will be evaluated according to intraoperative CTC levels. It might as well be interesting to develop this study including a laparoscopic approach that could reduce the tumor manipulation and, consequently, the CTC spread.

Regardless of the approach route, a very limiting aspect of pancreatic cancer surgery is the high local recurrence rate. There are currently different and novel lines of research that seek to optimize the effects of systemic treatment of pancreatic cancer by implementing the locoregional effect of chemotherapeutic agents. One of the ways is to facilitate the arrival of chemotherapeutic and/or immunotherapeutic drugs to tumor cells. For this, the use of various vehicles (lysosomes, exosomes, vectors, etc.) is proposed which, when administered systemically and loaded with drugs, lead them to tumor cells. However, these strategies often fail in their mission to get the medication to the neoplastic cell due to the dense stromal matrix that pancreatic adenocarcinomas have. This matrix is responsible for the poorly vascularized and immunosuppressive microenvironment characteristic of this type of tumor. Hence, research is currently being conducted on formulas that allow high concentrations of chemotherapy/immunotherapy and antistromal medication in the tumor itself to generate a synergistic antineoplastic effect. Based on the contributions made in the field of peritoneal carcinomatosis, using hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC), our research group has developed a biodevice (TARTESSUS®) (FISEVI-19004) that releases chemotherapy drugs on a scheduled basis. Applied locally after resection, this biodevice would release chemotherapeutic agents in a delayed and controlled manner to promote local permeation and reduce recurrences. These studies are currently in the development phase.

At present, another development to reduce the incidence of R1 and ensure a good lymphadenectomy is indocyanine green-guided surgery (Fig. 1.6). Fluorescent structures showed during operation allow the surgeon not only to identify potential lymphatic dissemination but also to be sure that resected mesopancreas tissue is free of tumor [51, 52]. In our experience, it has both served to facilitate the identification of lymphadenopathy or free margin, and to detect multicentric lesions not identified in the preoperative tests that have modified the expected surgical technique, changing the cephalic duodenopancreatectomy for a total duodenopancreatectomy.

To sum up, navigation tools must be key to achieving radical goals in pancreatic cancer oncological surgery. In both open and laparoscopic or robotic surgery, they should be incorporated progressively. In the same way as in chemotherapeutic medical treatment, the application of radiomics can play a crucial role in the personalization of treatments. The intraoperative incorporation of radiomics with artificial intelligence and machine learning developments, together with the current fluorescence, should contribute to important advances to carry out the surgical approach of each patient in a personalized way.

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