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ORIGINAL ARTICLE

Update on Management Periampullary/Pancreatic Head Cancer

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Abstract

Management of pancreatic head (ductal adenocarcinoma) and periampullary cancer is difficult owing to its insidious onset and hence late diagnosis, lack of significant diagnostic, predictive and prognostic biomarkers, and the inherent tumor biology of being relatively resistant to chemotherapy and radiotherapy. Surgery of this deep-seated gland is technically challenging and the procedure is called pancreaticoduodenectomy (PD). It involves removal of pancreatic head, duodenum, bile duct and gallbladder ± distal stomach. The reconstruction involves pancreatoenteric anastomosis (pancreaticojejunostomy or pancreaticogastrostomy), hepaticojejunostomy, and gastro/duodenojejunostomy. At times, vascular resection and adjacent organ resection are required for complete extirpation (R0) of the cancer. Over the years, surgical procedures used in the management of pancreatic cancer (PC) have been refined and with better anesthesia and perioperative and postoperative care, the operative mortality has dropped to < 5% but morbidity still remains close to 40%. The most common cause of severe morbidity is occurrence of postoperative pancreatic fistula. Post pancreatectomy hemorrhage and delayed gastric emptying are the other two major morbidities extending hospital stay and are at times life-threatening. New classification systems, better imaging, and new chemotherapeutic/targeted drug combinations for neoadjuvant/adjuvant treatment with/without refined radiotherapy techniques and centralization of treatment have helped in selecting the best patients for aggressive treatment with the aim of improving abysmally low overall survival. The present review highlights recent updates in the management of PC.

Keywords Pancreatic cancer · Periampullary cancer · Update · Incidence · Surgery · Chemotherapy · Radiotherapy · Novel agents · Biomarkers

Introduction

The incidence of pancreatic ductal adenocarcinoma in India is low. The International Agency for Research on Cancer (IARC) puts it around 1.16 per 100,000 population compared to over 7.52 in the USA (Fig. 1) (http://globocan.iarc.fr/Pages/Map.aspx).

Though the incidence of periampullary cancer is higher in India, the exact incidence is not known. Periampullary carcinoma arises around the confluence of the common bile duct with the main pancreatic duct and therefore may have a different anatomical origin: at the level of the pancreatic head (50–70% of the resected specimens), ampulla of Vater (20%), distal common bile duct (15–25%), and duodenum (10%). [1].

Despite slight improvements, the overall survival (OS) of patients with PC has not improved over the last two decades. Periampullary cancer has an overall better prognosis compared to PC due to different disease biology. A summary of the basic understanding of the recent management of ductal adenocarcinoma of the pancreatic head (PC) is presented below.

Screening

Because of the low incidence of PC in the general population, population-based screening has not been recommended. International Cancer of the Pancreas Screening (CAPS) Consortium is in consensus for a screening programme which should be able to detect T1N0M0 margin-negative PC and high-grade dysplastic precursor lesions (pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm) in high-risk individuals. Screening can be useful for first-degree relatives (FDRs) of patients with PC from a

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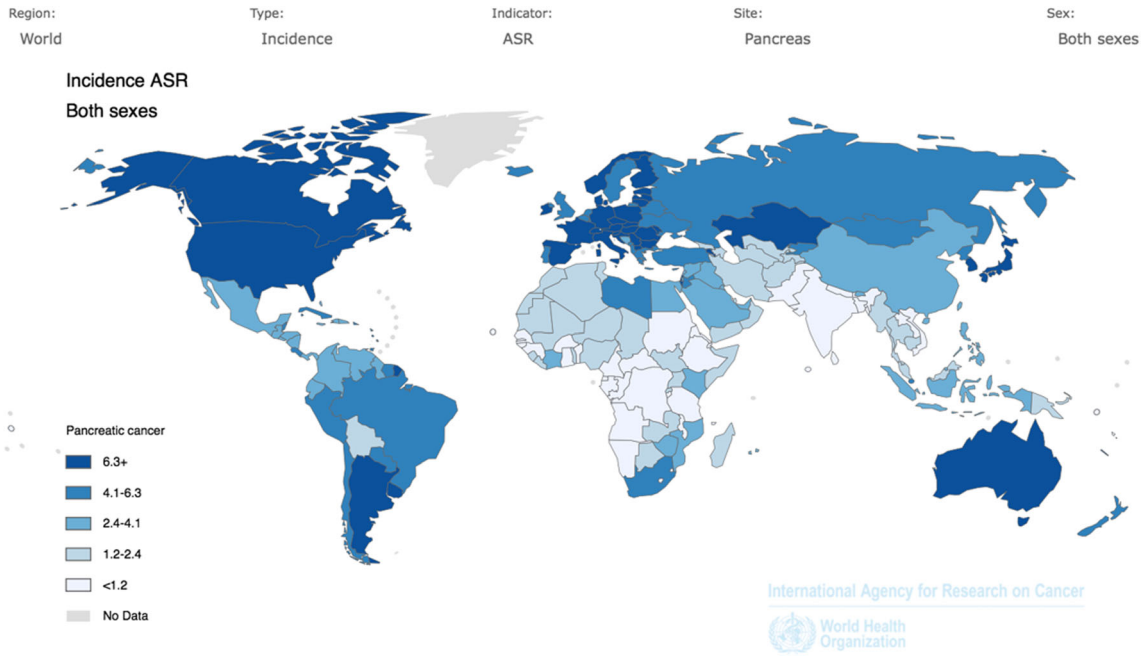

Fig. 1 Incidence of pancreatic cancer across the world [1]

familial PC kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and p16, BRCA2, and hereditary non-polyposis colorectal cancer (HNPCC) mutation carriers with ≥ 1 affected FDR. Still there is no consensus on the age to begin screening, screening intervals, and optimal modalities for screening or when to stop surveillance. There are significant differences in the criteria used for selecting candidates for surgical resection post screening and hence screening is recommended in high-volume centers with a multidisciplinary team preferably in a trial setting. The tools commonly used in initial screening include endoscopic ultrasonography (EUS) and/or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) but not computed tomography (CT) or endoscopic retrograde cholangiopancreatography (ERCP) [2]. Newer screening methods under research include micro RNAs [3], circulating cell free DNA and its methylation status [4], urine metabolites, and pancreatic juice analysis [5]. Interestingly, serum CA 19-9 is back as a biomarker as it may be elevated in patients up to 2 years before the diagnosis of PC [6].

Staging

Pancreatic protocol contrast-enhanced CT with submillimeter sections is the most preferred imaging modality for staging PC. Multiplanar 3-D reconstruction and thin cuts allow precise delineation of the hypodense PC within the pancreatic parenchyma and its relation with the adjacent vasculature. MR imaging is predominantly utilized for problem-solving in patients with isoattenuating pancreatic lesions or to better characterize indeterminate liver lesions identified at prior CT examinations or in patients allergic to contrast material [7]. EUS may be used as an adjunct in the detection of small tumors and in patients when the primary tumor is not visualized or its relation with adjacent vasculature is questionable [8].

The criteria defining resectability status are based on tumor interface with the surrounding vasculature and has been stratified in 3 groups namely, resectable, borderline resectable (BRPC), and unresectable (i.e., locally advanced or metastatic) [9, 10]. The National Cancer Comprehensive Network (NCCN) v2.2017 now recommends and endorses Intergroup criteria doing away with the subjective terms such as abutment and impingement [11] (Table 1).

Use of positron emission tomography (PET)/PET-CT and staging laparoscopy is still considered optional and may be used if there is suspicion of advanced/ metastatic disease, e.g., borderline resectable PC, markedly high CA 19-9 levels, large tumor, bulky lymphadenopathy, or highly symptomatic patient [11]. A Cochrane database meta-analysis of 16 studies involving 1146 participants revealed that adding laparoscopy (and histopathological confirmation of the suspicious lesion) to CT scan might decrease unnecessary laparotomy in 21% of patients deemed resectable by CT alone [13].

The Union for International Cancer Control (UICC) American Joint Committee on Cancer (AJCC) 8th edition has made substantial changes in the staging of PC. The T (Tumor) category is significantly revised paying emphasis on tumor size and number of positive nodes. Tumor size and nodal positivity are important prognostic indicators of tumor biology. Moreover, the criteria of resectability is removed from the T4 category, as the definition of resectability varies amongst institutions and is still evolving with advances in

Table 1 Staging of pancreatic cancer using radiographic criteria

Pancreatic cancer (head and uncinate process)	Intergroup criteria [12]	NCCN v2.2017 [11]
Resectable	SMV-PV: T-V-I < 180° SMA: No T-V-I	No arterial tumor contact CA, SMA, or CHA
	CHA: No T-V-I	
	Celiac Trunk: No T-V-I	No tumor contact with SMV or PV or ≤ 180° contact without vein contour irregularity
Borderline Resectable	SMV-PV: T-V-I ≥ 180° and/or reconstructable occlusion SMA: T-V-I < 180°	• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction
	CHA: Reconstructable short-segment T-V-I of any degree	• Solid tumor contact with the SMA of ≤ 180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning.
	Celiac Trunk: T-V-I < 180°	• Solid tumor contact with the SMV or PV of > 180°, contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable	SMV-PV: Unreconstructable Occlusion	• Distant metastasis (including non-regional lymph node metastasis)
	SMA: T-V-I ≥ 180°	• Solid tumor contact with SMA > 180°
	CHA: Unreconstructable	• Solid tumor contact with the CA > 180°
	Celiac Trunk: T-V-I ≥ 180°	• Solid tumor contact with the first jejunal SMA branch • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV

SMV superior mesenteric vein, *PV* portal vein, *SMA* superior mesenteric artery, *CHA* common hepatic artery, *CA* celiac axis, *T-V-I* tumor-vessel interface

surgical technique and multimodality therapy [14]. An interesting multi-institutional study published recently reanalyzed data from 3 high-volume centers in the USA and concluded that the proposed 8th edition changes for T and N (Node) classification will allow more comprehensible, statistically valid, and prognostic staging [15].

Biopsy and Preoperative Biliary Drainage

A biopsy confirmation of PC is not mandatory before resection in view of significant clinical and radiological suspicion of the disease. EUS-FNA is the preferred approach if required. A biopsy is however necessary if patient needs neoadjuvant or palliative chemo/chemoradiotherapy [16].

Biopsy in periampullary cancer is usually feasible as the tumor is accessible through UGI endoscopy. Sometimes, a brush cytology is required if no tumor is visualized.

Review of 6 randomized controlled trials (RCTs) and 5 meta-analysis by Lai EC et al. [17] and the DROP trial [18] indicated that routine preoperative biliary drainage showed no beneficial effect on the surgical outcome, but rather increased incidences of wound complications and infection were observed. In addition, the patient has the risk of post procedural complications most important of which is cholangitis. A selective approach of preoperative biliary drainage should be used in jaundiced patients suffering from cholangitis, severe pruritus, coagulopathy, and delay in surgery for over 1 week or before initiation of neoadjuvant therapy. Short metallic stents are preferred over plastic stents for their inert nature and longer patency. The optimal duration and modality of preoperative biliary drainage remain unclear.

Surgical Options

Pancreaticoduodenectomy (PD) is the standard of care for resectable pancreatic head and periampullary cancers and the only hope for cure. Ever since PD was first performed by Codvilla in 1898 [19, 20], this complex surgery has evolved over the last century and is now performed with very low mortality (< 5%) but the morbidity is still close to 40% [21, 22].

Classical Whipple's Versus Pylorus Preserving Versus Pylorus Resecting PD

Classical Whipple PD entails resection of the distal stomach, the duodenum and proximal jejunum, the head of the

pancreas, and the common bile duct along with the gallbladder. This surgery has been modified to preserve stomach (pylorus-preserving PD—PPPD) or to resect just distal to pylorus (pylorus-resecting PD—PRPD). First introduced by Traverso and Longmire in 1978, PPPD has been stated to achieve better QOL due to improved gastric emptying and hence nutritional status of the patient but the results have been inconsistent to date. RCTs comparing PPPD with classical Whipple PD have shown equivocal results vis-à-vis its common complication, delayed gastric emptying (DGE) [23–29].

Of late, various studies have reported the benefit of resecting the pylorus called PRPD that preserves most of the stomach and removes the often denervated pylorus resulting supposedly in reduced incidence of DGE versus PPPD [30, 31].

In Japan, it is named subtotal stomach-preserving PD (SSPPD), in which stomach is divided 2–3 cm proximal to the pylorus ring. SSPPD has been shown to have significantly lower incidence of DGE compared to PPPD in retrospective studies and although a trend favoring SSPPD versus PPPD was observed (DGE 12% versus 20% respectively) in a RCT, the difference was not significant [32, 33]. We practice PRPD in a large majority of our patients with < 2% incidence of DGE.

Extended Pancreatectomy

Extended pancreatectomy including venous (portal vein/superior mesenteric vein/inferior mesenteric vein), arterial (hepatic artery, superior mesenteric artery (SMA), celiac trunk), and/or adjacent organ resection (colon/small bowel/kidney/adrenal/liver/diaphragmatic crura) is feasible albeit with often higher morbidity (increased operative time, blood loss, blood transfusion, ICU/hospital stay, etc.) [34, 35] and lower OS rate compared with those undergoing a standard PD [36]. Venous resection is commonly done in high-volume centers in locally advanced PC. The aim being to achieve a R0 resection. Recent reports suggest that actual pathological invasion of the venous wall during portal venous resection portends grave prognosis [37]. Data on the impact of arterial resections on survival is unknown. Celiac axis or hepatic artery resection is performed more often and only a handful reports exist of SMA resection [38].

Post PD Reconstruction and Complications

The second part of the operation is restoration of continuity of the gut and entails 3 anastomoses: pancreatic remnant to either jejunum (pancreaticojejunostomy [PJ]) or stomach (pancreaticogastrostomy [PG]); hepatic duct to jejunum (hepaticojejunostomy); and stomach/duodenum to small intestine (gastro/duodenojejunostomy). A great heterogeneity exists amongst surgeons opting for PG versus PJ and a number of RCTs and meta-analysis have revealed variable results in terms of its most feared complication—postoperative pancreatic fistula (POPF) [39–44]. Further, PJ/PG may be done by a variety of techniques (over 70 modifications of PJ have been published [45])—invagination/dunking, duct-to-mucosa, binding, and PJ either end to end or end to side.

Several factors influence development of POPF and confound study conclusions. Broadly, they may be categorized into patient related (age, obesity, comorbidities like diabetes mellitus or cardiovascular disease, pancreatic texture—soft/firm/hard—pancreatic duct size); disease related (benign or malignant etiology); and surgery related (type of technique used, surgeon/hospital volume, use of perioperative somatostatin analogues, stents, glue, etc.). Hence, getting a completely homogenous population with significant number of patients and without any bias or confounding variables is extremely difficult. A comprehensive Cochrane database review recently published by Cheng et al. analyzed data from 10 RCTs involving 1629 participants who underwent PD [46]. No significant difference was found between PJ and PG in POPF rate, mortality, length of hospital stay, surgical re-intervention rate, and risk of any surgical complications. PJ had lower risk of postpancreatectomy hemorrhage (PPH) but a higher risk of developing an intra-abdominal abscess. There appeared to be some evidence in favor of improved quality of life (QOL) with PG.

Upcoming Role of Minimally Invasive PD

Minimally invasive PD (MIPD) has also made a headway in to this field and to date remains investigational. Although technically feasible in expert hands, its advantages over an open PD (OPD) are yet not confirmed. A recent systemic review and meta-analysis to compare MIPD vs OPD suggested that MIPD can be a reasonable alternative to OPD with the advantages of decreased blood loss, increased R0 resection, decreased DGE, decreased wound infection, and shorter hospital stay. However, MIPD should be performed at high-volume centers and more RCTs are needed to evaluate the efficacy and appropriate indications of MIPD [47].

A systematic review and network meta-analysis comparing different types of MIPD laparoscopic assisted, totally robotic, totally laparoscopic, or totally laparoscopic robotic assisted to OPD. The primary endpoint was postoperative mortality. The secondary endpoints were intraoperative, postoperative, and oncological outcomes. They concluded that safest MIPDs are those involving a robotic system which seems to have a promising role in ameliorating the outcomes of OPD, especially when compared to a laparoscopic approach. [48]

International Study Group of Pancreatic Surgeons

As can be appreciated, surgery for PC is complex and is beset with complications. There is considerable heterogeneity in

terms of definitions categorizing outcomes and complications. A need was felt to standardize various definitions and formulate a consensus on various aspects of management of PC so as to enable pooled data comparable across the world. An international working group of 37 pancreatic surgeons was thus initially formed involving experienced surgeons from high-volume centers across Europe, Japan, Australia, North America, and South America called The International Study Group of Pancreatic Surgery (ISGPS). After a thorough literature search and discussions, the group first published the final definition of POPF [49]. Thereafter, ISGPS has published various consensus statements on DGE (2007) [50]; PPH (2007) [51]; standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma (2014) [52]; extended pancreatectomy in pancreatic ductal adenocarcinoma (2014) [53]; BRPC (2014) [54]; the 2016 update of the International Study Group (ISGPS) definition and grading of POPF: 11 years after [55]; and pancreatic anastomosis after PD: a position statement (2016) [56].

Use of Perioperative Somatostatin Analogues

Recent systematic review and meta-analysis of somatostatin analogues after PD suggest that prophylactic treatment with somatostatin or pasireotide have a potential role in reducing incidence of POPF, while octreotide had no influence on the incidence of POPF [57].

Enhanced Recovery after Surgery Protocol

Enhanced recovery after surgery (ERAS) pathways are multimodal, evidence-based approaches to optimize patient outcome after surgery. It involves multidisciplinary team work to enhance patient's recovery and includes aggressive pain control, early ambulation, early initiation of oral diet, and thromboprophylaxis amongst others. ERAS was first started for elective colorectal surgery [58] and has now become the standard of perioperative care in most centers [59].

A systematic review and meta-analysis to assess the safety and efficacy of ERAS protocols compared with conventional perioperative care (CPC) in patients following PD shows that ERAS is as safe as CPC and improved recovery of patients undergoing PD, thus reducing in-hospital costs. General adoption of ERAS protocols during PD should be recommended [60]. We follow the ERAS protocol in our unit and have an ongoing thesis on the subject.

Neoadjuvant Treatment

Cumulative survival after 5 years is less than 5% and rises to 25% for radically resected patients; in this latter group, local recurrences occur in about 50% and distant metachronous metastases appear in more than 70% of patients [61, 62]. Completion of multimodality therapy is believed to be the optimal treatment. Neoadjuvant approach has certain advantages. The initiation of adjuvant chemotherapy is frequently delayed due to surgical complications, comorbidity, and prolonged recovery after PD and delay occurs in up to one fourth of eligible patients [63, 64]. Therefore, a higher proportion of patients may receive preoperative treatment compared to treatment in the adjuvant setting, and preoperative treatment may be better tolerated, resulting in higher rates of treatment compliance [65–67]. In addition, drug delivery is better in well-perfused tumor bed and there is an opportunity to assess drug response. However, there is a concern for disease progression during neoadjuvant treatment that may preclude curative resection and hence the "therapeutic window" may be lost. The contrary reasoning by advocates of neoadjuvant therapy is that it helps select the best subpopulation of patients that might benefit from further therapy [68, 69].

Neoadjuvant Therapy in BRPC

While chemotherapy provides control for microdisseminated disease and acts as radiosensitizer, radiotherapy provides locoregional control. Due to high likelihood of the presence of systemic micrometastasis and risk of R1 resection, neoadjuvant therapy is preferred in most cases with BRPC in an attempt to eradicate occult systemic disease, improve R0 resection and OS rates, and spare patients who develop metastases during the treatment to an otherwise futile surgery.

A meta-analysis by Gillen S et al. [70] reported that up to 33.2% of patients with locally advanced PC (including a large number of BRPC) underwent surgical exploration with resection (79% R0 resection rate) following neoadjuvant therapy and had median survival comparable to those with resectable PC and adjuvant chemotherapy (23.3 months versus 20.5 months respectively). Interestingly, it also found that progressive disease occurred in approximately 21% of patients in either group indicating similar tumor biology.

This paradigm of multimodality therapy in multi-institutional setting has been proven in a pilot study, Alliance for Clinical Trials in Oncology Trial A021101, in which the median survival of patients who received chemotherapy and radiation prior to anticipated pancreatectomy was 22 months, and 64% of operations achieved an R0 resection [71]. It is important to understand that the significant change in tumor size and anatomic extent post neoadjuvant treatment is rare [72]. One must therefore anticipate the need for vascular resection and reconstruction during a pancreatectomy for all patients with BRPC, even following neoadjuvant treatment [71]. The pathological response may however be high (pathological complete response (pCR) 13%; < 5% viable cancer cells 33%) [71] and hence patients with BRPC should be given a chance for resection post aggressive preoperative therapy in absence of overt metastatic disease.

The Alliance for Clinical Trials in Oncology with support from NCI is conducting a multi-institutional treatment trial for patients with BRPC (Alliance A021501). This trial will compare 8 cycles of mFOLFIRINOX (oxaliplatin, irinotecan, leucovorin, 5-fluorouracil) with 7 cycles of mFOLFIRINOX followed by short-course radiotherapy (SBRT/ HIGRT). The primary endpoint is 18-month OS and secondary end points being R0 resection rate, event-free survival rate, pCR rate, adverse effect profile, and QOL and to evaluate a novel image based risk classification [73].

Neoadjuvant Therapy for Resectable PC

Neoadjuvant therapy for resectable PC is a debatable issue to be addressed best in a trial setting. Few retrospective studies and phase II trials in resectable PC have been published with equivocal advantage in OS or R0 resection rates but showing disease progression in 10–25% patients [74]. The MD Anderson Cancer Center (MDACC), USA, still champions use of neoadjuvant treatment in most patients with PC.

A phase III NEOPA trial by Tachezy M et al. is currently recruiting patients with resectable PC to compare neoadjuvant gemcitabine chemoradiation therapy to upfront surgery followed by adjuvant treatment in both arms with 3 year OS as primary end point [75] (ClinicalTrials.gov NCT01900327). A phase II trial with R0 resection as the primary endpoint is also ongoing (ClinicalTrials.gov NCT01389440).

There are few trials investigating preoperative chemotherapy in the resectable population without the addition of radiation. A study by O'Reilly and colleagues from Memorial Sloan Kettering Cancer Center (MSKCC), USA, suggests that preoperative chemotherapy alone may also improve patient selection and disease control in patients with clearly resectable PC [76].

As of now, NCCN [11] does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. Selected patients who appear technically resectable but have poor prognostic features may be considered for neoadjuvant therapy preferably in a high-volume center. 3rd St. Gallen EORTC Gastrointestinal Cancer Conference expert panel also does not recommend neoadjuvant therapy in resectable PC [77].

Adjuvant Treatment

Survival for patients with resected PC has improved in the past several decades with the addition of adjuvant therapy compared to surgery alone and has been proven by multiple RCTs. However, there is a lack of consensus regarding the optimal approach to adjuvant therapy, namely, chemotherapy alone or chemotherapy combined with chemoradiation.

The Gastrointestinal Tumor Study Group (GITSG) [78] in 1985 was the first pivotal study showing a survival benefit for adjuvant chemoradiation (5-fluorouracil + RT versus observation alone). This was followed by various large multi-institutional trials involving 5-FU and gemcitabine with or without radiotherapy with mixed results like by the European Organization of Research and Treatment of Cancer (EORTC) [79], European Study Group for Pancreatic Cancer (ESPAC-1 [80], ESPAC-3 [81, 82], ESPAC-4 [83]), Radiation Therapy Oncology Group (RTOG 9704) [84], and CONKO-001(Charité Onkologie 001) [85] to name a few.

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (ClinicalTrials.gov NCT01013649). Patients without evidence of progressive disease after 5 cycles of gemcitabine-based chemotherapy are being randomized to 1 additional round of chemotherapy or 1 additional round of chemotherapy followed by chemoradiation with capecitabine or 5-FU. The primary endpoint is OS and the trial is likely to be completed by 2020. The Adjuvant Pancreatic Adenocarcinoma Clinical Trial (APACT) trial (NCT01964430) is evaluating nab paclitaxel and gemcitabine vs. gemcitabine alone to treat resected patients.

Data incorporated from recent evidences reasonably suggest adjuvant chemotherapy as standard of care with the role of chemoradiation still not clearly defined perhaps being indicated in situations with increased risk of local relapse such as R1 resection. However, with the improvement in techniques of radiation delivery, high-dose chemoradiation can be delivered with increased efficacy and reduced toxicity. Based on the results of the abovementioned studies, NCCN [11], European Society for Medical Oncology [86], and also 3rd St. Gallen EORTC Consensus panel [77] recommend adjuvant chemotherapy.

Palliation

New Drugs in Systemic Therapy for Metastatic PC

The 5-year OS for metastatic PC remains at 2%. A landmark trial by Conroy et al. (PRODIGE TRIAL) [87] established FOLFIRINOX as the standard of care for patients with ECOG performance status (PS) 0 to 1 and favorable comorbidity profile. In this trial, FOLFIRINOX was compared to standard gemcitabine arm and reported improved median OS (11.1 months vs 6.8 months).

MPACT, another landmark trial which compared the combination of gemcitabine + nab paclitaxel with gemcitabine alone, reported an improved median OS with the combination regimen (8.5 months vs 6.7 months) and established this as another first-line chemotherapy regimen in patients with ECOG PS 0 or 1 and favorable comorbidity profile [88].

As no randomized trial has yet been performed to establish the superiority of these two regimens, either of them is used as an alternative first-line regimen for metastatic carcinoma.

In another phase III, double-blind, placebo-controlled trial, patients on erlotinib (EGFR tyrosine kinase inhibitor) plus gemcitabine versus gemcitabine alone, showed small but statistically significant improvements in OS suggesting that only a small subset of patients benefit [89].

New Approach: Targeted Therapy

Considering the wide variety of signaling pathways dysregulated in PC and triggering its progression, targeted therapies have emerged as a possibility to augment available therapeutic strategies (Fig. 2) [90]. Although many of the studies on targeted PC therapies showed promising results in preclinical or clinical settings, most of them failed during phase II/III trials. Nevertheless, numerous phase I/Ib studies are still ongoing with many of them showing encouraging results and remain an area of active research.

Palliation of Jaundice

Biliary obstruction is found in approximately 65–75% patients with advanced and metastatic PC [91]. In case of anticipated limited survival, endoscopic biliary stenting is the best palliation. Plastic stents made of Teflon, polyurethane, or polyethylene are inexpensive, are effective, but are easily blocked (patency time approximately 133 days). Self-expanding metallic stents (SEMS) have a longer patency times (up to 278 days). SEMS may be uncovered, partially covered, or fully covered [92].

For patients in which unresectable disease is found at laparotomy, biliary enteric bypass is recommended. Hepaticojejunostomy or choledochojejunostomy is preferred over bypass of gall bladder for providing long-term relief.

Gastric Outlet Obstruction

Gastric outlet obstruction is reported to be occurring in 10–25% patients of advanced PC [91]. For patients with poor PS and shorter life expectancy, palliative endoscopic stenting or percutaneous endoscopic gastrotomy tube can be placed. For longer life expectancy of more than 3–6 months, palliative gastrojejunostomy is preferred. Prophylactic gastrojejunostomy is recommended for unresectable disease at laparotomy who are supposed to be at higher risk for developing gastric outlet obstruction.

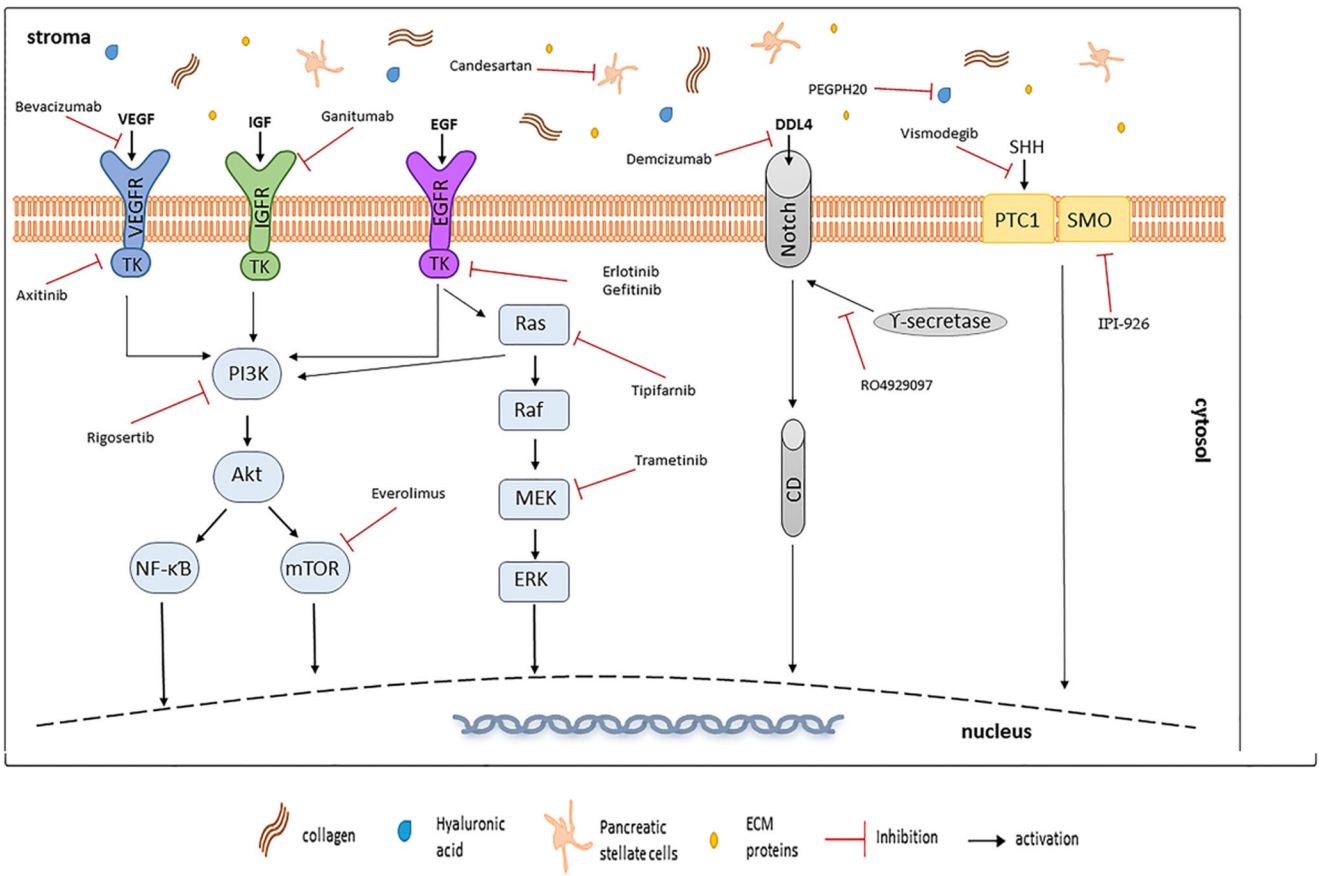

Fig. 2 Upcoming some of the targeted therapies in pancreatic cancer [90]

Pain Relief

Initial pain management is by non-opioid medications (WHO ladder) but the mainstay of pain management is liberal use of opioids. Severe progressive and refractory pain requires celiac plexus block/neurolysis (EUS guided is preferred/ percutaneous fluoroscopic or CT-guided).

Conclusions

Ongoing research in the field of PC emphasizes on centralization of sources for data collection, review, interpretation, and analysis; careful selection of homogenous patient cohorts; strict compliance for consensus definitions, e.g., for BRPC and complications; identification of biomarkers for early diagnosis and predictive of response to drugs; and primary outcome as OS for metastatic cancer trials for newer agents, tissue and serum banking etc. Management of PC should be attempted at high-volume centers with a multidisciplinary approach and teamwork to minimize complications/mortality and result in better patient outcomes.

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