Chapter 17
Pancreatic Cancer

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17.1 Overview

Pancreatic cancer most commonly refers to the carcinoma of the exocrine pancreas, a disease that presents a constant challenge in modern oncology, since it is characterized by significant morbidity and carries a uniformly ominous prognosis. Adenocarcinoma of the pancreas is largely perceived as inherently resistant to most of the currently available treatment options, hence needing a Multidisciplinary team (MDT) discussion to face the hydra that might defy easy solutions. Potentially resectable disease might necessitate a more aggressive multimodality approach as early stage detection makes cure plausible. Patients in the advanced and metastatic setting, however, do not share the opportunity to bask in a treatment with curative intent and palliation is the primary aim. Cumulative rise in knowledge of cellular and molecular biology and emerging evidence for the efficacy of new agents

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promise more potent treatment options and eligible patients with advanced disease are urged to participate in clinical trials. In this chapter, we sought to summarize existing knowledge about pancreatic cancer and present novel and future therapeutic strategies.

17.2 Essential Practice Aphorisms

Pancreatic cancer is a versatile disease with interesting anatomical and geographic topography that carries a dismal global prognosis, even for potentially respectable disease. Early stages lack significant symptoms to alert both the patient as well as the clinician, which results in a delay in diagnosis with pernicious effect and those diagnosed as an emergency presentation have a lower rate of survival [1, 2]. Moreover, failure in reliable validated biomarkers and screening processes reflects a strategic impediment resulting in more advanced presentation, technically challenging operations with increased risks, frequently misapplied or abandoned. Just 15–20 % of patients are candidates for a more aggressive treatment with curative intent at the time when diagnosis is reached. Even so, the 5-year survival following surgery for the localized node-negative disease fairly reaches 10 % in major trials conducted.

Nearly 90 % are adenocarcinomas arising from the exocrine ductal system (PDAC). The incidence rate for PDAC of the head has remained at 5.6 per 100,000, whereas the rate for body/tail has increased by 46 % (to 1.6 per 100,000) between 1973 and 2002. The majority of pancreatic carcinomas occur within the head/neck of the pancreas with much less affecting the body and even less the tail. For all stages combined, the 1-year survival rate remains at the discouraging 19 % and the 5-year survival does not exceed 4–6 %, with patients with pancreatic head cancer carrying higher survival rates compared with those with body/tail cancers [3].

It is hence not surprising that although it is the twelfth most common cancer in the world with 338,000 new cases (178,161 men and 159,711 women) diagnosed in 2012 worldwide, yet it is the seventh most common cause of cancer-related deaths. The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.2 per 100,000, while incidence and mortality have the least of improvement among cancer types in all epidemiology surveys over the last 40 years. Interestingly, it appears to have a distinct preference in the more industrialized parts of the world, affecting more the developed countries with 2.6 times higher rate compared with the less developed [4, 5].

17.3 Epidemiology and Statistics

Pancreatic cancer is an aggressive and abysmal disease with increasing frequency for both sexes over the last almost 30 years worldwide and a life expectancy counting in months. The disease carries one of the highest incident-to-mortality rates

among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world, respectively. 45,220 (22,740 men and 22,480 women) are the estimated new cases diagnosed in the USA in 2013 with 38,460 estimated deaths (19,480 men and 18,980 women), being the fourth leading cause for cancer-related deaths, representing the 6.6 % of all cancer deaths in this country[1]. European age-standardised incidence rates (per 100,000) have remained constant (around 9.0) since 1993 in the UK, however, 8,455 people have been diagnosed with pancreatic cancer in the year 2010, a number steadily rising from 7,684 in 2007 [4]. The very low incidence and death rates, on the other hand, in countries like Tanzania and Bangladesh (0.35 and 0.45 per 100,000 respectively) mainly reflect the major geographic diversity that this disease represents.

Pooled epidemiology data suggest that the 5-year survival for localized pancreatic cancer can reach the startling, for this disease, 24.1 %, however only a very small percentage (8.7 %) is diagnosed at such an early stage. This ends up in a disappointing 9 % for regional and 2 % for metastatic disease.

Pancreatic cancer is more common with increasing age and slightly more common in men than women (men:women 1.12:1). Age has a powerful influence on the risk of pancreatic cancer. It is rather uncommon in younger individuals, albeit random cases can still occur (less than 10–15 % of cases) and it is frequent in the elderly. Its frequency increases precipitously after the age of 50 years, with most patients being between 60 and 80 years old at the time of diagnosis with the seventh decade of age carrying the highest rates. While incidence is lower for those under the age of 50, the 1-year survival rate for this group of patients is markedly higher as well as the 5-year survival that drops considerably for those over 60 years. The median age at diagnosis is 71 years, 69 years in whites and 65 years in blacks. The incidence in Afro-Americans (17.6 men and 14.3 women per 100,000) is higher that whites in the USA (13.8 men and 10.7 women per 100,000), albeit more recent data suggest this racial difference show to abate [6]. Afro-Americans also have the highest death rates from the disease. The median age at death is 73 with the ages 75–84 carrying again the highest rates. Although some improvement is demonstrated over the last 40 years in survival curves, the scenery has not changed much with the 5-year relative survival rate still represented in single figure.

17.4 Risk Factors

17.4.1 Lifestyle Risk Factors

Interestingly, pancreatic cancer incidence has been associated with socio-economic deprivation although some studies do not share this notion [7, 8]. Bearing in mind the aforementioned geographic distribution of the disease, we then understand that relatively little is known yet regarding the risk factors contributing to pancreatic cancer. Epidemiologic studies have assisted, by providing data, in an attempt to

establish environmental and lifestyle factors as well as genetic predisposition associated with an increased risk for the disease.

17.4.1.1 Smoking

Smoking is the most common risk factor attributing to pancreatic cancer, a very much otherwise age-dependant disease. Data analysis from 12 case-control studies demonstrated statistically significant 2.2-fold (95 % confidence interval [CI] 5 1.71–2.83) increased risk of pancreatic cancer for current smokers compared with never-smokers [9]. Cigarette smoking attributes almost 25 % of all cases and showed to increase the risk by 27 % for every five cigarettes smoked per day [10, 11]. Tobacco "fingerprint" was clearly demonstrated in the genotyping of tumors resected from nonsmokers harboring a maximum of five mutations, whereas the tumors from smokers had as many as 49 mutations, albeit they did not yield any characteristic profile [12]. Smoking has also the debilitating effect of earlier onset of pancreatic cancer, since it has been identified that heavy smokers were diagnosed around age 62, almost a decade earlier than the average age of 71 (HR of 2.69 (95 % CI, 1.97–3.68, P = 0.019 for active smokers) [13]. Passive smoking, cigars and snuff are no less harmful wontedness. The European (EPIC) study showed that passive smoking can increase the risk of pancreatic cancer by 50 % and more devastating, that tobacco smoke children exposure on a daily basis incur double the risk of contracting pancreatic cancer later in life [14, 15]. Pipe smoking and smokeless tobacco are also believed to increase the risk [16].

Smoking cessation however important in reducing the risk of developing and dying from cancer, takes a number of years to abolish the unhygienic effect. A significant mitigating trend in risk is seen over time since stopping cigarette smoking. After 20 years, risk estimates are similar to that of nonsmokers (OR 0.98 (0.77–1.23) $p < 0.0001$) [9]. Furthermore, smoking may also account for the trend of female pancreatic cancer surge in the recent decades.

17.4.1.2 Alcohol Consumption

Evidence for a positive association between heavy alcohol consumption and the risk of pancreatic cancer has been demonstrated in pooled analyses. Compared with abstainers and occasional drinkers (<1 drink per day) where no confirmed link has been established, higher consumption levels lead to increased risk for pancreatic carcinogenesis (OR = 1.6, 95 % confidence interval 1.2–2.2 for subjects drinking 9 drinks per day) [17]. Analysis by type of alcohol showed that the risk was increased for consumers of more than 4 drinks of wine per day (OR = 1.5; 95 % CI 1.0–2.1; p value for trend 0.017), whereas no excess risk has been observed for consumption of beer.

17.4.1.3 Coffee Consumption

Although former data from older studies have suggested a potential association of coffee ingestion in the tumorigenetic process of pancreatic cancer, prospective data as well as a very recent meta-analysis have clearly demonstrated no appreciable connection between coffee drinking and this type of cancer [18, 19]. Despite caffeine and its byproducts have been accused of influencing cancer inception through DNA repair inhibition and mitotic event induction, roasted coffee is a complex mixture of a number of different chemicals and actually evidence may exist that it might also reduce pancreatic cancer risk, even with just 125 mL of coffee daily (RR, 0.96; 95 % CI: 0.90–1.02) [20].

17.4.1.4 Diet

Many studies have suggested the relationship of dietary habits and supplements with pancreatic cancer. Lower serum lycopene and selenium have been observed in individuals who later developed pancreatic cancer. However, a clear direct association has not been evinced between dietary or supplemental consumption of these nutrients [21]. The high intake of the so-called "Western" diet products, saturated fat and/or meat, smoked or processed meat in particular, seems to correlate with an increased risk, although it is hard to be absolute [22]. Observations and several studies have linked fresh fruits and vegetable intake with an inverse effect on risk for pancreatic cancer development and following a more balanced, high-quality diet, as scored by the HEI-2005 (consisting of higher fruit, vegetable and whole grains intake, milk, meat and beans, and oils found in fish, nuts and seeds combined with a much lower intake of saturated fat, sodium, solid fat, alcohol and added sugar) can have a protective effect by reducing the risk (HR 0.85, 95 % CI 0.74–0.97). Interestingly, the benefit appears to be higher for overweighed/obese men (BMI $\geq$25 kg/m^2) [23].

17.4.1.5 Obesity

Evidence that greater body fatness forms a convincing cause for pancreatic cancer is largely supported by a number of studies. Individuals aged 14–39 years who were overweight (a BMI of 25–29.9) (highest odds ratio [OR], 1.67; 95 % confidence interval [CI], 1.20–2.34) or obese (a BMI > or = 30) from the ages of 20–49 years (highest OR, 2.58; 95 % CI, 1.70–3.90) carry an associated increased risk of pancreatic cancer, independent of diabetes status. The association observed was stronger in men (adjusted OR, 1.80; 95 % CI, 1.45–2.23) than in women (adjusted OR, 1.32; 95 % CI, 1.02–1.70) and in ever smokers (adjusted OR, 1.75; 95 % CI, 1.37–2.22). Furthermore, subjects who were overweight or obese had an earlier onset of pancreatic cancer by 2–6 years (median age of onset was 64 years for patients with normal weight, 61 years for overweight patients [P = 0.02], and 59 years for obese patients

[P < 0.001]). Obesity at an older age was further linked to a lower overall survival in patients with pancreatic cancer [24]. Higher BMI has also been associated with more advanced disease at diagnosis, with 72.5 % of obese patients presenting with metastatic disease versus 59.4 % of healthy-weight patients ($\square\chi^2$ p = 0.02) [25]. Both general and abdominal fatness augment pancreatic cancer risk. Surprisingly however, among nonsmokers, risk increases even among persons within the normal BMI range and has an increment of 10 % for a five-point increase in BMI (1.10 [95 % confidence interval (CI) 1.07–1.14, I2 = 19 %]). Central obesity is also a significant risk factor (for a 0.1-unit increment in waist-to-hip ratio was 1.19 (95 % CI 1.09–1.31, I2 = 11 %) [26]. Moderate physical activity demonstrated an inverse relation (RR 0.45, 95 % CI 0.29–0.70) particularly for overweighed and obese subjects (BMI ≥25 kg/m^2).

17.4.2 Medical Conditions

17.4.2.1 Diabetes

A positive association between long-standing type 2 diabetes mellitus (DM2) and pancreatic cancer has been identified (OR for DM2 ≥4 years in a recent meta-analysis was 1.5 (95 % CI 1.3–1.8) and newly diagnosed with DM individuals have an eightfold higher likelihood of pancreatic cancer diagnosis within 3 years of meeting criteria for DM compared to the general population, implying that unveiling new-onset diabetes could serve to denote an early diagnosis of pancreatic cancer [27, 28]. Long-standing diabetes is a risk factor for pancreatic cancer (RR 1.94 95 % CI, 1.66–2.27 in the most recent meta-analysis) and new-onset diabetes can be an early manifestation of the disease [29, 30]. Pancreatic cancer induced hyperglycaemia may occur up to 24 months prior to the cancer diagnosis [27]. Several putative molecules with diabetogenic effect have been proposed in an attempt to establish a causal relation [31]. The prevalence of DM is markedly higher than in other well-known diabetogenic states such as morbid obesity, polycystic ovarian syndrome and pregnancy and existing strong epidemiologic evidence support the concept that pancreatic cancer-related DM can be distinguished from primary DM2, thus giving the opportunity to older patients with newly diagnosed DM to be screened for asymptomatic pancreatic cancer [27]. Patients with young-onset or type I diabetes have double the risk of pancreatic cancer (overall RR for pancreatic cancer 2.00, with 95 % CI 1.37–3.01). A causality relation can not be established in this setting, given the rare frequency of pancreatic cancer in people under 25, however, seems more likely that type I diabetes precedes pancreatic cancer [32].

Oral antidiabetic drugs (including metformin and sulfonylurea) may play a role in the relationship between DM2 and pancreatic cancer, too. A meta-analysis in 2012 demonstrated that metformin decreased the pancreatic cancer risk by 62 %, contrasted by a substantial independence from use of sulfonylurea [33]. However, data from the General Practice Research Database suggest that the decrease in pan-

creatic cancer risk associated with metformin is consistent only in women (adj. OR: 0.43, 95 % CI: 0.23–0.80) and that both sulfonylureas (≥30 prescriptions, adj. OR: 1.90, 95 % CI: 1.32–2.74) and insulin use (≥40 prescriptions, adj. OR: 2.29, 95 % CI: 1.34–3.92) is associated with an increased risk of pancreatic cancer [34]. Based on current knowledge, metformin may exhibit its beneficial effect by direct molecular mechanisms of action involving activation of the AMP-activated protein kinase (AMPK), a protein kinase sensitive to deviations in the AMP/ATP ratio, inhibition of the mTOR pathway and by interfering in cell polarity and cell division, further to controlling hyperglycemia and hyperinsulinemia. Metformin blocks the proliferative effects of insulin and IGF-1 by blocking the PI3K/Akt/mTOR signaling pathway and by inhibiting cell division [35].

17.4.2.2 Chronic Pancreatitis

Chronic inflammation of the pancreas is another risk factor for pancreatic cancer. A study from the International Pancreatitis Study Group reported 56 cases of pancreatic cancer in 2015 patients with chronic pancreatitis yielding a standardized incidence ratio (the ratio of observed to expected cases) of 26.3. The cumulative risk reached 1.8 % at 10 years and 4 % at 20 years, independent of the type of pancreatitis [36]. Interestingly, younger (<65 years) cases demonstrated stronger associations with previous (>2 years) pancreatitis (OR: 3.91, 95 % CI: 2.53–6.04) than the older (≥65 years) cases (OR: 1.68, 95 % CI: 1.02–2.76; P value for interaction: 0.006). This association was stronger for intervals between diagnoses of pancreatitis and pancreatic cancer of greater than 2 years, when individuals with a history of chronic pancreatitis had a nearly threefold increased risk of pancreatic cancer (OR: 2.71, 95 % CI: 1.96–3.74) and more potent at intervals of ≤2 years (OR: 13.56, 95 % CI: 8.72–21.90), entailing a potential causative role of chronic inflammation in the development of pancreatic cancer or even a delay in the diagnosis of pancreatic cancer [37]. Yet, the population attributable fraction was estimated at 1.34 % (95 % CI: 0.612–2.07 %), suggesting that a relatively small proportion of pancreatic cancer might be avoided if pancreatitis could be prevented [38].

17.4.2.3 Inflammatory Bowel Disease

Patients before the age of 25 hospitalised for ulcerative colitis carry an ominous sevenfold risk increase for pancreatic cancer in comparison to the general population, albeit this hardly reaches a double-fold increased risk for those hospitalised for ulcerative colitis at a later age [39]. Those suffering with Crohn's disease are at a 75 % increased risk of contracting pancreatic cancer and hospitalized patients above the age of 64 have a 3.3-fold increased risk of pancreatic cancer (95 % CI, 1.88–5.37) compared to younger patients (<25 years old) who run half the risk (1.54 95 % CI, 0.00–8.82) [40].

17.4.2.4 Gastric Ulcer and *H. pylori*

A diagnosis of gastric ulcer is linked to an increased risk of pancreatic cancer (RR, 1.83; 95 % CI: 1.13–2.97). The risk is highest for those whose cancer diagnosis is close in time to their gastric ulcer diagnosis (RR, 3.66; 95 % CI: 1.45–14 9.24), but can remain significantly increased even 10–19 years after gastric ulcer diagnosis (RR, 2.89; 95 % CI: 1.26–6.64) [41]. Particularly, subjects operated for their ulcer have a 2.1-fold increased risk for pancreatic cancer (95 % CI 1.4–3.1) 20 years after gastric resection, while vagotomy does not. A 20 % excess risk for pancreatic cancer (95 % CI 10–40 %) was also observed even in unoperated gastric ulcer patients, which increased to 50 % (95 % CI 10–110 %) 15 years after first hospitalization (p for trend = 0.03) [42]. It has been suggested that formation of carcinogenic molecules, e.g. nitrosamines, secreted from bacteria clonising the stomach postoperatively may have a causative effect [43].

Helicobacter pylori (H. pylori) seropositivity has demonstrated a weak, however, statistically significant association with pancreatic cancer [44]. Recent data from a meta-analysis have linked H. pylori infection to an increased risk of pancreatic cancer (OR 1.47, 95 % CI 1.2–1.8) [45]. A subgroup analysis failed to associate CagA positive H. pylori strains with an increased risk of pancreatic cancer. A connection between pancreatic cancer risk and CagA-negative H. pylori colonisation was found among individuals particularly with non–O blood type but not among those with O blood type (OR = 2.78, 95 % CI = 1.49 to 5.20, P = 0.0014; OR = 1.28, 95 % CI = 0.62 to 2.64, P = 0.51, respectively) [46]. Chronic hyperacidity has been proposed as a hypothetical mechanism to explain the relation of H. pylori infection and pancreatic cancer increased risk. However, there are studies that defy the aforementioned notion and data that prove no relation of duodenal ulcer to pancreatic cancer [41, 47].

17.4.2.5 Hepatitis B and C

Exposure to Hepatitis B virus has been shown to predispose to pancreatic cancer. Individuals with anti-HBc–positive serology have 2.5-fold increased risk (95 % CI, 1.5–4.2), those with past exposure to HBV with natural immunity a 2.3-fold (95 % CI, 1.2–4.2), and a fourfold increased risk (95 % CI, 1.4–11.1) exhibit those without natural immunity. Of interest, diabetes mellitus significantly modifies the risk of pancreatic cancer among patients with past exposure to HBV, who appear to have a 7.1-fold (95 % CI, 1.7–28.7) increased risk for pancreatic cancer [48]. Past exposure to Hepatitis C virus seems also to result in an increased risk of pancreatic cancer (OR = 1.26; 95 % CI, 1.03–1.50) [49]. Substantial variation between different geographical areas in seroprevalence of HBV/HCV-antigens/antibodies and genotypes require further investigation to validate these findings.

17.4.2.6 Periodontal Disease

Tooth loss and periodontal disease have been identified as risk factors for pancreatic cancer attributing a 50 % increase in risk (HR = 1.54, 95 % CI = 1.16–2.04) and a twofold increase (HR = 2.06, 95 % CI: 1.14, 3.75) respectively [50, 51]. Systemic inflammation, pathogenic invasion into the blood stream and impaired or hyperactive immune response to periodontal infection might give an interpretation of the liaison.

17.4.2.7 Aspirin and NSAID

Recent laboratory data adorn aspirin with a potential tumouricidal effect. However an epidemiologic report challenged this notion and investigated into whether both aspirin and NSAID increase the risk of pancreatic cancer. Processing data from the Nurses' Health study, raised the possibility of a dose-dependant tumourigenic effect of aspirin in women, who made significant use of more than 14 tablets on a weekly basis for at least 4 years (RR = 1.86, 95 % CI = 1.03–3.35) [52]. Despite these data, a number of studies have either found no connection between aspirin use and pancreatic cancer risk or even revealed an inverse correlation revealing a benefit with the use of even one tablet on a daily basis (OR 0.74, 95 % CI: 0.60–0.91, P 0.005), an effect that was valid even for low-dose aspirin consumers (OR 0.67, 95 % CI: 0.49–0.92, P 0.013), even after adjusting for cancer stage, smoking status, or body mass index [53–55].

17.4.2.8 Allergies

A surprising finding is that reported in people with a history of allergies, who carry a considerable reduced risk for pancreatic cancer (OR = 0.77; 95 % CI, 0.63–0.95). More surprisingly, common allergens such as the mold demonstrate marked inverse associations (OR = 0.49; 95 % CI, 0.32–0.75) and trends were shown for lower risks associated with increasing number of allergies (p = 0.0006) and severity of allergic symptoms (p = 0.003) [56]. Furthermore, allergies particularly related to atopy exhibit a reduced risk of pancreatic cancer (RR, 0.71; 95 % CI, 0.64–0.80), especially those affecting the skin and reactions to insect bites, hay fever and respiratory allergies other than asthma. Hence, the hyperactive immune system of allergic individuals may operate in an increased surveillance mode and protect against pancreatic cancer development [57].

17.4.2.9 Previous Cancers

On the report of a large pooled analysis, people run a higher risk of developing pancreatic cancer within 10 years of a diagnosis of pharyngeal, laryngeal, gastric, biliary, pulmonary, cervical, corpus uteri, bladder and ocular cancer and 10 years or later following a diagnosis of cancers of the stomach, colon, gallbladder, breast, cervix, placenta, corpus uteri, ovary, testis, bladder, kidney and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. These risk increases are probably partly due to the well-documented shared risk factor of tobacco use. The risk of pancreatic cancer was decreased however significantly after cancers of the rectum and the prostate. The elevated pancreatic cancer risk in young patients found among different types of cancer implies a genetic link. Radiotherapy treatment for the first cancer may also be an additional risk factor [58].

17.4.2.10 Psychological Stress

Epidemiologic studies have rarely been pre-occupied with the investigation of the potential detrimental role of psychological stress in the development of pancreatic cancer. Severe psychological stress induced by the drama of losing a child has been tested and was associated with a significant rise in pancreatic cancer risk (OR 1.09, 95 % CI; 1.02–1.17). Women and people already suffering psychiatric illness had the greatest risk increase after child loss. The risk was greater during the first 5 years after the loss (OR 1.27, 95 % CI; 1.12–1.45) providing some initial evidence that psychological stress could also account as a predisposing factor for pancreatic cancer [59]. Interestingly, it has also been implied that neurotransmitter responses to psychological stress may instigate pancreatic cancer progression through the activation of multiple cAMP-dependent pathways and concurrent suppression of endogenous GABA, which may act as a promising therapeutic target [60].

17.4.3 Hereditary Risk Factors

17.4.3.1 Familial Pancreatic Cancer

In addition to environmental and lifestyle factors, inherited genetic changes or a familial causative link can play an important role for pancreatic cancer. This is suggested by the fact that almost 5–10 % of patients report to have a first-degree relative with the disease. Individuals with a family history of pancreatic cancer are at a moderately increased risk of developing pancreatic cancer themselves (multivariate-adjusted odds ratios (ORs) = 1.76, 95 % (CI) = 1.19–2.61) [61]. People with at least one first degree relative diagnosed with pancreatic cancer have almost double the risk of people without pancreatic cancer in their family, which increases further if relatives were diagnosed before the age of 50 or if there are more than two cases in

the family (standardized incidence ratio reached, SIR 17.02, CI 95 % (7.34–33.5) [62]. However, a responsible specific gene defect, although implied, has not yet been identified and hence there is no genetic test available to early detect the susceptibility of certain individuals with a positive family history. Relatives of familial pancreatic cancer patients have an increased risk of developing other cancer types, such as breast (1.66-fold, 95 % CI 51.15–2.34), ovarian (2.05-fold, 95 % CI 5 1.10–3.49), and bile duct cancers (2.89-fold, 95 % CI 5 1.04–6.39) [63].

17.4.3.2 Hereditary Pancreatitis

Hereditary pancreatitis is a rare hereditary form of pancreatitis that accounts for a minority of pancreatic cancer cases, in which the patients suffer recurrent episodes of acute pancreatitis beginning in childhood, even before the age of five and which typically results in pancreatic insufficiency by early adulthood. It demonstrates two types of inheritance causing an autosomal dominant form, when mutations in the cationic trypsinogen gene (PRSS1) are identified, and an autosomal recessive form, when it is about mutations in the serine protease inhibitor gene (SPINK1) [64]. Hereditary pancreatitis remarkably increases by 58-fold (95 % CI (23–105) the risk of developing pancreatic cancer and attributes a cumulative risk (by the age of 70) of 30–44 %. Tobacco use and diabetes seem to further increase this risk. People with hereditary pancreatitis present a higher mortality rate compared to the general population and they often consider pancreatectomy as a prophylactic measure, however, total pancreatectomy associated risks and morbidity are serious co-variants in such a decision.

17.4.3.3 Pancreatic Cancer Hereditary Susceptibility Syndromes

A variety of different germline genetic syndromes have been identified and been linked to an increased risk of pancreatic cancer displaying a range of penetrance resulting in a lifetime risk for pancreatic cancer as well as for a number of malignancies. The contribution yet of these syndromes accounts for less than one out of five cases of pancreatic cancer, suggesting the potential existence of other yet unidentified susceptibility genes. They are particularly important because identification of a gene makes it possible to quantify the risk of pancreatic cancer, organize screening for highly susceptible individuals or early curable precancerous conditions. Besides, this is valuable for trial design and quantification of other associated malignancies. Noticeably, particular germline mutations may denote a susceptibility to certain chemotherapeutics or targeted therapies.

17.4.3.4 BRCA and PALB2 Hereditary Breast and Ovarian Cancer

Mutations in the BRCA gene family have been associated with malignancies, such as breast, ovarian, prostate, gastric and colon cancer. The prevalence of germline BRCA2 gene mutations in pancreatic cancer patients varies among different populations and is particularly high in individuals of Ashkenazi Jewish decent, mounting up to even 10 %. The BRCA2 gene mutations prevalence increases among pancreatic cancer patients alongside the increasing number of affected relatives. BRCA2 mutations can be found in as many as 12–16 % of patients with familial pancreatic cancer [65]. However, a reasonable number of pancreatic cancer patients with germline BRCA2 mutations report no breast or ovarian cancers running in their family revealing that evaluation of penetrance of these genetic alterations needs yet to be determined. The role of germline mutations in BRCA1 is less clear and although studies have suggested that also carriers itself a 2.26-fold (95 % CI 51.26–4.06) higher risk of pancreatic cancer, it is lower than the one observed with BRCA2 and needs to be further evident in literature as it may have significant clinical implications [66, 67].

PALB2 (partner and localizer of BRCA2) gene mutations have been identified in 1–3 % of familial pancreatic cancer kindred's. PALB2 mutation carriers are also associated with an increased risk of breast cancer, although, not all patients with pancreatic cancer who are found to have germline PALB2 mutations report a personal or family history of breast cancer. The PALB2 protein binds with BRCA2 protein and stabilizes it in the nucleus; the generated BRCA2/PALB2 complex is part of the Fanconi Anaemia DNA repair pathway that acts in double-stranded DNA repair, which may prove such tumours sensitive to DNA cross-linking agents [68]. The link between BRCA and PALB2 gene mutations with pancreatic cancer underlines the necessity of obtaining a good family history.

17.4.3.5 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hamartomatous polyps in the alimentary system and pigmented macules of the lips, buccal mucosa and digits. Germline mutations in PRSS1 and STK11 genes, associated with the syndrome, attribute an up to 26 % (95 % CI 0.4–0.47) cumulative risk (at age 70) and a 76 % (95 % CI 36–160; $p < 0.001$) relative risk of pancreatic cancer. Individuals with the Peutz-Jeghers Syndrome run a highly increased risk for pancreato-biliary cancer (RR 96 %; 95 % CI 53–174; $p < 0.001$) and would be good candidates for early neoplasia screening once this kind of tests become available [69].

17.4.3.6 Lynch Syndrome and Familial Adenomatous Polyposis (FAP)

Lynch syndrome is an autosomal dominant hereditary disease characterized by early onset colon cancer due to germline mutations in one of the DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2, or hMSH6/GTBP). Individuals with Lynch syndrome are found to have a predisposition for a variety of malignancies, such as endometrial, gastric, small intestinal, ureteral and pancreatic cancer. Families containing a mutation in a mismatch gene reported an 8.6-fold (95 % CI 5 4.7–15.7) increased risk of pancreatic cancer, corresponding to a cumulative risk of 1.31 % (95 % confidence interval [CI], 0.31–2.32 %) up to age 50 years and 3.68 % (95 % CI, 1.45–5.88 %) up to age 70 years compared with the general population [70]. Lynch syndrome kindreds might also benefit from screening and surveillance, especially since cancers that occurring in these frequently have microsatellite instability (MSI1) and a distinct poorly differentiated medullary histopathology, that despite their poor differentiation carries a relative good prognosis. Patients with FAP may also be at increased risk for pancreatic adenocarcinoma (RR 4.46; 95 % CL 1.2–11.4) as well as their risk relatives [71].

17.4.3.7 Familial Atypical Multiple-Mole Melanoma (FAMMM) Syndrome

Familial atypical multiple-mole melanoma (FAMMM) syndrome is a disorder associated with multiple nevi, cutaneous and ocular malignant melanomas, as well as pancreatic cancers and is characterized by germline mutations in the CDKN2A (also known as the multiple tumor suppressor-1) gene. Kindreds with a 19–base pair deletion in exon 2 of the p16/CDKN2A gene (the Leiden mutation) have a 38-fold increased risk of developing pancreatic cancer and lifetime (by age 75) 17 % risk [72]. This suggests that family members with known p16/CDKN2A gene mutation would benefit from regular skin examination for nevi and melanomas, which should be part of the clinical examination for these patients and their relatives.

17.4.3.8 Ataxia-Telangiectasia

Next-generation sequencing has recently made it possible to identify deleterious mutations in the ataxia telangiectasia mutated (ATM) gene that may play an important role in familial pancreatic cancer predisposition. The ATM protein is a serine/threonine kinase involved in DNA double strand break repair. The disease is caused by the inheritance of bi-allelic deleterious mutations in the ATM gene and has a reported carrier frequency of 0.5–1 % in the population. It is characterized by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctiva and skin, immunodeficiency, sensitivity to ionizing radiation and an increased rate of malignancies, in particular lymphoma and leukemia, but now has become evident that also increases the risk of pancreatic cancer [73].

17.4.3.9 Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a rare autosomal dominant cancer predisposition syndrome related to the development of a number of tumors of the soft tissue, ie sarcoma, osteosarcoma, as well as pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma, and leukemias. These often occur in childhood or young adulthood and survivors have an increased risk for multiple primary malignancies. It has also been associated with elevated risk for pancreatic cancer (RR 7.3, 95 % CI; 2–19, $p = 0.006$) [74]. Besides, CDKN2A is implicated in the TP53 pathway. Chompret criteria or Dutch recommendations do not incorporate pancreatic cancer for TP53 mutation testing.

17.4.3.10 ABO Blood Group

Blood group is determined by the presence or absence of glycoproteins (antigens) that are expressed on the surface of erythrocytes and several other cells, including pancreatic cancer cells and is a hereditary characteristic that has been linked with the risk of several gastrointestinal tumours, including pancreatic cancer. People with blood groups A, AB, or B were interestingly found to have a moderately increased risk of developing pancreatic cancer compared to those with group O (adjusted hazard ratios for incident pancreatic cancer 1.32 [95 % CI; 1.02–1.72], 1.51 [95 % CI; 1.02–2.23], and 1.72 [95 % CI; 1.25–2.38], respectively) [75]. Albeit, a causative mechanism has not yet been elucidated, a genome-wide association study managed to identify variants in the ABO blood group gene (locus on 9q34 marked by the SNP rs505922) linked to a per-allele odds ratio of 1.20 for pancreatic cancer (95 % CI; 1.12–1.28) [76].

17.5 Pathophysiology

A number of clinically and pathologically distinct neoplasms arise in the pancreas. These neoplasms can be broadly divided pathologically into those that are typically solid and those that are usually cystic. This categorization parallels the primary radiologic appearances of these neoplasms, and it helps narrow the clinical differential diagnosis. Specific pathologic diagnoses within each of these two broad categories have important implications for patient management and prognosis. The treatment recommendations in the “Treatment” section of this review are specific for invasive ductal adenocarcinoma (“pancreatic cancer”) and may not apply completely to some of the other tumor types that can arise in the pancreas.

17.5.1 Solid Tumors

17.5.1.1 Invasive Ductal Adenocarcinoma

The commonest solid tumor is the invasive pancreatic ductal adenocarcinoma (PDAC), more commonly called "pancreatic cancer. In this type of cancer the neoplastic cells form glands (adenomas) and infiltrates the pancreatic tissue. These cancers are usually firm and solid and a number of their neoplastic cells can be extended far beyond the main tumor. Almost all adenocarcinomas infiltrating the nerves and extend along the perineural spaces. Another significant characteristic of these cancers is that they have the tendency to invade the small veins and locoregional lymph nodes. Those characteristics result in easy metastasis to the regional lymphatic spaces and the liver. This is the reason why most of the invasive ductal adenocarcinomas have already spread beyond the pancreas by the time of diagnosis and are not suitable for surgical resection.

The invasive ductal adenocarcinoma of the pancreas is the trigger for an intense desmoplastic reaction. This desmoplastic reaction is composed of inflammatory and endothelial cells, fibroblasts and provokes a significant increase of the interstitial fluid pressure within the tumor [77, 78]. This elevated pressure of the interstitial fluid considered as a barrier to perfusion of the tumor and that can explain the low attenuation seen on contrast-enhanced imaging. The elevated pressure can also act as a barrier to the permeation of therapeutic agents [79, 80]. The desmoplastic reaction should be taken seriously into account by the oncologists when planning the treatment of adenocarcinoma, because even the best therapeutic agents are not effective if they do not reach the tumor cells.

17.5.1.2 Other Solid Pancreatic Tumors

Adenosquamous Carcinoma

Adenosquamous carcinoma is very aggressive type with poor prognosis. In spite of its aggressiveness and its poor prognosis, many patients with an adenosquamous carcinoma may still benefit from surgical resection of the tumor [81, 82]. Their main characteristic is that in addition to neoplastic cells, they tend to have a large component of squamous differentiation [81].

Colloid Carcinoma

Colloid carcinoma is also referred as gelatinous carcinoma. It is an infiltrating ductal epithelial tumor that produces mucin and is composed usually of cuboidal or columnar neoplastic cells. Their characteristic image is that of floating cells in mucin pools and this type of tumor have no ovarian type stroma [77]. They almost

always arise in association with intraductal papillary mucinous neoplasms (IPMNs), and they have a much better prognosis than invasive ductal adenocarcinomas [83]. The better prognosis of the colloid carcinomas is related to their tendency to present clinically at a lower stage than invasive ductal adenocarcinomas [84].

Medullary Carcinoma

Medullary carcinoma is composed of poorly differentiated cells, which are characterized by frequently extensive necrosis, pushing tumor borders, and lymphocytic inflammatory cell infiltrates. Under the microscope we can see pleomorphic nuclei with variable nucleoli. Some of the medullary carcinomas demonstrate microsatellite instability, and patients are more likely to have a history of cancer in their family or other syndromes associated with cancer, such as Lynch syndrome [85]. It carries a better prognosis than invasive ductal adenocarcinoma.

Signet Ring Carcinoma

This type of pancreatic cancer is extremely rare and usually aggressive, occurring in less than 1 % of pancreatic carcinomas. It entails individual neoplastic cells with a prominent mucin globule, giving a "signet ring" appearance to the cells [77]. Signet ring carcinomas except of pancreas can arise as well from breast or stomach, both of which can metastasize to the pancreas. For that reason the clinicians should be aware, because their metastasis can mimic a pancreatic primary.

Undifferentiated Carcinomas

Undifferentiated carcinomas and undifferentiated carcinomas with osteoclast-like giant cells are very aggressive carcinomas associated with a very poor prognosis for patients [77].

17.5.1.3 Pancreatic Neuroendocrine Tumors (PanNET)

NETs are the second most common type of solid neoplasms of the pancreas but they are less aggressive than invasive ductal adenocarcinomas. Their 10-year survival rate is 45 % [77]. These neoplasms are clinically important since some may be associated with genetic predisposition syndromes such as von Hippel Lindau (VHL) and the Multiple Endocrine Neoplasia 1 (MEN1). Another reason of their clinical importance is that some PanNETs produce endocrine hormones. Those hormones circulating into the bloodstream provoke some clinical syndromes such as glucagonomas and insulinomas. Usually these are referred as functional PanNETs. The PanNETs are often well demarcated, soft, and solid neoplasms. The neoplastic cells

of NETs are rich in vascularization and microscopically form trabeculae or nests. This rich vascularity explains the tendency of Pancreatic NETs to enhance with contrast.

The prognosis and management of functional NETs depends on the clinical syndrome produced, the topography of the tumor and if the NET has spread to lymph nodes near the pancreas or to other parts of the body such as the liver, lung, peritoneum, or bone. The most important prognostic factors for NETs are tumor stage and grade. The stage of PanNET is determined by the size and the metastatic potential and the grade by the proliferation rate of the tumor cells [86].

17.5.1.4 Pancreatoblastoma

Pancreatoblastoma is a rare form of pancreatic cancer. They are typically large, solid and soft tumors and usually occur in childhood ranging from 2 to 20 cm carrying a relatively good prognosis [77].

17.5.1.5 Acinar Carcinoma of the Pancreas

It is a rare usually solid malignant exocrine tumor and is associated with increased serum lipase. Typically arise in the head of the pancreas and unfortunately is associated with poor prognosis [77].

17.5.2 Cystic Tumors

The second broad category of pancreatic tumors is the cystic neoplasms. During the last years and with the extensive use of the Computer Tomography scan more and more patients have been diagnosed with cystic lesions in pancreas [87]. Many of those cysts are neoplastic and some of them will progress to invasive carcinomas if they will be left without treatment. For that reason, cystic neoplasms of the pancreas are giving us the opportunity to treat pancreatic neoplasia before an invasive cancer develops.

There are four main types of pancreatic cystic neoplasms:

1. Intraductal Papillary Mucinous Neoplasms (IPMNs)
2. Mucinous Cystic Neoplasms (MCNs)
3. Solid Pseudopapillary Neoplasms (SPNs).
4. Serous Cystic Neoplasms (SCNs)

17.5.2.1 Intraductal Papillary Mucinous Neoplasms

This type of cystic neoplasm grows within the larger pancreatic ducts and the tumor cells produce a thick fluid. If they are left untreated they can progress from low grade dysplasia to high grade dysplasia and to invasive cancer. The patients should be followed up carefully, especially those who have had an IPMN resected in the past, because of their high risk for developing an invasive tumour [88].

17.5.2.2 Mucinous Cystic Neoplasms MCNs

This type of neoplasm arises in the tail of pancreas and occurs almost exclusively in women. Mucinous Cystic Neoplasms are composed of columnar mucin producing epithelium supported by ovarian type stroma and they do not arise in the pancreatic duct system. This ovarian type stroma connective tissue resembles the tissue normally found in the ovary. They are measuring between 6 and 10 cm. MCNs are composed from a large number of small cysts filled with thick mucin and this formation gives them their characteristic appearance. They can progress from low grade dysplasia to high grade and to invasive tumor such as the IPMNs. They should certainly be followed up carefully.

17.5.2.3 Solid Pseudopapillary Neoplasms

Solid Pseudopapillary Neoplasms are low grade malignant neoplasms typically round, measuring around 2–15 cm. The neoplastic cells of the lesion usually have uniform nuclei. Necrosis can occur in neoplasm and as cell death usually occurs distant from blood vessels a pseudopapillae can be formed. SPNs typically affects young women [89].

17.5.2.4 Serous Cystic Neoplasms

Serous Cystic Neoplasms are almost always entirely benign and they grow at slow pace. Should they grow large enough they can compress the nearby organs and then cause symptoms. SCNs may be associated with von Hippel-Lindau Syndrome and usually are found in the tail of the pancreas. They are formed from glycogen rich cuboidal cells which compose straw coloured fluid cysts. We can follow them up with safety and they should be resected only if they are large or if they cause symptoms [90].

17.5.3 Genes Associated with Pancreatic Neoplasias

Apart from BRCA there are four more cardinal genes associated with pancreatic cancer.

17.5.3.1 K-RAS Mutation

K-RAS is an oncogene on chromosome 12 that codes a protein called GTPase. This protein plays an important role in differentiation, proliferation and survival of cell through the mitogen-activated protein kinase (MAPK) pathway. *K-Ras* mutation can be observed in up to 95 % of invasive ductal adenocarcinomas [91, 92]. *K-Ras* point mutation can be detected early on in codons 12, 13 and 61, since it is one the first genetic events that can be occur in PDAC. Those codons can be easily identified and this is the reason why *K-Ras* could be one the basic gene- tests for early diagnosis of pancreatic neoplasia, when early detection can deem the disease still curable [93].

17.5.3.2 The p16/CDKN2A Gene

The *p16/CDKN2A* gene is associated with family history of pancreatic cancer. *CDKN2A* is a tumor suppressor gene located on chromosome 9p and is not active in 95 % of pancreatic neoplasms. This gene produces the protein p16 whose role is very important in cell cycle regulation, because p16 delays the progression of cells from G1 phase to S.

In pancreatic neoplasia the *CDKN2A* gene is losing his ability to produce p16 and as a result we can notice continuous unrestricted cell growth and proliferation of malignant cells [91].

17.5.3.3 Tumor Protein 53

TP53 is another important tumor suppressor gene associated with pancreatic cancer. Is located in chromosome 17p and drives the production of protein 53 (p53). This protein can be found in the nucleus of the cells and regulates their division by direct binding with DNA. The significant role of p53 lies into that after cell exposure on radiation, ultraviolet rays or toxic materials defines if the damaged DNA should be repaired or the cell will self-destruct (apoptosis). *TP53* is not activated in 75 % of pancreatic cancers and this decrease of activity can be observed early during the development of pancreatic tumor [91].

17.5.3.4 SMAD4 Tumor Suppressor Gene

The last major gene that can be identified in pancreatic cancer is the *SMAD4*. This gene was known previously as DPC4 and is located on chromosome 18q [94]. *SMAD4* mutation can be observed in approximately 55 % of pancreatic neoplasms and plays a significant role in the function of TGF-B proteins (transforming growth factor beta). TGF-B proteins can regulate the differentiation, motility and proliferation of the cell. They can also promote angiogenesis and inhibit immune function of the cells. *SMAD4* gene mutation that is associated with poor prognosis in pancreatic neoplasms [95, 96].

17.6 Signs and Symptoms

Establishing a diagnosis of pancreatic cancer can be a complex process, posing a significant challenge to the clinician. Symptoms usually do not appear in the early stages, as the disease can remain silent until it spreads invading surrounding tissues or giving distant metastasis, or occasionally, signs and symptoms can be misinterpreted as presentation of other clinical conditions. Due to the diagnostic difficulties, pancreatic cancer recognition is usually achieved at advanced stages, which in combination with the aggressive clinical course of the disease, determine its poor prognosis. Delay in the diagnosis of pancreatic cancer by GPs or specialists, finally results in about 50 % of pancreatic cancer patients presenting as emergency cases, while only 11 % of patients are diagnosed through the 2-week referral system [97]. Symptoms and clinical features, if present, depend on the size and location of the tumour, as well as the presence of metastasis. More than one half of cases have distant metastases at the time of diagnosis. Additionally, initial signs and symptoms can be associated with resectability and prognosis of pancreatic cancer [98]. Lesions in the head of pancreas are often curable, as they can cause obstructive jaundice when they are still located inside the pancreatic gland, while patients with tumours in the body or tail generally present either with weight loss or vague pain, or even with symptoms associated to metastasis.

Painless and steadily increasing obstructive jaundice, due to biliary duct obstruction, is mainly associated with surgically resectable tumours in the head of pancreas, with more than two thirds of pancreatic cancers counting for this subcategory. The situation leads to increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The urine is dark because of its high levels of conjugated bilirubin, while lack of stercobilinogen in the bowel results in pale-coloured faeces. Patients can experience pruritus, nausea, anorexia, and bruising caused by vitamin K malabsorption and reduced production of clotting factors. Body and tail tumors are much less likely to cause obstructive jaundice. Epigastric pain that radiates to the back may be present. Tumours in the body and tail usually do not cause symptoms until they present as locally advanced disease, extending to the peritoneum and spleen, or causing duodenal obstruction. Other symptoms include onset of diabetes, acute pancreatitis, steatorrhea and depression.

Physical examination findings may be normal. An enlarged, palpable gallbladder and the presence of painless jaundice (*Courvoisier's sign*) is up to 90 % specific, but only 55 % sensitive for malignant obstruction of the bile duct. Hepatomegaly is a common finding in advanced disease, while patients may present with ascites, palmar erythema, and spider angioma. Other findings associated with advanced or metastatic pancreatic cancer include left supraclavicular lymphadenopathy (*Virchow's node*) and recurring superficial thrombophlebitis (*Trousseau's sign*) [99].

17.7 Diagnosis

17.7.1 Imaging Modalities

17.7.1.1 Ultrasound

Abdominal ultrasound (U/S) is an inexpensive, widely available imaging modality, mainly useful at the beginning of the diagnostic approach. Additionally, it is not invasive and lacks any kind of complications. U/S is the first examination in a patient with jaundice or abdominal pain, usually determining the aetiology of biliary dilatation, and either excluding or raising the suspicion for benign and malignant obstructions. The accuracy of conventional U/S for diagnosing pancreatic tumors is only 50–70 %, percentage that is seriously affected by the operator's experience. Body and tail tumours are even more difficult to detect, due to the absence of biliary dilatation and the presence of bowel gas [100–102]. If the existence of a pancreatic mass cannot be excluded, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should be used for further evaluation, as discussed below.

17.7.1.2 Computed Tomography (CT): Conventional and Multidetector CT (MDCT)

Recent advances in technology have improved the accuracy of CT, with a reported sensitivity between 76 % and 92 % for diagnosing pancreatic cancer [103]. Due to the hypovascularity of pancreatic tumours, contrast agents should be always used, unless contraindicated. Multidetector CT (MDCT) provides higher image resolution than conventional CT. This technique allows better visualization of the pancreatic adenocarcinoma in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein [104, 105]. Indirect signs, such as atrophic distal parenchyma, and abrupt cut off of the pancreatic duct dilatation (*interrupted duct sign*) are suggestive of pancreatic cancer. Extrahepatic biliary dilatation and pancreatic duct dilatation (*double duct sign*) may also be helpful [106]. The reported sensitivity, specificity and positive predictive value of the method, for predicting the resectability of pancreatic cancer, were 100, 72 and 89 %, respectively [107].

MDCT with intravenous contrast is generally considered as the imaging procedure of choice for initial evaluation of patients suspected to have pancreatic cancer [108]. Main disadvantage of CT/MDCT remains the limited ability to detect isoattenuating tumours or small metastases to the liver or peritoneum [104, 106]. Even though pancreatic protocol CT is widely regarded to be superior to non-pancreatic protocol contrast MDCT for determining resectability, there is currently insufficient direct evidence to support this [109].

17.7.1.3 Magnetic Resonance Imaging (MRI)

MRI is a useful tool in imaging for pancreatic cancer, when a definite diagnosis cannot be established with ultrasound or MDCT. Due to their hypovascularity, pancreatic tumours are hypo intense on T1-weighted images in the venous phase, while they appear isointense on delayed images because of slow wash-in of contrast medium, usually gadolinium. MRI is superior to MDCT in detecting cystic lesions, isoattenuating or smaller tumours, and has better sensitivity in the presence of pancreatic fatty infiltration [110]. However, no statistically significant difference between the sensitivity of these two methods has been shown, overall (86 % for CT vs. 84 % for MRI), while their combination does not offer any additional diagnostic advantage. MRI is a radiation free, but expensive imaging method. Thus, the choice of MRI or CT usually depends upon local experience and availability [111].

17.7.1.4 Magnetic Resonance Cholangiopancreatography (MRCP)

A 3-D image of the pancreaticobiliary tree can be obtained with magnetic resonance cholangiopancreatography (MRCP), which is based on magnetic resonance technology. MRCP is very useful for detecting ductal narrowing, suggestive for the presence of a pancreatic tumour, or ruling out the existence of stones as a cause of biliary or pancreatic duct dilatation, while it can often contribute to the differential between chronic pancreatitis and pancreatic adenocarcinoma [112, 113]. It is as sensitive as Endoscopic Retrograde Cholangiopancreatography (ERCP) in the detection of pancreatic cancer, but lacks of complications, unlike ERCP [114].

17.7.1.5 Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is considered as a diagnostic, as well as therapeutic modality in patients with pancreatic cancer. Besides imaging, ERCP is helpful in the establishment of pancreatic cancer diagnosis using brush cytology and tissue biopsy samples. Although brush cytology has a limited sensitivity of 35–70 % for the diagnosis of pancreatic cancer, the triple sampling combination of brush cytology, FNA and forceps biopsy of a stricture diagnosed during ERCP, improves the overall sensitivity to 77 % [115]. The placement of a biliary stent with ERCP provides palliation of jaundice, and offers a less interventional alternative choice to surgery, especially in cases of

unresectable cancers. In these circumstances, patients will benefit from chemotherapy with/without radiation. ERCP is also helpful preoperatively in resectable cancers. ERCP has a limited role in the staging of pancreatic cancer. Among the complications of this method, acute pancreatitis, gastrointestinal bleeding and perforation are the most common. ERCP plus EUS have been associated with a high diagnostic value for the detection of pancreatic neoplasms compared to ERCP or EUS alone [116].

17.7.1.6 Positron Emission Tomography (PET)

Positron emission tomography (PET) scanning is a molecular imaging modality, using tissue accumulation of the radiotracer 18-fluorodeoxyglucose (FDG), a glucose analogue, as indicator of the metabolic activity of a lesion. Consequently, cancer can be distinguished from a benign lesion, or even inflammation, due to the higher accumulation of FDG. Sensitivity and specificity of this method range between 46–71 % and 63–100 %, respectively [117]. There are controversial studies regarding the superiority of PET scan compared to CT in identifying metastatic disease [118, 119]. However, PET scan is more sensitive for patients follow-up after chemoradiotherapy, as well as for estimation of disease recurrence [120–122]. PET/CT, offering a better image resolution than PET scan, has a higher reported sensitivity and specificity compared to conventional imaging for tumour staging and detection of metastases (89 % and 100 %, respectively), while the positive and negative predictive values of the method for pancreatic cancer were 91 % and 64 %, respectively [123].

17.7.1.7 Endoscopic Ultrasound (EUS)

Endoscopic Ultrasound (EUS) is the method used for establishing diagnosis when the other conventional methods have failed, or their findings are only suggestive for pancreatic cancer or non-specific. EUS also offers the ability to obtain specimens for histopathological diagnosis using EUS-guided fine needle aspiration (EUS-FNA). The specimens are subjected to cytologic examination and special immunostaining can be used for suspected neuroendocrine tumors [124]. The reported sensitivity of EUS-FNA for diagnosing pancreatic cancer ranges from 80 % to 95 % in various studies [125–127]. EUS-FNA was shown to be superior to ERCP for tissue sampling due to its higher success rates and less procedure-related complications [128]. The presence of obstructive jaundice and that of underlying chronic pancreatitis seem to reduce the accuracy of EUS-FNA for diagnosing pancreatic cancer. Especially in patients with both characteristics, the diagnostic accuracy of EUS-FNA is significantly lower [129]. EUS has a remarkable role in staging and is considered as an accurate pre-operative tool in the assessment of resectability in patients with pancreatic cancer. EUS also plays a role in identification and biopsy of locoregional metastatic lymph nodes [130, 131]. However, EUS has a limited

accuracy for diagnosis of venous involvement by pancreatic cancer [132]. It was also shown that the presence of a biliary stent reduced the T-stage accuracy of EUS to 72 % [133]. EUS elastography, which is considered as a recent and promising advance in GI endoscopy, is a non-invasive technique that measures tissue elasticity in real time [134]. EUS shares the same complications of other endoscopic procedures.

In conclusion, MDCT is the initial imaging method of choice in patients with clinical suspicion for pancreatic cancer. MRI stands as an alternative method when definite diagnosis is not achieved with MDCT. MRCP can be helpful in clarifying the nature of a biliary stricture, while ERCP also offers the ability to apply interventional techniques. EUS can set with the highest accuracy a definite diagnosis, apart from being a very useful tool for staging and determination of resectability. PET/CT, if available, can provide additional information regarding resectability, by ruling out metastatic disease. Finally, diagnostic laparoscopy may decrease the rate of unnecessary laparotomy in patients with pancreatic cancer found to have resectable disease on conventional imaging [135] (Fig. 17.1).

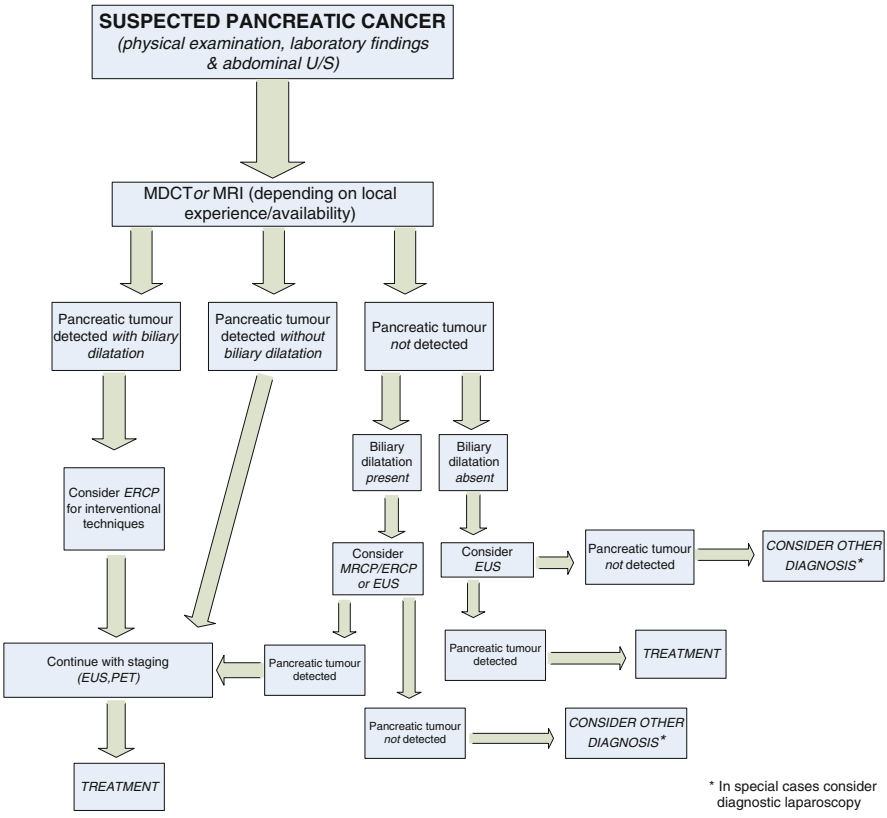

Fig. 17.1 Proposed diagnostic algorithm for pancreatic cancer

17.7.2 Serological Diagnosis

The current broadly used serological marker for the diagnosis of pancreatic cancer in clinical practice is carbohydrate antigen 19.9 (CA19-9), which is a sialylated Lewis A-active pentasaccharide detected on the surface of mucins in pancreatic cancer patients serum. Although elevated CA19-9 levels have been associated with the presence of pancreatic or biliary cancer, there are many benign situations in which this marker is increased [136]. CA19-9 is not a suitable marker to be used in screening of asymptomatic subjects for pancreatic cancer, due to its relatively poor sensitivity and specificity. CA19-9 is considered a helpful tool in differential diagnosis of pancreatic cancer from chronic pancreatitis with high sensitivity and specificity [137, 138]. As early recurrence can be expected in patients with high preoperative levels of CA19-9, measurement of CA19-9 has a significant prognostic value before the therapeutic decision of resection, while persistent elevated marker levels after resection are indicative of remnant disease [139–141]. CA 19-9 may serve as an in vivo marker for chemoradiotherapy sensitivity [142]. Additionally, CA19-9 values can be useful in distinguishing benign from malignant intraductal papillary mucinous tumors [143]. The diagnostic value of CA19-9 is limited in obstructive jaundice [144]. Overall, CA19-9 is not an adequate marker for the diagnosis of patients with pancreatic cancer, and according to the American Society of Clinical Oncology Tumor Markers Expert Panel, CA19.9 is recommended only for monitoring response to treatment [145, 146].

Although other promising markers have been reported for pancreatic cancer diagnosis, none of them has entered clinical use. This is mainly due to low sensitivity or specificity of these markers. The specific pathophysiology and micro-architecture of pancreatic cancer, which is poorly vascularized, might prevent certain molecules from passing into the circulation. Additionally, combining existent tumor markers with new ones, did not provide applicable panels [147]. Markers that have been investigated in diagnosis of pancreatic cancer include the carbohydrates CA 50, CA 125, CA 195, and CA 72-4. Other proteins, like MIC-1, PAM4, OPN, HSP27, TPS, TSGF, CAM17.1, PF4, and CEACAM1 have been studied with encouraging results, although not showing superiority to CA19-9. Consequently, despite testing many markers or their combinations, none of them has been implemented for clinical routine use besides CA 19-9 [148]. As curative resection is only possible in early stages of pancreatic cancer, an urgent need for novel serum markers for pancreatic cancer screening still remains.

17.8 Treatment Options

Pancreatic cancer is a complex disease with a wide diversity of patient population. Optimal multidisciplinary treatment approach much depends on a careful and accurate initial staging. Patients with limited disease extent (mainly Stage I/II disease)

will be serious candidates to undergo surgical resection followed by adjuvant therapy or neoadjuvant therapy, albeit the latter still remains controversial. However, it might be the treatment of choice for the Stage III borderline resectable cancers prior to resection. Patients with Stage III locally advanced disease may be treated with chemotherapy and/or chemoradiotherapy, although, carefully selected patients can still be considered for surgical resection. Yet, the vast majority of these patients will develop metastatic disease. Patients with Stage IV disease and good performance status (PS) may proceed to systemic therapy, while those with poor PS shall be given best supportive care (BSC).

17.8.1 Localised Disease-Surgical Perspective

Although patients with localized PDAC disease will most benefit from a complete resection of the primary lesion, a number of different factors can affect the decision of surgery when selecting patients. The systemic nature of PDAC at diagnosis, the relatively low chance of long-term survival and the impact of pancreatectomy on quality of life are factors that need to be carefully assessed. Since the majority of these patients have locally invasive and/or micrometastatic disease at the time of operation, they run a high risk of both local and systemic recurrence following an operation with a potentially curative intent and a significant morbidity in 40–65 % of patients and mortality up to 5 % [149, 150]. Furthermore, despite improvements in surgical techniques over the last decades and perioperative patient care, pancreatic surgery is still associated with substantial perioperative morbidity and in-hospital mortality as well as significant impact on complete recovery to a normal quality of life, which can take up to 2–3 months even in the absence of any complication.

This is also important to consider for the formulation of a management plan and the implementation of neoadjuvant therapy through patient evaluation by a multidisciplinary team. Several factors, including stage, overall performance status, tumor biology, influence the final decision and significant comorbidities and age (>70 years) can determine the ability of a patient to tolerate a major operation or a neoadjuvant approach [151]. Extensive metastatic disease at the time of diagnosis, locally infiltrative and rapidly progressing tumors indicate aggressive biology and in general, patients even with an early-stage but aggressive tumor biology are unlikely to benefit from local therapy such as surgical resection. Although, there is still no validated marker to characterize this aggressive biology, low serum CA19-9 levels and wild-type *SMAD4* gene status can identify patients with a more favorable tumor profile.

The appropriate operation required for a given patient is mainly determined by the location of the tumor. Pancreaticoduodenectomy (Whipple operation) is the surgery of choice for lesions arising in the head of the pancreas, while a distal pancreatectomy with an en bloc splenectomy may be required for tumors in the tail. However, masses of the neck and body may require a pancreaticoduodenectomy, distal pancreatectomy or, rarely, a total pancreatectomy. Other partial resections,

like central pancreatectomy or enucleation techniques do not result in an sufficient lymphadenectomy and are not considered to have a potentially intent. Minimally invasive approaches offer, at least in theory, the merits of less scarring, less postoperative pain, less wound complications, and an earlier return to normal activity and despite the complexity of most pancreatectomies have recently been gaining ground, albeit their role in the management of patients with pancreatic cancer is not yet clear [152]. Pancreaticoduodenectomy morbidity rate has discouragingly remained between in the range of 45 %, even at high volume centers, where results show significantly better outcomes. The common postoperative morbid complications include delayed gastric emptying (15 %), wound infection (8 %), pancreatic fistula (5 %), cardiac events (4 %), abdominal abscess (4 %), bile leakage (4 %), haemorrhage (4 %), sepsis (2 %) and all other complications in less than 2 % of patients. The median survival rate still lingers in less than 2 years (18 months) with a 5-year survival of around 20 %. Negatively affecting factors include positive resection margin, histological grade and tumor size of 3 cm or greater (HR 1.6, $p<0.001$) and regional lymphadenopathy (HR 1.3, $p=0.05$) [153]. However, emerging non-operative biliary decompression and endoscopic therapies such as stents and non-invasive celiac plexus blocks have facilitated the drastic reduction of elective surgical palliation.

17.8.2 Neoadjuvant Therapy

Neoadjuvant therapy remains controversial in pancreatic cancer treatment, although theoretically it presents many advantages, especially in borderline resectable tumors. Among the advantages, it is considered that preoperative chemotherapy allows an early treatment of micrometastatic disease and may also induce tumour regression, reducing the risk of R_1 resection or relapse after surgery. Other potential advantages include a reduced risk of peritoneal tumour implantation during surgery, and the chance of an in vivo assessment of tumour chemosensitivity. Finally, neoadjuvant treatment allows a better patient selection identifying those patients for whom surgery is unlikely to provide any benefit [12]. However, several studies have shown that resection after neoadjuvant chemoradiation (CRT) is associated with increased postoperative stay. It is finally important to note that in order to initiate neoadjuvant therapy, histological confirmation of pancreatic adenocarcinoma is required, unlike surgical resection [154].

Several studies have evaluated the role of neoadjuvant chemotherapy, radiotherapy, or combination of both in resectable pancreatic cancer. A phase II randomized trial studying patients with resectable PDAC receiving gemcitabine alone or a combination of gemcitabine with cisplatin, showed that the response rate and overall survival (OS) were better in combination arm [155]. Neoadjuvant CRT with gemcitabine concomitant to RT was studied on patients with localized pancreatic cancer. Median OS for the whole patients population was 22.7 months while patients who underwent surgery had a median OS of 34 months [156]. A phase II trial evaluated

the combination of cisplatin and gemcitabine followed by gemcitabine-based CRT in patients with resectable PDAC. The median OS of all patients from the date of diagnosis was 17.4 months while patients who completed CRT and underwent surgery had a median OS of 31 months [157]. Also paclitaxel in combination with radiotherapy has been tested in patients with resectable PDAC, with moderate results [158]. Overall, patients who completed neoadjuvant CRT and underwent surgery had a higher chance of achieving R_0 resection and a higher overall survival when compared to patients from historical data that underwent surgery without receiving therapy. Nevertheless, CRT may not effectively decrease distant metastasis, as shown by the high rate of distant failure in these studies. Consequently, the role of neoadjuvant therapy in patients with resectable pancreatic cancer has not yet been clearly defined. Prospective controlled randomized trials are needed so as to estimate the benefit of neoadjuvant strategies compared to conventional adjuvant strategies. Presently, the use of neoadjuvant therapies should be considered in the context of a multidisciplinary approach, in order to identify patients at high risk for recurrence.

Borderline resectable pancreatic cancers (BRPC) have been recently defined as cancers with limited involvement of the mesenteric vessels. In this setting, resection may be technically possible, but carries a higher risk of R_1 resection and early recurrence. Chemoradiotherapy is a common approach in such cases and seems to improve the percentage of patients undergoing radical resection. In a study, 7 out of 18 of BRPC patients who received gemcitabine-based chemoradiotherapy were finally resected. Chemoradiotherapy did not increase perioperative morbidity and mortality [159]. In another study, patients were treated with gemcitabine, docetaxel, and capecitabine followed by 5-FU based chemoradiotherapy with IMRT. Eleven patients (64.7 %) out of 17 underwent resection and eight patients (47 %) achieved an R_0 resection. The median progression-free survival and OS were 10.48 months and 15.64 months, respectively [160]. Forty borderline resectable pancreatic cancer patients were treated with combined capecitabine-based chemoradiation. A total of 16 patients (46 %) proceeded to surgery, with 88 % having an R_0 resection and median overall survival of 23 months [161]. A chemoradiotherapy regimen including gemcitabine and oxaliplatin on 68 BRPC and locally advanced pancreatic cancer (LAPC) patients was studied, and R_0 resection was achieved in 36 of 43 patients that underwent surgery. The median overall survival was 18.2 months for all patients and 27.1 months for those who underwent resection [162]. The benefit of neoadjuvant therapies in BRPC was retrospectively reviewed between 1999 and 2006. Patients received neoadjuvant chemotherapy followed by radiation in combination with either 5-fluorouracil (5-FU), gemcitabine, capecitabine, or paclitaxel. Patients who completed the whole therapy including surgery had a significantly better clinical outcome (median OS of 40 months), compared to a median survival of 13 months in unresected patients. These results confirm a positive effect of neoadjuvant treatment in this setting, however, the high rates of disease relapse claim for more effective future treatments [163].

In LAPC patients, neoadjuvant gemcitabine-based combinations have proved to induce higher response rates compared to single agent gemcitabine [164]. A phase

II trial, evaluated gemcitabine and oxaliplatin combination in LAPC patients, and after treatment, 39 % of patients underwent curative resection, with a 69 % of R_0 resections. Median OS of patients who underwent tumor resection was 22 months compared with 12 months for those without resection [165]. In another study, patients received either cisplatin, epirubicin, 5-fluorouracil/capecitabine, and gemcitabine or the same regimen with docetaxel substituting epirubicin for 6 months, followed by radiotherapy. A high response rate was observed (47 %) while stable disease was reported in 42 % of patients [166]. A recent systematic review evaluating 111 trials that included 4,394 pancreatic cancer patients, suggested that neoadjuvant treatment may be able to induce conversion to resectability in about one-third of LAPC patients [167]. In patients with borderline resectable or nonresectable pancreatic cancer, neoadjuvant therapy may achieve down-sizing of the tumour, increasing the probability of R_0 resections. Current data is not sufficient to define an optimal regimen in this setting. Combination chemotherapy appears to achieve higher response rates, while there is no strong evidence to support that chemoradiotherapy is superior to chemotherapy alone. More effective chemotherapeutic regimens, like FOLFIRINOX and nab-paclitaxel, are now tested, but the efficacy of these treatments remains to be determined in prospective clinical trials.

17.8.3 Adjuvant Treatment

17.8.3.1 Practice Establishing Studies

Despite the intensity of the approaches with curative intent, PDAC demonstrates very high rates of both locoregional, most commonly the superior mesenteric artery margin, and distal recurrence necessitating postoperative therapy in the effort to reduce this risk. Patients typically need a period of 6–8 weeks to recover or might take even longer, much depending on the occurrence of adverse events. The optimal adjuvant treatment for PDAC patients remains elusive and there is still no worldwide consensus on which regimen is more effective than others, however, 6 months of a 5-FU–based or gemcitabine-based chemotherapy is an appropriate standard option. Application of 5-FU- or gemcitabine-based chemoradiation (CRT) (45 Gy directed to the tumor bed, surgical anastomoses and peripancreatic nodes with an additional 5–15 Gy boost to the tumor bed) during the postoperative period could be considered an option for R1 resections and patients whose risk of locoregional recurrence is higher. Moreover, the optimal time and sequence of AT is still debatable, yet, since the vast majority of patients will relapse with synchronous distant metastases, systemic treatment gains a priority followed by CRT, should the patient remain disease free after completion of chemotherapy [3].

In spite of the recent advances in the metastatic setting (discussed later in the metastatic disease), adjuvant treatment has lagged behind and despite that a variety of different agents and their combinations have been tested 5-FU or gemcitabine-based scheme remains the golden standard. Historical trials established the role of

adjuvant therapy, however, have not managed to definitely address issues like optimal sequence, modality and regimen [168–170]. Next generation studies have evaluated the benefit of adjuvant systemic chemotherapy. The CONKO-001 multicenter randomized phase III trial from the group at Charite Onkologie Group in Germany randomized 368 patients to either adjuvant intravenous gemcitabine for a total of 6 cycles or observation, achieving nearly a doubling of median disease-free survival (DFS) (13.4 vs 6.9 months, respectively; $p<0.001$), and improved median OS (22.8 vs 20.2 months, $p=0.005$) thus establishing its pivotal role in the management of patients in this setting [171]. Another study recently with a very similar design randomized 119 Japanese patients to receive either adjuvant gemcitabine or resection only with comparable results to the CONKO-OO1 trial [172]. However, despite the fact that median DFS was significantly improved (median DFS, 11.4 vs 5.0 months; HR = 0.60 (95 % CI: 0.40–0.89); $p=0.01$), with an acceptable toxicity profile, the trial failed to show an OS improvement (median overall survival, 22.3 vs 18.4 months; HR = 0.77 (95 % CI: 0.51–1.14); $p=0.19$). Differences in the sample size, the number of cycles of chemotherapy, weeks from operation to randomization and inclusion criteria regarding tumor markers applied.

The European Study Group for Pancreatic Cancer (ESPAC) investigators similarly conducted a study comparing GEM vs 5-FU (ESPAC-3v2) [173]. This was originally designed as a three-arm study, in which patients were randomized to receive a 6-month course of 5FU/LCV (leucovorin), the same duration of GEM or observation alone. However, as data emerged from other adjuvant trials regarding the benefits of adjuvant chemotherapy for PDAC, the observation alone arm was dropped. Still, ESPAC-3 represents the largest trial of its kind with a total of 1,088 patients randomized between the two treatment arms of bolus 5-FU daily with leucovorin for 5 days every 4 weeks or GEM weekly for 3 weeks every 4 weeks for 6 cycles in total. The OS was 23.0 months in the 5-FU group and 23.6 months in the gemcitabine group, with higher rates of stomatitis and diarrhea in the 5-FU group and higher rates of hematologic toxicity in the gemcitabine group, but without any difference in quality of life. Taken together, the CONKO and ESPAC trials established both 5-FU and GEM as effective options for adjuvant chemotherapy. Yet, the median OS for patients with resected pancreatic cancer dishearteningly remains approximately 20–22 months.

The role of adding radiation therapy in the adjuvant setting is still controversial and debatable between the coasts of the Atlantic. The Gastrointestinal Tumor Study Group (GITSG) trial in the 1980s was the first trial to show a survival benefit for adjuvant chemoradiation [168]. In this trial, patients with resected pancreatic cancer were randomized to either observation or to chemoradiation. Chemoradiation included a 40-Gy split course of radiation with a 2-week break after 20 Gy, given with concurrent bolus 5-FU (500 mg/m^2 on days 1–3 of each 20-Gy course of RT), followed by additional weekly 5-FU for 2 years or until progression. The median OS was 21 months in the treatment arm compared to 11 months in the observation arm (adjusted $p=0.03$) and actuarial 2-year survival rates (43 % vs 18 %). Criticism however arose for the relatively low RT dose, the small number of patients, and the fact that 25 % of the patients on the treatment arm did not begin postoperative treat-

ment for more than 10 weeks following resection, mostly secondary to poor or delayed postoperative recovery. Following closure of the study, an additional 30 patients were registered on the combined modality arm and a subsequent report that included these and the original 43 confirmed the initial survival benefit. The European Organization for Research and Treatment of Cancer (EORTC) trial randomized patients to observation or to chemoradiation with 40-Gy split course given identically to the GITSG trial, with continuous infusion 5-FU (25 mg/kg/day) during the first course of radiation therapy, and for 0, 3, or 5 days of the second course (depending on toxicities) [169]. Although the OS was 12.6 months in the observation arm compared to 17.1 months in the treatment arm, this difference was not statistically significant neither was the 5-year survival (22 % vs 28 % for control and treated patients, respectively, $p=0.208$). However unlike the GITSG trial patients did not receive maintenance chemotherapy.

A third large multicenter trial (ESPAC-1; $n=289$) examined the role of both CHT and CRT in this setting [170]. The study used a 2-by-2 factorial design whereby patients were randomly assigned after surgery to 1 of 4 options: CHT alone, CRT alone, CRT followed by CHT or neither. It is worthwhile mentioning that ESPAC-1 used the GITSG RT regimen (AP/PA split course 20/10 + 20/10, although up to 60 Gy could be given, physician judging the final treatment dose), as did also the researchers in the EORTC trial. The four arms were ultimately combined in two comparison groups: CHT vs no CHT and CRT vs no CRT. With approximately 71 patients in each arm, patients who received CHT (5FU/LCV) had a significantly improved median OS over no treatment arm (20.1 vs 15.5 months, respectively; $p=0.009$). Surprisingly enough, patients on the CRT arm had a trend towards worse outcome (median OS: 15.9 vs 17.9 months, respectively; $p=0.05$). Interestingly, CRT did not reduce the risk of local relapse in this study. Investigators of the ESPAC-1 trial concluded that although CHT should be embraced as the standard of care following PDAC resection, CRT should not routinely be used, due to its deleterious effect. Of note, this study was heavily criticized because of a great deal of nonadherence within the trial, the suboptimal delivery and dosing of RT that potentially negated any survival benefit conferred by CRT with longer time-to-treatment in the CRT group and inclusion of R1 patients.

A separate study (RTOG 9704) conducted in the United States by the Radiation Therapy Oncology Group (RTOG) compared GEM with bolus 5-FU in the postoperative setting, in an effort to improve on chemoradiation therapy; patients on both arms received CRT (5040 cGy with concurrent continuous 5-FU infusion) between their first and second cycles of prescribed CHT [174]. Notably, for tumors located in the pancreatic head (388 out of 451 patients), those in the GEM group had a non statistically significant benefit in median OS that became more pronounced on multivariate analysis ($p=0.05$), with 3-year survival rates of 31 % vs 22 % in the 5FU group. Despite an initial trend to survival benefit for GEM, there has been no difference noticed in OS between GEM and 5FU at closure, whereas it has demonstrated a significantly more toxic profile (Grade 4 hematologic; 5-FU 1 % vs GEM 14 %). It has to be noted that despite criticism regarding difficulties in data interpretation due to surgical and pathology issues resulting from the lack of standardization,

RTOG has established the importance of CA 19-9 in the management of PDAC patients, demonstrated improved local failure compared to earlier studies (25 % for the gemcitabine arm and 30 % for the 5-FU arm) and implied that higher radiation doses might be more effective in preventing local recurrence. The primary mode of failure, however, remained distant metastasis, occurring in >70 % of patients, which highlights the need for better systemic therapies.

The limited systemic therapy options in the adjuvant setting have been expanded by a breakthrough phase III randomized trial with GEM versus S-1 for patients with resectable disease (The Japanese Adjuvant Study Group of Pancreatic Cancer; JASPAC-01 study) after the safety and efficacy committee recommended early reporting of the results [175]. The study enrolled 385 Japanese patients with stage II and III disease over a period of 3 years and achieved its primary endpoint to prove S- 1 non-inferior to GEM ($p < 0.0001$ for non-inferiority, $p < 0.0001$ for superiority). The 2-year survival rates were 70 % vs 53 % for S-1 and GEM, respectively, with lower relapse rates in the S-1 arm. The 2-year relapse free survival rates were 49 % vs 29 % for S-1 and GEM, respectively and S-1 proved to be well-tolerated, with over 70 % of patients completing the therapy and significantly fewer deaths. The S-1 emerges as a potential alternative to standard GEM-based adjuvant CHT with the limitation of S-1's broad application in the West, secondary to metabolic differences between Asian and Caucasian ethnic groups, requiring use of potentially lower doses of the drug for Caucasian patients, as gastrointestinal side effects of S-1 are more severe among them. One possible explanation for this difference is that the pharmacokinetics are affected by polymorphisms in cytochrome CYP2A6 and consequently 5-FU concentrations in the plasma are more likely to be elevated in patients from Western countries. Hence, S-1 could be considered an alternative treatment option for populations of Asian origin, but still needs to be attested in appropriately de- signed trials, before it is immediately available for use to non-Asian populations.

Improvements in the delivery of radiation therapy now also offer more hope and newer technologies such as IMRT or SBRT that use multiple, modulated beams of radiation can limit the dose to surrounding normal structures and organs at risk and deliver higher doses of radiation to the tumor bed. The increased use of more 3-dimensional (3D) conformal planning has led to more focused radiation fields, and it has now become feasible to deliver higher doses of continuous chemoradiation without increasing toxicities. Data presented from 2 high-volume surgical centers combined, Johns Hopkins University and Mayo Clinic, reported on 1,272 patients who had undergone surgical resection for pancreatic cancer and received postoperative CRT with a median dose of 50.4 Gy [176]. Both studies combined and independently demonstrated an improved survival and increased locoregional control with chemoradiation when compared to surgery alone (median survival 21.1 vs. 15.5 months, $p < 0.001$; 2- and 5-year OS 44.7 vs. 34.6 %; 22.3 vs. 16.1 %, $p < 0.001$). Chemoradiation merits were once again more evident in margin-positive and node-positive. Yet, this once more did not address the ongoing issue of optimal adjuvant modality, where the role of chemoradiation is less clear, leaving chemo-based systemic treatment as the upfront management plan [177].

17.8.3.2 Novel and Future Postoperative Approaches

Several smaller trials have also looked at other systemic therapies and used combinations of agents that have shown efficacy in the metastatic setting. The CAPRI trial integrated immunomodulation in the evaluation of adjuvant chemotherapy with 5FU versus CRT using cisplatin, interferon alpha-2b and 5FU, followed by 5FU [178]. One hundred twenty two patients were randomized, the median survival for 5FU/LCV was 28.5 months (95 % CI, 20.4–38.6 months), and the 2-year survival rate was 54 % over a recruitment period of 3 years. The chemoradioimmunotherapy regimen has negatively affected the quality of life, because of its profound grade III/IV toxicity. Despite trial's failure to show any significant difference with respect to OS, the 3.6-month longer median survival underlines the potentially beneficial role of this experimental regimen for selected patients and raised questions on the importance and time of surgery as well as predictive marker innovation. Based on their biological properties numerous different agents, including taxanes, oral fluoropyrimidines, epothylons and targeting molecules, have been tested alone or in several combinations, yet, despite the initially promising results the majority failed to incorporate into practice and its use is rendered questionable.

Most recent data suggest that future perspectives have to focus on patient selection and more personalized approaches in an attempt to address the dispute over best treatment option. Low matrix metalloproteinase-7 (MMP-7) serum levels predicted an OS benefit from adjuvant GEM (HR = 1.39 (1.05–1.83), p = 0.0001), but not 5-FU, implementing that patients with low MMP-7 serum levels might have a better chance benefiting from adjuvant GEM rather than 5FU [179]. MMP-7 is involved in the breakdown of extracellular matrix (ECM), tissue remodeling and plays a critical role in tumor progression via activation, degradation and shedding of non-ECM. An immunotherapy approach integrated to standard treatment seems promising, safe and demonstrates an OS that compares favorably with already published data in the literature for resected pancreatic cancer. Hyperacute immunotherapy approach (Algenpantucel-L) combined with chemotherapy (mean 12 doses, range 1–14) has been tested in the adjuvant setting demonstrating survival benefit (the 12-month disease-free survival was 62 %, and the 12-month overall survival was 86 %) [180]. The agent is well tolerated with a favorable toxicity profile and there is currently interest to evaluate its effectiveness for upfront use in multimodality approach in a phase III trial. A single-center phase II study, of 5-FU based chemoradiation combined with a pancreatic cancer vaccine of irradiated granulocyte-macrophage colony stimulating factor (GM-CSF) transfected allogenic whole-cell tumor lines conducted, has resulted in a median OS of 24.8 months (95 % CI, 21.2–31.6) and patients who showed a CD8+ T-cell response to post-immunotherapy induction mesothelin demonstrated a higher likelihood of achieving prolonged disease free status. Additional boost immunotherapy given at regular intervals beyond 1 year postoperatively offer innovative concept in the treatment of respectable disease. Other vaccines such as K-Ras mutant vaccines and MUC1 peptide-loaded dendritic cell vaccines also have shown early promising results that need however to be reproduced in larger scale trials.

The integration of predictive and prognostic biomarkers in the management of PDAC is of paramount importance since it can facilitate the recognition and selection of those patients who will benefit the most and stratify patients into optimal disease management. Genomic analysis and research into the cellular uptake of GEM suggests that levels of human equilibrative nucleoside transport protein 1 (hENT1) alters resistance and predict sensitivity to the treatment, while expression of other ribo- nucleotide reductase 1 (RRM2) and excision repair cross complementing gene 1 (ERCC1) are independent prognosticators associated with reduced relapse free survival (RFS) and OS after resection of pancreatic cancer [181]. Deleted in Pancreatic Cancer locus 4 (DPC4)/SMAD4 tumor suppressor gene status at initial diagnosis may contribute to patient selection. Loss of SMAD4 expression was highly correlated with widespread metastasis resulting in poor prognosis, whereas intact SMAD4 expression was highly correlated with a locally destructive phenotype [95]. C-X-C chemokine receptor type 4 (CXCR-4) is another independent negative prognostic factor and a predictor of distant relapse suggesting that anti-CXCR4 targeting therapies could be a promising approach in combination with cytotoxic chemotherapy in the adjuvant setting [182]. A growing body of evidence has established the role for systemic chemotherapy in the adjuvant setting and there is cumulative rise in knowledge of cellular and molecular biology. Vigorous efforts have been made to evaluate less toxic regimens and incorporate new agents into our arsenal against a disease with ominous prognosis even at earlier stages.

17.8.4 Systemic Treatment for the Metastatic Disease

Despite the improved understanding of pancreatic cancer biology, the early detection rate remains low. Almost 70 % of patients are diagnosed with advanced disease upon diagnosis and there is no doubt that systemic chemotherapy remains the standard of care in our armamentarium. The available data for first line treatment are robust (OS: 6–11 months), meanwhile the evidence for second line treatment is supported mainly by phase II and retrospective studies with poor survival expectancy (OS: 3–9 months) [183].

17.8.4.1 Chemotherapy

Gemcitabine Monotherapy and Combination Regimens

By the landmark study of Burris et al. in 1997, gemcitabine (GEM) became the standard of care. 63 patients received GEM *vs.* bolus 5-fluorouracil (5-FU) (n = 63). Survival (5.6 *vs.* 4.4 months, p = 0.0025) and clinical benefit (regarding performance status and pain management, 23.8 *vs.* 4.8 %, p = 0.0022) were observed [184].

Combination therapies involving platinum analogs, 5-FU, and other agents have been investigated in phase II and III trials. However, most of these failed to reveal a

significant survival benefit, and only improvement in PFS and ORR was revealed [185]. Therefore, the combination approach remains a matter of debate. Furthermore, the major criticism relates with studies' underpowered statistical design. In this context, meta-analyses performed comparing GEM alone *vs.* GEM+cytotoxic or GEM+platinum analog or GEM+5-FU showed risk reduction for the combination arms (HR: 0.91; 95 % CI, 0.85–0.97/HR: 0.85; 95 % CI: 0.76–0.96, p = 0.010/ HR: 0.90; 95 % CI: 0.81–0.99, p = 0.03, respectively). No risk reduction was derived by GEM-Irinotecan combination [186, 187]. GEM + Docetaxel+Capecitabine (GTX) combination showed encouraging results in retrospective studies with median (m) OS reaching 11.3 months [188]. Prospective studies are warranted to evaluate the efficacy of this promising regimen.

Reni and collaborators investigated the cisplatin, epirubicin, 5-FU, GEM regimen (PEFG) *vs.* monotherapy. Improved survival at 1 year (38.5 *vs.* 21.3 %) and in addition PFS at 4 months (60 *vs.* 28 %, HR: 0.46) for the combination arm were reported [189]. Moore et al. evaluated the combination of erlotinib to GEM. A statistically significant improvement of PFS (HR = 0.77, p = 0.004) and OS (HR =0.82, p = 0.038) derived, but the improvement in m OS (6.24 *vs.* 5.91 months) was clinically meaningless and debatable. It should be also noted that patients with a rash grade >2, usually developed during the first 2–4 weeks of treatment, had the greatest benefit compared with the patients without rash (10.5 *vs.* 5.3 months) [190]. In addition, GEM plus cetuximab or inhibitors of angiogenesis combinations (aflibercept, axitinib, bevacizumab, sorafenib, sunitinib) failed to show any benefit [191–194]. Unfortunately, phase III studies failed to confirm phase II encouraging data focusing on angiogenesis pathway.

Von Hoff and coworkers investigated the nab-paclitaxel and GEM combination *vs.* GEM alone in MPACT trial. Eight hundred sixty one patients were studied. For the combination arm clear superiority was demonstrated with regard to m OS (8.5 vs. 6.7 months, HR: 0.72; 95 %, 0.62–0.83; p < 0.001), m PFS (5.5 *vs.* 3.7 months, HR: 0.69; 95 % CI, 0.58–0.82; p < 0.001) and RR (23 vs. 7 %, p < 0.001). Grade 3 or higher most common events were neutropenia (38 *vs.* 27 %), neuropathy (17 *vs.* 1 %) and fatigue (17 *vs.* 7 %) [195]. The rationale of nab-paclitaxel administration is based on SPARC (secreted protein acidic and rich in cysteine) protein binding which is overexpressed in the cancer microenvironment. Thus nab-paclitaxel by depleting tumor stroma renders a high concentration of chemotherapeutic agent in the tissue [196, 197].

5-FU/Capecitabine Combination Regimens

The continuous 5-FU infusion and Oxaliplatin combination vs. single arms of both 5-FU and Oxaliplatin offered benefit with regard to mOS (9 *vs.* 2.4 *vs.* 3.4 months, respectively) [198]. Furthermore, similar results were derived by the comparison of CapOx *vs.* CapGEM *vs.* GEMOX for PFS (4.2, 5.7, 3.9) and OS (8.1, 9, 6.9 months, respectively) [199]. Further studies evaluated protracted vs. bolus 5-FU and

combination with Cisplatin or Mitomycin C [200, 201]. No survival improvement was revealed.

Irinotecan Doublet Combinations

In a phase II study, by a FOLFIRI regimen clear benefit was derived for OS, PFS and ORR [202]. On the contrary, GEM+ Irinotecan regimens did not offer any improvement [203].

FOLFIRINOX Combination

In PRODIGE 4/ACCORD 11, a randomized phase III trial, conducted by Conroy and collaborators, a three drug combination FOLFIRINOX (infusional 5-FU/folinic acid, irinotecan, oxaliplatin) was evaluated vs. GEM alone. Improvement was derived for OS (11.1 vs. 6.8 months, HR: 0.57, $p<0.001$), PFS (6.4 vs. 3.3 months, HR: 0.47, $p<0.001$) and ORR (31.6 vs. 9.4 %, $p<0.001$). Grade 3 or higher most common events for the combination arm were neutropenia (45.7 *vs.* 21 %, $p<0.001$), febrile neutropenia (5.4 *vs.* 1.2 %, $p=0.03$), sensory neuropathy (9 *vs.* 0, $p<0.001$) and diarrhea (12.7 *vs.* 1.8, $p<0.001$) [204].

17.8.4.2 Immunotherapy

The unmet medical need to improve survival in pancreatic cancer patients directed research to investigate the field of immunotherapy. Unfortunately, promising data obtained by phase I and II studies of MUC1, CEA antigen pulsed dendritic cell vaccines or a telomerase peptide vaccine (GV1001) with GM-CSF did not translate into a statistically and clinically survival improvement when tested in phase III studies [205–208]. Preliminary results in a phase IB study that investigated GVAX [irradiated pancreatic cancer cells modified to elude granulocyte-macrophage colony-stimulating factor (GM-CSF) and produce an anti-tumor immune response] + Ipilimumab vs Ipilimumab alone appeared encouraging (5.5 *vs.* 3.3 months) [209]. GVAX and CRS207 (a listeria based vaccine) translated to a survival benefit (6.1 *vs.* 3.9 months, HR: 0.59, $p=0.0172$) which was more clear among patients treated in third line (5.7 *vs.* 3.9 months, HR: 0.29, $p=0.0003$) [210].

17.8.4.3 Future Directions

Targeting the stroma that interferes with the weak drug penetration and confers chemo-resistance appears an attractive target. Sonic Hedgehog pathway plays an important role in this context. In addition, TGF-B – instead of its critical role in pathogenesis, metastasis and angiogenesis- is an important partner in stromal

regulation. Furthermore, the Notch pathway, Histone de-acetylation and DNA hypermethylation are thought to be important targets in pancreatic cancer. Results of PARP inhibitors in patients with BRCA1,2 mutations, and clarification of data on metformin's use are strongly awaited.

Although various therapy combinations have been found to improve survival expectancy significant toxicity is often associated. Young patients or in good performance status are candidates for GEM+ nab-paclitaxel or FOLFIRINOX combinations. To those with modest or poor performance status single agent GEM could be the option. Moreover, for patients with poor performance status best supportive care could be the alternative.

17.9 Palliation

17.9.1 Quality of Life

Pancreatic cancer carries a dismal prognosis at even the early stage and patients usually have a limited follow-up before they progress on to a more advanced stage. Therefore, much attention is focused upon palliation and symptom control and the decision to treat a patient with more aggressively must always take into account the impact upon a patient's quality of life (QoL). Toxicities from treatment may also contribute to the patient's symptom profile despite any clinical benefit response deriving from it. Several comprehensive report forms exist to evaluate patient's QoL, however, EORTC has developed a disease specific QoL module for pancreatic cancer (EORTC QLQ-PANC26), which has 26 questions and must be used in conjunction with the generic instrument EORTC Quality of Life Questioinnaire-C30 (EORTC C-30). Yet, its utility is strongly restricted both in research and clinical practice, since patients particularly with severe and disabling disease as it is often difficult to complete. Supportive management of symptoms must be initiated early and aggressively to ensure patient comfort with early involvement of the palliative care facilities [211].

Pancreatic cancer frequently presents with pain even as initial symptom at the time of diagnosis. Initial assessment of pain should include evaluation of the intensity, frequency, duration, exacerbating and/or alleviating factors as well as a comprehensive history of current and previous pain medications along with documentation of any side effects encountered on these medications. This should be completed by clinical examination to influence decisions on implementation of the appropriate pharmacologic or procedural interventions. Patient symptoms may also complement as prognostic signs for treatment success and mortality and their response to symptom control may act as predictors of disease extent and response [212].

Albeit, palliative care or pain team should be actively involved in the management of symptoms like pain, the attending physician should be trained and feel

comfortable starting the initial analgesic regimen. Opioids are generally thought the mainstay of pharmacologic management of pancreatic cancer pain. Initial therapy shall preferably consist of a short-acting opioid such as morphine or oxycodone. Collateral comorbidities of the patient like chronic kidney damage and/or hepatic impairment should also be taken into account when selecting the appropriate agent. A sustained-release opioid, along with a short-acting opioid for breakthrough pain, may be the next step of actions mainly in patients whose pain has been roughly under control, those with constant pain or those sleeping problems due to pain. Common side effects of opioids include sedation, constipation, pruritus, nausea, xerostomia and testosterone suppression in those on long-term therapy. Constipation is commonly addressed with stool softeners or bowel motility-promoting agents.

However, more advanced techniques might be needed for pain control. The most common and effective procedural intervention for is celiac plexus block [213]. Patients with pain refractory to increasing doses of opioids and those who suffer debilitating opioid-mediated side effects seem to benefit most from a celiac plexus block. Most patients relish a >3 month period of pain relief on initial celiac plexus neurolysis yields, yet, subsequent celiac plexus neurolysis may be feasible in selected patients, its efficacy is seriously mitigated by disease progression. More invasive techniques such as intrathecal delivery of analgesia, via an implantable intrathecal drug delivery systems (IDDSs), might prove helpful especially for patients who have not achieved adequate pain relief. IDDSs managed to control pain, significantly relieve common drug toxicities, and improve survival in patients with refractory cancer pain [214].

Physical symptoms like fatigue, anorexia, cachexia, gastric outlet obstruction, insomnia, decreased appetite, dysgeusia, indigestion and certainly pain heavily impact on pancreatic cancer patients's psychology. Additionally fear of disease recurrence, severity or advanced stage is pervasive and can render the patient emotionally unstable. Depression is a common condition up to one fifth of patients and become debilitating since data suggest that patients who are depressed are more likely to have suboptimal treatment or poor response. Notably, depression may as well precede initial diagnosis raising that this might equally be a result of chemicals released by the tumor and not just a consequence of the psychological burden of the diagnosis [215]. Regardless of etiology, appropriate early detection and treatment is of paramount importance for the immense suffering it causes.

17.9.2 End of Life

Pancreatic cancer is a disease with a grim natural history and albeit the aim for health care providers is prolonging life, assisting patients and their families when in distress through the arduous transitions precipitating all too often is equally as important. The multidisciplinary team decision to discontinue treatment is equally disappointing most of the times for both patients and their families as it is for doctors and it should involve patient, family, friends, and the healthcare team. However,

it is important to clarify that ending cancer treatment does not necessarily mean ending care. A hospice placement is frequently recommended when prognosis is no longer than 6 months. It addresses all aspects of a patient and family's needs, including the physical (eg, pain relief), psychological, social, and spiritual or may be given at home. Nowadays, advanced services such as hospital to home care also exist and facilitate the serene transition to home reducing their suffering.

Synopsis: Take Away Messages

It is the twelfth most common cancer type but the seventh cause of death due to cancer with 10–20 % familial or hereditary cases and increasing incidence. It carries one of the highest incident-to-mortality rates among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world. Lifestyle factors like tobacco use, alcohol, obesity and diet form significant risk factors. Several medical conditions and hereditary diseases predispose to pancreatic cancer as does the occurrence of other cancer types. Point mutations, especially of the KRAS family do occur and drive oncogenesis through the MAP-kinase pathway in addition to Tumor Suppressor Gene inactivation such as p16, p53, DPC4/SMAD inactivation and BRCA2 mutations. The research on further molecular events in pancreatic carcinogenesis (overexpression of EGFR, VEGF, MMPs, COX-2, hedgehog signaling, IGF-1 pathways) has not yet manage to produce any fruit in clinical practice. Resectable and early stage disease still carries the best chances of long-term survival and by that we mean mostly small tumors mainly in the head of the pancreas without any extrapancreatic spread, patent SMV and PV, definable tissue plan between the tumor and regional arterial structures (including the celiac axis and SMA). Neoplasms of the tail are considered of high risk for peritoneal seeding despite their potentially smaller size. Yet, locoregional and distant recurrence frequency reaches 80 %.

Systemic treatment established by a German group (CONKO-001) and several meta-analyses demonstrated superiority of postoperative gemcitabine compared to surgery alone for patients with resected pancreatic cancer and is the mainstay of adjuvant therapy in Europe; however, combined CRT is preferred in the USA, based on historical trials and single center experiences. Based on ESPAC-3 both weekly gemcitabine and 5-FU/LV can be considered appropriate adjuvant treatment. CRT might have a role to play in node positive, borderline resectable or palliation in advanced unresectable disease. Targeted therapies have largely failed to produce any substantial outcome. The interest for treatment of the metastatic disease has been revived by the introduction of combinations like FOLFIRINOX and nab-paclitaxel for patients with good performance status, absence of biliary obstruction and no infectious complications after addressing the problem of significant expected toxicity. Other alternatives with combination capecitabine and GEM or GEM single agent have conferred some modest benefits. Treatment on relapse or progression is not equally well established, but second line options include 5-FU-based regimens, such as FOLFOX, FOLFIRI or even single-agent capecitabine in patients who cannot tolerate combination treatments.

The majority of patients present with a wide variety of symptoms, which need to be addressed early on and patient and their family requires receiving support, both physical and psychological. Early Palliative Care and Pain team involvement is highly recommended, since prognosis is dismal and relapse highly likely. Health care professionals and attending clinicians need to be actively involved and a network of professional is required to promptly address patient's needs. Course of events and overall management plan should involve a variety of specialties within the MDT. MDT shall also take the decision for no further oncologic treatment and arrange for patient's appropriate placement for end of life therapies.

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