

# Locally Advanced Pancreatic Ductal Adenocarcinoma: Challenges and Progress

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**Abstract:** Pancreatic ductal adenocarcinoma (PDAC) is one of the major causes of death in the Western world, and it is estimated to become the second leading cause of tumour-related mortality in the next 10 years. Among pancreatic cancers, ductal adenocarcinomas are by far the most common, characterised by a challenging diagnosis due to the lack of initial and pathognomonic clinical signs. In this scenario, non-metastatic locally advanced pancreatic cancer (LAPC) accounts for a large proportion of all new pancreatic ductal adenocarcinoma diagnoses. There is no consensus on a common definition of LAPC. Still, it usually includes tumours that are not resectable due to vascular involvement. As of today, treatment is limited, and the prognosis is very unfavourable. Curative-intent surgery remains the gold-standard even if often jeopardized by vascular involvement. Continuing progress in our understanding of LAPC genetics and immunology will permit the development of different treatments, targeted or combined, including radiation therapy, hadrontherapy, targeted immunotherapies or new chemotherapies. A multidisciplinary approach combining various fields of expertise is essential in aiming to limit disease progression as well as patient outcome. Using a narrative literature review approach, the manuscript explores the most up-to-date knowledge concerning locally advanced pancreatic ductal adenocarcinoma management.

**Keywords:** pancreatic cancer, risk factors, treatment, hadrontherapy, surgery

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a deadly malignancy characterised by a somber prognosis. Its incidence is increasing drastically, classed worldwide as the 14th most common cancer and the 7th highest cause of tumour-related mortality. In 2018, 458,918 diagnoses and 432,242 deaths from PDAC had been estimated worldwide<sup>1</sup> and by 2030, PDAC is forecasted to be the second leading cause of cancer deaths in the US.<sup>2</sup> PDAC is the most frequent type of pancreatic neoplasm, representing 80% to 85% of all malignant pancreatic neoplasms. The absence of specific symptoms and the aggressiveness of the disease are the two main limitations for early diagnosis.<sup>3</sup> As it happens today in most clinical disciplines,<sup>4–6</sup> a multidisciplinary approach is essential for the management of PDAC, due to the need for primary prevention, importance of an early diagnosis, and the complexity of treatment given that, even combined with radiotherapy, traditional therapeutic strategies have not prolonged the 5-year survival rates (less than 30%)<sup>7</sup>. As of today, curative-intent surgical resection remains the only potential for cure. However, at initial presentation, only 15–20% of patients feature a surgically resectable tumour and, additionally, 45–50% of patients experience an openly metastatic disease.<sup>8</sup> The remaining 25–30% of patients show either borderline

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resectable (BRPAC) or locally advanced (LPAC) pancreatic cancer.<sup>9</sup> This condition opens up the concept of pancreatic tumour resectability by dividing the progression of pancreatic cancer into BRPAC, LPAC or advanced pancreatic cancer (APAC). As a general principle, the estimation of PDAC resectability should always be driven by the ability to obtain negative resection margins (R0 margins).<sup>10</sup> BRPAC has been defined as a condition that encompasses a spectrum of patients ranging from “resectable” to LPAC disease. For these patients, a microscopically positive margin (R1) resection is considered relatively more likely, primarily due to the relationship between the primary pancreatic tumour and the surrounding blood vessels. LPAC is defined as a tumoural condition involving the celiac trunk, or having a tumour-to-artery interface  $>180^\circ$  and/or involvement of SMV/PV with no reconstruction options. APAC/LPAC is finally defined as an unresectable pancreatic tumour with metastasis.<sup>11</sup> This situation entails to an unmet therapeutic challenge for developing new treatments. This review covers the most up-to-date knowledge of non-metastasized locally advanced pancreatic ductal adenocarcinoma (LPAC) and, in particular, of providing an overview of how new therapies or new therapeutic strategies will guide multidisciplinary disease management. Furthermore, this study also aims to highlight current shortcomings concerning this pathology, which is not yet fully understood.

## Epidemiology

PDAC is one of the deadliest malignancies worldwide<sup>1</sup> and one of the major concerns is its growing incidence in the Western world. This is supported by the group driven by Saad et al<sup>12</sup> which, using data from the USSEER (United States Surveillance, Epidemiology, and End Results Program), found that between 1973 and 2014, PDAC incidence rates increased around 1.03%/year. This is the reason why pancreatic cancer is forecasted to become the second most frequent cause of cancer-related death in the United States by 2030.<sup>2,13</sup>

Although incidence rates vary considerably in different countries, the highest age-standardised incidence has been detected in industrialised regions such as North America and Europe, and the lowest in less developed areas of Africa and South Central Asia.<sup>14</sup> These trends have been confirmed by Wong et al<sup>15</sup> who emphasized the positive correlation between the higher human development index and PDAC incidence.

The wide disparity between countries in the incidence of pancreatic cancer indicates how environmental factors may be essential for PDAC development.

PDAC is known as having a complex multistep and multifactorial aetiology linked to the interaction between genetic background as well as environmental susceptibility. The risk of PDAC increases with age in both sexes, the majority of patients who develop PDAC being older than 45 (90% are  $>55$  yrs and 70%  $>65$  yrs), and is diagnosed at a median age of around 70 years old.<sup>16</sup>

## Risk Factors

Although knowledge of the risk factors involved in pancreatic cancer development is poor, some conditions have been associated with an increased risk of pancreatic cancer. Environmental and genetic risk factors have been reported, as already mentioned.<sup>17</sup>

The most important environmental risk is cigarette smoking,<sup>8</sup> with approximately 20% of pancreatic cancers that can be attributed to tobacco use. In 2012 a pooled analysis was performed by Bosetti et al<sup>18</sup> reporting a positive association between PDAC and cigarette smoking (OR: 1.2, 95% for former smokers; OR: 2.2, 95% for current smokers). Interestingly, this group has also shown that 20 years of smoking cessation are necessary to reduce the risk of PDAC to the level of never-smokers. These trends have been similarly reported by Lynch et al (OR: 1.8, 95% for current smokers).<sup>19</sup> Electronic-cigarette smoke (ECS), meant to provide unburnt nicotine, has been found, in an experimental model, to cause lung cancer in mice.<sup>20</sup> Even if today it is too early to have convincing data, it will be of great interest, due to widespread use, to analyse the impact of ECS on PDAC onset in the near future.

## Obesity

Large pooled analysis and meta-analyses have confirmed the positive association between obese patients (body mass index [BMI] of 30 or more) and pancreatic cancer risk.<sup>21–23</sup> Given that obesity often mirrors an energy imbalance with a caloric overload, three main mechanisms have been proposed to promote pancreas tumourigenesis:

- hormonal and inflammatory effects associated with hyperglycemia, insulin resistance and a chronic inflammatory state.<sup>24,25</sup>
- diet both due to calory intake<sup>26</sup> and a dietary pattern rich in meat and dairy.<sup>27,28</sup>

- reduced physical activity.<sup>29</sup>

Overall, studies have concurred that obesity is a risk factor of PDAC (OR:1.33, 95%).<sup>30</sup>

## Diabetes

Type 2 diabetes mellitus (T2DM) is a well-known risk factor for pancreatic cancer, being both a consequence and a prognostic factor for pancreatic cancer. A meta-analysis of 88 cohort studies reported a 94% increase in the risk of pancreatic cancer in individuals with T2DM compared to euglycemic individuals.<sup>31</sup> The underlying mechanisms have yet to be fully elucidated. Insulin resistance drives to hyperinsulinemia and high levels of insulin-like growth factor-1 (*IGF-1*),<sup>32,33</sup> exploiting PDAC tumourigenesis by the expression of IGF-1 receptors (*IGF-1r*) on PDAC cellular membranes.<sup>34</sup> As suggested by Li et al<sup>35</sup> insulin itself could play an active role in increasing cell proliferation and glucose consumption.<sup>36</sup> In parallel, it has been proposed that insulin could activate specific *IGF-1r* signalling pathways to mediate cell proliferation and inhibition of apoptosis on tumoural cell surface.<sup>37</sup>

Besides all ongoing studies on PDAC, several trials involve small as well as large animals to investigate the pancreatic parenchyma. Among small animal studies, a variety of experiences emerge on islet transplantation,<sup>38</sup> pancreatic transplant<sup>39</sup> and ischemic preconditions.<sup>40,41</sup> Pancreatic diseases and the possible innovative cure and clinical protocols, including hadrontherapy, stand as a top priority for the scientific community.<sup>42</sup>

## Alcohol Consumption

In the past, principally due to difficulties of investigation, PDAC has been inconsistently associated with alcohol consumption. Nowadays, interesting epidemiological studies have shown a positive association between alcohol intake and pancreatic cancer. In 2018, increased risk for PDAC was reported for heavy drinking habit (>60 g/day), with a hazard ratio of 1.77. It has also been shown that this risk is greater in case of a liquor or beer assumption, but interestingly not with wine. In parallel, this risk was not modified by smoking habits.<sup>43</sup>

The abovementioned risk factors are summarised in the following Table 1.

## Inherited Pancreatic Cancer Syndromes

Inherited risk factors are responsible for at least 5–10% of pancreatic adenocarcinomas.<sup>44</sup> Some genetic variations

**Table 1** Risk Factors

Environmental Risk Factor	
Cigarette Smoking and Other Tobacco Products <sup>8,18–20</sup>	
Obesity	Hormonal and inflammatory effects <sup>24,25</sup> Diet <sup>26–28</sup> Reduced physical activity <sup>29</sup>
Type 2 diabetes <sup>31–35,37</sup> Alcohol Consumption <sup>43</sup>	

have been identified as important dominant risk factors, even if not all hereditary pancreatic cancer cases can be tied to a known mutation.<sup>45</sup> The most important syndromes increasing risk for pancreatic cancer include the hereditary breast-ovarian cancer syndrome (*BRCA1* and *BRCA2* genes), familial adenomatous polyposis (*APC* gene), Lynch syndrome (hereditary non-polyposis colorectal cancer) (*MLH1*, *MSH2*, *MSH6* and *PMS2* genes), and Peutz-Jeghers Syndrome (*STK11*).

### Hereditary Breast-Ovarian Cancer Syndrome (HBOC)

HBOC syndrome is an autosomal dominant disorder associated to an increasing risk for breast cancer (47–55%), ovarian cancer (17–39%) and other cancers, including pancreatic cancer, and is mainly caused by germline mutation in *BRCA1* or *BRCA2* mutations. Data about prevalence of PDAC among *BRCA* mutation carriers are heterogeneous, but a study which performed *BRCA* testing on an unselected collected cohort of 306 patients showed that 4.6% of them had pathogenic *BRCA1* or *BRCA2* germline variants.<sup>46</sup>

### Familial Adenomatous Polyposis (FAP)

FAP syndrome is an autosomal dominant entity caused by germline mutation of the adenomatous polyposis coli (*APC*) gene and characterized by the development of numerous adenomatous polyps arising mainly from large intestine epithelium. Patients with FAP have a risk, of almost 100%, of developing colorectal carcinoma by the fourth decade of life,<sup>47</sup> and a risk of developing PDAC 4.5 times more than the general population.<sup>48</sup>

### Lynch Syndrome (LS)

LS, also known as hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant condition caused by germline mutation of genes encoding for mismatch repair (*MMR*) such as *MLH1*, *MSH2*, *MSH6* and *PMS2*.<sup>49,50</sup> An alteration of the genes responsible for

DNA repair leads to an increase in error rate during replication from 100 to 1000 times, involving areas containing repetitive sequences (microsatellites sequences). These alterations have been associated with the presence of wild-type *KRAS* and *p53* genes, with cumulative risk of PDAC in LS patients around 3.7% (versus 1.5% of general population).<sup>51,52</sup>

### Peutz-Jeghers Syndrome (JPS)

JPS is an autosomal dominant inherited condition deriving from the germline mutation in the *STK11* oncosuppressor gene<sup>53</sup> and associated with a high risk for developing PDAC. Patients usually exhibit a mucocutaneous hyperpigmentation (oral mucosa, lips and digits) and pathognomonic intestinal hamartomatous polyps. Furthermore, this syndrome puts people at increased risk for developing digestive or genital cancers,<sup>54</sup> estimated as high as 93% without specific medical surveillance. PDAC is fully part of this group of neoplasms that can occur in patients with JPS, with a relative risk reported to be as high as 132.<sup>55</sup> With such a high relative risk, Peutz-Jeghers syndrome is considered as the hereditary syndrome with the highest risk of developing pancreatic adenocarcinoma.

### Genetic Counselling and Risk Assessment

Due to the aggressiveness of this disease, a screening program and genetic counselling is highly recommended for PDAC cases with a suspicion of genetic predisposition (5–10%).<sup>56</sup>

### Histopathology and Molecular Pathways

The World Health Organization (WHO) classification,<sup>57</sup> classified pancreatic cancers into different groups based on:

- i) the macroscopic features (intraductal, solid, cystic);
- ii) type of cell line differentiation (acinar, ductal, endocrine) that is crucial to understand the clinical outcome and biological behaviour of the tumour;
- iii) immunophenotypically characteristics, sometimes necessary to define the differentiation line.

By taking into account the most common histotypes, in the following Table 2, we summarise the WHO classification

Although in the pancreatic parenchyma, the ductal component is only 20–30%, PDAC is the most frequent pancreatic tumour representing up to 90% of all pancreatic neoplasms.<sup>58</sup> Macroscopically, PDCA appears as a solid, hard consistency and shaded margin mass with a colour

**Table 2** Common Histotypes of Pancreatic Cancers

Simplified Histological Classification
Ductal adenocarcinoma
Mucinous cystic neoplasm
Serous cystadenoma
Intraductal papillary mucinous neoplasm
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Intraductal papillary mucinous neoplasm with an associated invasive carcinoma
Intraductal tubule-papillary neoplasm with associated invasive carcinoma
Pancreatoblastoma
Serous cystadenocarcinoma
Mixed acinar/ductal/neuroendocrine carcinoma
Solid-pseudopapillary neoplasm
Neuroendocrine neoplasms

ranging from yellow to brown encompassing hemorrhagic, necrotic, and/or microcystic areas.<sup>59</sup> The anatomical site of presentation (head, body, tail, ampulla, peri-ampullary tissue and inferior third of the common bile duct) influences clinical outcomes. Indeed ampullary carcinomas have generally a better prognosis than those arising in other sites.<sup>60</sup> Microscopically, PDAC is characterised by atypical tubular glands with heterogeneous growth patterns including clear-cell or cribriform component that with the tumour grading, which may have an impact on patient survival.<sup>61</sup> According to WHO, the histopathological tumour grading for pancreatic cancer considers the architecture (tubular, cribriform and duct-like structures, solid growth), cell shape (cylindrical, cubic, polygonal, pleomorphic, spindle) and amount of mucin (retained, partial loss, complete loss) nuclear polymorphism (slightly, moderately or very polymorphous) and the number of mitoses (1–5/10 HPF, 6–10/10 HPF or >10/10 HPF).<sup>57</sup> Immunophenotypically, MUC1, MUC4, MUC5A, CA125, CEA, CA19-9 CK7, CK19, CK18 and sometimes CK20 are usually expressed in PDAC.<sup>59</sup>

### Variants of PDAC

Several variants of PDAC exist distinguished according to the molecular pathogenesis as follow:

- Similar molecular pathogenesis:
  - Adenosquamous carcinoma: characterised by a squamous component of up to 30% with a minimum number of glandular ones, an

immunohistochemistry positivity for p40 of squamous cells and a worse prognosis than classical PDAC.<sup>57</sup>

- Anaplastic (undifferentiated) carcinoma: characterised by solid growth, polymorphic cells (including multinuclear giant tumour cells), and positivity for pan-cytokeratin (Pan-CK) and vimentin with an E-cadherin loss. In case of rhabdoid differentiation, it is *KRAS* wildtype and *SMARCB1* mutated.<sup>59,62</sup>
- Undifferentiated carcinoma with large-duct type carcinoma (resembling non-invasive cystic cancer),<sup>63</sup> signet-ring cell carcinoma (expression of nucleus dislocated in the periphery by big cytoplasmic vacuoles of mucin),<sup>64</sup> osteoclastic giant cells (showing histiocytic giant cells positive for CD68) and micropapillary carcinoma (looking like breast carcinoma with an expression of MUC1 in the stroma-facing cell surface and a e-cadherin/galectin-3 cytoplasmic staining).<sup>59</sup>
- Different molecular pathogenesis
  - Hepatoid adenocarcinoma resembling morphologically and immunocytochemically hepatocellular carcinoma.<sup>59</sup>
  - Colloid carcinoma characterised by tumour cells fitted in great mucin pools and usually associated with high-grade intestinal-type intraductal papillary neoplasm (IPMN).<sup>59</sup>
  - Medullary carcinoma associated with microsatellite instability showed a poor differentiation and an invasive and syncytial pattern of growth.<sup>65</sup>

## Molecular Subtyping of PDAC

Over the years, different molecular classification has been proposed thanks to the introduction of high-throughput techniques and the better knowledge of the pathogenetic role of the PDAC-related genes *KRAS*, *TP53*, *SMAD4*, and *CDKN2A*.<sup>66</sup> Based on the molecular characteristics of PDAC, several authors conducted an interesting molecular classification approach that we summarised below. The molecular classification by Collisson et al<sup>67</sup> identified subtypes of PDAC which are different for outcomes and therapeutic response (Table 3): classical, quasi-mesenchymal, and exocrine-like.

Another molecular classification is described by Bailey et al<sup>68</sup> according to genomic analysis: 1) squamous type, characterised by *TP53* and *KDM6A* mutations,

**Table 3** Summary of Molecular Subtypes

Molecular Subtypes	Features	Clinical Outcome	Therapeutic Response
Classical	High expression of epithelial and adhesion-related genes	Best prognosis	Gemcitabine-resistant; Erlotinib-sensitive
Quasi-Mesenchymal	High expression of mesenchyme-related genes	Worst prognosis	Gemcitabine-sensitive; Erlotinib-resistant
Exocrine-like	High expression of tumour cell-derived and genes-linked to digestive enzyme	Intermediate prognosis	Not reported

**Note:** Data from Collisson et al.<sup>67</sup>

upregulation of the *TP63ΔN* transcriptional network, hypermethylation; 2) pancreatic progenitor type expressing *FOXA2/3*, *PDX1* and *MNX1* genes implicated in early pancreatic development 3) immunogenic type displayed upregulation of immune networks; 4) aberrantly differentiated endocrine exocrine (ADEX) type: showed upregulation of genes involved in *KRAS* activation, exocrine (*NR5A2* and *RBPJL*) and endocrine differentiation (*NEUROD1* and *NKX2-2*). Waddell and colleagues<sup>68</sup> proposed a further molecular subtype classification according to genomic stability: 1) termed stable with <50 rearrangements located randomly through the genome; 2) locally rearranged with at least 50 somatic rearrangements clustered on one or few chromosomes; 3) scattered containing 50–200 structural rearrangements spread in genome entirety; 4) unstable with >200 structural rearrangements. Considering the stroma, Moffit et al<sup>69</sup> described “normal” and “activate” stroma subtypes with a good and poor prognosis, respectively. In “normal” stroma there is high expression of markers for stellate cells, smooth muscle actin, vimentin, and desmin; in the “activated” stroma there are several genes linked to macrophages (integrin ligand ITGAM and chemokine ligands CCL13- CCL18), associated to tumour progression (released protein SPARC, WNT family members WNT2- WNT5A, gelatinase B MMP9, and stromelysin 3-MMP11) and is also characterised by the presence of fibroblast activation protein FAP. Comparing the gene signatures of the above-mentioned classification, it can be observed a non-perfect

overlap. As well reported by Primavesi et al<sup>66</sup> several working groups used different terminologies as well as different approaches to define biological-similar subtypes and, the definition of consensus genetic models among different classifications is desirable to find new diagnostic and tailored treatment options.

## Mutation in Carcinogenesis of Pancreatic Cancer

Early lesion of PDAC can be classified into microscopic (pancreatic intraepithelial neoplasia - PanIN - and atypical flat lesions-AFL) and macroscopic (IPMN-, mucinous cystic neoplasms - MCN - and intraductal tubule-papillary neoplasms - ITPN) precursors whose grading is defined by the importance of cytological atypia. The progression from normal pancreatic tissue to tumour consists of a defined sequence of histopathological and biological events in which the carcinogenesis is the result of a gradual accumulation of multiple and consecutive molecular alterations such as oncogene-activation, inhibition of tumour suppressor genes, gene mutations.<sup>59</sup> Since the number of PanIN associated with high-grade dysplasia is increased in patients with a family history of PDAC, these precursor lesions are hypothesized to occur at a very young age.<sup>66</sup>

### K-RAS

The mutation of *KRAS* (also called *K-Ras 2*, *Ki-Ras*, *c-K-ras*, or *c-Ki-ras*) is an early event in the carcinogenesis and reported up to 95% of PDAC. *KRAS* is a small (21KDa) GTP-ase physiologically quiescent and linked to GDP; when GTP replaces GDP, *KRAS* could active numerous downstream effectors that guide tumour progression: RAF family kinase (RAF1, BRAF, and ARAF) which in turn activate MEK1-MEK2 kinases, that phosphorylate and activate ERK1 and ERK2 kinases. ERKs phosphorylate several proteins of whom ELK1 and c-JUN. *KRAS* mutation of codon G12, G13, or Q61 makes *KRAS* constitutively active, typically occurs in early low-grade PanIN-1 lesions, and is associated with minimal cytological architectural atypia.<sup>70</sup> Clinical studies show that *KRAS* mutation is associated with a poor response to Gemcitabine administered as first-line chemotherapy and poorer survival.<sup>71</sup> *KRAS* is mutated in about 95% of advanced PDAC.<sup>66</sup>

### CDKN2A

*CDKN2A* (*p16-INK4a*, *MTS-1*, or *CDK4I*) is a tumour suppressor that inhibits the progression into the cell cycle by

inactivating cyclin D-CDK4 and cyclin D-CDK6 complexes that regulate G1/S phase checkpoint. The inactivation of *CDKN2A* occurs in 98% of cases of sporadic PDAC and is caused by a different kind of mutation (loss of heterozygosity, homozygous deletion, or promoter silencing). Alteration in *CDKN2A* is an early event in the pathogenesis and indeed is also described in pre-neoplastic PanIN-2 lesions. Inherited *CDKN2A* mutations are associated with the familial atypical multiple mole melanoma (FAMMM) syndrome and a greater risk of pancreatic cancer.<sup>61,70,72</sup>

### TP53/SMAD4/BRCA2

*TP53* (*p53* or *antigen NY-CO-13*) is a tumour suppressor which modulates the answer to cytotoxic stress by stopping the progression into the cell cycle, arresting growth arrest or inducing apoptosis. *TP53* mutation occurs up to 70% of pancreatic cancers and is found in PanIN-3 lesions. Clinical studies observed a worse prognosis in p53 mutated-PDAC<sup>73</sup> and a significant improvement of progression-free survival (PFS) in patients with *TP53* wild-type.<sup>74</sup> *SMAD4* (also known as *DPC4* or *MADH4*) is a tumour suppressor protein and a downstream effector of TGF-beta which translocates to the nucleus as heterotrimeric complex promoting the inhibition of growth. Alterations of *SMAD4* are reported up to 50% of pancreatic cancer of whom 30% are caused by homozygous deletion. The authors reported a prognostic role of *SMAD4* inactivation in terms of overall survival.<sup>75</sup> *BRCA1* (also known as *RNF53*) and *BRCA2* (also known as *FANCD1*) are involved in PDAC carcinogenesis. *BRCA1* is a tumour suppressor which regulates the answer to DNA damage and the progression in the G2/M cell cycle. *BRCA1* mutation occurs in not more than 7% of pancreatic cancer patients, it is associated with familiar cancers and is quite uncommon as sporadic event.<sup>76</sup> *BRCA2* mutation is found in at most 7–10% of familiar PDAC; few cases of sporadic somatic mutations are reported. *BRCA2* is involved in double-strand break repair during the S phase of the cell cycle, centrosome duplication, and cell death.<sup>76</sup> Several clinical studies are performed to evaluate the prognostic and predictive role of *BRCA2* in PDCA. There are two emblematic cases of an increased sensitivity of *BRCA2*-mutated-PDCA to DNA-intercalating agents.<sup>77,78</sup>

## Clinical Presentation, Signs and Symptoms

Pancreatic cancer is generally defined as a “silent cancer”; hence, in most cases, symptoms and signs arise when the

disease has already progressed to an advanced stage. Here, symptoms are non-specific and vague: patients complain about fatigue, abdominal pain and anorexia, responsible for late diagnosis. However, the clinical presentation is mostly dictated by tumour location within the pancreas and the degree of involvement of surrounding anatomy. In fact, diagnosis is typically made much earlier when the tumour arises in the head of the pancreas with obstruction of the biliary tract rather than in the body or the tail. Sudden and generally painless obstructive jaundice is indeed the most common sign of pancreatic head cancer and pruritus is reported as the most distressing symptom in this subset of patients. Sometimes physical examination can reveal a palpable gallbladder (Courvoisier's sign) suggesting the presence of mechanical obstruction of the distal common bile duct.<sup>79</sup>

Instead, the onset of pain may represent a clinical marker of local tumour progression, being it usually related to the extension in the retroperitoneal space with infiltration of the celiac plexus. It is often reported as the first clinical symptom referred from patients with body or tail tumours whose progressive growth has trespassed the pancreatic capsule posteriorly and, with that, spread into the peripancreatic tissues. Direct involvement of major splanchnic vessels is common at this stage. The different setting of clinical presentation between head and body/tail pancreatic tumours account for the different size of the primary lesion that these neoplasms can show at the time of diagnosis; however, tumour size is not the only determinant for resectability and, accordingly, prognosis, as described later. Likewise, body and tail location, cancers of the uncinate process lack early symptoms and bear the worst prognosis because of their close proximity to superior mesenteric vessels which is responsible for a particular dissemination pattern that leads to liver metastasis and lymph node spreading at an earlier course of the disease.<sup>80</sup>

Pain is located in the mid-epigastric region and radiated to the back. Typically described as relentless, it can be exacerbated in lying position and in some patients by food ingestion too.

Weight loss is also seen in the advanced stage of the disease, and its cause may be found in cancer-related anorexia or pancreatic exocrine insufficiency with malabsorption and steatorrhea. When weight loss occurs in the early stage, it may be related to delayed gastric emptying due to larger size tumours predominantly grown on the duodenal side thus determining endoluminal obstruction. These patients often complain of nausea and recurrent

vomit too. Moreover, newly onset of diabetes in euglycemic subjects or worsening of known diabetes can often precede the diagnosis of pancreatic cancer. Ascites and a palpable mass in the epigastrium characterise the most advanced clinical pictures of this tumour.

Depression is reported to be more frequent in patients with pancreatic cancer than in patients with other neoplastic diseases. This might be explained with the typical delay of diagnosis of this disease. High incidence of suicide, almost 11 times higher than the remainder of the population, has been reported in male patients with pancreatic adenocarcinoma.<sup>81</sup>

Migratory thrombophlebitis (Trousseau sign), venous thrombosis, or marantic endocarditis are also reported in patients with pancreatic cancer sometimes as the first clinical presentation.

## Diagnostic Investigation

Tumour's characterization, staging, and determination of resectability, surgical planning, reassessment after neoadjuvant treatment (NAT) are the drivers of proper management for advanced PDAC.<sup>82</sup> Contrast-enhanced Multi-Detector Computed Tomography (MDCT) of chest and abdomen is the main, first-line radiological investigation capable of addressing all the above issues when performed by expert radiologists.<sup>82,83</sup> Thin-section (<3 mm) multi-Phase Image acquisition based on specific pancreatic protocols and followed by multiplanar reconstructions is recommended to optimize the assessment of the primary lesion, including its local and distant stage, with an overall diagnostic accuracy around 90%.<sup>82–84</sup> Being resectability mostly dictated by vascular involvement, MDCT has the highest specificity, sensitivity, positive and negative predictive values (82–100%, 70–96%, 89%, and 100%, respectively) for determining if and to which extent the circumference of critical peripancreatic vessels is affected.<sup>82</sup> Despite the persistent lack of consensus on the definition of “borderline resectable” and, to a lesser degree, of “locally advanced” tumours, MDCT remains the preferred modality to address vascular invasion.<sup>83</sup> The high-quality distinction between vascular “abutment” (tumour contact  $\leq 180^\circ$  of vessel circumference) and “encasement” (contact  $> 180^\circ$ ) can be seen on multiplanar-reformatted images, as well as distortion in the contour or shape of vessels indicating possible infiltration by tumoural tissue.<sup>85</sup> Contrast-enhanced endoscopic ultrasound (CEUS) may be as much reliable as MDCT for this aim though limited by local availability, operator's

dependency, and presence of anatomical variants in regional vasculature. Therefore, its use is not routinely recommended.<sup>85</sup> Arterial variations, if any, should be comprehensively described in MDCT reports. Contact of atypical hepatic or mesenteric arteries with the primary lesion may dictate variations of the standard surgical technique (ie, to allow safe reconstructions, avoid vascular injury) or even rule out resectability in some cases.<sup>85</sup> On the other hand, MDCT may fail in detecting tiny liver or peritoneal metastases.<sup>82</sup> Current NCCN guidelines still suggest staging laparoscopy, with or without intraoperative ultrasound, when high suspicion of distant disease is raised clinically.<sup>83</sup> Magnetic Resonance (MR) is a valuable alternative to MDCT for staging and resectability assessment, especially in the setting of MR angiography, having comparable sensitivity and specificity rates (89% each).<sup>85</sup> However, its use is mostly restricted to patients with known allergy to iodinated contrast or with attenuating tumours in which MDCT has lower accuracy.<sup>83</sup> Chest X-Ray or non-contrast CT can be used as surrogate tools for chest staging when iodinated contrast medium is contraindicated. Also, MR may help the characterisation of uncertain pancreatic lesions and synchronous small liver nodules appearing indeterminable at MDCT. Specific MR applications, such as Diffusion-weighted Imaging (DWI) and contrast enhancement with Gadoteric acid, are extremely efficient for these aims.<sup>82,85</sup> When a histological diagnosis is needed, EUS with fine-needle aspiration/biopsy (EUS-FNA/FNB) is preferable to US or CT-guided percutaneous approach due to its higher diagnostic yield (over 90% in patients with negative US/CT-guided FNA) and safety profile as to the risk of peritoneal seeding.<sup>83,84</sup> Brushing of the common bile/main pancreatic duct can also be performed during ERCP in patients requiring biliary stenting, although the sensitivity rate does not exceed 40% according to the available data.<sup>83,86–88</sup> Positron Emission Tomography combined with CT (PET/CT) for diagnosis and staging of PDAC is poorly helpful and should be used selectively in addition to MDCT and/or MR.<sup>82–84</sup> However, it may be of help in the evaluation of response to NAT or in the follow-up of resected patients.<sup>82–84</sup> Patients receiving NAT should be reassessed with MDCT and/or MR despite morphological criteria indicating clinical response are still unclear. Tumour size and attenuation lack specificity due to the inflammatory reaction causing oedema, fibrosis, and necrosis; instead, reduction in the extent of tumour-vessel contact seems to be more reliable in predicting

resectability if evident on MDCT/MR.<sup>85</sup> Recently, the combination of PET with MR (PET/MR) has shown better results compared with PET/CT for staging and post-NAT re-evaluation in advanced PDAC patients.<sup>82</sup> Reliable, specific biomarkers are still lacking at present. Carbohydrate Antigen 19–9 (CA19-9) has a limited role for diagnosis due to its high false-positive rate and poor specificity for PDAC. Instead, it is useful during post-surgical follow-up and after NAT as a prognostic tool for, respectively, recurrence or resectability.<sup>84</sup> Recently, several serum cytokines, proteins, or cancer cell targets have been proposed, alone or combined, as novel potential biomarkers for PDAC that need to be tested on large scale to prove their sensitivity and specificity are higher as expected.<sup>84</sup>

## Medical and Surgical Treatment

In the panorama of locally advanced pancreatic cancer treatments, there are several therapeutic options in the literature. Such therapies may be divided into two groups, the standard ones and those still being tested and validated. This section aims to analyse a variety of the possible therapeutic proposals for the 30% of patients who have locally advanced stage ductal pancreatic cancer without distant metastases.<sup>89,90</sup>

We may assume that all patients in this stage of disease today would receive induction chemotherapy.<sup>91</sup> In 2016 Suker et al demonstrated that LAPC treated with FOLFIRINOX has a very far superior efficacy compared to the previous therapeutic regimens.<sup>92</sup> In the last decades, for the first time, new therapeutic regimens have been able to impact on the survival of pancreatic cancer also in its locally advanced form.<sup>93</sup> Systematic chemotherapy stands as the standard for patients with LPAC. The evolution of treatments started with fluorouracil (5-FU), which represented the most commonly used treatment until 1996 when Gemcitabine was approved with a modest improvement in survival rate and disease-related symptoms.<sup>94</sup>

Surgery still stands as the only one potentially curative therapy for pancreatic cancer. New multi-agent chemotherapy regimens, such as Gemcitabine with nab-paclitaxel and FOLFIRINOX, have the aim to be able to determine a downstaging of the disease, allowing surgery to be performed.<sup>83</sup> For this reason, as of today, such treatments are widely used to treat LAPC patients. The duration of these systemic therapies is quite well defined in metastatic disease (disease progression or cumulative limiting toxicity), lasting 4–6 months as an average. For LAPC, there seems to be a lack of knowledge on the ideal duration of



the treatment. All the recommendations about the duration of treatment are based on quite old studies on single chemotherapy agents.<sup>95</sup> Therefore, there is a call to perform new studies on the topic.

As said, the effect of treating these patients with therapy periods of less than 4 months or greater than 6 months is currently unknown. Tuli et al analysed the impact of duration of combination therapy on survival of patients with LAPC, suggesting that a treatment lasting for at least 6 or more months may increase the survival outcomes.<sup>96</sup>

While such new systemic therapies look more promising and effective than in the past, surgical resection remains the mainstay of cure also for LAPC. In practice, the goal of systemic treatment is to achieve resectability. The resectability rate of LAPC after combination therapies is around 30%.<sup>97,98</sup> It is well known that patients with LAPC who undergo surgical resection after chemotherapy show an improved survival outcome compared with those who are not able to achieve resection.<sup>99</sup> The role of vascular resection in the treatment of LAPC is well defined by Oba et al in 2020.<sup>100</sup> Pancreatic cancer is a systemic disease from the beginning. The development of a new neoadjuvant treatment that improves the survival rate has to be deeply considered. There are probably primary resectable PDACs with bad biology which do not qualify for surgery and locally advanced cancers, with good biology, that should be treated with aggressive surgical operations. The research community should invest in defining better prognostic, patients-related, and biological criteria to select the best ideal candidate for surgery.

## Radiotherapy

Historically, locally advanced pancreatic adenocarcinoma (LPAC) has been treated with conformal fractionated radiotherapy (CRT), and conventional fractionation (1.8–2 Gy/fraction) up to a total dose of 50.4 Gy. Treatment target were large fields, including gross tumour volume and regional nodal areas plus further margins, keeping into account the mobility of abdominal structure.

Unsatisfactory results, with reported locoregional control rates between 50 and 70%, have been described with such low doses, not sufficient for a radioresistant tumour, known as one of the “big killer”.<sup>101</sup> The intrinsic radioresistance of PDAC is related to the high percentage of its hypoxic cells. To overcome pancreatic cancer radioresistance there are two possible modalities:

1. The association of RT to chemo-therapeutic agents to selectively sensitise the tumour to radiations.

2. The dose escalation to the target by increasing the total dose with conventional fractionation (2 Gy per fraction) or the dose per fraction (hypo-fractionated RT regimens). The advantage of associating radiations to chemotherapy has been demonstrated by the LAP07 randomised trial, which showed significantly improved local control in LAPC patients treated by chemoradiotherapy compared to patients treated by chemotherapy alone.<sup>102</sup>

Dose escalation in pancreatic cancer is limited by its anatomical location and by the proximity to bowel loops, duodenum, and stomach, all organs in motion-sensitive to radiations, so the prescription dose to target volume is necessarily limited by the dose constraints of the surrounding OARs.

Technological advances in radiation delivery, with more conformal dose distribution and lower side effects, allow to partially overcome these limits.

Intensity-modulated RT (IMRT) allows the RT dose to conform to the shape of the target volume by modulating the radiation beam into smaller volumes. The possibility to concentrate higher radiation doses on the tumour, while lowering the dose to surrounding normal critical structures, opened the way to dose escalation.

Krishnan et al described the clinical benefit of escalating the dose using fractionated IMRT in a population of 200 LAPC patients: who received biological equivalent dose (BED) >70 Gy showed better outcomes in terms of overall survival and locoregional relapse-free survival compared to patients treated with lower BED.<sup>103</sup>

In a retrospective study on 205 patients treated by IMRT (n=134) and 3D-CRT (n=71) significant lower gastrointestinal toxicity < G2 was found in the IMRT group (16% versus 34%, p< 0.001) compared to the patients treated with conventional 3D conformal technique, while keeping median prescription dose higher in the IMRT group (56 Gy vs 50.4 Gy).<sup>104</sup>

Further, stereotactic body RT (SBRT), a method of external beam radiotherapy, allows to precisely deliver a high radiation dose to the target, by using a single fraction or few fractions of RT, by prescribing a large dose per fraction, which is known to be biologically more effective on tumour cells response. The potential advantages of hypo-fractionation are based on the assumption that DNA of the healthy tissue easily repairs the damages of the oxidative effects from RT, while tumoural cells, due to their impairment in repairing genomic alterations, cannot.

In contrast to conventional RT, in SBRT dose is delivered only to the primary tumour and involved nodal

disease, if, in proximity, no elective regional node regions are irradiated. A further short course of RT by SBRT may bring potential benefits to patients in terms of overall survival by shortening the treatment RT course, reducing the time off of the multi-agents chemotherapy. While the early experience with pancreatic SBRT demonstrated significant gastrointestinal toxicity,<sup>105</sup> in more recent studies, SBRT has shown improvement in tolerability by de-escalating dose and decreasing target volumes.

In prospective trials of SBRT delivered alone, median OS range between 5.7 and 19 months, better outcomes are reported when SBRT is delivered after chemotherapy (median OS between 10.3 and 20 months).<sup>106,107</sup>

Since single fraction, compared to multiple fractions and lower dose/fraction, is related to worst outcomes and side effects, fractionated SBRT is preferred to single-fraction stereotactic RT. Further, fractionated SBRT might be more advantageous because it allows the re-oxygenation of hypoxic tumour cells and redistribution of resistant tumour cells into more radiosensitive cell cycle phases.<sup>108</sup> Heavy particles, by protons and carbon ions, are emerging as promising treatment RT modality in radioresistant cancers,<sup>109–116</sup> such as pancreatic tumours.<sup>117–121</sup>

Proton therapy, thanks to its intrinsic physical selectivity, allows delivering dose to the target with no exit dose in the beam path. This translates in a lower dose to surrounding organs and in the possibility of increasing the dose to the target volume with theoretically lower toxicity and better local outcomes.<sup>122,123</sup> Clinical data about proton therapy in pancreatic cancer are still scarce.

In locally advanced, unresectable pancreatic cancer, the largest studies with proton radiotherapy are still limited to mono-institutional Japanese experiences. In a retrospective analysis of 42 patients with LAPC treated with proton RT and concurrent chemotherapy, with dose ranging between 50 Gy RBE and 67.5 Gy RBE in 25 fractions, based on the tumour location, after a median follow-up of 14 months (range: 2.4–47.6) no grade 3 or higher late adverse effects were reported. OS at 1 and 2 years was 77.8 and 50.8% with median survival time of 25.6 months, while the LC rate at 1 and 2 years, respectively, of 90.1 and 76.7% with a median time to local recurrence of more than 36 months.<sup>124</sup>

In opposite the other experiences by proton therapy were less advantageous in terms of gastrointestinal toxicities.

Terashima et al in a Phase I II study treated PDCA with proton radiotherapy with doses up to 70.2 Gy (RBE) in 26

fractions and concomitant Gemcitabine with a relatively high toxicity rate > G3, 8 cases (10%) reported of late gastric ulcer and haemorrhage.<sup>125</sup>

Such data were supported by Takatori et al in a separate retrospective analysis focalised on gastrointestinal complications of 91 patients treated by proton radiotherapy at Hyogo Medical Center. Acute ulcers were reported in almost 50% of the patients, but late > G3 intestinal side effects in only 3 patients.<sup>126</sup>

Carbon ions are high linear energy transfer (LET) radiations able to deposit higher energy in the target, compared to conventional photons (low LET radiation), producing significantly more DNA damages to malignant cells, because of their higher relative biological effectiveness (RBE).<sup>110,118</sup>

Further, the type of damage is different. Whereas photon irradiation leads to indirect DNA damage through the creation of free radicals against the DNA, carbon ion radiotherapy (CIRT) leads to direct DNA damage without an intermediary.

This mechanism leads to the well-known oxygen-dependence of conventional, photon-based radiation, such that hypoxic tumours are radioresistant. Because carbon ions do not require oxygen to damage DNA, CIRT is more effective on hypoxic cells. Thus, because of the superior dose distribution, high RBE, and resistance to hypoxia, CIRT is a promising radiotherapy modality that may improve local control without compromising normal tissues, especially in classically radioresistant tumours.<sup>116,118,127</sup>

Furthermore, from the physical point of view heavy particles, thanks to their steep dose gradient deposit all the dose in the target volume while keeping a very low dose to the surrounding organs.

Clinical published data about CIRT in pancreatic cancer are limited to Japanese centres.

After a dose-escalation study on 26 patients treated pre-operatively by CIRT (30 to 36.8 Gy[RBE], in 8 fractions, 4 fractions/week),<sup>120</sup> Shinoto et al started a dose-escalation trial to treat LAPC patients by CIRT up to 55.2 Gy[RBE], over 3 weeks; concurrent Gemcitabine (1000 mg/m<sup>2</sup>) was administered. Treatment was generally well tolerated with better local control and overall survival in those patients who received at least 45.6 Gy[RBE], compared to those who received lower doses. In this study, two-year survival at the highest radiation dose levels was 54%, and two-year survival in the cohort of stage III patients treated with at least 45.6 Gy[RBE], was 48%. Median OS was 19.6 months, with 1- and 2-year OS rates in all patients, respectively, of

73% and 35%. Gastrointestinal toxicity greater than G3 (ulcer) was reported in only 1 patient (1%).<sup>128</sup>

Such promising results in terms of outcomes and toxicities are confirmed by a retrospective multi-institutional study involving Japanese institutions within the study group called “Japan Carbon ion Radiation Oncology Study Group (J-CROS)”. In this study were included 72 LAPC patients treated in three Japanese centres with 52.8 Gy [RBE], or 55.2 Gy [RBE], in 12 fractions. After a median follow-up period of 14.7 months (range, 3.2–37.5), the OS rates were 73% at 1 year, and 46% at 2 years with a median OS of 21.5 months. The three institutions had similar independent results in terms of both LC, OS, and toxicity. Only 1 patient (1%) developed grade 3 duodenal ulcer and no grade 4–5 toxicity was reported.<sup>119</sup> Clinical results of particle therapy in LAPC are reported in Table 4.

There are no randomised trials yet showing statistically better outcomes for LAPC of CIRT compared to other conformal RT modalities with photons, but results from Japanese centres are certainly promising and may hopefully represent

hope for treatment of disease with such a poor outcome. PIOppo trial is an ongoing Italian Prospective, Phase II, Multicentre, Single-Arm Study that aims to evaluate the efficacy and the feasibility of 3 cycles of FOLFIRINOX neoadjuvant chemotherapy followed by a short-course CIRT for resectable or borderline resectable pancreatic adenocarcinoma.<sup>118</sup>

## Conclusions

While significant progress in medical knowledge has been made in its management, PDAC is still regarded as one of the deadliest malignancies. This is due to factors such as the lack of early diagnostic markers, delayed detection, diverse genetics and rapid metastasis. In the era of integrated oncological therapies, especially pancreatic cancer, is living and will have a new therapeutic era.<sup>42,117</sup> Hadrontherapy appears promising in terms of outcomes and toxicities,<sup>122</sup> also in the neoadjuvant schedule.<sup>118,120</sup> There is a call for new biological therapies, target treatment as soon as new biotechnological tools for biomarkers that may, in the future, influence the survival of this neoplasm.

**Table 4** Particle Therapy Studies

Authors	Type of Study	Particle	Number of Patients	Dose/Fractionation/Chemotherapy	Overall Survival	Toxicity > G3 (Number of Patients)
Terashima et al, 2012 <sup>125</sup>	Mono-centric Prospective; Phase I-II,	Proton	50	P1: 50 GyE/25 fractions (5), P2: 70.2 GyE/26 fractions (5), P3: 67.5 GyE/25 fractions (40), All with concurrent gemcitabine	1-year:76.8% P3 patients: 1-year:78.8%	P1 G3 Anorexia (1) G3 Epigastralgia (1) P2 G3 Anorexia (1) G3 gastric ulcer (1), P3: G3 Anorexia (4) G3 GI ulcer (3); G5: death from GI bleeding (1)
Shinoto et al, 2016 <sup>129</sup>	Mono-centric Prospective, Phase I	Carbon ions	71	43.2–55.2 GyE/12 fractions, Gemcitabine	1-year: 73%, 2-year: 35% Median:19.6 months	G3 Anorexia (6), G3 gastrointestinal (1)
Shinoto et al, 2018 <sup>128</sup>	Mono-centric retrospective study	Carbon ions	46	55.2 GyE/12fractions, Gemcitabine	2-year: 53% Median:25.1 months	G3 anorexia (1); G3 gastrointestinal (2)
Kawashiro et al, 2018 <sup>119</sup>	Multi-centric retrospective study	Carbon ions	72	52.8 GyE or 55.2 GyE 12 fractions Concurrent Gemcitabine (in 78% pts)	1 -year: 73% 2 -year: 46% Median: 21.5 months	G3 anorexia (2); G3 duodenal-ulcer (1)

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