Management of Pancreatic Cancer and Cholangiocarcinoma

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Preface

Pancreatic cancer and biliary tract cancer are typical intractable cancers. The prognoses of these cancers are still extremely poor. In particular, pancreatic cancer is the seventh leading cause of cancer death in the world. Various approaches have been attempted to improve the clinical outcomes for pancreatic cancer and biliary tract cancer. In diagnosis, in addition to the examination of risk factors, gene analysis using next-generation sequencing is widely attempted. Endoscopic retrograde cholangiopancreatology and endoscopic ultrasound are indispensable for the early diagnosis of cancers. In treatment, new systemic therapies are developed each year. Perioperative anticancer treatment has also been introduced. As a result, the possibilities of conversion surgery are expanding, which might improve long-term survival. Moreover, various advances in radiation therapy have been made, contributing to improved efficacy and safety. These anticancer treatments cannot be performed without appropriate endoscopic management for malignant biliary obstruction or gastric outlet obstruction, which is often encountered in patients with pancreatic cancer and biliary tract cancer. Self-expandable metal stents play a major role in the management of both biliary obstruction and gastric outlet obstruction. Furthermore, in recent years, local endoscopic treatments such as biliary radiofrequency ablation have been actively performed.

In this book, we have collected insights from Japanese experts on the latest diagnosis and treatment of pancreatic cancer and biliary tract cancer. In addition, the members of Springer Nature devoted great effort for publishing the book. We would like to take this opportunity to thank all those who cooperated in the publication of this book. There are few books that cover such a wide range of topics, including diagnosis, anticancer drugs, and endoscopic management, as this book. Therefore, we sincerely hope that this book will be useful for the daily clinical practice of many physicians worldwide and, as a result, will enable better management of patients suffering from pancreatic cancer and biliary tract cancer.

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Tokyo, Japan — Yousuke Nakai
Tokyo, Japan — Hiroyuki Isayama

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Part I

Current Topics in Epidemiology and Examinations of Pancreatic Cancer and Cholangiocarcinoma

Risk Factors for Pancreatic Cancer and Cholangiocarcinoma

1

Tsuyoshi Hamada and Yousuke Nakai

Abstract

Carcinomas arising in the pancreatobiliary system have been extremely aggressive and unable to be identified at an early stage of the disease in a majority of cases. We have witnessed the rising incidence of those carcinomas, particularly in developed countries worldwide. Moreover, the effects of chemotherapeutic agents have been quite limited in those cancer types. As a result, the prognosis of patients diagnosed with pancreatic and bile duct carcinomas has been poor. Therefore, there is a great need to establish primary prevention strategies through investigating risk factors and developing risk stratification systems for healthy individuals. In the microenvironment of gastrointestinal cancers including pancreatic and bile duct carcinomas, tumor cells evolve interacting continuously with exogenous and endogenous epidemiological factors as well as immune cells and microorganisms. Recent studies have revealed distinctive molecular subtypes of pancreatic and bile duct carcinomas, and heterogeneity in clinical characteristics and treatment response across the subtypes. Therefore, an integrative approach is warranted to explore a specific repertoire of risk factors for each subtype and tailor the prevention approach in the era of multi-omic technologies and precision oncology.

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1.1 Risk Factors for Pancreatic Cancer

1.1.1 Introduction

Pancreatic cancer currently represents the seventh leading cause of cancer-related deaths worldwide [1] with increasing incidence in developed countries [2–5]. The regional difference in the incidence of pancreatic cancer may be attributable to that in a variety of factors including lifestyle factors (e.g., dietary patterns and smoking) and resultant metabolic syndrome as well as genetic factors, compering risks of deaths, and screening practices. Despite efforts to improve clinical outcomes of pancreatic cancer *via* intensive chemotherapeutic regimens including FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine plus nab-paclitaxel [6–9], the prognosis of patients diagnosed with pancreatic cancer remains poor [3], resulting in nearly equal rates of incidence and mortality associated with this malignancy [1]. Therefore, primary prevention of pancreatic cancer is of considerable importance to reduce the mortality associated with this malignancy. Identifying risk factors, particularly modifiable risk factors, would not only provide insights into the pathogenesis of pancreatic cancer development but also help implement surveillance strategies of this highly lethal malignancy. In this section, we review risk factors for pancreatic cancer (Fig. 1.1).

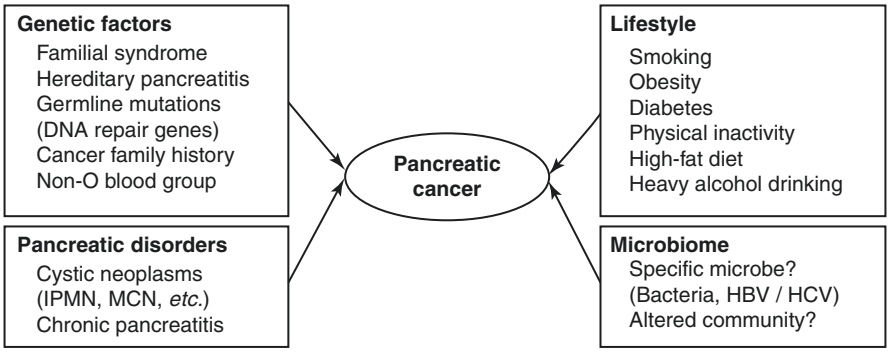

Fig. 1.1 Major risk factors for pancreatic cancer. There may exist interactions between multiple factors. *HBV* hepatitis B virus, *HCV* hepatitis C virus, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm

1.1.2 Genetic Factors

According to the American College of Gastroenterology (ACG) guidelines [10], the risk of familial pancreatic adenocarcinoma should be considered for individuals who (1) have a known familial syndrome or germline mutation associated with elevated risk of pancreatic cancer, (2) have two relatives (including at least one first-degree relative) with pancreatic adenocarcinoma or ≥3 relatives with pancreatic cancer, or (3) have a history of hereditary pancreatitis. Herein, the familial syndromes associated with the risk elevation include hereditary breast-ovarian cancer syndrome (due to mutations in *BRCA1* or *BRCA2*), familial atypical multiple mole melanoma syndrome (due to mutations in *CDKN2A* [*p16*]), Peutz-Jeghers syndrome (due to mutations in *STK11*), and Lynch syndrome (due to mutations of DNA mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*) [11, 12]. Hereditary pancreatitis is driven by germline mutations in *PRSS1* [11, 12]. Germline mutations in genes responsible for DNA damage response (e.g., *ATM*) and DNA repair (e.g., Lynch syndrome-associated genes and *PALB2*) have also been associated with the risk of pancreatic cancer [11, 12]. These genetic variants are highly penetrant but only account for a small subset of pancreatic cancer cases. Therefore, the ACG guidelines recommend genetic testing of *BRCA1/2*, *CDKN2A*, *PALB2*, and *ATM* for patients with suspected familial pancreatic cancer [10].

Individuals with a family history of pancreatic cancer are at higher risk of this malignancy compared to those with no family history with a relative risk of 1.7 to 2.4 [13–17]. In addition, individuals with family members diagnosed with other cancer types may carry moderately elevated risk of pancreatic cancer. Those cancer types include colorectal cancer, breast cancer, and melanoma, and the abovementioned familial syndromes may underline the associations [16–18]. Epidemiological studies also suggest a weak association of a family history of prostate, gastric, or liver cancer with pancreatic cancer risk [15, 17], but the reported association has been inconsistent, requiring further research. Individuals of Ashkenazi Jewish ancestry, who may harbor founder mutations in *BRCA1*, *BRCA2*, *MSH2*, and/or *MSH6* [19–21], are associated with higher risk of pancreatic cancer compared to those of other ancestries. In a population-based study in the United States, the association of family history of colorectal or breast cancer appeared to be augmented and limited in Ashkenazi Jews [18]. This study underlines the potential of self-reported information on family history in identifying individuals with founder mutations among Ashkenazi Jews.

Epidemiological and subsequent genetic studies suggest that individuals can be stratified by ABO blood groups in terms of the risk of developing pancreatic cancer in the future [22–25]. ABO blood group is defined by the types of antigens on the surface of red blood cells, which are inherently determined by alleles of the *ABO* gene at chromosome 9q34.2. The glycosyltransferase encoded by the *ABO* gene catalyzes the transfer of carbohydrates to a protein backbone (the H antigen) on red blood cells. Within large prospective cohorts in the United States, individuals with non-O blood group (A, B, or AB *vs.* O) had hazard ratios of 1.32 (95% confidence interval [CI], 1.02–1.72), 1.72 (95% CI, 1.25–2.38), and 1.51 (95% CI, 1.02–2.23),

respectively [22]. A subsequent meta-analysis yielded similar results with summary odds ratios of 1.2 to 1.4 for non-O blood groups (*vs.* blood group O) [26]. In genome-wide association studies, variants in the *ABO* locus were associated with the risk of pancreatic cancer [23, 24]. Specifically, the allele T for the SNP rs505922, which was in complete linkage disequilibrium with the O allele of the *ABO* locus, was associated with a lower risk of pancreatic cancer. Mechanistic evidence points to the role of the glycosyltransferase in regulating intercellular adhesion, cellular membrane signaling, and/or inflammatory and immune responses [27, 28], which may orchestrate the carcinogenic process in various organs. Given these lines of evidence, ABO blood group can be a biomarker for the risk of developing pancreatic cancer in the future.

1.1.3 Pancreatic Disorders (Cystic Lesions and Chronic Pancreatitis)

Pancreatic disorders may have the potential of progressing to pancreatic cancer or provoking malignant transformation of pancreatic cells. Several types of cystic neoplasms have served as precursor lesions of pancreatic cancer. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasm potentially progress to pancreatic carcinoma [29–32]. IPMNs have been incidentally identified on imaging studies in a majority of cases [33] and have been associated with the risk of pancreatic cancer with the incidence rate of 4–8% reported in longitudinal cohort studies [34–37]. The current international consensus guidelines recommend surgical pancreatic resection for patients with IPMNs harboring so-called "high-risk stigmata" (i.e., obstructive jaundice, enhancing mural nodule >5 mm, or the main pancreatic duct >10 mm) [30]. The dilated main pancreatic duct has been a strong predictor for development of pancreatic cancer among patients without high-risk stigmata [36–38]. It should be noted that patients with IPMNs are at higher risk of concomitant pancreatic ductal adenocarcinoma as well as IPMN-derived carcinoma [39, 40]. Therefore, this patient population should be referred to long-term surveillance programs. Other rare cystic neoplasms harboring malignant potential include solid pseudopapillary neoplasms and cystic neuroendocrine tumors [31, 32].

Patients with chronic pancreatitis have been predisposed to the risk of pancreatic cancer [41–43]. Chronic pancreatitis occurs based on fibroinflammatory process in the pancreas owing to genetic predispositions including germline mutations in *PRSS1* and *SPINK1* as well as lifestyle factors including heavy alcohol drinking and cigarette smoking [41]. Long-term inflammatory reactions in the pancreas cannot only cause exocrine and endocrine pancreatic insufficiency, but also provoke pancreatic carcinogenesis. Higher incidence of pancreatic cancer has been documented in patients with chronic pancreatitis compared to the general population [44]. In a meta-analysis, individuals with chronic pancreatitis appeared to be at approximately 16-fold increased risk of pancreatic cancer compared to unaffected individuals [45].

1.1.4 Epidemiological Factors

A wide spectrum of epidemiological factors have been reported to associate with the risk of pancreatic cancer with various levels of potential carcinogenic effects. Overall, heathy lifestyle may reduce the risk of developing pancreatic cancer in the future [46].

Smoking has been one of the strongest risk factors for pancreatic cancer. Cigarette smokes contain a number of carcinogens that can induce DNA damage and chemicals that can suppress host immune response to tumors [47, 48]. On average, current smokers may have 1.5 to 2.1-fold increased risk of pancreatic cancer (with mild dose–response relationship) compared to nonsmokers [49]. Importantly, the risk appeared to be reduced according to the duration of smoking cessation [49].

Pancreatic cancer has been one of the adiposity-related malignancies and therefore, management of body composition throughout the life course plays a key role in minimizing the likelihood of pancreatic carcinogenesis [50]. Obese and diabetic people have been associated with increased risk of pancreatic cancer [51–54]. Evidence implicates that chronic inflammatory changes in the pancreas due to altered glucose metabolism may promote initiation and progression of pancreatic neoplasms [55–57]. A meta-analysis has demonstrated that the risk of pancreatic cancer may almost double among diabetic individuals compared to nondiabetic individuals [54]. It is plausible that longer-term diabetes results in higher incidence of pancreatic cancer, but the association of the duration of diabetes and pancreatic cancer risk has not been reported consistently [52–54]. Similarly, studies point to the elevated risk of pancreatic cancer associated with physical inactivity [51]. Physical activity may exert a preventive effect on pancreatic cancer development particularly for obese individuals [51]. The biological mechanism through which physical activity may reduce pancreatic neoplasm has remained to be elucidated, but alterations of insulin- and/or inflammation-related signaling pathways may underlie the association [58].

Dietary patterns have potential relevance to the risk of pancreatic cancer [59, 60]. There may exist a positive association of consumption of red and processed meat with the risk of pancreatic cancer [61], and an inverse association of folate intake [62]. In addition, adherence to high levels of the Healthy Eating Index 2005 or Mediterranean dietary pattern appears to have protective effect on pancreatic carcinogenesis [63, 64]. Given the incidence rate of pancreatic cancer in the general population and the modest risk reduction associated with dietary modifications, a considerably large number of participants are required in trials designed to examine dietary interventions as such few trials have been conducted on the topic. In the Women's Health Initiative Dietary Modification randomized trial involving approximately 50,000 postmenopausal women in the United States, a dietary intervention aiming to reduce total fat intake and increase intake of vegetables, fruits, and grains successfully reduced 30% risk of pancreatic cancer among overweight or obese women [65].

Excess alcohol drinking may cause malignant transformation of pancreatic cells. In a dose–response meta-analysis, heavy alcohol drinking, but not low- to

intermediate-level drinking, is associated with elevated risk of pancreatic cancer compared to no alcohol drinking [66]. The risk of pancreatic cancer appeared to start to rise when daily alcohol consumption exceeded approximately >15 g per day and to be limited to liquor drinkers [66].

1.1.5 Microbiome

There is an ongoing debate on altered microbial flora in relation to pancreatic carcinogenesis [67, 68]. In the human body, the microbiota represents an interactive ecosystem that consists of a tremendous number of microorganisms interacting continuously with host cells including immune cells [69, 70]. Ample evidence supports the role of endogenous and exogenous microorganisms in the pathogenesis of various neoplasms [71–73]. Recent studies implicate that specific microorganisms or dysregulated microbial communities may exert tumorigenic effects not only in the affected organs but also in distant organs (e.g., the colorectal microorganisms in relation to pancreatic cancer [74–77]). Recent studies point to the microbiome localized within the pancreatic tumor that may play etiological roles in development and progression of pancreatic cancer. In mouse models of pancreatic cancer, ablation of microbiome in the tumor resulted in immunogenic reprogramming including a decrease in myeloid-derived suppressor cells, an increase in M1 macrophages, and activation of $CD8^+$ T cells, and tumor suppression [78]. A metagenomic analysis based on 16S rRNA gene sequencing on tumor samples of patients with pancreatic cancer has demonstrated specific bacteria enriched in the tumor (e.g., *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*) and the higher diversity among long survivors [79]. In a landmark study, the researchers identified specific fungi in tumor tissue of pancreatic carcinoma (e.g., *Malassezia* spp.), and modulation of the fungal composition resulted in suppression of pancreatic tumor cells [80].

Infections with hepatitis B virus and hepatitis C virus have also been implicated in development of pancreatic cancer as well as that of hepatocellular carcinoma [81, 82]. However, the association with pancreatic cancer has been inconclusive [83, 84]. Carriers of *Helicobacter pylori*, which can cause atrophic gastritis and gastric cancer, may be at higher risk of pancreatic cancer compared to non-carriers [85], but the association has not been observed consistently [86, 87].

1.1.6 Discussion

Pancreatic cancer has been associated with unfavorable clinical outcomes in patients [3]. In the current medical practice, owing to the nature of pancreatic cancer progressing without specific early symptoms and the lack of effective screening modalities, pancreatic cancer is often identified at advanced stage when the disease is nonresectable and thus incurable. Given the increasing global burden of pancreatic cancer [2–5], there is an urgent need to establish risk stratification systems and refine surveillance programs. It is of considerable importance to intervene

modifiable risk factors including cigarette smoking, obesity, and diabetes, and to consider the intensity of surveillance based on risk factors including genetic dispositions. However, future research is warranted to develop a prognostic model that can integrate individual-level information on the reported risk factors and tailor surveillance programs to maximize the effectiveness. Comprehensive gene expression profiling has revealed distinct molecular subtypes of pancreatic cancer that may represent heterogenous patterns of postdiagnosis progression and treatment response [88]. Collisson et al. defined three molecular subtypes (classical, quasimesenchymal, and exocrine-like) [89], Moffitt et al. defined two subgroups (basal and classical) [90], and Bailey et al. defined four subtypes (squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine) [91]. It should be noted that all these classifications have prognostic abilities in patients with pancreatic cancer and that there are substantial overlaps across the classifications. In addition, a subsequent analysis suggests that the exocrine-like, immunogenic, and aberrantly differentiated endocrine exocrine subtypes are likely artifact signals due to contamination of non-neoplastic cells in cellularity-low tumor and stroma [92]. From the therapeutic perspective, the PARP inhibition may specifically benefit patients with pancreatic cancer harboring mutations in *BRCA1* or *BRCA2* [8]. While rare in pancreatic cancer [93], *KRAS* G12C mutation may guide a highly specific molecular-targeted therapy, sotorasib [94]. In parallel with these lines of evidence, risk factor profiles may differ by molecularly defined subtypes of pancreatic cancer, and therefore, consideration of the heterogeneity of the subtypes would facilitate effective prevention against specific tumor subtypes [69, 95]. In addition, the inter-tumor heterogeneity highlights the importance of precision oncology approach for prevention, surveillance, and treatment of pancreatic cancer. In summary, integrated and multidisciplinary approach is desired to implement strategies for early detection of pancreatic cancer in average-risk populations as well as high-risk populations and improve clinical outcomes of this malignancy overall [96, 97].

1.2 Risk Factors for Cholangiocarcinoma

1.2.1 Introduction

Cholangiocarcinoma represents a heterogeneous collection of carcinomas arising from the biliary epithelium and is anatomically classified as intrahepatic (arising in the intrahepatic bile ducts), perihilar (arising in the extrahepatic bile ducts proximal to the bifurcation of the cystic duct), or distal (arising distally to the bifurcation of the cystic duct) cholangiocarcinoma based on the location of the bile duct involved [98]. Intrahepatic cholangiocarcinoma is the second most common primary hepatic malignancy following hepatocellular carcinoma. It should be noted that perihilar and distal cholangiocarcinomas have been dealt collectively as extrahepatic cholangiocarcinoma in a majority of epidemiological studies. Within the disease entity of cholangiocarcinoma, tumor behavior may differ by the location of the primary tumor in the biliary tree. Compared to risk factors for pancreatic cancer, risk factors

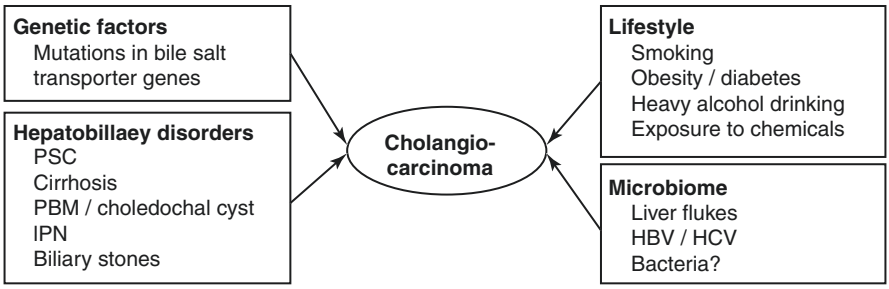

Fig. 1.2 Major risk factors for cholangiocarcinoma. There may exist interactions between multiple factors. *HBV* hepatitis B virus, *HCV* hepatitis C virus, *IPN* intraductal papillary neoplasm, *PBM* pancreatobiliary maljunction, *PSC* primary sclerosing cholangitis

for cholangiocarcinoma remain relatively unexplored. This may be due to the fact that cholangiocarcinoma has been more common in Asian countries than in Western countries [99] where there have been a number of ongoing population-based cohort studies. Genetic differences and geographical variations in risk factors may underlie this inter-regional heterogeneity in the incidence of cholangiocarcinoma. Moreover, intrahepatic cholangiocarcinoma and hepatocellular carcinoma have been analyzed collectively as liver cancer in several epidemiological studies due to the lack of detailed information on differential diagnoses of these carcinomas as such the number of studies investigating the incidence of cholangiocarcinoma has been relatively limited. In this section, we summarize current evidence on risk factors for cholangiocarcinoma (Fig. 1.2).

1.2.2 Microbiome (Infectious Diseases)

Parasitic infections, particularly infections with hepatobiliary flukes such as *Opisthorchis viverrini* and *Clonorchis sinensis* have been major risk factors for cholangiocarcinoma [100, 101]. These species are typically transmitted through consumption of raw or undercooked freshwater fish. In a meta-analysis of case-control studies, patients with cholangiocarcinoma had 4-fold higher likelihood of the parasitic infections compared to the controls [102]. The limited number of patients diagnosed with cholangiocarcinoma in cohort studies precluded a robust statistical assessment. Nonetheless, the parasitic infections as the etiology of cholangiocarcinoma have been a public health issue that is highly specific for Southeast Asian countries, particularly for Thailand.

Viral infections have been implicated in development of cholangiocarcinoma. Infections with hepatitis B virus and hepatitis C virus have been associated with increased risks of intrahepatic and extrahepatic cholangiocarcinomas. In a meta-analysis, the viruses were both associated with the risk of intra- and extrahepatic cholangiocarcinomas [103]. These associations may be partly due to increased risk of combined hepatocellular-cholangiocarcinoma driven by the hepatitis viruses

[104]. Emerging evidence points to Epstein-Barr virus, which has been associated with gastric and nasopharyngeal carcinomas, as a pathogenic microbe in cholangiocarcinogenesis [105].

Emerging evidence links dysregulation of the gut microbiome to a variety of neoplastic and non-neoplastic diseases throughout the human body [71–73]. Given that microorganisms in the gastrointestinal tract potentially migrate into the biliary system and/or provoke biliary inflammation through the gut–liver axis, there may be a possibility that the dysbiosis of the microbial communities can provoke hepatobiliary diseases [74–76, 106]. Accumulating evidence points to suppressive effects of dysregulated microbiome on local and systemic antitumor immune reactions in the context of carcinogenesis [73, 107, 108]. However, etiological roles of the microbiome in cholangiocarcinogenesis just started to be investigated [109, 110].

1.2.3 Genetic Factors

Mutations in genes encoding bile salt transporter proteins (e.g., *ABCB11* [BSEP, bile salt export pump], *ATP8B1*, and *ABCB4*) result in cholestasis, which provokes chronic inflammation and carcinogenesis in the biliary system [111]. However, germline mutations in those genes are responsible for a small fraction of cholangiocarcinoma cases. Therefore, genome-wide association studies are warranted to identify other hereditary genetic dispositions associated with the risk of cholangiocarcinoma and implement risk stratification through genetic testing for early detection of this extremely aggressive malignancy.

A meta-analysis of case-control studies suggests an association of family history of any cancer with the risk of developing cholangiocarcinoma [112]. However, these findings were limited by the case-control study designs and the inclusion of only studies conducted in Thailand. The risk of cholangiocarcinoma among individuals with a family history of this malignancy has not been examined in large studies. Taken together, there has not been sufficient evidence supporting intense surveillance for family members of cholangiocarcinoma.

1.2.4 Pancreatobiliary and Inflammatory Disorders

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology, which is characterized by progressive stenosis of intra- and extrahepatic bile ducts [113, 114]. Progression of biliary strictures may not only result in decompensated cirrhosis requiring liver transplantation but also associate with development of cholangiocarcinoma with lifetime incidence of up to 20% [114–116]. Therefore, patients with PSC should be referred to long-term surveillance, and endoscopic retrograde cholangiopancreatography with brush cytology should be carried out when there are any imaging findings that are suggestive of cholangiocarcinoma (worsening clinical symptoms, worsening cholestasis, or a dominant stricture, etc.) [117].

Cirrhosis refers to an advanced stage of chronic liver failure and has been associated with the risks of cholangiocarcinoma and hepatocellular carcinoma, irrespective of underlying etiology. As expected, the association of cirrhosis with the incidence of cholangiocarcinoma appeared to be stronger for intrahepatic cholangiocarcinoma than for extrahepatic cholangiocarcinoma with pooled odds ratios of 15 and 3.8, respectively [118].

Pancreatobiliary maljunction (PBM) is defined as a congenital condition characterized by the communication of the pancreatic and bile ducts outside the duodenal wall, and results in reflux of pancreatic juice into the biliary system due to the compromised sphincter function [119]. Long-term inflammatory reaction in the biliary epithelium may cause carcinogenesis [120]. It is difficult to identify PBM cases without bile duct dilatation, but thickening of the inner layer of the gallbladder can be a diagnostic clue [121]. Surgery (cholecystectomy with or without resection of the extrahepatic bile duct) has been recommended for patients diagnosed with PBM to reduce the future risk of cholangiocarcinoma [119, 121]. Choledochal cysts are hereditary biliary disorders characterized by cystic dilation of intra- and/or extrahepatic bile ducts, which are derived based on the PBM. A meta-analysis suggests >26-fold elevated risk both for intra- and extrahepatic cholangiocarcinomas among individuals with choledochal cysts compared to non-affected individuals [118]. Caroli's disease is also an inherited disorder, which is derived from ductal plate malformation and is characterized by cystic dilatation of intrahepatic bile ducts. Patients with this disease have been considered to be at elevated risk of cholangiocarcinoma [122]. Owing to the rarity of Caroli's disease, the risk of cholangiocarcinoma associated has not been reported in large studies, but the overall incidence was reported to be 6.6% [122].

Intraductal papillary neoplasms of the bile duct have been considered as a biliary counterpart of IPMNs of the pancreas. Due to the rarity of this type of neoplasm, its clinical outcomes remain unexplored. However, it has been considered that this neoplasm may represent a stepwise progression from adenoma to carcinoma through accumulation of molecular alterations [123].

Biliary stones have been recognized as risk factors for development of cholangiocarcinoma. Choledocholithiasis has been associated with presence of intra- and extrahepatic cholangiocarcinomas conferring relative risks of >10 [118]. Cholelithiasis has been also associated with presence of intra- and extrahepatic cholangiocarcinoma, but relative risks have been numerically smaller than for choledocholithiasis [118]. Although biliary inflammation and cholestasis as underlying mechanisms are plausible, the evidence has been derived from case-control studies that were subject to a bias due to secondary biliary stone formation following cholangiocarcinoma. A further prospective study is warranted on this topic.

Other disorders associated with development of cholangiocarcinoma include inflammatory bowel diseases including ulcerative colitis and Crohn's disease (irrespective of concomitant PSC) and chronic pancreatitis [118].

1.2.5 Epidemiological Factors

Long-standing adiposity (i.e., excess body weight) can cause carcinogenesis in various organs throughout the body [124]. The association of obesity itself with the risk of cholangiocarcinoma appears to be weak or null [118]. Diabetes mellitus has been considered as a modest risk factor for cholangiocarcinoma overall with a relative risk of 1.6 (2.0 and 1.6 for intra- and extrahepatic cholangiocarcinomas, respectively) [125]. Patients with nonalcoholic fatty liver disease are at modestly elevated risk of cholangiocarcinoma (relative risk, 2.0–2.1 for all, intrahepatic, or extrahepatic cholangiocarcinoma) [126].

Cigarette smoking can provoke malignant transformation of the biliary epithelium. Despite substantial heterogeneity in definitions of smoking status across the prior studies, meta-analyses suggest that smokers may be predisposed to 1.3-fold higher risk of intrahepatic cholangiocarcinoma and 1.7-fold higher risk of extrahepatic cholangiocarcinoma compared to nonsmokers [118]. Future studies should examine to what extent smoking cessation can decrease the elevated risk of cholangiocarcinoma due to tobacco exposure.

Excess alcohol consumption may increase the possibility of developing cholangiocarcinoma by causing chronic liver diseases (e.g., cirrhosis) and/or exploiting direct carcinogenic effect on the biliary epithelium. Ethanol in alcoholic beverages is metabolized in the liver, and the metabolites are excreted into the biliary system. However, the effect of the metabolites on the biliary epithelium in the context of carcinogenesis has not been fully investigated. Despite considerable heterogeneity in definitions of alcohol exposures across the prior studies, pooled relative risks comparing alcohol drinkers vs. nondrinkers in meta-analyses were 3.2 and 1.8 for intra- and extrahepatic cholangiocarcinoma, respectively [118]. Further research is warranted to examine doses and types of alcoholic beverages in relation to the risk of cholangiocarcinoma.

Dietary patterns have not been fully investigated in relation to incidence of cholangiocarcinoma. All individuals are continuously exposed to these epidemiological factors, and hence, research in this field may have considerable clinical relevance as the data derived would help us to consider and lower the attributable risk of diet in cholangiocarcinoma in general populations.

Given modest risk increase due to the presence of each epidemiological risk factor described, research incorporating a wide spectrum of lifestyle factors is warranted to implement effective prevention strategies through lifestyle interventions.

Long-term occupational exposure to certain chemicals as a risk factor for cholangiocarcinoma has attracted public attention in Japan. High incidence of cholangiocarcinoma has been reported recently among workers in printing companies (termed “occupational cholangiocarcinoma”) [127] who are routinely exposed to potentially mutagenic chemicals including 1,2-dichloropropane and dichloromethane [128, 129]. Pathological and molecular features of occupational cholangiocarcinoma include unique trinucleotide changes, high mutation burden, and multicentric tumorigenesis [130, 131]. To prevent this occupational hazard, preventive programs

at the workplace should be improved, and periodical medical check-up should be conducted prudently [127].

1.2.6 Discussion

The incidence of cholangiocarcinoma has been rising worldwide [132]. Prognosis of patients diagnosed with cholangiocarcinoma has been poor due to difficulties in identifying this malignancy at an early stage of the disease. Gemcitabine-based chemotherapy regimens have been used for advanced or metastatic cases [133–135], but their clinical effectiveness has been quite limited. Therefore, it is mandatory to identify risk factors for cholangiocarcinoma and stratify individuals in terms of risk of developing this malignancy for better clinical outcomes of the patients. Recent exome-wide analyses based on high-throughput sequencing technologies have revealed distinct genetic aberrations that may contribute to the development and distinct characteristics of cholangiocarcinoma [99, 136–138]. Currently, clinical evaluation is ongoing for a number of agents including molecular targeted agents for FGFR and IDH pathways [139, 140]. Of note, a clinical trial has demonstrated survival benefits of the small-molecule targeted inhibitor of mutated *IDH1*, ivosidenib, in patients with advanced cholangiocarcinoma harboring *IDH1* mutation [141]. Therefore, there may be a possibility that risk factors may differentially impact incidences of tumor subtypes classified by molecular signatures as well as those defined by anatomical location of the primary origin. Consideration of the heterogeneity of the subtypes would help to develop strategies of prevention, surveillance, and treatment for specific subtypes of cholangiocarcinoma, thereby improving the outcomes of patients with cholangiocarcinoma overall.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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Detection Strategies and Examination of Early Pancreatic Cancer

2

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Abstract

Early diagnosis is essential to improve the prognosis of patients with pancreatic cancer (PC). A long-term prognosis should be expected in patients with PC of <10 mm. Main pancreatic duct (MPD) dilatation and pancreatic cystic lesions are important indirect findings that should be considered. Endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) are recommended to diagnose small tumor lesions that are difficult to be directly detected with external ultrasonography (US) and computed tomography (CT). Thereafter, EUS-guided fine-needle aspiration should be performed when a tumor lesion is detected using EUS. When localized irregular MPD stenosis, caliber MPD changes, and branch duct dilatation are detected, ERCP followed by pancreatic juice cytology is recommended. EUS and MRCP play important roles in detecting local irregular stenosis of the MPD or small cystic lesions in PC in situ, which is undetectable on cross-sectional images. Subsequently, ERCP and associated serial pancreatic juice aspiration cytologic examination obtained using endoscopic nasopancreatic drainage may be useful in the diagnosis of very early-stage PC. Additionally, collaborations between special doctors in pancreatic diseases and general practitioners play an important role in the early detection of PC.

Keywords

Early pancreatic cancer · EUS · SPACE · MRCP

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Abbreviations

CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
EUS-FNA	Endoscopic ultrasonography-guided fine-needle aspiration
IPMN	Intraductal papillary mucinous neoplasm
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PC	Pancreatic cancer
PCIS	Pancreatic cancer in situ
US	Ultrasonography

2.1 Introduction

Generally, the prognosis of patients with pancreatic cancer (PC) has been poor according to the results of recent studies. However, in patients with stage 0 PC corresponding to intraepithelial PC or those with tumor diameter of <1 cm, the 5-year survival rate has been reported as >80% [1]. Early PC diagnosis is expected to improve the prognosis in the future. Recently, clinical guidelines (CGL) for PC published by the Japan Pancreas Society (JPS) have been revised in 2019 [2]. A new algorithm or statement for the early PC diagnosis has been announced. In this study, diagnostic approaches for early-stage PC have been reviewed.

2.2 Clinical Features and Image Findings of Early-Stage PC

Conventionally, reports on early-stage PC have been extremely limited, and its clinical features and image findings have been unclear. The Japan Study Group on the Early Detection of Pancreatic Cancer (JEDPAC) was established in 2014. In 2018, the JEDPAC reported 200 surgically resected cases of early-stage PC (51 stage 0 and 149 stage I) at 14 Japanese high-volume centers [3]. In this report, 50 (25%) cases were symptomatic, 30% had risk factors such as intraductal papillary mucinous neoplasm (IPMN), diabetes mellitus (DM), and smoking (Table 2.1), and 51% were diagnosed at an early stage while assessing and examining for other diseases such as chronic hepatitis, DM, and coronary artery diseases. About half of these cases led to early diagnosis based on ultrasonography (US) and computed tomography (CT) findings such as the main pancreatic duct (MPD) dilatation. DM has been conventionally known as a risk factor for PC. Recently, many asymptomatic PC cases had been diagnosed within 2 years after the onset of abnormal glucose resistance [2]. The American Gastroenterological Association had reported that the occurrence of new-onset DM or worsened hyperglycemia in such surveillance cases with risk factors would certainly warrant additional examinations including CT, magnetic resonance imaging (MRI), or endoscopic ultrasonography (EUS) [4]. In the future, surveillance systems of imaging tests should be established for the early

Table 2.1 Risk factors of early-stage PC (revised from reference [3])

Risk factors	Number of patients (%)
Diabetes mellitus	64 (32)
Smoking	62 (31)
Chronic pancreatitis	30 (15)
Heavy alcohol consumption	26 (13)
Obesity	13 (7)
Family history of pancreatic cancer	9 (5)

Table 2.2 Imaging modalities and findings for the diagnosis of early-stage PC (revised from reference [3])

Modalities	Findings	All patients (%) (n = 200)	Stage 0 (%) (n = 51)	Stage I (%) (n = 149)
US		135/200 (67.5)	34/51 (66.7)	101/149 (67.8)
	MPD dilatation	101/135 (74.8)	26/34 (76.5)	75/101 (74.3)
	MPD stenosis	27/135 (20.0)	2/34 (5.9)	25/101 (24.8)
	Tumor	71/135 (52.6)	3/34 (8.8)	68/101 (67.3)
CT		196/200 (98.0)	50/51 (98.0)	146/149 (98.0)
	MPD dilatation	156/196 (79.6)	36/50 (72.0)	120/146 (82.2)
	Tumor	101/196 (51.5)	5/50 (10.0)	96/146 (65.8)
	Focal fatty changes	82/196 (41.8)	21/50 (42.0)	61/146 (41.8)
MRI		173/200 (86.5)	46/51 (90.2)	127/149 (85.2)
	MPD dilatation	143/173 (82.7)	34/46 (73.9)	109/127 (85.8)
	Tumor	78/173 (45.1)	5/46 (10.9)	73/127 (57.5)
EUS		173/200 (86.5)	41/51 (80.4)	132/149 (88.6)
	MPD dilatation	153/173 (88.4)	35/41 (85.4)	118/132 (89.4)
	MPD stenosis	98/173 (56.6)	28/41 (68.3)	70/132 (53.0)
	Tumor	132/173 (76.3)	10/41 (24.4)	122/132 (92.4)
ERCP		141/200 (70.5)	47/51 (92.2)	94/149 (63.1)
	MPD dilatation	114/141 (80.9)	39/47 (83.0)	75/94 (79.8)
	MPD stenosis	112/141 (79.4)	39/47 (83.0)	73/94 (77.7)
FDG-PET		61/200 (30.5)	11/51 (21.6)	50/149 (33.6)
	FDG accumulation	31/61 (50.8)	1/11 (9.1)	30/50(60.0)

US, ultrasonography; MPD, main pancreatic duct; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; FDG-PET, fluorodeoxyglucose-positron emission tomography

PC diagnosis among patients with abnormal glucose resistance. When diagnosing patients with IPMN without mural nodules, an efficient follow-up is required to determine any concomitant PC lesions. Kamata et al. reported that the 3- and 5-year rates of IPMN-concomitant PC development are 4.0% and 8.8%, respectively, and the value of semiannual EUS to diagnose early-stage IPMN-concomitant PC [5].

As for imaging findings from JEDPAC study (Table 2.2), MPD dilatation or irregular stenosis detected using CT, magnetic resonance cholangiopancreatography (MRCP), or EUS is important for the detection of early-stage PC. Among these findings, MPD dilatation detected using US was the most important initial finding for the early PC diagnosis. US may be limited to detect MPD stenosis. EUS, MRCP, and endoscopic retrograde cholangiopancreatology (ERCP) had a favorable visibility in detecting MPD stenosis [6]. EUS also showed high visibility of tumor regions

in stage I PC. EUS is recommended even when US and CT cannot directly detect a mass lesion. EUS showed slightly low echoic tumor regions in 24% of patients with stage 0 PC. These observations indicated that changes in the diagnostic algorism for early-stage PC are required to identify MPD irregular stenosis or dilatation using EUS or MRCP in addition to detecting tumor regions using US or CT.

2.3 Cytological Diagnosis of Early-Stage PC

In early-stage PC with a tumor lesion, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been widely performed for its cytological or histological confirmation. Recent studies have reported preoperative cytological findings in early-stage PC. The sensitivity of EUS-FNA for PC of <10 mm ranged from 84 to 96% [3, 7, 8]. Recently, needle tract seeding (NTS) performed after the preoperative EUS-FNA for the pancreatic body and tail cancer has been reported. Yane et al. reported that 3.4% of patients with PC who underwent preoperative EUS-FNA were diagnosed with NTS [9]. For resectable PCs located in the pancreatic body or tail, EUS-FNA should be carefully performed to prevent NTS.

Diagnosing PC without a mass lesion is difficult using various imaging modalities. In the last 10 years, certain patients with stage 0 PC have been diagnosed by cytodiagnosis using pancreatic juice [10–12]. Iiboshi et al. first reported the high accuracy to diagnose stage 0 PC by repeated cytodiagnosis using pancreatic juice obtained followed by endoscopic nasopancreatic drainage (ENPD) [13]. Recently, Satoh et al. termed this diagnostic procedure as the serial pancreatic juice aspiration cytologic examination (SPACE) [14]. In the JEDPAC study, 72% of patients with stage 0 were confirmed as malignant using SPACE [3]. Recently, studies reported on SPACE with favorable sensitivity (62.3–82.4%) for the diagnosis of early-stage PC [3, 13, 15–17]. These observations strongly suggest that SPACE should improve the sensitivity of cytology for early-stage PC. However, the pancreatic juice cytological method including SPACE may be associated with complications, such as post-ERCP pancreatitis (PEP) [13, 15, 17, 18]. Recently, a randomized controlled trial comparing 4- with 5-Fr ENPD catheters to reduce the incidence of complications suggested that the former may reduce the incidence of PEP [19]. Additionally, SPACE has some problems that need to be solved, such as self-decannulation, pancreatic juice processing from the pancreatic head or tail, difficult identification of the appropriate placing position, displacement, and false-positive pancreatic juice cytodiagnosis. In the future, further multicentric prospective studies should evaluate the appropriate number of samples, placing position of the ENPD tube into the MPD, and size of the ENPD tube [20].

2.4 Pathological Features of Early-Stage PC

Recent reports on pathologic features of early-stage PC have been limited. Patients with pancreatic cancer in situ (PCIS) could be classified into three types as follows: flat (F), low papillary (LP), and mixed. Those with the LP type may demonstrate a tendency than those with the F type to spread into the MPD and branch duct. Patients

with PCIS with the LP type may tend to change into invasive PC after metastasizing intraductally. Conversely, patients with the F type may tend to invade with minimal intraductal metastasis [21]. These observations suggested that patients with LP-type PCIS might tend to metastasize into MPD, and its pathological features were also reflected in imaging findings, with a long irregular MPD stenosis detected using MRCP or EUS.

In patients with stage 0 or I PC cases, focal parenchymal atrophy and fatty replacement around cancer lesions were frequently detected with contrast-enhanced CT [22, 23]. The JEDPAC data showed that 42% of 200 patients with early-stage PC also had local fatty changes (Table 2.2). Recently, EUS findings and pathological characteristics of 16 patients with PCIS were reported. Hypoechoic areas, including a 10- to 11-mm hypoechoic mass, around the MPD stricture were observed in 56% of patients with PCIS using EUS. Histopathologically, subepithelial inflammatory cell infiltration and fibrosis were present in all patients with PCIS. From these observations, PCIS may cause localized inflammation and fibrotic changes around the pancreatic duct, resulting in local pancreatitis, and pancreatic fatty infiltration in the background of the pancreas. EUS may offer a satisfactory resolution to demonstrate pancreatic changes in patients with PCIS [24]. In contrast-enhanced CT, local pancreatic atrophy, and fat deposition were commonly found. Recently, a total of 46 patients strongly suspected of early-stage PC without nodule on imaging were evaluated according to ten factors of CT, MRI, EUS, and ERCP [25]. These observations strongly suggested that focal pancreatic atrophy and hypoechoic areas surrounded by MPD strictures are important indirect findings for the diagnosis of stage 0 PC (Fig. 2.1).

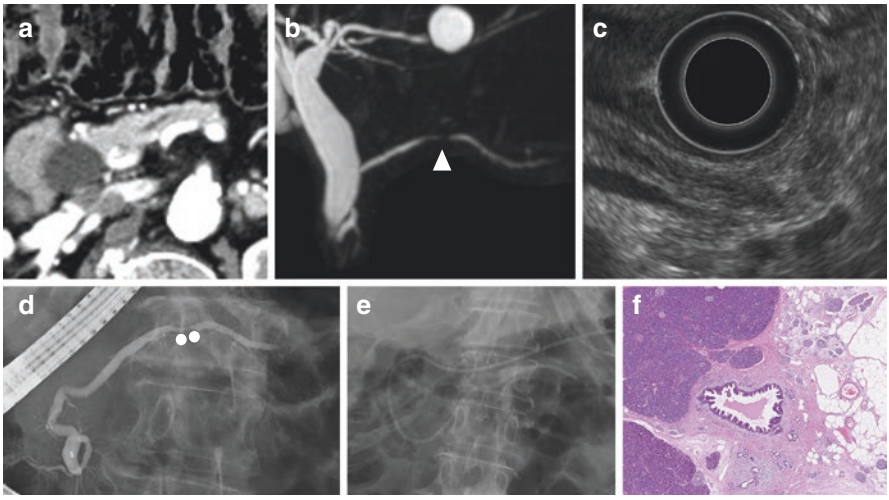

Fig. 2.1 A case with stage 0 pancreatic cancer (a 60-year-old woman). Dynamic CT demonstrated MPD dilatation only (**a**). MRCP revealed irregular MPD stenosis (white arrow) in the pancreatic body (**b**). EUS also revealed irregular MPD stenosis. No tumorous lesion was detected (**c**). ERCP confirmed an irregular MPD stenosis, and a sequential ENPD was performed for SPACE (**d**, **e**). Cytologic examination positively confirmed adenocarcinoma, and distal pancreatectomy was performed. PCIS was histologically detected in the irregular MPD stenosis (white circles in **d**) (**f**)

2.5 Statements and Detection Strategies of Early-Stage PC in Japan

The 2016 CGL committee for PC by JPS firstly proposed some statements for the clinical question on PC with long-term survival [26]. Long-term prognosis is expected in patients with PC of <10 mm. MPD dilatation and pancreatic cystic lesions are important indirect findings. When a small tumor lesion cannot be directly detected with US and CT, EUS, and MRCP is recommended to examine any tumor lesions. EUS-FNA should be performed when a tumor lesion is detected using EUS. When the localized irregular MPD stenosis, caliber MPD changes, and branch duct dilatation are detected, ERCP followed by pancreatic juice cytology is recommended. The 2019 CGL for PC by JPS supported these statements for the diagnosis of early-stage PC. The newest diagnostic algorithm for PC in the CGL 2019 is shown in Fig. 2.2 [2]. In this CGL, three statements are related to EUS, and two statements are related to ERCP.

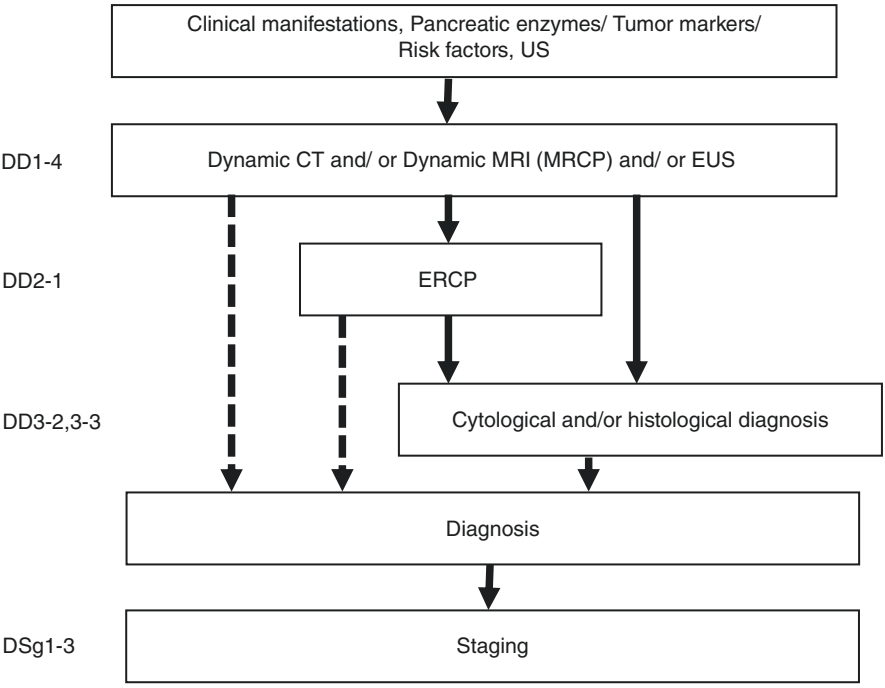

Fig. 2.2 Algorithm for the diagnosis of pancreatic cancer (revised from reference [2]). US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography

2.6 Collaborations Between Specialists and General Practitioners for Early-Stage PC in Japan

JPS firstly published the diagnostic algorithm for PC in 2006. At that time, the Onomichi Medical Association (OMA) had experienced difficulties in diagnosing PC at an early stage due to the lack of specialists for pancreatic diseases (SPD) despite the increased number of patients with PC. In 2007, OMA decided to establish a social program for the early diagnosis of PC (Onomichi project), with collaborations between SPD in central hospitals and general practitioners (GP) [27]. SPD in central hospitals educated GP on risk factors in CGL for PC, abnormal US findings such as MPD dilatation or pancreatic cystic lesion, and MRCP and EUS values. If GP encountered a patient with these problems, they consulted SPD in central hospitals for further examination of the whole pancreas. From January 2007 to September 2017, a total of 555 of 12,307 suspected patients (4.5%) were histologically diagnosed with PC. Of these 555 patients with PC, 24 had stage 0 and 40 had stage I PC. After starting this Onomichi project, the surgical resection and 5-year survival rates of PC in Onomichi area significantly improved [28]. Recently, as the basic concept of the Onomichi project expands in other rural regions in Japan, some Japanese medical associations, such as Osaka, Kagoshima, Matsue, Obihiro, Kawasaki, and Kishiwada, attempted to establish the new regional medical networks for the early diagnosis of PC. The Kishiwada–Katsuragi project with collaborations between medical centers and GP used clinical findings of 244 enrolled patients between 2014 and 2016. Among them, 28 PCs including 15 early stage ones were detected [29]. These observations suggested that collaborations between SPD and GP in the medical association play an important role in the early detection of PC. In the future, regional networks between SPC and GP in medical associations for the early PC diagnosis are essential in every local area in Japan.

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Biomarkers for Pancreatic Cancer and Cholangiocarcinoma

3

Takahiro Kishikawa

Abstract

The lack of highly sensitive biomarkers for pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) hampers improvement of their prognosis. Therefore, convenient and accurate diagnostic, prognostic, and predictive biomarkers that reflect pathophysiological or physiological processes are required. In this chapter, recent developments in protein, glycoprotein, and circulating nucleic acid biomarkers of PDAC and CCA are highlighted. In addition, new classes of biomarkers, circulating tumor cells (CTCs), and extracellular vesicles (EVs) have a potential to reflect the molecular and genetic characteristics of primary tumors. Importantly, recent advances in sequencing and -omics techniques, such as proteomics and metabolomics, have enabled assessment of the extremely small number of nucleic acids or proteins in CTCs or EVs, which provides the molecular landscape of tumors and suggests therapeutic targets in a timely manner. To date, no single marker has yet been approved for clinical use, with the exception of carbohydrate antigen 19-9, however, further advances in omics-based techniques and validation in large patient cohorts should result in the development of effective and widely usable markers in near future, which enhance the diagnosis, treatment-response prediction, and prognosis of PDAC and CCA.

Keywords

Biomarker · Pancreatic cancer · Cholangiocarcinoma · Extracellular vesicles · Circulating tumor cells · Circulating nucleic acids

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3.1 Introduction

Biomarkers can be assayed to detect malignant diseases, monitor their course, and select treatment strategies. They reflect the physiological status of a cell at a given time and change during the course of pathogenesis [1]. The complex cellular, intercellular and organ-specific mechanisms of tumorigenesis vary according to the type of malignant tumor, which explains the diversity of prognoses and success rates of cancer treatment [2, 3]. Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignant tumors and a leading cause of cancer-related deaths; also, its prevalence is increasing worldwide. The incidence of PDAC is almost equal to its mortality rate, ascribable to delayed diagnosis, absence of effective screening methods, and the aggression and therapeutic resistance of the disease [4]. Cholangiocarcinoma (CCA) accounts for 3% of all gastrointestinal cancers arising from the intra- or extrahepatic bile duct. Although the incident rate is relatively rare, especially in European countries, the diagnostic and treatment options are inadequate. CCA is typically asymptomatic in the early stages and tends to be diagnosed at an advanced stage. The tumor recurrence rate after resection is low and CCA has a higher mortality rate than other major digestive cancers [5]. The incidence of CCA has gradually increased in recent years worldwide.

Importantly, there has been no notable improvement in the prognosis of PDAC and CCA in this decade; the 5-year survival rate is 9–10% and 7–20%, respectively, which are extremely low compared to other cancers [2]. Therefore, research on the pathogenetic mechanisms and discovery of novel biomarkers could improve the prognosis by enabling accurate and highly sensitive detection at an early stage, selection of the most effective treatment based on their molecular profiles, and timely evaluation and prediction of the treatment response.

Compared to tissue biomarkers, circulating biomarkers possess several advantages for screening, sample collection being easy and non-invasive; moreover, the possibility of repeated sample collection enables longitudinal monitoring of disease progression. Notably, the rapid prevalence of "-omics" technologies have revealed the mechanisms and networks underlying carcinogenesis, facilitating the discovery of nucleic acid and protein biomarkers (Fig. 3.1).

3.2 Currently Used Biomarkers for PDAC and CCA

Carbohydrate antigen 19-9 (CA19-9), a sialylated Lewis blood group antigen, is the most widely used diagnostic and prognostic biomarker for various types of cancer, including those of the colon, stomach, and pancreas [4]. CA19-9 is currently the only biomarker approved by the United States Food and Drug Administration (FDA) for PDAC and CCA. Although its sensitivity and specificity are sufficient for predicting the response to chemotherapy or detecting recurrence after surgical resection, CA19-9 is not suitable as a diagnostic biomarker of early-stage pancreatic and bile duct cancers [4]. The serum level of CA 19-9 varies according to the secretor status and Lewis genotype; the CA19-9 level is not elevated in Lewis blood type-negative individuals with tumors. Carcinoembryonic antigen (CEA), a glycosylphosphatidyl-inositol-anchored

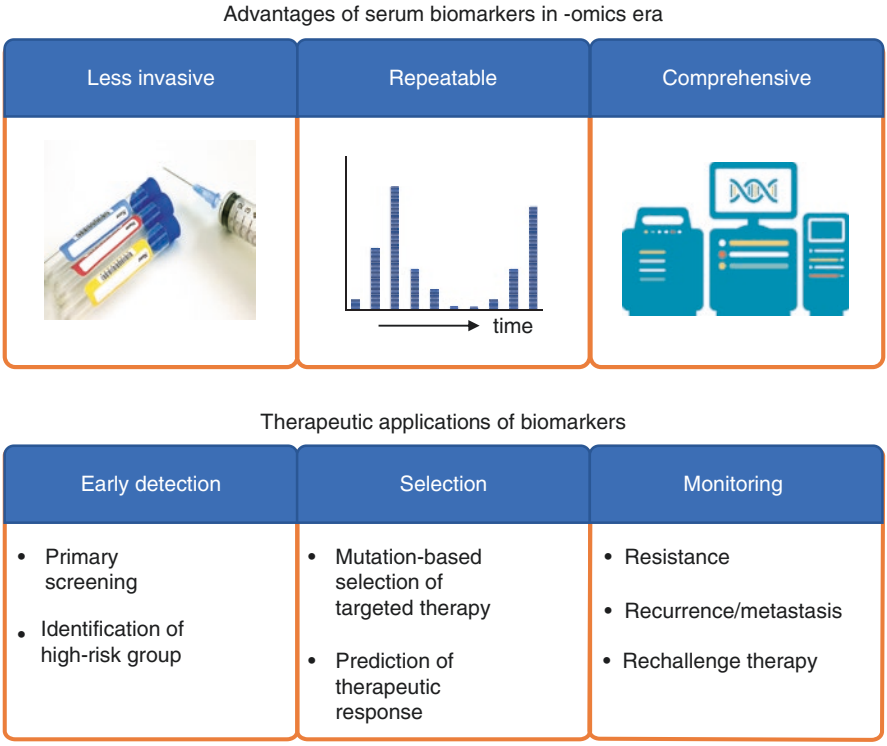

Fig. 3.1 Advantages of circulating biomarkers and their therapeutic applications

cell-surface glycoprotein, is used as a diagnostic and prognostic biomarker in, for instance, colorectal, breast, gastric cancer. Although an increased level of CEA has been reported in more than 60% of patients with PDAC, and its specificity was enhanced in combination with CA 19-9, the sensitivity was lower than that of CA 19-9 alone [6]. Studies of CEA in patients with CCA failed to demonstrate its superiority as a diagnostic and prognostic marker (sensitivities 50% and 30%, respectively) [7]. Importantly, glycoprotein biomarkers are not specific to PDAC or CCA, being also related to other benign or malignant pathologies, such as cholangitis, obstructive jaundice, chronic hepatitis, and chronic pancreatitis. This hampers the discrimination of malignant tumors from benign inflammatory diseases. Therefore, a highly specific and sensitive diagnostic biomarker is urgently needed to enable earlier diagnosis and improve the outcomes [8, 9].

3.3 Other Protein Markers for PDAC and CCA

Glycosylation, one of the most common co- and posttranslational modifications, is crucial for a variety of biological processes, including intercellular adhesion, cell migration, cell–cell signaling, host–microbial interactions, and inflammation.

Aberrant glycosylation is associated with the development and progression of various cancers and is characteristic of serum glycoproteins in patients with cancer. As a result, altered glycans or their carrier proteins in specific tissues are used as biomarkers for various types of cancer [10]. Mucins, a large family of highly glycosylated proteins, are overexpressed in several types of cancer, and can be used as early biomarkers or for staging. Importantly, secreted mucins—such as MUC1, MUC5AC, and MUC16—are the main carriers of CA19-9, indicating mucins to be potential diagnostic biomarkers of cancer [11]. In fact, the serum MUC5AC level was elevated in patients with CCA, and those patients had a significantly worse prognosis than those without serum MUC5AC [12]. Also, serum MUC3A is a candidate diagnostic and prognostic biomarker for extrahepatic CCA, and is superior to CA19-9 and CEA in this regard [13]. Overexpression of MUC1 and aberrant expression of MUC4 are associated with PDAC development and progression [14]. Wang et al. demonstrated that the serum N-glycan status, including peak10 and NA3F2, has greater diagnostic utility than CA19-9 in patients with extrahepatic CCA [15].

A large number of proteins have been studied as serum biomarkers of PDAC or CCA. Macrophage inhibitory cytokine 1 (MIC-1) is a member of the transforming growth factor superfamily implicated in macrophage activation. Using a sensitive enzyme-linked immunosorbent assay, Koopman et al. demonstrated that MIC-1 and CA 19-9 are independently predictive of PDAC with a sensitivity and specificity of 71–90 and 78–94%, respectively [16]. A receiver operating characteristics analysis showed that MIC-1 was significantly superior to CA 19-9 for differentiating patients with pancreatic cancer from healthy controls, but not from those with chronic pancreatitis or CCA. Moreover, a recent meta-analysis of 14 studies showed that serum MIC-1 has comparable diagnostic accuracy to CA19-9 for PDAC [17].

Prevalence of proteomics technologies enables identification of novel biomarkers for asymptomatic PDAC. Several serum/plasma biomarkers—such as prolyl 4-hydroxylation of α-fibrinogen peptides, galectin-3-binding protein (LGALS3BP), insulin-like growth factor-binding protein (IGFBP)2 and IGFBP3, C4b-binding protein α-chain (C4BPA), serum osteopontin (OPN), and tissue inhibitor of metalloproteinase 1 (TIMP-1)—reportedly discriminate early stage of pancreatic cancer from normal or precancerous cystic lesions [18, 19]. A proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor (TNF) superfamily also has potential as a biomarker. The serum level of APRIL is increased in pancreatic cancer, with a sensitivity of 70.1% and specificity of 85.5% [20]. Additionally, the sensitivity and specificity are increased when APRIL is combined with CEA and CA 19-9. Other potential biomarkers of PDAC have been identified in pancreatic juice, such as matrix metalloproteinase (MMP)-7, Anterior Gradient 2 (AGR2), S100A6, telomerase activity, serine proteinase-2 pre-protein (PRSS-2), and pancreatic lipase-related protein-1 (PLRP-1) [21]. It is also reported that in the serum of patients with CCA, MMP7, IL-6, Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1), and SSP411 levels are abnormally elevated and suggested as diagnostic and prognostic biomarkers [22]. Furthermore, by secretome analysis of patients with PDAC or CCA, Le Large et al. showed that plasma thrombospondin-2 (THBS2) is a promising biomarker and demonstrated a greater discriminatory power when used in combination with CA19-9 [23].

Metabolomic biomarkers are also useful for identifying high-risk individuals in the general population. Honda et al. reported that plasma/serum apolipoprotein A2 (apoA2) isoforms, a major component of high-density lipoproteins, are promising biomarkers for early PDAC or precancerous lesions. Proteomic approaches have revealed that the specific isoform ratio of apoA2 (apoA2-ATQ/AT) is significantly reduced in the serum/plasma of patients with pancreatic cancer compared to healthy individuals, even in the early stages of the disease or in the presence of precancer cystic tumors [24].

3.4 Circulating Tumor Cells

Circulating tumor cells (CTCs) originating from the primary tumor are transported in the bloodstream to distant organs, which can cause metastases [25]. However, the number of CTCs in the blood is extremely small which necessitate highly sensitive and specific enrichment techniques. Indeed, over 40 of novel platforms have been developed which vary in terms of their targets (such as surface antigens), complexity, and flexibility. Although the number of CTCs is relatively small in patients with PDAC, a meta-analysis of nine cohort studies of CTCs in patients with PDAC showed that 43% had CTCs in peripheral blood; those patients had a significantly worse progression-free survival (PFS) and overall survival [26]. Notably, CTCs have been detected in some patients with pre-adenocarcinomatous disease (>30%) [27]. Although few studies have addressed CTCs as diagnostic and/or prognostic biomarkers of CCA, 17–25% of patients showed an elevated number of CTCs; importantly, the number of CTCs was associated with survival [5].

Additionally, advances in whole-genome or transcriptome amplification and genome-wide analysis platforms enable high-resolution analyses of the genome or transcriptome of a single cell, revealing hitherto obscured biological complexity [28]. These techniques are suitable for analysis of CTC. Indeed, CTCs are not only diagnostic biomarkers but also reflect the molecular and genetic characteristics of tumors. For example, Frances et al. performed RNA-seq of purified CTCs from patients with PDAC and demonstrated their potential for identifying patients who will benefit from novel therapeutics targeting the molecular pathways enriched in CTCs [29]. Yu et al. developed targeted single-cell next-generation sequencing without whole-genome pre-amplification, which enables characterization of CTCs by accurate evaluation of single nucleotide DNA variants [30]. Moreover, CTCs enriched by a non-labeling method from the bloodstream of patients with cancer show different metabolomic profiles to organ-specific tumors, as determined by living single-cell mass spectrometry [31].

3.5 Extracellular Vesicles

Extracellular vesicles (EVs) are lipid-bound vesicles secreted by cells into the extracellular space. The three main subtypes of EVs are microvesicles, exosomes, and apoptotic bodies, which are differentiated by their biogenesis, release pathways, size,

content, and function. Exosomes, typically of diameter 50–150 nm, contain proteins and genetic material that can be isolated and analyzed as biomarkers [32]. The theoretical advantages of exosome analysis in liquid biopsy are that exosomes have a longer circulating half-life than circulating cell-free nucleic acids, such as circulating tumor DNAs (ctDNAs) and cell-free RNAs, and cancer cells constantly secrete exosomes into the peripheral circulation, which is thus enriched in tumor-associated exosomes compared to those from normal cells. Depending on their cell and tissue of origin, exosomes contain a unique mixture of proteins, lipids, and nucleic acids and they mediate cell-to-cell communications by transferring their contents between cells.

Profiling the nucleic acid content of exosomes (exoDNA) can provide useful information on the mutational landscape of established cancers and enable their early detection. In particular, KRAS mutation is present in over 90% of primary PDAC, and so is a good target of ctDNA-based assays. There have been several recent advances in measuring platforms, including the digital PCR and targeted next generation sequencing (NGS). Digital PCR assays on microfluidic platforms are quantitative and highly sensitive and can be used extensively to quantify single cancer-specific mutation. For a larger number of loci, targeted sequencing using PCR amplicons have been used, which can increase the depth of target read and reduce costs compared to entire exome sequencing [33]. These innovative technologies enable to detect ctDNA or exoDNA as low as 0.1% in the blood. Indeed, a larger proportion of patients with localized PDAC showed detectable KRAS mutations in exoDNA than previously reported in ctDNA [34].

Circulating non-coding RNAs are also candidate biomarkers for PDAC and CCA. Micro-RNA (miRNA) is an 18–22-nucleotide non-coding RNA detectable in biofluids which modulates the posttranslational expression of tumor-suppressor genes or oncogenes [35]. Further, miRNA circulates in the blood encapsulated in exosomes. For instanse, a large study of blood miRNA as a biomarker of PDAC revealed a sensitivity and specificity of a diagnostic panel comprising miR-145, miR-150, miR-223, and miR-636 of 85% and 48%, respectively [36]. However, insufficient validity was obtained for early-stage PDAC.

Exosomal proteins are also important players in PDAC diagnosis. Melo et al. reported that glypican-1 (GPC1) was enriched in PDAC exosomes. The circulating $GPC1^+$ exosome level was significantly increased in patients with pancreatic cancer compared to healthy controls and had a sensitivity and specificity for diagnosing PDAC of 100%. By contrast, the serum CA19-9 level cannot distinguish patients with PDAC from those with benign pancreatic disease [37]. Moreover, exosomal forms of epidermal growth factor receptor released from pancreatic cancer cells can be used to monitor treatment response [38].

3.6 Biomarker-Based Selection of Targeted Therapies

By means of specific inhibitors of the oncogenic pathways dysregulated in tumors, molecular-targeted therapy is expected effective against cancer with relatively few toxicities. Precise evaluation of mutational and transcriptional landscape within the

tumor is thus essential to choose and administrate these specific drugs appropriately.

BRCA2 and BRCA1 mutations cause higher risk of PDAC. Somatic BRCA2 mutations are described to occur in almost 4–7% of patients with PDAC. BRCA genes mutations are associated with defect in homologous recombination repair of DNA double-strand breaks and confer sensibility to poly adenosine diphosphate-ribose polymerase (PARP) inhibition which leads to accumulation of DNA damage and tumor cell death [39]. Indeed, PARP inhibitor Olaparib achieved a longer PFS in patients with metastatic PDAC who had a germline BRCA1 or 2 mutation [40].

The FGF pathway regulates cell proliferation, migration, and angiogenesis. Alterations in genes encoding fibroblast growth factor receptors (FGFRs) can promote aberrant FGF pathway activation and tumorigenesis. FGFR fusions and translocations are driver mutations in CCA and are present in 13–17% of intrahepatic CCAs. Pemigatinib, which targets FGFR2 rearrangement or fusion, was recently approved by the FDA [41]. Isocitrate dehydrogenase (IDH)1/IDH2-specific inhibitors are important in the treatment of CCA. IDH mutations cause metabolic reprogramming and production of the oncometabolite, D-2-hydroxyglutarate (D-2HG), resulting in epigenetic effects and malignant transformation of cells. The blood D-2HG level may be a useful diagnostic biomarker and predictive of the response to selective IDH1 and IDH2 inhibitors [42].

On the other hand, several serum proteins and non-coding RNAs are reported to predict or monitor the emergence of resistance to chemotherapy. A meta-analysis shows that 18 microRNAs have possible contributions to chemoresistance, in particular, miR-21 showing a hazard ratio for gemcitabine resistance of 2.061 [43]. Additionally, soluble vascular cell adhesion molecule-1 (sVCAM-1), which is increased with gemcitabine treatment promotes the resistance to the drug through the attraction of macrophages into the tumor [44]. Longitudinal monitoring of these markers enables early identification and adaptive modifications to treatments.

3.7 Conclusion and Future Perspectives

A variety of biomarkers for PDAC and CCA have been discovered over the past decade, but none are used routinely in the clinical setting. Our improved understanding of the tumor biology and microenvironment of PDAC and CCA has enabled biomarker detection. A number of novel classes of circulating biomarkers, such as metabolites, cell-free DNAs, circulating non-coding RNAs, CTCs, and EVs, that recently show their diagnostic potential, have been discovered utilizing advanced sequencing and -omics techniques in this decade (Fig. 3.2). Although the cost needs to be reduced to facilitate routine omics-based biomarker measurement, combinations of several markers or diagnostic panels would increase the sensitivity and specificity, not only for detecting emerging neoplasms but also for facilitating genetic and physiologic characterization of individual tumors. Importantly, the monitoring of mutational or molecular markers with serial sample collection can provide

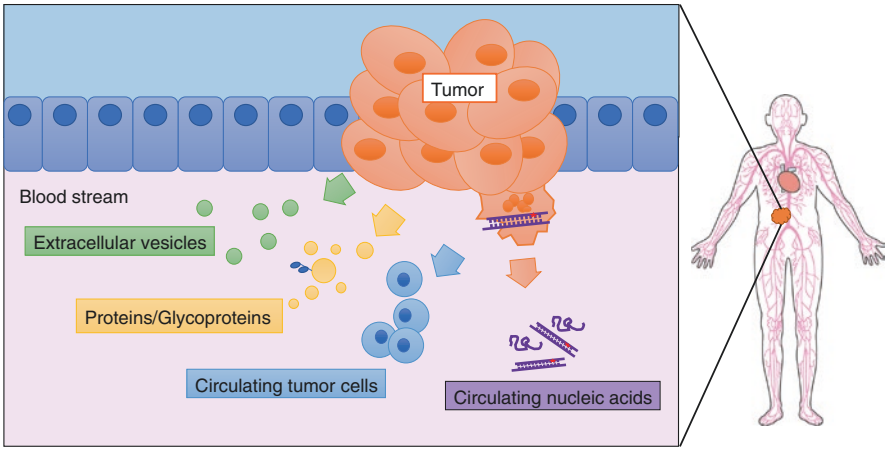

Fig. 3.2 Types of circulating biomarkers

therapeutic information, such as prediction of resistance and indication of secondary target molecules.

Although further improvements in procedures and validation in a larger cohort are required for their clinical use, the discovery of more specific and sensitive markers could improve the quality of care and, ultimately, the survival of patients with PDAC and CCA.

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4 Recent Advances of Precision Medicine in Pancreatic Cancer and Cholangiocarcinoma

Masashi Kanai

Abstract

In June 2019, two comprehensive genomic profiling (CGP) tests, "OncoGuide NCC Oncopanel System" and "FoundationOne CDx", were approved with reimbursement in Japan. Before returning the CGP results to patient by attending physicians, a review by expert panel, which comprises multidisciplinary experts, is mandatory for reimbursement. It takes about 4–8 weeks from the order of CGP test to the return of the result to the patient, so it is relevant to select the candidate patients and to order CGP test at appropriate timing. Although the proportion of patients who were found to harbor any actionable mutations by CGP test are still limited in pancreatic or biliary tract cancer, NCCN guidelines of pancreatic cancer now recommend CGP test for any patients with unresectable pancreatic cancer who are eligible for systemic chemotherapy. In the near future, precision medicine using CGP tests will be more relevant in the field of pancreatic and biliary tract cancer treatment.

Keywords

Precision medicine · Comprehensive genomic profiling · Tumor agnostic · BRCA Homologous recombinant repair (HRR) deficiency · MSI-H · NTRK fusion · TMB-H

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4.1 Introduction

Mutational signatures greatly differ between individual patients with pancreatic and biliary tract cancer and have a large influence on clinical response to chemotherapy [1–3].

With the recent development of next generation sequencing (NGS) technologies, it has become possible to scan multiple cancer-related genes at a time using tens of nanograms of DNA extracted from tiny tissues such as biopsy sample [4–6]. Comprehensive genomic profiling (CGP) tests, which comprise more than hundreds of cancer-related genes, are designed to comprehensively analyze gene mutations in cancer tissues and utilize the genomic data for treatment selection [6].

In Japan, CGP tests begun at several academic institutions as self-financed medical care or research purpose around 2015. In June 2019, two CGP tests, "OncoGuide NCC Oncopanel System (NCC Oncopanel)" and "FoundationOne CDx (F1CDx)" were approved with reimbursement and are now available in designated hospitals for cancer genomic medicine by the Ministry of Health, Labour and Welfare [7].

4.2 Features of Two Reimbursed CGP Tests

The main features of NCC Oncopanel and F1CDx are summarized in Table 4.1. Major differences between two panels are as follows. First, F1CDx requires only tumor samples, while NCC Oncopanel analyzes tumor and blood samples in pairs. Therefore, NCC Oncopanel can distinguish between somatic and germline

Table 4.1 Comparison of two reimbursed comprehensive gene panel test

	OncoGuide NCC Oncopanel	FoundationOne CDx
Required specimen	Tumor tissue (FFPE) and peripheral blood	Tumor tissue (FFPE)
Required tumor content	20% or higher	
Number of genes	114	324
Role of companion diagnostics	None	EGFR, ALK, MET, ROS1 (non-small cell lung cancer), BRAF (melanoma), ERBB2 (breast cancer), KRAS/NRAS (colorectal cancer), BRCA1/2 (ovarian cancer), NTRK1/2/3 (solid tumors)
Evaluation of microsatellite instability	None	Yes
Determination of secondary findings	BRCA1/2, TP53, STK11/LKB1, MLH1, MSH2, APC, VHL, RET, PTEN, RB1, TSC1, SMAD4, NF1, PALB2, SMARCB1	None
Reimbursements	560,000 JPY	

mutations. CGP tests potentially reveal germline mutations associated with hereditary tumors in 3–10% of patients, and these are called secondary findings, which require genetic counseling for relatives as well as patients [8, 9]. For example, when an inactivated mutation of *BRCA2*, which is known to increase the risk of pancreatic cancer, is reported in F1CDx, an additional test using peripheral blood is required to determine whether it is derived from germline or not. Second, F1CDx has a role of companion diagnostic test, while NCC Oncopanel does not. Third, F1CDx can return the status of microsatellite instability (MSI) high, which is a tumor-agnostic biomarker for immune-checkpoint inhibitor, Pembrolizumab, while NCC Oncopanel cannot.

4.3 Required Tissue Samples

Except for patients who undergo surgery, biopsy samples obtained by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) are the main source for CGP test in pancreatic cancer [10]. Several groups reported high success rate of CGP test using EUS-FNA samples in pancreatic cancer [11–13]; however, since pancreatic cancer cells are surrounded by abundant stroma components, it is not rare to see the patients whose tissue sample does not meet the criteria for CGP test due to low tumor content in daily clinical practice.

4.4 Liquid Biopsy

CGP tests targeting circulating tumor DNA (ctDNA) present in peripheral blood, which is called liquid biopsy, have been implemented as self-financed medical care or research purpose at some academic and local institutions in Japan. FoundationOne Liquid CDx covers more than 300 cancer-related genes, which number is almost equivalent to those of tissue panels. Liquid biopsy could be an alternative option for patients whose tissue samples are not available or are disqualified for tissue panel tests due to low tumor content or poor DNA quality [14]. Results of liquid biopsy can reflect the current mutation signature of the tumors spreading in the whole body and its turnaround time (TAT) is shorter, usually less than 2 weeks.

In contrast, since the amount of ctDNA is positively correlated with tumor volume in the whole body, liquid biopsy could return false-negative results if tumor volume is small.

4.5 Eligible Patients for CGP Test and Optimal Timing of Its Application

Eligible patients for CGP test are restricted to those with solid tumors for which there is no standard treatment or those with locally advanced or metastatic cancer who have completed standard treatment (includes patients expected to complete

the treatment), and who are judged by the attending physician to have a strong likelihood of being suitable for chemotherapy after CGP test, based on their general condition including organ function. In addition, CGP test results must be reviewed by molecular tumor board called "Expert Panel (EP)," which comprises multidisciplinary specialists (medical oncologists, pathologists, medical geneticists, genetic counselors) for its clinical interpretation. Before returning CGP results to patient by attending physicians, a review by EP is mandatory for reimbursement. Therefore, it usually takes nearly 6–8 weeks from ordering CGP test to returning its results to patients [7]. Considering the dismal prognosis of patients with pancreatic and biliary tract cancer, ordering CGP test after the completion of standard treatment is too late to utilize its results. Since eligible patients include those who are expected to end the standard treatment, attending physicians do not have to wait until the completion of standard treatment. Instead, it is relevant to select patients who will remain eligible for chemotherapy 6–8 weeks after ordering CGP test.

4.6 Clinical Benefit of CGP Tests in Pancreatic Cancer

Recently, a large prospective study enrolling more than 1000 patients with pancreatic cancer who underwent CGP tests (Know Your Tumor registry trial) are published [15]. Mutations that have potential matched drugs are called "actionable (druggable) mutations" and the most common actionable mutations reported in this study were homologous recombinant repair (HRR) related genes, which could confer the sensitivity to platinum drugs or PARP inhibitors, and 14% of patients (152/1083) harbored any inactivating mutations in HRR related genes. The overall survival of the patients who received matched drugs based on actionable mutations was 30.9 months ($n = 46$), which was significantly longer compared to 18.1 months of those who did not ($n = 143$) with a hazard ratio of 0.42 (95% confidence interval [CI], 0.26–0.68, $p = 0.0004$) [15]. Based on these results, NCCN guidelines now recommend undergoing CGP test for any patients with unresectable pancreatic cancer who are eligible for systemic chemotherapy [16].

Measurements of germline *BRCA* mutations have been approved by FDA as a positive biomarker for PARP inhibitor, Olaparib. A large randomized phase III study (POLO study) demonstrated that maintenance therapy using Olaparib after the response to platinum-based chemotherapy significantly improved progression-free survival for patients with metastatic pancreatic cancer who harbored germline *BRCA* mutations (hazard ratio 0.53, 95%CI, 0.35–0.82, $p = 0.0004$) [17].

MSI-high (MSI-H), NTRK fusion gene or tumor mutation burden-high (TMB-H), all of which are known FDA approved tumor-agnostic biomarkers for immune-checkpoint inhibitor for MSI-H and TMB-H or TRK inhibitor for NTRK fusion gene [18–20]. However, the proportion of patients who harbor these alterations are very low in pancreatic cancer and prevalence of MSI-H and NTRK fusion gene is estimated to be less than one percent (Table 4.2) [21, 22].

Table 4.2 FDA approved biomarkers for pancreatic cancer

Gene marker	Prevalence in pancreatic cancer	Matched drugs
MSI-H	0.7% (20/2698) [21]	Pembrolizumab
NTRK fusion	0.1% (15/11989) [22]	Entrectinib
TMB-H (≧10/Mb)[a]	1% (25/2483) [27]	Pembrolizumab
Germline BRCA1/2 inactivating mutation	7% (247/3315) [17]	Olaparib

[a]Data represents the proportion of patients with TMB 20/Mb or higher

Table 4.3 FDA approved biomarkers for biliary tract cancer

Gene marker	Prevalence in biliary tract cancer	Matched drugs
MSI-H	1.6% (23/1017) [21]	Pembrolizumab
NTRK fusion	0.15% (6/3905) [22]	Entrectinib
TMB-H (≧10/Mb)	1.9% (28/1456) [27][a]	Pembrolizumab
FGFR2 fusion/rearrangement	7.4% (20/272) [28][b]	Pemigatinib[a]
IDH1 activating mutation	13% (45/5393) [29][b]	Ivosidenib[a]

[a]Data represents the proportion of patients with TMB 20/Mb or higher
[b]Data of intrahepatic cholangiocarcinoma

4.7 Clinical Benefit of CGP Tests in Biliary Tract Cancer

Clinical benefits of CGP test for biliary tract cancer have also been investigated as a subgroup analysis of the basket trial (MOSCATO-01 trial) [23, 24]. Among 43 patients with biliary tract cancer who were enrolled in the MOSCATO-01, 34 patients (79%) were able to complete CGP test while nine patients (21%) canceled CGP test due to biopsy failure (n = 4) or low tumor content (n = 5). Actionable mutations were reported in 23 patients (68%), and 18 patients received matched therapy. Although the sample size is limited, 33% of the response rate was promising. In addition to tumor-agnostic biomarkers of MSI-H, NTRK fusions, and TMB-H, there are two FDA approved biomarkers, FGFR2 fusion/rearrangement and IDH1 mutation for biliary tract cancer (restricted to intrahepatic cholangiocarcinoma) [25, 26]. FDA approved biomarkers for biliary tract cancers are summarized in Table 4.3.

In the near future, precision medicine using CGP tests will be more relevant in the field of pancreatic and biliary tract cancer treatment.

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Part II

Anti-cancer Treatments for Pancreatic Cancer

Chemotherapy for Locally Advanced and Metastatic Pancreatic Cancer

5

Yousuke Nakai

Abstract

Pancreatic cancer is still one of the most intractable cancers and 80% of pancreatic cancer are unresectable, either locally advanced or metastatic, at the time of diagnosis. The current standard regimens for metastatic disease are FORFIRINOX and gemcitabine plus nab-paclitaxel. However, there is controversy about treatment for locally advanced disease, second-line chemotherapy, and treatment selection in elderly patients. For locally advanced disease, chemoradiotherapy is considered as a treatment option but the evidence is lacking and the same two regimens of FOLFIRINOX and gemcitabine plus nab-paclitaxel are used as the community standard. For second-line chemotherapy, a combination of nanoliposomal irinotecan, folinic acid, and fluorouracil is one of the evidence-based regimens but sequential treatment of FOLFIRINOX and gemcitabine plus nab-paclitaxel is also utilized in clinical practice. Finally, treatment selection in elderly and frail patients is still an unanswered question and needs further investigation in this globally aging population.

Keywords

Chemotherapy · FOLFIRINOX · Gemcitabine plus nab-paclitaxel · Locally advanced · Metastatic · Nanoliposomal irinotecan · Pancreatic cancer

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5.1 Introduction

Pancreatic cancer is still one of intractable cancer with a 5-year survival rate of 5–10% and the numbers of incidence and mortality of pancreatic cancer are close. Despite investigation for early detection of pancreatic cancer, about 80% of pancreatic cancer are unresectable, either locally advanced or metastatic, at the time of diagnosis. In those patients with advanced pancreatic cancer, systemic chemotherapy is the current standard of care. Since a pivotal randomized controlled trial (RCT) by Burris in 1997 [1], gemcitabine had long been the standard regimen for advanced pancreatic cancer. After a series of RCTs failed to overcome gemcitabine, the superiority of two combination regimens of FOLFIRINOX [2] and gemcitabine plus nab-paclitaxel [3] were demonstrated in metastatic pancreatic cancer and are now utilized as the current standard of care in clinical practice. Herein, we review the current status of chemotherapy for locally advanced and metastatic pancreatic cancer.

5.2 Metastatic Pancreatic Cancer

Systemic chemotherapy is the treatment of choice in metastatic pancreatic cancer (Fig. 5.1). Intensive regimens are utilized in young and fit patients, while less intensive regimens are selected to avoid severe toxicity in elderly and frail patients. FOLFIRINOX and gemcitabine plus nab-paclitaxel are two standards of care regimens in young and fit patients.

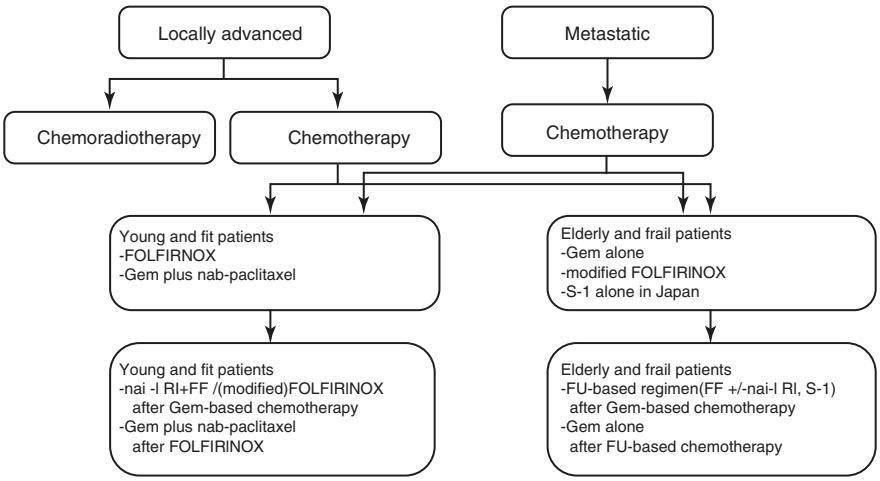

Fig. 5.1 Treatment flowchart of advanced pancreatic cancer. FF, fluorouracil and folinic acid; Gem, gemcitabine; IRI, irinotecan

5.2.1 FOLFIRINOX

FOLFIRINOX, a combination of folinic acid, 5-FU, oxaliplatin, and irinotecan, is one of the standards of care regimens in metastatic pancreatic cancer. After promising results of single arm phase II trial of FOLFIRINOX [4], phase II/III RCT of PRODIGE4/ACCORD 11 [2], demonstrated the superiority over gemcitabine: response rate (RR) of 31.6% vs. 9.4%, progression-free survival (PFS) of 6.4 vs. 3.3 months, and overall survival (OS) of 11.1 vs. 6.8 months. The quality of life was also better in FOLFIRINOX. In terms of safety, however, severe hematologic adverse events were more common in FOLFIRINOX, such as neutropenia (45.7%), febrile neutropenia (5.4%), and thrombocytopenia (9.1%). Nonhematologic adverse events were also common; diarrhea (12.7%) and sensory neuropathy (9.0%).

Given the increased adverse events despite the enrollment of patients 75 years or younger with good performance status (PS), a modified regimen of FOLFIRINOX was developed to mitigate adverse events while maintaining the efficacy of the original FOLFIRINOX regimen. In one of the modified FOLFIRINOX regimens [5], a bolus of 5-FU is omitted, and the dose of irinotecan is reduced. In a single arm study of this modified FOLFIRINOX regimen in 69 Japanese patients, RR was 37.7%, PFS was 5.5 months and OS was 11.2 months, which was comparable to the phase II study of the original FOLFIRINOX in Japanese patients [6]. Meanwhile, the rate of neutropenia and febrile neutropenia decreased from 77.8 and 22.2% in the original FOLFIRINOX [6] to 47.8 and 8.7% in the modified FOLFIRINOX [5]. Although there has been no head-to-head comparison between the original and modified FOLFIRINOX regimens, the modified FOLFIRINOX is one of the treatment options in clinical practice, especially in elderly patients or depending on UGT1A1 genotyping [7].

5.2.2 Gemcitabine Plus Nab-Paclitaxel

Nab-paclitaxel is an albumin-bound nanoparticle formulation of paclitaxel and can reportedly deliver higher doses of paclitaxel into pancreatic cancer. A combination regimen of gemcitabine plus nab-paclitaxel is another standard regimen for metastatic pancreatic cancer since a phase III study showing a significant improvement of PFS (5.5 months vs. 3.7 months) and OS (8.5 months vs. 6.7 months) over gemcitabine alone [3]. In terms of safety, grade 3 or higher adverse events were more often reported such as neutropenia (38% vs. 27%), leukopenia (31% vs. 16%), fatigue (17% vs. 7%), and peripheral neuropathy (17% vs. 1%). Of note, peripheral neuropathy resulted in discontinuation of nab-paclitaxel in 8% and dose reduction in 10%. Management of peripheral neuropathy is important to maintain dose intensity of nab-paclitaxel in cases with good response and medications such as mirogabalin, pregabalin, and duloxetine are used in clinical practice, but control of peripheral neuropathy remains an unsolved issue.

5.2.3 Selection Between FOLFIRINOX and Gemcitabine Plus Nab-Paclitaxel

Both FOLFIRINOX and gemcitabine plus nab-paclitaxel are recommended as a first-line chemotherapy for metastatic pancreatic cancer but there has been no head-to-head comparison between two regimens. Conflicting data have been reported but a systematic review [8] suggested longer OS in FOLFIRINOX with the mean weighted difference of 1.15 months but the risk of mortality and PFS were comparable. In the analysis of toxicity, gemcitabine plus nab-paclitaxel caused less neutropenia, febrile neutropenia, and nausea but FOLFIRINOX caused less neurotoxicity and anemia. Therefore, there is no consensus on which regimen should be selected as a first-line chemotherapy. Factors other than safety and efficacy can affect treatment selection such as the cost of more antiemetics and pegfilgrastim in cases with severe neutropenia and the need for central venous access port in FOLFIRINOX. In summary, the current real-world data does not support the benefits of one regimen over the other and the treatment selection still depends on patients' and physicians' preferences.

Recently, it was reported that patients with DNA damage response (DDR) gene mutations including BRCA mutations [9, 10] or with a family history of pancreatic cancer [11] might benefit from platinum-including chemotherapy such as FOLFIRINOX. Thus, a family history of cancer can provide important information for treatment selection and should be carefully evaluated.

5.2.4 Intraperitoneal Chemotherapy in Patients with Peritoneal Dissemination

The prognosis of pancreatic cancer with peritoneal dissemination is extremely poor with a reported median survival of 6 weeks [12]. Despite above-mentioned progress in systemic chemotherapy in metastatic pancreatic cancer, the improvement of survival in this condition is less prominent. Intraperitoneal chemotherapy using paclitaxel is a treatment option in peritoneal dissemination and its efficacy has been reported in ovarian cancer [13] and gastric cancer [14]. We previously reported intraperitoneal paclitaxel in addition to systemic chemotherapy of S-1 and paclitaxel in gemcitabine-refractory pancreatic cancer with malignant ascites [15]. In this phase II study, malignant ascites had disappeared or decreased in 69% of patients, including complete resolution in 15%. Cytology of ascites turned negative in 31%. However, PFS and OS were 2.8 months and 4.8 months, respectively, suggesting the need for patient selection and intensive systemic chemotherapy. Thus, a phase I/II study of intraperitoneal paclitaxel in combination with systemic gemcitabine plus nab-paclitaxel is now ongoing. Phase I part of this study demonstrated promising results both locally and systemically: The cytology turned negative in 67% and RR was 25% and PFS was 5.4 months. Satoi et al. also investigated intraperitoneal paclitaxel for pancreatic cancer and reported conversion surgery in 8 out of 46 patients (17%), including 7 patients with R0 resection [16]. Thus, local delivery of intraperitoneal chemotherapy appears to have a role to control peritoneal dissemination.

5.3 Locally Advanced Pancreatic Cancer

Locally advanced pancreatic cancer has more treatment options than metastatic pancreatic cancer: Chemotherapy, chemoradiotherapy, and induction chemotherapy followed by chemoradiotherapy but there is no consensus on which approach is superior yet. Due to the lack of valid evidence in induction chemotherapy and no superiority of chemoradiotherapy in the LAP07 trial [17], systemic chemotherapy is often selected as a community standard for locally advanced pancreatic cancer (Fig. 5.1). In the LAP07 trial, two randomizations were conducted; first randomization of induction chemotherapy, either gemcitabine alone or in combination with erlotinib, and second randomization of continued chemotherapy or chemoradiotherapy. The median OS was not significantly different: 16.5 months in chemotherapy group and 15.2 months in chemoradiotherapy. A more recent Japanese randomized phase II trial, JCOG1106 [18], compared radiotherapy with concurrent S-1 with or without induction gemcitabine chemotherapy and suggested chemoradiotherapy without induction chemotherapy might provide better 2-year survival (36.9% vs. 18.9% without vs. with induction chemotherapy).

Although FOLFIRINOX and gemcitabine plus nab-paclitaxel are selected in clinical practice similar to metastatic pancreatic cancer, those regimens were less investigated in patients with locally advanced pancreatic cancer. No RCTs have proved superiority of these two regimens over gemcitabine.

In a systematic review of FOLFIRINOX for locally advanced pancreatic cancer [19], PFS was 15.0 months and OS was 24.2 months. Meanwhile, gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer was evaluated in a multicenter prospective phase II trial, LAPACT [20], and PFS and OS were 10.9 months and 18.8 months, respectively. Surgical resection after chemotherapy was performed in 25.9% after FOLFIRINOX [19] and 15% after gemcitabine plus nab-paclitaxel [20], respectively. A randomized phase II trial comparing modified FOLFIRINOX and gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer (JCOG1407) [21] is now ongoing in Japan.

A combination of gemcitabine and S-1 was also investigated in Japan by three randomized controlled trials [22–24], and in a pooled analysis of the three trials [25], OS was 11.83 months for gemcitabine and 16.41 months for gemcitabine and S-1 with a hazard ratio of 0.708 ($P = 0.022$), suggesting the role of this regimen in locally advanced pancreatic cancer. A neoadjuvant chemotherapy of gemcitabine and S-1 demonstrated superiority over upfront resection for resectable pancreatic cancer in a Japanese phase II/III study (Prep-02/JSAP-05) [26], too. Based on these promising results of gemcitabine and S-1, we further investigated a combination of gemcitabine, S-1 and leucovorin (GSL) both in borderline resectable [27] and in advanced pancreatic cancer [28]. In locally advanced pancreatic cancer, GSL combination therapy demonstrated efficacy comparable to FOLFIRINOX and gemcitabine plus nab-paclitaxel with PFS of 12.7 months and OS of 26.1 months.

Thus, the standard chemotherapy is yet to be determined for locally advanced pancreatic cancer. Given the longer treatment duration compared to metastatic pancreatic cancer, evaluation of chemotherapy and chemoradiotherapy for locally

advanced pancreatic cancer should be focused on safety and the quality of life in addition to efficacy. Furthermore, the rate of conversion surgery is important for long-term survival.

5.4 The Role of Monotherapy

Intensive chemotherapy is the current standard of care in advanced pancreatic cancer but in most clinical trials the evidence is lacking in a subgroup of elderly patients with poor performance status. Since those patients cannot tolerate intensive chemotherapy, monotherapy can be a treatment option. Gemcitabine monotherapy had long been the standard regimen and in Japan non-inferiority of S-1, an oral fluoropyrimidine, was reported, too [24].

There are no standard criteria to choose monotherapy vs. intensive combination therapy in advanced pancreatic cancer. In general, treatment selection was based on age, PS, comorbidity, and so on. We previously reported comorbidity rather than age was associated with poor prognosis in gemcitabine-based chemotherapy [29]. More recently, the usefulness of comprehensive geriatric assessments (CGAs) are reported in elderly patients and are evaluated in prospective trials [30].

5.5 Second-Line Chemotherapy

Despite advancement of intensive first-line chemotherapy for advanced pancreatic cancer, most patients experience disease progression and second-line chemotherapy receive in patients fit for further treatment. However, robust data on second-line chemotherapy are scarce but some randomized controlled trials were reported in this setting: CONKO-003 trial [31], PANCREOX [32], SOX [33], IRIS [34], GRAPE trial [35], and NAPOLI-1 trial [36].

First of all, CONKO group demonstrated the role of second-line chemotherapy over best supportive care (BSC) alone [37]. In this randomized controlled trial of 46 patients with gemcitabine-refractory pancreatic cancer, OFF (oxaliplatin, folinic acid, and fluorouracil) showed OS of 4.82 months compared to 2.30 months in BSC group. Subsequently, in CONKO-003 trial, FF (folinic acid and fluorouracil) and OFF (oxaliplatin and FF) were compared in patients with gemcitabine-refractory pancreatic cancer. Time to treatment failure (2.0 months vs. 2.9 months) and OS (3.3 months vs. 5.9 months) were significantly longer in OFF group, confirming the role of OFF regimen in gemcitabine-refractory pancreatic cancer. However, the following PANCREOX trial [32] failed to demonstrate the benefits of additional oxaliplatin to fluorouracil and leucovorin by comparing mFOLFOX6 and FU/LV as second-line chemotherapy after gemcitabine-based chemotherapy. PFS was similar (3.1 months vs. 2.9 months) but OS was inferior in mFOLFOX6 (6.1 months vs. 9.9 months).

In Asian countries, S-1 [38, 39] is another option for gemcitabine-refractory pancreatic cancer. The addition of oxaliplatin or irinotecan to S-1 was investigated in randomized controlled trials. In a randomized phase II trial of 271 patients with gemcitabine-refractory pancreatic cancer [33], SOX (S-1 and oxaliplatin) did not demonstrate superiority to S-1 alone: PFS was 3.0 months vs. 2.8 months and OS was 7.4 months vs. 6.9 months in SOX vs. S-1 groups. Similarly, the addition of irinotecan to S-1 (IRIS) [34] did not lead to significantly better efficacy in the same setting. PFS was 3.5 months vs. 1.9 months and OS was 6.8 months vs. 5.8 months in IRIS and S-1 group. Furthermore, GRAPE trial [35] evaluated the addition of leucovorin to S-1 (SL) in 603 patients with gemcitabine-refractory pancreatic cancer and again failed to demonstrate the superiority of SL to S-1 alone. PFS was 3.9 months vs. 2.8 months and OS was 7.6 months and 7.9 months in SL vs. S-1 group. Thus far, no study has proved S-1-based combination therapy was superior to S-1 monotherapy in this setting.

After those negative or conflicting data, the NAPOLI-1 trial [36] was reported in 2016, which was a phase III trial of nanoliposomal irinotecan (nal-IRI) monotherapy, fluorouracil, and folinic acid (FF) and the combination in patients previously treated with gemcitabine-based chemotherapy. OS was 4.9 months with nal-IRI monotherapy, 4.2 months with FF and 6.1 months with nal-IRI plus FF. Major grade 3–4 adverse events of nal-IRI plus FF were neutropenia (27%), diarrhea (13%), and fatigue (14%), which is acceptable in this setting.

Since the NAPOLI-1 trial [36], this combination regimen of fluorouracil, leucovorin and nal-IRI is used as one of the standard of care regimens for second-line chemotherapy after gemcitabine-based regimen. In clinical practice, meanwhile, sequential treatment of two standard regimens (FOLFIRINOX and gemcitabine plus nab-paclitaxel) is also used as the community standard. Retrospective studies suggested the sequence of those two regimens (FOLFIRINOX followed by gemcitabine plus nab-paclitaxel, or vice versa) did not matter [40, 41]. However, the chance to receive second-line chemotherapy was higher if gemcitabine plus nab-paclitaxel was given first (45% vs. 56%, $P = 0.036$) [41]. Due to the limited tolerability of second-line chemotherapy after prolonged intensive first-line chemotherapy, modified FOLFIRINOX after first-line gemcitabine plus nab-paclitaxel was also evaluated [42] with PFS of 3.9 months and OS of 7.0 months. However, grade 3–4 toxicities were still high: Neutropenia in 42.3% and febrile neutropenia in 5.8%. We also reported a retrospective comparison of S-IROX [43], a combination of S-1, leucovorin, irinotecan, and oxaliplatin, with modified FOLFIRINOX as second-line chemotherapy after first-line gemcitabine plus nab-paclitaxel. PFS was 7.8 months vs. 5.7 months and OS was 14.2 months and 11.5 months in the S-IROX and modified FOLFIRINOX groups. Patients with PFS > 6 months in first-line gemcitabine plus nab-paclitaxel demonstrated favorable OS by S-IROX. Grade 3–4 neutropenia was less observed in S-IROX (26.3% vs. 42.9%). Since S-IROX can be administered without need for the central venous access port, it should be further investigated in prospective studies.

5.6 Future Perspective

The advancement of systemic chemotherapy has led to modest improvement in prognosis of advanced pancreatic cancer. OS extended roughly from 6 to 12 months in metastatic disease [44] and 12 to 24 months in locally advanced disease when intensive chemotherapy is tolerated. Currently, the role of molecular target therapy and immunotherapy is limited in the management of pancreatic cancer, and cytotoxic agents still play a central role. However, there remain many unanswered questions. What is the best sequential regimen? Any role for radiation in locally advanced disease? What is the best treatment for elderly or frail patients and how can we evaluate frailty? We need more robust data to answer those clinically important questions in the future.

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Neoadjuvant Therapy for Resectable and Borderline Resectable Pancreatic Cancer

6

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Abstract

Neoadjuvant therapy (NAT) is an emerging strategy for treating potentially resectable pancreatic adenocarcinoma (PA). Although a strong rationale and many theoretical advantages of NAT have been identified for patients with PA, the results of prospective studies have considerably varied. Recently, a multicentric Japanese group conducted a randomized control trial (PREP02/JSAP05) and clearly demonstrated the significant survival benefit of neoadjuvant chemotherapy compared with that of upfront surgery for resectable and borderline resectable PA. This treatment strategy aims to decrease tumor burden, which may provide a higher rate of R0 resection, and intervene early with systemic chemotherapy to suppress micrometastases, which may be undetectable on preoperative radiological images but may emerge within a short postoperative period. Currently, various institutes are championing further efforts to clarify an optimal NAT regimen or an appropriate period for NAT and achieve better patient selection for particular therapies in patients with potentially resectable or borderline resectable PA. This promising approach provides a paradigm shift in the management of PA wherein NAT can be the new standard of care for patients with PA.

Keywords

Pancreatic cancer · Neoadjuvant therapy · Resectable pancreatic cancer · Borderline resectable pancreatic cancer · Chemotherapy · Chemoradiotherapy

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6.1 Introduction

Pancreatic adenocarcinoma (PA) is the second leading cause of cancer-related death in the Western world and remains one of the most lethal cancers with an overall 5-year survival rate of approximately 5% [1–3]. Although most patients with PA are diagnosed with a locally advanced tumor or distant metastases and are indicated for systemic chemotherapy, patients with a radiological appearance of resectable disease (accounting for approximately 20%) undergo radical pancreatectomies followed by adjuvant therapy as a standard treatment. This strategy provides a survival benefit, with the 5-year overall survival exceeding 40% in patients with resectable PA [4, 5]. Recently, in patients with resectable PA cohort, a novel treatment strategy called neoadjuvant therapy (NAT) is considered to modestly improve overall survival and thus has been introduced in clinical practice. Currently, various institutions or hospitals are championing efforts to cure more patients by early intervention with potent cytotoxic treatments such as preoperative FOLFIRINOX or gemcitabine plus nab-paclitaxel (GnP) [6, 7]. In fact, a multicentric Japanese group clarified the superiority of NAT in prolonged overall survival for patients with potentially resectable PA, compared with conventional upfront surgery combined with adjuvant therapy [8–10].

The presumable benefits of NAT are considered to decrease tumor burden, which may provide a higher rate of R0 resection, and to boost early treatment for micrometastatic diseases, which may be undetectable on preoperative radiological findings but may be detected in early postoperative period [11]. For patients with disease progression during NAT, non-curative surgical resection and its associated risks can be avoided. Furthermore, NAT shows a promising advantage in compliance with drug administration. In an adjuvant setting, approximately 25–40% of patients with surgical complete resection cannot receive postoperative treatment as initially planned because of prolonged surgical complications and delayed recovery after surgery [12–14]. Conversely, in a neoadjuvant setting, 73–100% of patients are expected to complete a full regimen of planned NAT [15–21]. NAT has no adverse effects on operative morbidity or mortality. In fact, a decreased incident of postoperative complications, such as anastomotic fistulas, have been reported in patients after NAT, which is caused by the firmer pancreatic texture owing to the long-term obstruction of the pancreatic duct and chronic pancreatitis [22–24]. Finally, an analysis of a national database of medical costs and patient survival in the United States suggested that the introduction of NAT in clinical practice resulted in lower costs and provided an economic advantage compared with upfront surgery [25].

In this chapter, we focus on this multimodal approach and discuss the existing status of NAT for patients with potentially resectable PA.

6.2 Preoperative Estimation for Surgical Resectability

It is essential to accurately assess resectability at the time of diagnosis to identify the most appropriate treatment strategy to maximize survival in patients with PA. Two definitions for a resectable tumor have been proposed: one is from the joint consensus guidelines of the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society for Surgery of the Alimentary Tract

[26] and the other is the MD Anderson Classification [27]. The former has been revised by the National Comprehensive Cancer Network (NCCN), and these NCCN definitions have been widely accepted and approved by the International Study Group of Pancreatic Surgery [28]. According to these criteria, resectability is decided based on radiological findings of the involvement of critical adjacent vessels, i.e., the celiac axis (CA), superior mesenteric artery (SMA), and superior mesenteric vein (SMV) and portal vein (PV) (Table 6.1). This detailed investigation can be accomplished only by high-quality cross-sectional imaging using CT or MRI.

Table 6.1 NCCN pancreatic adenocarcinoma guidelines version 1.2021 defining resectability

Resectability status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA])	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity
Borderline resectable	*Pancreatic head/uncinate process*	• 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 CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction	
	• Solid tumor contact with the SMA of ≤180°	
	• Solid tumor contact with variant arterial anatomy (e.g., 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 noted if present, as it may affect surgical planning	• Solid tumor contact with the inferior vena cava (IVC)
	Pancreatic body/tail	
	• Solid tumor contact with the CA of ≤180°	
	• Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category)	
Locally advanced	*Head/uncinate process*	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
	• Solid tumor contact with SMA >180°	
	• Solid tumor contact with the CA >180°	
	Pancreatic body/tail	
	• Solid tumor contact of >180° with the SMA or CA	
	• Solid tumor contact with the CA and aortic involvement	

CA celiac axis, *CHA* common hepatic artery, *SMA* superior mesenteric artery, *PV* portal vein, *SMV* superior mesenteric vein
Adopted to: https://www.nccn.org/professionals/physician_gls/default.aspx

In general, resectable PA shows no arterial tumor contact with or without venous involvement (SMV or PV <180°), and borderline PA is specifically characterized by semi-circumferential abutment (<180°) of the SMA and/or CA. Only 15–20% of overall patients with PA show a primarily resectable tumor at diagnosis.

Several biological factors, including occult distant metastasis or regional lymph node involvement, lead to early postoperative metastases and dismal prognosis. Even if radiological investigations suggest a resectable tumor, patients with high carbohydrate antigen (CA) 19–9 levels >500 U/mL or an Eastern Cooperative Oncology Group performance status of 2 (indicating poor prognosis) may be considered to have borderline resectable PA [29]. Thus, especially for high-risk patients, surgical resection combined with NAT is appropriate to increase the possibility for prolonged survival.

6.3 Potentially Resectable Tumors

Upfront surgery combined with adjuvant therapy has been widely accepted as a standard treatment for resectable PA. Adjuvant therapy is administered to patients who undergo curative resection and completely recover from surgery without early postoperative recurrence. Several randomized controlled trials (RCTs) have proposed the superiority of adjuvant therapy with new agents, with median overall survival of 46.5 months (S1) [4] and 54.4 months (modified FOLFIRINOX) [5]; however, eligible patients in these trials comprised only those who pass the surgical selection (Fig. 6.1A-a). Patients who did not undergo surgical resection owing to gross distant metastases noted during laparotomy or who did not recover owing to postoperative complications were excluded from this cohort and those patients are generally expected to have poor prognosis.

Recently, many ongoing clinical trials have been attempting to clarify the efficacy of NAT in patients with PA, and a multicenter randomized clinical trial by a Japanese study group reported the superiority of NAT in overall survival for patients with potentially resectable PA compared with conventional upfront surgery with adjuvant therapy [9, 10]. In the course of NAT followed by surgical resection, there are other patient selections in addition to the surgical selections mentioned above (Fig. 6.1B-b). Patients with disease progression or insufficient recovery during NAT are not indicated for surgical resection and have poorer prognosis. In retrospective or case series studies evaluating the efficacy of NAT, the survival outcome of patients with only resected PA after NAT was analyzed (Fig. 6.1B-c), and a better survival trend was noted because of the exclusion of patients with poor prognosis. Prospective studies should include patients with the radiological appearance of resectable PA and potentially resectable PA (Fig. 6.1B-d), and they should be designed according to intention-to-treat (ITT) analysis to reduce the selection bias for accurate survival analysis. In short, resected PA is not necessarily equal to potentially resectable PA, and objective cohorts for evaluating adjuvant therapy in RCTs (Fig. 6.1A-a) are not necessarily equal to those with ITT analysis when evaluating the efficacy of NAT in RCTs (Fig. 6.1B-d).

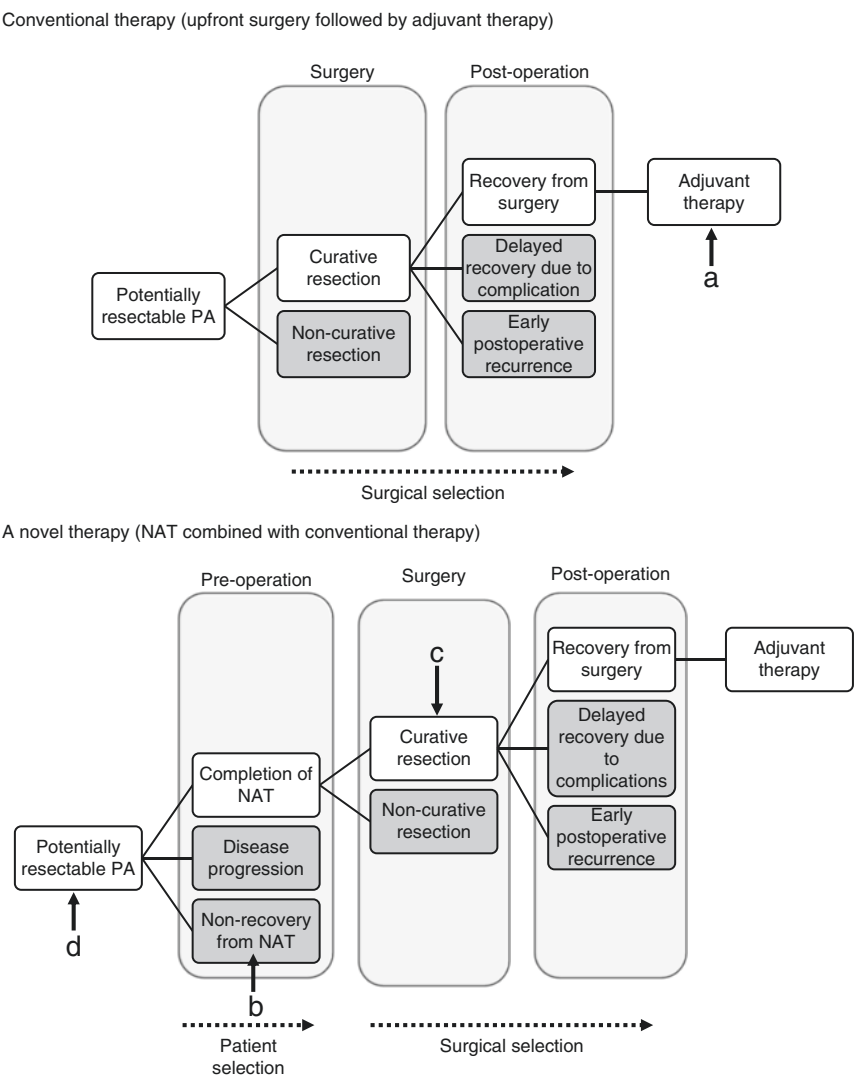

Fig. 6.1 Patient selection for conventional (**A**) and neoadjuvant therapy (**B**). The gray box represents excluded cases for postoperative adjuvant treatment. Non-curative resection includes cases with unresectable tumors at laparotomy or resectable tumors with a macroscopic positive margin (R2 resection) or metastatic disease (M1). Eligible patients in randomized controlled trials (RCTs) to evaluate the efficacy of adjuvant therapy consist of only patients who pass these surgical selections (**A-a**), while eligible patients in RCTs to evaluate NAT include all patients with a radiological appearance of resectable PA (**B-d**), and the RCTs are designed based on intention-to-treat (ITT) analysis to reduce selection bias for accurate survival analysis. It is incorrect to directly compare survival outcomes across both trials since the objective cohorts in both trials are not completely matched: one is resected PA and the other is potentially resectable PA

6.4 Prospective Studies for NAT and Adjuvant Therapy

Several prospective Phase II trials of NAT for potentially resectable PA have reported favorable R0 resection and survival rates based on ITT analyses (Table 6.2) [15, 16, 18, 30–41]. All these trials demonstrated that compared with historical surgical data, patients who completed neoadjuvant chemotherapy or chemoradiotherapy (CRT) and had no radiographic appearance of progression before surgery had a higher possibility of achieving R0 resection and prolonged overall survival. Early trials tested neoadjuvant chemotherapy, not CRT, in suppressing occult metastatic disease before surgery. Palmer et al. conducted a Phase II trial in which patients with potentially resectable PA with NAT [16], i.e., either gemcitabine alone or in combination with cisplatin. Only 38% of patients in the gemcitabine cohort underwent curative resection compared with 70% in the combination of gemcitabine and cisplatin, without significant differences in postoperative complications. Other trials also identified the superiority of combination therapy over monotherapy, with high resection and survival rates. Regarding CRT, combined regimens using two or more agents do not necessarily result in improved survival compared with monotherapy. Heinrich et al. reported the safety and effect of NAT with a similar chemotherapy regimen associated with improved quality of life and nutritional status [32]. Turrini et al. [34] and Pipas et al. [35] reported the results of their Phase II study of NAT using CRT. Motoi et al. conducted a prospective Phase II trial of NAT using gemcitabine plus S1 (GS) in a multicenter randomized controlled study [39]. This regimen was well-tolerated and induced a favorable outcome without radiotherapy. O'Reilly et al. also reported results of a combination therapy of gemcitabine plus oxaliplatin [37], suggesting a longer survival rate according to both the ITT and the per-protocol analysis.

In the adjuvant setting, modified FOLFIRINOX, as well as S1, is one of the most commonly used regimens [4, 5]. Both treatments had a positive survival effect in patients who underwent curative surgical resection, with median survival times of 46.5 and 54.4 months, respectively. These results appear to be compatible or superior to those found when treating with NAT in the prospective trial; however, this interpretation is incorrect. Prospective analysis to identify an appropriate regimen of adjuvant therapy is based on a patient cohort that can achieve surgical resection and completely recover from surgical treatment (Fig. 6.1A-a), while an objective cohort to evaluate the efficacy of NAT should include all patients having potentially resectable PA (Fig. 6.1B-d), including a subpopulation that did not undergo surgical resection owing to disease progression or that underwent surgical resection but could not start adjuvant therapy owing to prolonged postoperative complications. In the analysis of the efficacy of adjuvant therapy, the selected patient cohort is enrolled, therefore the survival outcomes tend to be preferable, compared with ITT analysis to evaluate NAT efficacy. RCTs are the only method for discriminating between survival outcomes after upfront surgery and those after NAT by directly comparing two arms of patients with potentially resectable PA to avoid the influence of selection bias.

Table 6.2 Prospective studies of NAT for resectable and borderline resectable PA

Author	Resectability	N	Regimens	Resection rate	OS (ITT)	Reference
Phase II study						
Talamonti MS	R, BR	20	Gem + RT	85%	18	[30]
Mornex F	R, BR	41	5FU/Cis + RT	63%	9.4	[31]
Palmer	R,BR	50	Gem	38%	9.9	[16]
			Gem/Cis	70%	15.6	
Heinrich S	R	28	Gem/Cis	80%	26.5	[32]
Varadhachary GR	R	90	Gem/Cis + RT	66%	17.4	[18]
Evans DB	R	86	Gem + RT	74%	22.7	[15]
Landry J	R, BR	21	Gem + RT	24%	19.4	[33]
			Gem/Cis/5FU (5FU + RT)		13.4	
Turrini O	R	34	DOC + RT	50%	15.5	[34]
Pipas JM	R, BR	37	Gem/Cet + RT	76%	17.3	[35]
Motoi F	R, BR	36	Gem/S1	87%	19.7	[36]
O'Reilly EM	R	38	Gem/Ox	71%	27.2	[37]
Okano K	R, BR	57	Gem/S1	73%	N.R.	[38]
Motoi F	R, BR	101	Gem/S1	73%	30.8	[39]
Tsai S	R, BR	130	FOLFIRINOX	82%	38	[40]
			FOLFIRINOX			
			Gem/Nab-P			
			Cap/Nab-P			
			CRT			
Eguchi H	R	63	Gem/S1 + RT	86%	55.3	[41]

(continued)

Table 6.2 (continued)

Author	Resectability	N	Regimens	Resection rate	OS (ITT)	Reference
Phase III study						
Golcher H	R	30	Gem/Cis + RT	63%	17.4	[42]
		33	Upfront surgery	70%	14.4	
Casadei R	R	18	Gem + RT	61%	22.4	[43]
		20		75%	19.5	
Jang JY	BR	27	Gem + RT	63%	21	[44]
		23		78%	12	
Versteijne E	R, BR	119	Gem + RT	62%	17.1	[45, 46]
		127		72%	13.7	
Unno M	R, BR	182	Gem/S1	77%	36.7	[8–10]
		180		72%	25.7	

R resectable, *BR* borderline resectable, *Gem* gemcitabine, *RT* radiation, *5FU* 5-fluorouracil, *Cis* cisplatin, *DOC* docetaxel, *Cet* cetuximab, CAP, *OX* oxaliplatin, *Nab-P* nab-paclitaxel, *CRT* chemoradiotherapy, *N* number in the cohort, *N.R.* did not reach the median time, OS (ITT), median overall survival in months by intention-to-treat analysis, *HR* hazard ratio

Currently, many ongoing RCTs are examining the efficacy of NAT compared with that of upfront surgery (Table 6.2) [8–10, 42–46]. Most modalities in these RCTs are CRT and not chemotherapy. Golcher et al. [42] and Casadei et al. [43] reported the results of an RCT using CRT as NAT, but neither of them showed significant differences. A possible reason could be the difficulty in recruiting patients or small cohort sizes. Jang et al. [44] found a positive outcome by targeting only patients with borderline resectable PA in an RCT using CRT. Versteijne et al. [45] conducted an RCT for patients with resectable and borderline resectable PA (PREOPANC-1 trial), and their results showed significant improvements in R0 resection, locoregional recurrence, pathological lymph node metastases and disease-free survival rates, although this trial did not meet the primary endpoint [46].

Unno and Motoi conducted an RCT (PREP02/JSAP05) using chemotherapy (GS). A total of 362 patients with resectable or borderline resectable PA were randomly assigned to NAT or upfront surgery [8–10]. NAT significantly prolonged the median overall survival compared with upfront surgery (36.7 vs. 26.6 months, $p = 0.015$); however, there was no significant difference in resection rates between the two arms and no operative mortality. Interestingly, compared with upfront surgery, NAT significantly reduced the incidence of pathological nodal metastases and postoperative hepatic recurrence. This novel strategy of NAT using GS has great potential as a new standard for potentially resectable PA. Among these RCTs analyzing NAT and upfront surgery, the resection rates after upfront surgery were comparable, ranging from 70 to 78%, while the resection rate after NAT showed a difference between chemotherapy and CRT. The resection rate after CRT ranged from 61 to 63%, which was approximately 10% lower than that of upfront surgery. Only preferred cases for CRT might benefit from the advantage of local treatment. On the other hand, the resection rate after chemotherapy was 77%, which did not decrease compared with that after upfront surgery. In contrast to the efficacy of CRT, potentially resectable PA could benefit from chemotherapy because of its systemic nature.

6.5 Optimal Agent or Regimens for NAT for Potentially Resectable PA

The most reliable regimens for unresectable PA are FOLFIRINOX or GnP [47, 48]. Both regimens provided evidence of prolonged survival time in patients with advanced PA. These regimens could be strong candidates for NAT for potentially resectable PA. Currently, many clinical trials are trying to confirm the superior effects of these combination regimens for resectable PA. When treating unresectable PA, we usually set the primary endpoint as the improvement in overall survival; however, in the neoadjuvant setting, the treatment efficacy in terms of response rate or progression-free survival (PFS) should be weighted more because the tumors would be resected after NAT over a short period. FOLFIRINOX is a valuable treatment option in preoperative therapy for borderline resectable or unresectable PA, and it results in a significantly better tumor control and resection rate than other

treatments. Resection rates after FOLFIRINOX were 60.8% compared with those after other treatments (48.0%) [49]. In a meta-analysis, FOLFIRINOX provided better resection and R0 rates of 25.9% and 78.4%, respectively, in patients with locally advanced PA [50]. GnP is also expected to be administered as NAT to patients with potentially resectable PA. The initial results showed that NAT using GnP was safe and feasible [40]; however, the clinical benefit has not yet been clarified. Both FOLFIRINOX and GnP regimens might be potential candidates for NAT for potentially resectable PA, and their clinical survival benefits should be investigated in multicentric prospective trials.

Several studies have shown that GS induced a higher response rate and longer PFS. Ueno et al. [51] and Ozaka et al. [52] indicated significantly higher response rates and longer PFS with GS in a randomized trial; therefore, in the PREP02/JSAP05 trial, GS regimens were applied as an arm of NAT. Gemcitabine and oxaliplatin and the combination therapy of gemcitabine plus capecitabine have also shown significantly higher response rates and a longer PFS [24, 53]. More clinical trials are urgently needed to confirm the best protocol for NAT in patients with PA.

6.6 Optimal Regimens for NAT: Chemotherapy or CRT?

CRT was expected to be a valuable modality for local disease control, and many prospective non-randomized trials using CRT have been conducted; however, none of the trials reported positive survival benefits compared with chemotherapy [42–44, 46]. One of the main reasons for the positive outcome of the PREP02/JSAP05 trial is maybe that the preoperative systemic delivery of cytotoxic agents might suppress the progression of liver micrometastases.

The lower resection rate after CRT might be because of a reduced dose of systemic chemotherapy during combination with radiotherapy. As a NAT regimen for patients with borderline resectable PA, systemic chemotherapy of FOLFIRINOX followed by CRT showed sufficient feasibility and improved survival [7, 54]. This concept is referred to as total NAT, and this strategy might provide further survival benefits for patients with resectable PA [55].

6.7 Optimal Duration for NAT

In the PREP02/JSAP02 trial, two cycles of GS resulted in significant survival benefits for patients with potentially resectable PA. Most previously reported trials for potentially resectable PA used a 2-month period of NAT [9, 37, 39, 41]; however, additional treatment might only induce more prolonged survival time in super-responders to preoperative chemotherapy. A surrogate marker reflecting treatment efficacy is crucial to select appropriate patients for additional treatment.

Radiological response defined by the Response Evaluation Criteria in Solid Tumors, would be a candidate to surrogate the endpoint. Radiological assessments, which can be performed before and after preoperative treatment, are potential tools

to evaluate treatment efficacy during clinical decision-making for surgical resection. However, a radiological complete response is rarely shown even after multimodal treatment for PA [7, 41].

Serum tumor markers are also promising candidates as surrogate markers. CA19-9, which is elevated in most patients with PA, is widely accepted as a valuable tumor marker. Several reports indicated that a decreased CA19-9 value to the normal range after surgery is associated with longer survival and a lower hepatic relapse rate [56, 57]. The decreased marker levels after NAT reflect a good response and longer overall survival [11].

6.8 Conclusion

Neoadjuvant chemotherapy might be beneficial as a standard treatment for patients with potentially resectable PA. Various randomized controlled studies should be performed to comprehensively assess the indications and effects of NAT, and we must make further efforts to cure more patients with resectable PA.

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Adjuvant Chemotherapy for Pancreatic Cancer

7

Masato Ozaka

Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most difficult cancer to treat. The resection rate for patients with resectable PDAC is 15–20%. However, outcomes for resectable PDAC have improved dramatically over the past 13 years. Perhaps the most important factor in this has been the success of a number of adjuvant chemotherapy developments. In this chapter, we will discuss the reach and future prospects of postoperative adjuvant chemotherapy for PDAC, introducing an important randomized controlled trial (RCT) of adjuvant chemotherapy for PDAC.

Keywords

Pancreatic cancer · Adjuvant chemotherapy · Gemcitabine · S1 · FOLFIRINOX

7.1 History of Postoperative Adjuvant Chemotherapy

A list of important clinical trials of adjuvant chemotherapy for PDAC and their results is shown in Table 7.1.

7.1.1 ESPAC-01

In 1994, the European PDAC Research Group (ESPAC) published a 2-2-factor design to compare the relative benefits of adjuvant chemotherapy, chemoradiation,

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Table 7.1 Important clinical trials of adjuvant chemotherapy for PDAC

Study	Year	Treatment arms	Number of patients	MST (months)	*p*-value
ESPAC-01	2004	No CRT	144	17.9	0.05
		CRT	145	15.9	
		No chemotherapy	142	15.5	0.009
		5FU/FA	147	20.1	
CONKO-001	2007	Gem	179	22.1	0.06
		Observation	175	20.2	
JSAP-02	2009	Gem	58	22.3	0.19
		Observation	60	18.4	
RTOG 0704	2008	5FU/FA-CRT-5FU/FA	230	16.9	0.34
		Gem-CRT-Gem	221	20.5	
CapRI	2012	5FU+ CDDP+IFNa2b+RT	64	26.5	0.95
		5FU/FA	68	28.5	
ESPAC-03	2010	5FU/FA	551	23.0	0.39
		Gem	537	23.6	
JASPAC-01	2016	Gem	190	25.5	0.0001
		S1	187	46.5	
ESPAC-04	2017	Gem	366	25.5	0.032
		Gem+Cap	364	28.0	
PRODIGE 24-ACCORD/ CCTG PA.6	2018	Modified FOLFIIRNOX	247	54.4	0.003
		Gem	246	35.0	
APACT	2019	Gem+nab PTX	433	40.5	0.045
		Gem	433	36.2	

MST median survival time, *CRT* chemoradiation, *5FU* 5-fluorouracil, *FA* folinic acid, *Gem* gemcitabine, *CDDP* cisplatin, *IFNa2b* interferon alpha-2b, *RT* radiotherapy, *Cap* capecitabine, *mFOLFIRINOX* modified FOLFIRINOX (5-fluorouracil + leucovorin + irinotecan + oxaliplatin), *nab PTX* nab paclitaxel

or chemotherapy after chemoradiation with observation alone, in an attempt to answer the question about adjuvant chemotherapy once and for all initiated [1]. For more realistic treatments and to improve patient numbers, ESPAC had clinicians select two randomized schemes: (1) no chemoradiation or chemoradiation, and (2) no chemotherapy or chemotherapy. The final results were published in two separate publications: a report 21 in which the results of all 541 patients from three parallel randomized trials were pooled, and a report 22 focusing on 289 patients randomized to two three-factor designs. In the first pooled analysis, there was no difference in survival when comparing 175 patients who received postoperative chemoradiation with 178 who did not (median overall survival (OS), 15.5 months vs. 16.1 months, respectively). In contrast, postoperative adjuvant chemotherapy alone was associated with a significant survival benefit in 238 patients compared with 235 patients (median OS, 19.7 months vs. 14 months, respectively). There was no benefit of chemoradiation and a trend toward poorer survival in the chemoradiation group (2-year survival rates were 29% vs. 41% in the chemoradiation group and 5-year survival rates were 10% vs. 20% in the no chemoradiation group). Local recurrence

rates were similar in both groups, and it was noteworthy that there were more recurrences overall in the chemoradiation group (84% vs. 74%) and shorter recurrence-free survival (RFS) (10.7 months vs. 15.2 months). It is also noteworthy that 33% of patients who received adjuvant chemotherapy did not complete all six courses and 17% did not receive any chemotherapy at all. The median OS for patients who received and did not receive chemotherapy were 20.1 months and 15.5 months, respectively. The final data of ESPAC-01 is listed in Table 7.1 [2].

7.1.2 CONKO-001

CONKO-001 is an RCT that compared a group of patients who received adjuvant chemotherapy with gemcitabine hydrochloride (gemcitabine; GEM) after gross radical resection of PDAC with a surgery alone group. The results of the study, which was mainly conducted in Germany and included 368 patients, were published in 2007 and showed that the GEM group had a significantly better ($p < 0.001$) RFS as the primary endpoint [3]. In the secondary endpoint of OS, the GEM group showed only a favorable trend ($p = 0.06$), but subsequent reports based on long-term follow-up showed that adjuvant GEM chemotherapy significantly prolonged not only RFS, but also OS [4]. Meanwhile, in Japan, the JSAP-02 trial randomized 119 patients with gross radical resection of PDAC to surgery alone or postoperative adjuvant chemotherapy with GEM. Unlike CONKO-001, this study used three courses of adjuvant chemotherapy with GEM, and the results, published in 2009, showed that, like the original results of CONKO-001, GEM significantly prolonged RFS (median RFS: 11.4 months in the GEM group, compared to 5.0 months in the surgery alone group, $p = 0.01$) [5].

7.1.3 RTOG 9704

The RTOG 9704 phase III trial investigated the effect of the addition of GEM to adjuvant chemoradiation with 5-fluorouracil (5-FU) on survival in patients with resected PDAC. Median OS of 388 patients with pancreatic head carcinoma was 20.5 months in the GEM group versus 16.9 months in the 5-FU group [6, 7]. When compared with the individual treatment groups in the ESPAC-1 trial, one may suggest better survival times associated with chemotherapy than with chemoradiation. The Journal of the National Cancer Institute then drew the conclusion that only few data were in favor of adjuvant chemoradiation for PDAC.

7.1.4 CapRI

Between 2004 and 2007, the CapRI trial investigated chemoradio-immunotherapy with 5-FU, cisplatin, and interferon alfa-2b plus radiotherapy followed by 2 cycles of 5-FU compared to 6 cycles of 5-FU monotherapy in a total of 132 patients with

resected PDAC [8]. Median OS was comparable between patients receiving chemoradio-immunotherapy and those receiving 5-FU monotherapy (26.5 months vs. 28.5 months). Considering substantial adverse events in the chemoradio-immunotherapy, the authors concluded that this treatment cannot be recommended.

7.1.5 ESPAC-3

ESPAC-3 study is a head-to-head comparison between 5-FU/folinic acid (FA) as used in ESPAC-1 and GEM as used in CONKO-001 was undertaken within the ESPAC-3 trial (version 2). A total number of 1088 patients was randomized to either adjuvant chemotherapy with GEM or 5-FU/FA for 6 months after resection for PDAC [9]. At a median follow-up time of 34.2 months, median OSs were similar between the two chemotherapy arms (23.0 months for 5-FU/FA group versus 23.6 months for GEM group). However, grade 3/4 toxicities were almost halved in the GEM group compared to the 5-FU/FA group (7.5% vs. 14%). Consequently, from then on adjuvant chemotherapy using GEM was recommended as the treatment of choice in PDAC patients following upfront surgery.

The combined results of 458 randomized PDAC patients from the ESPAC-1, ESPAC-1 plus, and early ESPAC-3 (version 1) trial results were also used to estimate the effectiveness of adjuvant 5-FU/FA compared to surgery alone using meta-analysis. Median OS was 23.2 months with 5-FU/FA versus 16.8 months with surgery alone, supporting adjuvant chemotherapy with 5-FU/FA in PDAC [9].

7.1.6 JASPAC 01

JASPAC 01 is a large comparative study in Japan comparing patients who received adjuvant chemotherapy using GEM (GEM group) with those who received adjuvant chemotherapy using S-1 (S-1 group) after gross radical resection of PDAC. In JASPAC 01, the dosage and schedule of GEM were the same as in CONKO-001, while S-1 was administered at a dose of 80–120 mg/day, depending on body surface area, orally for 28 days. The study was conducted in four courses, each with a 14-day break. The study was initiated as a non-inferiority trial, but was discontinued after an interim analysis showed significantly better OS in the S-1 group than in the GEM group and was presented at the 2013 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. The results were published in a journal in 2016 after all enrolled patients had been in the group for 5 years [10]. According to the report, the 5-year survival rates and median OS for each group were 24.4% and 25.5 months in the GEM group and 44.1% and 46.5 months in the S-1 group, with a hazard ratio (HR) of 0.57 (95% confidence interval (CI), 0.44–0.72, $p < 0.001$ for non-inferiority, $p < 0.001$ for superiority) for S-1 versus GEM. JASPAC 01 showed that S-1 alone significantly and substantially improved survival after resection of PDAC compared to GEM alone.

A companion study to JASPAC 01 examined the impact of human equilibrative nucleoside transporter-1 (hENT1) and dihydropyrimidine dehydrogenase (DPD)

expression on prognosis. There have been scattered reports that hENT1 is a useful biomarker for GEM and DPD is a useful biomarker for S-1 [11]. However, in a prospective study of JASPAC 01 specimens, Okamura et al. found no difference in prognosis between high and low hENT1 expression in the GEM group; in fact, in the S-1 group, the prognosis of the low hENT1 group was significantly better than that of the high hENT1 group, and the expression of DPD was significantly higher than that of GEM. The results showed that there was no prognostic value in either the hENT1 or S-1 groups [12]. From these results, Okamura et al. concluded that hENT1 and DPD are not useful biomarkers of the choice of S-1 or GEM alone as adjuvant chemotherapy regimens for PDAC, but hENT1 is a significant prognostic factor in the S-1 group [13].

7.1.7 ESPAC-4

ESPAC-4 is a large European RCT comparing GEM alone with the combination of GEM plus capecitabine as adjuvant chemotherapy after resection of PDAC. The GEM was administered similarly to CONKO-001, with the GEM plus capecitabine group receiving the same dosing schedule of GEM plus capecitabine at 1660 mg/m^2/day orally for 21 consecutive days with a 7-day break, for a total of 6 courses. The results showed that the median OS was 25.5 months in the GEM group and 28.0 months in the GEM plus capecitabine group, HR 0.82 (95%CI, 0.68–0.98, $p = 0.032$), indicating that adding capecitabine significantly prolonged survival compared to GEM alone [14].

7.1.8 PRODIGE 24-ACCORD/CCTG PA.6

This large RCT conducted in France and Canada compared GEM alone (similar dosing schedule to CONKO-001) with modified FOLFIRINOX as adjuvant chemotherapy in PDAC. A total of 493 patients were enrolled, with the primary endpoint of disease-free survival (DFS), which was repeated for 12 courses of 14 days following administration of oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, irinotecan 150 mg/m^2 (at least day l), and 5-FU 2400 mg/m^2 (48 h continuous) [15]. The median DFS was 12.8 months in the GEM group and 21.6 months in the modified FOLFIRINOX group, with a HR of 0.58 (95%CI, 0.46–0.73, $p < 0.001$). The median OS was 35.0 months in the GEM group and 54.4 months in the modified FOLFIRINOX group, with a HR of 0.64 (95%CI, 0.48–0.86, $p = 0.003$) shown to be a significant improvement.

7.1.9 APACT

The APACT trial was an international RCT comparing GEM plus nab-paclitaxel as adjuvant therapy to GEM alone, the results of which will be presented at the 2019 American Society of Clinical Oncology Annual Meeting [16]. The GEM group

received GEM on a schedule similar to that of CONKO-001, and the GEM + nab-paclitaxel group, nab-paclitaxel 125 mg/m^2 and GEM 1000 mg/m^2 were administered intravenously on days 1, 8, and 15, followed by a 1-week break, for a total of 6 courses of 4 weeks each. The primary endpoint was DFS based on independent imaging review, and the secondary endpoints were OS and the rate of serious adverse events. 866 patients were enrolled, and the median DFS based on independent imaging review was 19.4 months in the GEM plus nab-paclitaxel group and 18.8 months in the GEM group, with a HR of 0.88 (95%CI, 0.729–1.063, $p = 0.182$), which was not significant. The median OS was 40.5 months in the GEM plus nab-paclitaxel group and 36.2 months in the GEM group, with a HR of 0.82 (95%CI, 0.680–0.996, $p = 0.045$).

7.2 Future Perspectives

Based on the results of the CONKO-001 study, the 2009 edition of the Japanese PDAC Treatment Guidelines stated that adjuvant chemotherapy with GEM is a useful, safe, and effective treatment for PDAC. The results of JASPAC 01 indicated that adjuvant chemotherapy was recommended for the first time because of its relatively good results in terms of efficacy. Subsequent to the JASPAC 01 results, the 2013, 2016, and 2019 editions of the PDAC Clinical Practice Guideline and subsequent editions recommend (1) adjuvant chemotherapy, (2) S-1 alone is recommended for the regimen of adjuvant chemotherapy, and (3) recommendation to use GEM alone for patients who are intolerant to S-1, etc. As the result, the use of adjuvant chemotherapy after surgery for PDAC and the use of S-1 or GEM as a regimen has been widely accepted as a consensus in Japan. In contrast, Western guidelines are somewhat different. For example, the National Comprehensive Cancer Network Guidelines recommend category 1 of modified FOLFIRINOX, GEM plus capecitabine, GEM alone, or 5-FU plus FA. This may be strongly influenced by the fact that S-1 is not preferred in the Western countries because diarrhea is more prevalent as an adverse event when used in Caucasians than in Asian races.

In the 2019 edition of the PDAC Practice Guidelines, the combination chemotherapy of GEM plus capecitabine and modified FOLFIRINOX therapy was also described in the statement as “suggested to be done.” The reason for “suggested” instead of “recommended” is that both regimens are only covered by health insurance for unresectable PDAC in Japan, and there are no data on their clinical use in Japanese patients as adjuvant therapy for PDAC. Regarding the HR of GEM plus capecitabine versus GEM alone, the combination chemotherapy of GEM plus capecitabine was much less effective than S-1 alone, and the modified FOLFIRINOX regimen had a HR similar to that of S-1 alone (Table 7.1), but the adverse events were more severe and the regimen was less effective than S-1 alone and complex. For these reasons, it is unlikely that the combination chemotherapy of GEM plus capecitabine or modified FOLFIRINOX will be widely used as adjuvant chemotherapy for PDAC in the very near future under the current insurance system in Japan. The development of new adjuvant regimens will require the reimbursement

of FOLFIRINOX and GEM plus nab-paclitaxel for resectable PDAC or the introduction of entirely new agents.

The choice of S-1 or GEM for postoperative adjuvant therapy in individual cases may also be an important issue. Previous reports have suggested that hENT1 and DPD might be useful biomarkers for this purpose. However, Okamura et al. using prospectively enrolled JASPAC 01 specimens found that patients with low hENT1 expression in the S-1 group had a better prognosis, contrary to previous reports that hENT1 may be a good biomarker for GEM and DPD may be a good biomarker for S-1. How to proceed with the individualization of adjuvant chemotherapy for PDAC remains an important issue.

BRCA1 and BRCA2 are the most common of the known genetic mutations involved in familial PDAC. In advanced unresectable PDAC, some studies reported significantly improved OS and response to platinum-based treatment in BRCA-positive PDAC. Platinum-based anticancer drugs bind directly to DNA, causing DNA double-strand breaks. Therefore, cells that lack BRCA1 or BRCA2 have a deficiency in the repair of DNA double-strand breaks. Although not approved in Japan, postoperative genetic testing may provide a useful alternative to FOLFIRINOX and S1. BRCA mutations have been reported in about 5% of PDACs, but as with BRCA, more than 10% of PDAC patients have homologous recombination DNA damage repair deficiency (HRD) related gene mutations. For these patients, as well as for those with BRCA mutations, platinum has been reported to be effective, and individualization by genetic testing may be necessary in the near future for selection of adjuvant chemotherapy for PDAC.

7.3 Conclusion

Over the past two decades, outcomes for resectable PDAC have improved significantly. This is largely due to the development of highly effective postoperative adjuvant chemotherapy. However, compared to other cancers, the results are poor and there is a need to develop more effective adjuvant chemotherapy for resectable PDAC.

It is also true that the development of new agents for unresectable advanced PDAC has been difficult. There is also a need for the development of individualized improvements that will allow existing treatments to be delivered to a more optimal patient population.

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Conversion Surgery in Pancreatic Cancer

8

Akio Saiura

Abstract

Unresectable pancreatic ductal adenocarcinoma (UR-PDAC) is divided into metastatic PDAC (mPDAC) and locally advanced PDAC (LA-PDAC). Conversion surgery (CS) has been gaining more attention due to the advent of effective systemic chemotherapy and surgical innovation of pancreatectomy with vascular resection and reconstruction. A significant improvement in overall survival has been reported in retrospective and prospective cohort studies. However, there are no robust data which indicate the clear benefit of CS and no consensus of the indication and optimal timing of CS for initially unresectable pancreatic cancer. Several prospective clinical trials are ongoing to clarify the benefit of CS for UR-PDAC.

Keywords

Pancreatic ductal adenocarcinoma · Conversion surgery · Locally advanced pancreatic cancer · Arterial reconstruction

8.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most devastating diseases, with a 5-year survival rate of less than 10%, which is the worst of all carcinomas, and it will become the second leading cause of cancer-related death by 2030 [1, 2]. Surgical resection is the only treatment for potential cure, however, more than 80%

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of patients with pancreatic cancer are deemed unresectable at the time of diagnosis. PDAC starts to metastasize systemically from an early stage, and can be assumed to be a systemic disease. For patients with resectable PDAC, a strategy of upfront surgery and adjuvant chemotherapy is the standard approach, with a 5-year survival rate after resection of 10–20% [3]. Neoadjuvant therapy (NAT), including neoadjuvant chemotherapy (NAC) or neoadjuvant chemo-radiotherapy (NAC-RT), is widely used for borderline resectable PDAC (BR-PDAC). For unresectable PDAC (UR-PDAC), improvement of prognosis was reported with the advent of gemcitabine (GEM), and a higher response rate and improvement of overall survival were shown by administration of strong anticancer agents, such as gemcitabine plus nab-paclitaxel (GnP) and FOLFIRINOX (fluorouracil [5-FU], leucovorin [LV], irinotecan [IRI], and oxaliplatin) [4, 5].

In the last decade, downstaging surgery or conversion surgery (CS) in patients with initially UR-PDAC who responded to systemic chemotherapy is increasingly reported [6]. To date, there are no robust data that indicate the clear benefit of CS and no consensus of the indication and optimal timing of CS for UR-PDAC. CS is a concept that has begun to be used in liver metastases from colorectal cancer. Due to the development of systemic chemotherapy, systemic chemotherapy is given to patients who cannot be resected or are difficult to resect, and resection is performed after obtaining a certain response. Although systemic chemotherapy can improve the prognosis, complete remission is still rare, and CS aims, not only to improve the prognosis, but also to achieve cure. In 1996, Bismuth et al. first reported downstaging surgery in the case of liver metastasis from colorectal cancer, and reported that CS can cure about 20–30% of cases [7]. In the field of pancreatic cancer, conversion surgery is being increasingly reported after the introduction of more effective systemic chemotherapy regimens [8]. In this chapter, we review previous reports on CS for UR-PDAC and discuss the current status and the problems of CS in the treatment of PDAC.

8.2 Definition of Unresectable Pancreatic Cancer

To date, there are several definitions of UR-PDAC [9–11]. UR-PDAC is divided into metastatic PDAC (mPDAC) and locally advanced PDAC (LA-PDAC). Resectability of PDAC without distant metastases is defined according to the local spread of the tumor to the portal and major arteries [11]. Unreconstructable tumor involvement of the superior mesenteric vein/portal vein is regarded as unresectable or LA-PDAC. Arterial involvement is divided into superior mesenteric artery (SMA) system and celiac artery (CA) system, and tumor contact with SMA or CA > 180° is defined as LA-PDAC (Fig. 8.1). Although anatomical classification is useful in technical resection, it is inadequate in predicting prognosis. The problem is the difficulty of determining the effect of chemotherapy on pancreatic cancer. Apparent radiographic extent of the tumor does not change significantly, even in patients with pathological response [12], and current radiological diagnosis cannot accurately

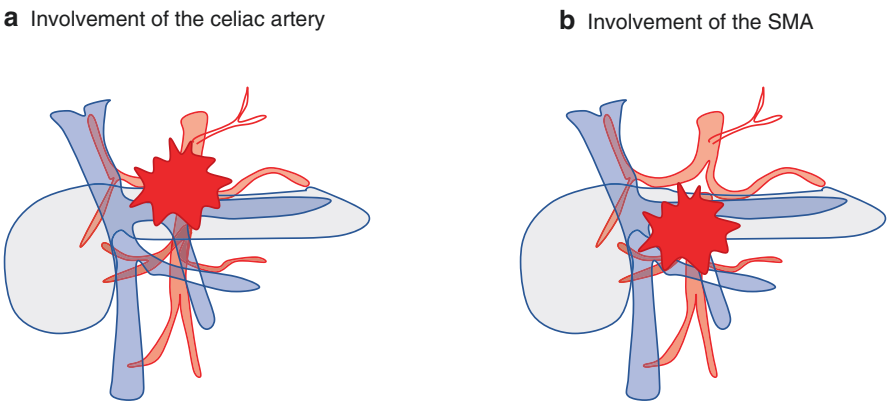

Fig. 8.1 Criteria defining resectability status according to arterial factor in LA-PDAC. (**a**) Tumor in the pancreatic body and tail involves celiac artery. (**b**) Tumor involves SMA > 180°

measure the tumor response to chemotherapy [13]. There is growing evidence that biochemical response is a good predictor for long-term outcomes after conversion therapy. CA19-9 is the only biomarker currently available in clinical practice, and many reports suggest that preoperative CA19-9 level is a good prognostic factor for pathological response and survival after CS [14]. The biological malignancy of the tumor must be taken into consideration independently of anatomical factors, such as the degree of tumor progression and, even if it is technically resectable, it is biologically very malignant. Unfortunately, very few biomarkers can currently be used as indicators of biological malignancy; CA19-9 is the only biomarker that can be trusted at this time. The International Pancreatic Society (IAP) has proposed resection criteria that include biological resection indications and host factors, in addition to anatomical resection indications [15]. One problem is that about 10–15% of patients do not secrete CA19-9 at all.

8.3 Conversion Surgery for LA-PDAC

Conversion surgery after neoadjuvant therapy has been increasingly performed and reported on after the introduction of effective chemotherapy. The reports of conversion surgery for advanced pancreatic cancer are shown in Table 8.1 [16, 18, 19, 21]. LA-PDAC was the main target of conversion surgery. There have been no randomized controlled trials, and the optimal timing and preoperative treatment regimen for conversion surgery are still unknown. Satoi et al. reported that preoperative treatment for more than 8 months was an indicator of favorable long-term outcomes after conversion surgery [17]. FOLFIRINOX or GnP was the standard regimen and offered an improved chance of resection compared to gemcitabine [24]. All studies indicated who responded to preoperative treatment, however, the precise preoperative indication for CS was not fully determined.

Table 8.1 Reports of conversion surgery for advanced pancreatic cancer

Authors	Year	Total number	Resected patients	Resection rate (%)	R0	R0 rate (%)	CR (%)	Regimen	RT	BR (%)	LA (%)	M1 (%)	MST in resected (months)
Strobel et al. [16]	2012	257	120	47	42	35	5	GEM-based	+	0	100	0	24
Satoi et al. [17]	2013	159	58	36	48	83	12	GEM	+	0	71	29	39
Blazer et al. [18]	2015	43	22	51	19	86	5	FFx	+	42	58	0	NA
Marthey et al. [19]	2015	77	28	36	25	89	NA	FFx	–	0	100	0	22
Rombouts et al. [a] [20]	2016	365	103	28	29	77	7	FFx	+/–	0	100	0	24
Natsume et al. [21]	2019	434	18	4	16	89	11	FFx/GnP	–	0	44	56	NA
Maggino et al. [22]	2019	680	93	14	54	58	NA	FFx, GnP, GEMOX	+/–	39	61	0	41
Murphy et al. [23]	2019	49	42	86	34	81	7	FFx+losartan	+	0	100	0	33

BR, borderline-resectable pancreatic cancer; CR, complete response; FFx, FOLFIRINOX; GEM, gemcitabine; GEMOX, gemcitabine plus oxaliplatin; GnP, gemcitabine plus nab-paclitaxel; LA, locally advanced pancreatic cancer; M1, metastatic pancreatic cancer; MST, median survival time; NA, not analyzed; RT, radiotherapy

[a]Systematic review

Postoperative morbidity and mortality after CS were not increased in many reports compared to conventional pancreatectomy [17]. The rate of CS ranged from 4 to 86%, and R0 rate in patients who underwent resection was between 35 and 89%. Pathological complete response was observed in 5–12% of resected cases. Median survival after CS was reported to be 22–41 months. Currently, contrast-enhanced computed tomography (CT) is the standard imaging modality for the evaluation of tumor extension. Major pathological response was reported to be a good prognostic factor [25, 26].

8.4 Conversion Surgery for Metastatic PDAC

Metastatic PDAC (mPDAC) has been an absolute contraindication for surgery, and the reports of CS for mPDAC are limited (Table 8.2). The Heidelberg group published their aggressive surgical approach to oligometastatic pancreatic cancer with liver and distant lymph node metastases. They defined oligometastasis as 1–3 liver metastases that could be easily resected or para-aortic lymph node metastases. However, overall survival was poor even in patients with CS, with the median survival after CS of 12 months [29]. In a recent review analyzing the impact of CS focusing on oligometastatic disease to the liver, increased survival in selected oligometastatic patients treated with CS compared to chemotherapy alone was reported (23–56 months vs. 11–16.4 months), suggesting a potential role for CS in a tailored and multimodal approach to treating pancreatic cancer patients [31]. Satoi et al. reported on a prospective phase 2 study looking at the impact of intraperitoneal chemotherapy for PDAC with isolated peritoneal metastases [27]. CS was performed in eight patients (24%), and the OS of patients who underwent CS was significantly better than that of patients who did not undergo surgery (MST; 27 vs. 14 months, respectively, $P = 0.0038$). A randomized phase 3 trial is ongoing.

Table 8.2 Reports of conversion surgery for mPDAC

Authors	Year	Patients	Resected	RR (%)	Location of distant metastases				MST (months)
					HEP (%)	LN (%)	PER (%)	PUL (%)	
Satoi et al. [27]	2016	33	8	24	0	0	100	0	16.3
Crippa et al. [28]	2016	127	11	9	100	0	0	0	39
Hackert et al. [29]	2017	NA	128	NA	66	34	0	0	12
Wright et al. [30]	2016	1147	23	2	70	0	9	26	18

HEP, hepatic; LN, lymph node; MST, median survival time; NA, not analyzed; PER, peritoneal; PUL, pulmonary; RR, resection rate

8.5 Techniques of Conversion Surgery for PDAC

LA-PDAC is considered unresectable due to extended local infiltration toward major vessels. Portal vein resection is widely accepted as a standard procedure for advanced PDAC and can be safely done in high-volume centers [32]. In 1993, Nakao and Takagi reported isolated pancreatectomy as a radical operation for pancreatic head cancer, including portal vein resection and reconstruction, which was the first report of the artery-first approach [33]. The artery-first approach, which has been widely used as a standard approach for pancreatic head cancer, can facilitate the use of portal vein resection and arterial resection (AR) [34]. Arterial resection is still a challenging procedure and a hurdle for CS for LA-PDAC [35]. Technically, a tumor might be "resectable" using the complex surgical technique of arterial resection and reconstruction in some patients with LAPC, however, it is associated with poor long-term outcomes. Therefore, it is considered unresectable from an oncological point of view. In 1977, Fortner et al. reported a regional pancreatectomy as a radical operation for LAPC, combined with portal vein resection (Type I) and/or combined arterial resection and reconstruction (Type II) [36]. The short-term outcome of pancreatic resection concomitant with vascular resection has been improved by advances in surgical techniques; however, long-term results were not improved, and these procedures had not been widely accepted in the last century [33]. AR during pancreatectomy is associated with poor short- and long-term outcomes, and should be limited to highly selected patients [37–39]. In the era of modern pancreatic surgery and multimodal therapy, short- and long-term outcomes have improved, and AR for PDAC has been revisited.

Arterial involvement is assessed by contrast-enhanced CT preoperatively. Inoue et al. reported tailored dissection (level 1–3) around major arteries depending on the tumor extension, and level 3 arterial dissection is indicated in patients with PDAC infiltrating the perivascular connective tissue [40]. Diener et al. named level 3 dissection a "divestment technique," which is an alternative to arterial resection (Fig. 8.2) [41, 42].

The celiac axis and the common hepatic artery are the most frequently resected major arteries in CS with AR and resected by the Appleby procedure or distal pancreatectomy with celiac axis resection (DP-CAR) [43]. The Appleby procedure, which was first reported as an en bloc resection of the celiac axis combined with distal pancreatectomy and subtotal gastrectomy for locally advanced gastric cancer, was applied to locally advanced pancreatic body/tail PDAC. Hirano et al. reported favorable long-term outcomes, with a 5-year survival rate of 42% for patients who underwent the Appleby procedure for locally advanced pancreatic body and tail cancer, and named it DP-CAR [44]. There are a series of reports of DP-CAR, however, high rates of postoperative mortality and morbidity were reported in single- and multi-institutional studies, with the mortality rate ranging from 3 to 10% (Table 8.3). Ischemic complication was the main cause of mortality, and to date, the procedure of DP-CAR has not been standardized. To minimize ischemic complications, DP-CAR preserving left gastric artery (LGA) flow by preserving or reconstructing the LGA was developed (Fig. 8.3) [50].

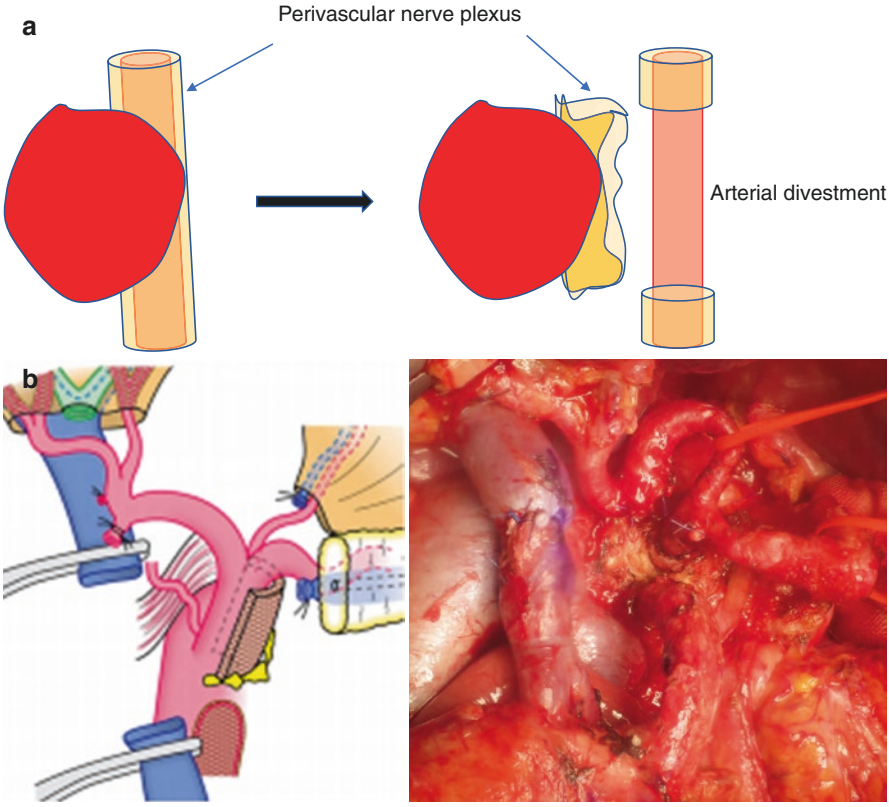

Fig. 8.2 Level 3 dissection (divestment technique) around the artery. (**a**) The perivascular nerve plexus was resected circumferentially with the tumor. (**b**) The nerve plexus around the CHA and splenic artery has been peeled off circumferentially and the nerve plexus around SMA has been detached hemi-circumferentially on the tumor side. Portal vein has been resected and reconstructed directly

Resection and reconstruction of the SMA is a more challenging procedure and rarely indicated due to its high morbidity and mortality [43]. Arterial reconstruction can be done by direct end-to-end anastomosis in case of short segment resection. If direct anastomosis is not feasible, it should be done using interposition graft or other arteries, such as the right gastroepiploic artery, the middle colic artery, the splenic artery, or jejunal artery [37, 51].

8.6 Summary

Although reports of conversion cases in pancreatic cancer are increasing, robust evidence is still lacking. CS is indicated in highly selected patients with favorable prognosis who responded well to NAT. Given the number of cases and the

Table 8.3 Recent reports of DP-CAR

Authors	Year	Patients	LGA preservation/ reconstruction (%)	Operation time (min)	Blood loss (ml)	Ischemic complication (%)		Mortality rate (%)
						Stomach	Liver	
Nakamura et al. [45]	2016	80	6.3	436	880	29	6	5
Okada et al. [46]	2018	50	46	342	500	10	56	8
Oba et al. [47]	2018	21	100	515	565	2	0	0
Klompmaker et al. [a] [48]	2019	191	12	350	560	11	23	9.5
Yoshitomi et al. [49]	2019	38	0	350	1274	10	3	3

LGA, left gastric artery
[a]Multicenter study

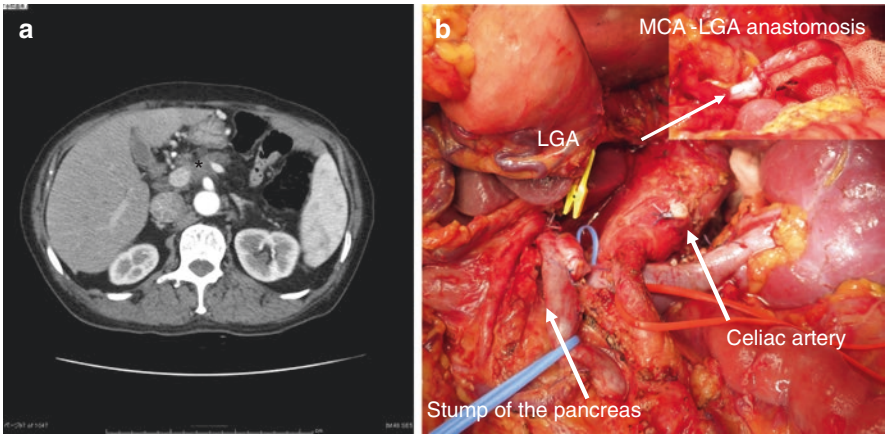

Fig. 8.3 A 63-year-old patient with locally advanced PDAC invading the celiac axis undergoing DP-CAR. After six cycles of GnP, the tumor had shrunk well, however, low-density area *still remained around the celiac artery (**a**). Anatomical orientation is indicated in the image (**b**). After removal of the specimen, the left gastric artery (LGA) was anastomosed to the medial colic artery (MCA) using microsurgical techniques

complexity of treatment, randomized controlled trials are assumed to be very difficult to conduct. In order to show the efficacy of CS, it is necessary to report many "cure cases" with long-term survival without therapy after CS.

The Pancreatic Cancer Preoperative Treatment Study Group stated that a prospective observational study has been conducted of the resectability, safety, and effectiveness of resection for pancreatic cancer that was unresectable at the first visit and for which non-surgical therapy was successful for a certain period of time, and the planned number of 100 cases has already been registered (UMIN000017793). As a clinical study of the Federation of Asian Clinical Oncology (FACO), a registered observational study of pancreatic cancer patients judged to be resectable by FOLFORINOX therapy or GnP combination therapy for unresectable pancreatic cancer is ongoing (UMIN000035668). CS could gain more attention as a potential curative treatment in a multimodal therapy in the era of precision medicine [52, 53].

8.7 Conclusion

Conversion therapy has been gaining more attention due to the advent of effective systemic chemotherapy. A significant improvement in overall survival has been reported in retrospective and prospective cohort studies. However, it should be evaluated in a prospective clinical trial to offer more robust data in the future.

Conflicts of Interest and Source of Funding None declared.

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Radiotherapy for Pancreatic Cancer

9

Shigeru Yamada and Makoto Shinoto

Abstract

Due to the rapid progress of treatment equipment, radiotherapy has become possible to treat with high dose concentration and high biological effect (cell killing effect). By using these new radiotherapy devices, the results of radiotherapy for gastrointestinal cancer have improved and the indications have expanded in recent years. Pancreatic cancer, on the other hand, is located near many radiation-sensitive organs such as the stomach and duodenum and is a highly radioresistant disease, and the role and indications of radiotherapy have long been debated and are still present under investigation. The life-prolonging effect of radiotherapy has not yet been clearly demonstrated, but it has been shown to lead to improved local control. In this chapter, we will introduce radiotherapy for pancreatic cancer, focusing on the heavy-ion radiotherapy that we are performing.

Keywords

Pancreatic cancer · 3D-CRT · IMRT · SBRT · IGRT · Proton · Heavy-ion Carbon-ion

Abbreviations

3D-CRT	Three-dimensional conformal radiation therapy
BR	Borderline resectable
CIRT	Carbon-ion radiotherapy
CRT	Chemoradiotherapy

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DLT	Dose-limiting toxicity
EBRT	External-beam radiotherapy
GEM	Gemcitabine
Gy (RBE)	Gray (relative biological effectiveness)
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
LAPC	Locally advanced pancreatic cancer
MTD	Maximally tolerated dose
NT	Neoadjuvant therapy
OS	Overall survival
PR	Potentially resectable
SBRT	Stereotactic body radiotherapy
UP	Upfront surgery

9.1 Introduction

Radiotherapy, surgery, and chemotherapy are called the three major treatments for cancer. However, radiotherapy for gastrointestinal cancer has not often been indicated for curative treatment except for squamous cell carcinoma such as esophageal cancer and anal cancer. In recent years, the treatment results of surgical therapy and radiotherapy, which are local therapies, have been remarkably improved due to the remarkable development of therapeutic devices. In surgical therapy, less invasive treatments have been developed by laparoscopic surgery and robotic surgery, and the indications for these treatments have been expanded. On the other hand, with the rapid progress of equipment in radiotherapy, it has become possible to treat with excellent spatial dose distribution and high biological effect (cell-killing effect). By using these new radiotherapy devices, the results of radiotherapy for gastrointestinal cancer have improved and the indications have expanded in recent years. Pancreatic cancer is a highly treatment-resistant disease that is located near many radiation-sensitive organs such as the stomach and duodenum. In the treatment of pancreatic cancer, high-precision radiotherapy and particle beam therapy using photon beams have become widespread, and chemotherapy and molecular-targeted therapy have recently become widespread in combination with immunotherapy. The role and indications of *radiotherapy* for pancreatic cancer have long been debated and are still under investigation. The effect of prolonging the survival of radiotherapy has not yet been clearly shown, but it has been shown to lead to improved local control [1–5]. This chapter introduces radiotherapy for pancreatic cancer.

9.2 Modalities for Radiotherapy

9.2.1 Advances in Radiotherapy

In the 1970s, the introduction of high-energy X-ray irradiators (linear accelerators: Linac) using linear accelerators progressed in Japan, and proton and fast

neutron radiotherapy were started. Methods of planning and delivering radiotherapy have advanced to allow more precise irradiation of target tumors of complex shapes.

Early treatment used a two-dimensional treatment planning based on flat images and radiation beams with uniform intensity cross-sections sequentially directed to the target tumor along two or three intersecting axes. Collectively, these methods are called conventional external beam radiotherapy. In the 1990s, the technology for increasing dose concentration rapidly developed, and the technology for improving the position matching accuracy advanced, and the era of high-precision radiotherapy entered. The main new radiotherapy methods are introduced below.

9.2.1.1 Three-Dimensional Conformal Radiation Therapy: 3D-CRT

Conformal therapy is radiation therapy that creates a high-dose volume that is exactly "confirm" to the target volume of interest while minimizing the dose to critical normal organs [6]. The 3D-CRT is a method of irradiating radiation from multiple directions according to the shape of the tumor using a multi-leaf collimator (MLC) using a 3-D CT image for treatment planning. It is possible to reduce the exposure dose to surrounding normal tissues and increase the irradiation dose to the target tumor, which is still the standard for many treatment sites today. Unlike IMRT, which will be described later, the dose intensity in the irradiation field is uniform, so it is difficult to obtain a dose distribution that matches the complex target tumor shape.

9.2.1.2 Intensity Modulated Radiotherapy: IMRT

It is an evolution of the above 3D-CRT, and was developed for the purpose of increasing the dose concentration to the tumor using ordinary high-energy X-rays. This is a treatment method that presents an optimal dose distribution to the lesion by irradiating a beam with non-uniform radiation intensity spatially and temporally from multiple directions based on a reverse treatment plan [7, 8]. The treatment plan of IMRT specifies the dose limit and irradiation direction for each normal tissue, changes the radiation intensity in each irradiation field, and presents the optimum dose distribution. Rotating IMRT (Volumetric Modulated Arc Therapy: VMAT) is becoming popular as an even more advanced method of IMRT. It is an advantage that it is possible to irradiate a complex target tumor more accurately compared to 3D-CRT, but there is a problem that a low dose area is widened.

9.2.1.3 Image-Guided Radiotherapy: IGRT

When applying IMRT, which has a high irradiation system, to the treatment of trunk tumors, it is necessary to deal with position changes due to respiratory movement and changes in surrounding organs. Immediately before or during irradiation, image information (CT, X-ray fluoroscopy, etc.) is used to measure and correct the displacement of tumors, bones, markers, etc., and the amount of displacement of the irradiation position determined in the treatment plan is obtained [9, 10]. This is a treatment that corrects the position of the radiation therapy couches. By increasing the accuracy of radiotherapy, it becomes possible to narrow the irradiation field

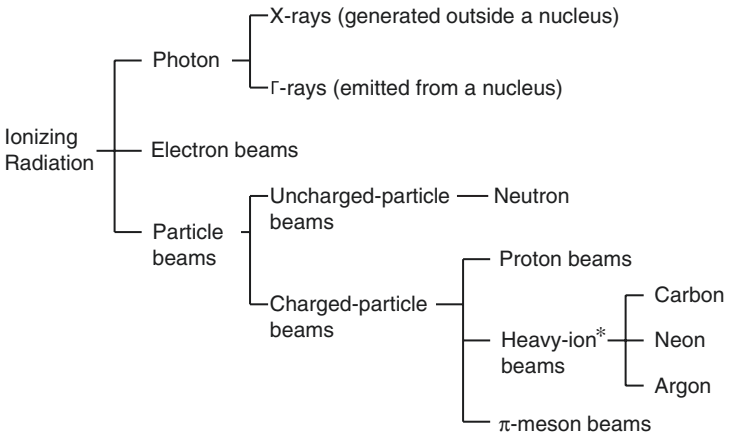
more than before, and the irradiation dose to the surrounding normal tissues is reduced, and as a result, adverse reactions can be reduced.

9.2.1.4 Stereotactic Irradiation: SRI

Stereotactic irradiation (SRI) is radiotherapy that irradiates with high accuracy by maintaining accurate position. A concept advocated by a brain surgeon in 1951, was developed with a different idea from ordinary radiation therapy [11]. Of the stereotactic radiotherapy, stereotactic radiosurgery (SRS) is defined as one fraction, and SRI is defined as two or more fractions. SRI was originally a treatment for intracranial lesions, but is also used for tumors of the trunk such as the liver or lung. More recently, its use in the treatment of the pancreas has expanded rapidly. When SRI is applied to the trunk, it is called Stereotactic body radiotherapy (SBRT). SBRT usually results in a higher dose per irradiation (7.5–20 Gy) and a lower total number of irradiations [1–8] as a result. It is possible to finish the treatment in a short period of time. SRI treatment devices include gamma knife and cyberknife, but it is also performed in ordinary linac.

9.2.1.5 Charged Particle Therapy (Proton Beam Radiotherapy, Heavy-Ion Radiotherapy)

In Japan, particle beam therapy was started at the National Institute of Radiological Sciences (currently QST) in 1978, followed by the particle beam medical science center at the University of Tsukuba in 1983. Figure 9.1 shows the classification of radiation used in cancer treatment. Generally, particles heavier than electrons are accelerated at high speed and are called particle beams. Furthermore, an accelerated nucleus (ion) whose atomic number is heavier than 1 is called a heavy ion beam. Figure 9.2 shows the deep dose distribution from the skin in the body due to various radiations used for treatment. Unlike X-rays, particle beams (proton beams,



*Heavy-ion beams: Accelerated nuclei heavier than atomic number 1 at high speed

Fig. 9.1 Types of radiation used for treatment

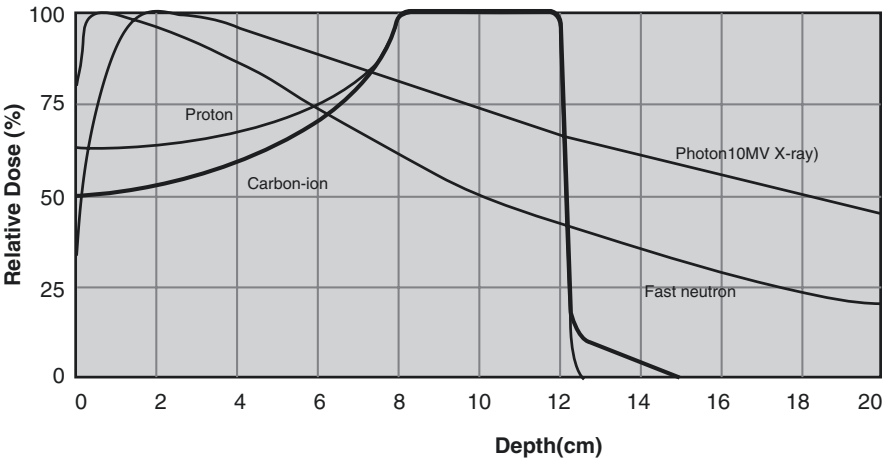


Fig. 9.2 Depth-dose distribution in various radiation

heavy-ion beams) have a special dose distribution called the Bragg peak [12, 13]. This property allows particle beams to avoid the highly radiosensitive organs such as gastrointestinal tract, bladder, and spinal cord around the cancer and to irradiate only the cancer with a sufficient dose. Furthermore, heavy-ion particles have a high biological effect because they are heavier than protons, and therefore have a high cell-killing effect on radioresistant cells in the DNA synthesis stage, hypoxic cells, or cancer stem cells [14, 15]. It has the characteristic of being recognized. Due to these characteristics, heavy-ion beams can selectively irradiate only cancer tissues with radiation having a high cell-killing effect.

The clinical application of heavy-ion radiotherapy using a medical accelerator was started at the National Institute of Radiological Sciences (NIRS) in 1994, and was approved for advanced medical treatment in 2003 [16, 17]. Public insurance coverage for heavy-ion radiotherapy for bone and soft tissue tumors was approved in 2016, and from April 2018, public insurance coverage was also applied for treatment for head and neck tumors and prostate cancer. Currently, six facilities are in operation: Hyogo Ion Beam Medical Center, Gunma University, Saga HIMAT, Ion-beam Radiation Oncology Center in Kanagawa, and Osaka Heavy Ion Therapy Center, and treatment is scheduled to start at Yamagata University. The main indications for heavy ion beam for gastrointestinal cancer are liver cancer, pancreatic cancer, esophageal cancer, and locally recurrent colorectal cancer.

9.3 Radiation Therapy for Pancreatic Cancer

9.3.1 Resected Pancreatic Cancer: Adjuvant Approach

In a clinical trial conducted by The Gastrointestinal Tumor Study Group (GITSG) to examine the efficacy of adjuvant therapy after resection of pancreatic cancer, 22

patients received no treatment and 21 received CRT. The median overall survival (OS) for the treatment group was 20 months and the control group was 11 months, demonstrating that adjuvant CRT is beneficial in prolonging prognosis [18]. However, subsequent clinical trials with an increased number of cases did not show the effectiveness of CRT [19–22].

In the results of clinical trials of adjuvant gemcitabine (GEM) alone versus GEM-based CRT after curative resection for pancreatic cancer conducted by EORTC, there was no difference in toxicity, but there was also no difference in disease-free survival (DFS), and OS. However, the local recurrence rate was shown to be significantly lower at the CRT arm, 11% at the CRT arm, and 24% at the control arm [22].

A meta-analysis of adjuvant therapy with Stocken DD et al. also did not show an additional effect on survival by adding radiotherapy to postoperative chemotherapy [23]. However, subgroup analysis showed that the CRT group was more effective in patients with positive resection margins than the chemotherapy group. Morganti et al. analyzed 514 patients with pancreatic ductal adenocarcinoma (PDAC) (T1–4; N0–1; M0) treated with surgical resection with macroscopically negative margins (R0–1) followed by adjuvant CRT [24]. Patients were classified into four groups by dose (group 1: <45 Gy, group 2: ≥ 45 and <50 Gy, group 3: ≥ 50 and <55 Gy, group 4: ≥ 55 Gy). The median OS was shown to increase to 13.0 months, 21.0 months, 22.0 months, and 28.0 months, respectively, as the dose increased ($p = 0.004$).

From the above results, it was suggested that postoperative irradiation may be effective for patients with positive resection margins or when the irradiation dose is high.

9.3.2 Potentially Resectable Pancreatic Cancer: PRPC

Upfront surgery (UP) followed by adjuvant chemotherapy has long been the standard treatment for PDAC [25, 26]. However, pancreatectomy is a complex and highly invasive procedure that prevents a significant proportion of patients from receiving adjuvant therapy due to postoperative complications or poor general conditions [27, 28].

Therefore, recently, non-surgical treatment before pancreatectomy has become popular for the purpose of improving complete microscopic tumor resection and local control rate and expanding the indications for resection [29].

Early trials focused primarily on neoadjuvant CRT [30–32]. Results from prospective clinical trials showed that neoadjuvant CRT for potentially resectable pancreatic cancer (PRPC) tended to prolong survival, but not significantly [33, 34] (Table 9.1). Retrospective studies suggest that CRT improves local region control compared to chemotherapy alone [35, 36]. However, due to the dramatic improvement in chemotherapy for PDAC, only chemotherapy is increasingly used without radiotherapy before surgery, especially for patients with PR tumors [37–39] (Table 9.1). In the era of more effective systemic chemotherapy, the role of neoadjuvant CRT in the management of PDAC remains poorly understood today and controversial.

Table 9.1 Comparison of outcome for potentially resectable pancreatic cancer treated with radiotherapy or/and chemotherapy

Study	Study design	Year	*N*	RT regimen Dose(Gy)/Fr	Neoadjuvant CT	Resection rate (%)	R0 resection rate (%)	MST (M)	*p* value
Golcher et al. [33]	Ph2	2015	33	–	–	69.7	47.8	14.4	0.96
			33	55.8 Gy/31 fr	GEM/CDDP	57.6	52.6	17.4	
Casadei et al. [34]	Ph3	2015	20	–	–	75	33.3	19.5	0.97
			18	54 Gy	GEM	61	45.5	22.4	
Cloyd et al. [36]	Retrospective	2016	27	–	GEM/CAP/5FU	–	66.7	28.4	0.33 (NoRT vs. RT) 0.41 (30 Gy vs. 50.4 Gy)
			224	30 Gy/10 fr	GEM/CAP/5FU	–	74.6	33.7	
			221	50.4 Gy/28 fr	GEM/CAP/5FU	–	77.6	38.2	
Reni et al. [37] PACT-15	Ph2/3	2018	56	–	–	87.5	32.3	20.4–25.1	0.022
			32	–	PEXG(CDDP/EPI/GEM/CAP)	84.4	63.0	38.2	
Unno et al. [38]	Ph2/3	2019	182	–	–	72.2	–	26.6	0.015
			182	–	GEM/S1	76.9	–	36.7	
Versteijne et al. [41] PREOPANC	Ph3	2020	68	–	–	79	59	15.6	0.83
			65	36 Gy/15 fr	GEM	68	66	14.6	

RT, radiotherapy; N, number; MST, median survival time; M, months; Ph, phase; CT, chemotherapy; CDDP, cisplatin; GEM, gemcitabine; EPI, epirubicin; CAP, capecitabine; 5FU, 5-fluorouracil; S-1, Tegafur/Gimeracil/Oteracil

Cloyd et al. have performed a meta-analysis of randomized controlled trials (RCTs) for neoadjuvant therapy (NT) for PRPC and borderline resectable pancreatic cancer (BRPC) [40]. Of the six RCTs, including 850 patients, 411 (48.3%) received NT, and 439 (51.6%) received UP. In all studies included, NT was GEM-based: four used CRT and two used chemotherapy (CT) only. Of the six trials, four were for PR tumors, 1 was for BR tumors, and 1 was for PRPC and BRPC. The median OS pooled in all studies was higher in patients who received NT than in UP (25.4 months (95% confidence interval (CI) 22.4–28.7) vs. 19.4 (95% CI 17.2–21.8), $p < 0.001$) (Table 9.1). Furthermore, this effect was shown to be independent of the NT type (CT or CRT). Versteijne et al. performed neoadjuvant CRT (with GEM) versus immediate surgery for PRPC and BRPC (Randomized Phase III PREOPANC Trial) [41] (Table 9.1). Median OS with treatment intent was 16.0 months with neoadjuvant CRT and 14.3 months with immediate surgery (hazard ratio (HR), 0.78; 95% CI, 0.58–1.05; $p = 0.096$). The predefined subgroup of patients with PRPC showed no significant difference in OS. Neoadjuvant CRT had significantly better progression-free survival (PFS) and locoregional failure-free intervals, and had a significantly lower incidence of pathological lymph node metastases, perineuronal infiltration, and venous infiltration.

The effectiveness of neoadjuvant CRT for PRPC is still controversial. In the future, it is expected that increasing the dose of radiation by advances in radiation technology or changing the combined chemotherapy to a new regimen may contribute to survival rates.

9.3.3 Borderline Resectable Pancreatic Cancer: BRPC

The results of clinical trials involving patients with BRPC should be carefully interpreted, as previous clinical trials have different definitions of resectability for pancreatic cancer. Several non-randomized trials and meta-analyses examining the efficacy of neoadjuvant therapy for BRPC have shown promising results for R0 resection and survival. From these results, the neoadjuvant approach to BR tumors appears to be particularly beneficial for BRPC [42–47] (Table 9.2).

Jang et al. conducted a multicenter Korean randomized multicenter phase 2/3 study for BRPC comparing neoadjuvant CRT with GEM and upfront surgery for BRPC [48] (Table 9.2). CRT underwent GEM-based neoadjuvant CRT (54 Gy external beam radiation). Twenty-seven patients were assigned to neoadjuvant therapy and 23 were assigned to the upfront surgery group. The 2-years survival rate and median OS were significantly better with neoadjuvant CRT than with upfront surgery [40.7%, 21 months vs. 26.1%, 12 months, HR 1.495 (95% CI) 0.66–3.36), $p = 0.028$]. R0 resection rates were also significantly higher in the neoadjuvant CRT group than in upfront surgery ($n = 14$, 51.8% vs. $n = 6$, 26.1%, $p = 0.004$).

A predefined subgroup of patients with suspected borderline PRPC in the PREOPANC trial also showed a significant improvement of OS and DFS in neoadjuvant CRT [41] (Table 9.2).

Table 9.2 Comparison of outcome for borderline resectable pancreatic cancer treated with radiotherapy

Study	Study design	Year	*N*	RT regimen Dose(Gy)/Fr	CT	Resection rate (%)	R0 resection rate (%)	MST (M)	*p* value
Dholakia et al. [45]	Retrospective	2013	50	50 Gy/25 fr	FLX→CAP	58	93	17.2	–
Katz et al. [46]	Ph2	2016	22	50.4 Gy	FLX→CAP	69	93	21.7	–
Nagakawa et al. [43]	Ph2	2017	29	50.4 Gy	GS	70	95	22.4	–
Pietrasz et al. [42] AGEO-FRENCH	Retrospective	2019	57	–	FLX	–	–	35.5	0.007
			49	54 Gy/30 fr	FLX	–	–	57.8	
Jang et al. [48]	Ph2/3	2018	23	–	–	79	26.1	12	0.028
			27	54 Gy	GEM	63	40.7	21	
Versteijne et al. [41] PREOPANC	Ph3	2020	59	–	–	64	13	13.2	0.029
			54	36 Gy/15 fr	GEM	52	79	17.6	

FFX FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan), *CAP* capecitabine, *GS* gemcitabine and S-1, *N* number, *RT* radiotherapy, *CT* chemotherapy, *MST* median survival time, *M* months, *Ph* phase

9.3.4 Locally Advanced Pancreatic Cancer: LAPC

The main RCTs for LAPC are summarized in Table 9.3. GITSG is conducting a RCT of LAPC comparing radiation alone and 5FU + irradiation (40 Gy, 60 Gy) [49]. Median OS was 22.9 weeks in the radiation alone (60 Gy) group, 42.2 weeks in the 5FU + 40 Gy group, and 40.3 weeks in the 5FU + 60 Gy group, indicating a significant prolongation of survival in the CRT group compared to the radiation alone group. In addition, GITSG compared the survival rates of the streptozotocin, mitomycin-C, and 5FU (SMF) and radiation combined with 5FU groups for LAPC [50]. The 1-year survival rate was 19% in the SMF alone group and 41% in the CRT group, indicating that the survival rate was significantly higher in the CRT group. In Japan as well, a RCT was conducted to verify the effectiveness of external-beam radiotherapy (EBRT) with concurrent continuous 5FU infusion for LAPC [51]. EBRT with concurrent continuous 5FU infusion increased the length and quality of survival as compared to no CRT. Although these results do not provide high-quality evidence, until the 1900s, 5FU combination CRT was recommended as the standard treatment for LAPC.

In the 2000s, new anticancer agents such as GEM, capecitabine and S-1 (5FU, Tegafur, and Potassium Oxonate) were developed. CRT, which is a combination of these anticancer drugs instead of 5FU and radiotherapy, is often used. Li et al. conducted a RCT comparing the effects of the efficacy and tolerability of concurrent CRT for LAPC: GEM versus 5FU [52]. The median OS and median time to progression were 14.5 months and 7.1 months for the GEM concurrent CRT group and 6.7 months and 2.7 months for the 5FU concurrent CRT group ($p = 0.027$ and $p = 0.019$, respectively). GEM concurrent CRT is more effective than 5FU concurrent CRT for LAPC. Loehrer PJ et al. (ECOG) conducted the clinical trial to evaluate the role of radiotherapy with concurrent GEM compared with GEM alone in patients with localized unresectable pancreatic cancer [53]. In this study, 37 patients were randomly assigned to GEM alone and 34 patients were assigned to GEM plus radiation. The incidence of grades 3 and 4 toxicities was not different between the two groups. Median OS was 9.2 months in the GEM alone group and 11.1 months in the GEM plus radiation (1.8 Gy/fr for a total of 50.4 Gy) group. The results of this study showed that the addition of radiotherapy to GEM improved OS and was acceptable toxicity in patients with LAPC.

On the other hand, FFCD/SFRO performed Phase III trial comparing intensive induction CRT (60 Gy, infusional 5FU, and intermittent cisplatin) followed by maintenance GEM with GEM alone for LAPC [54]. The result was OS was shorter in the CRT arm than in GEM arm [median OS 8.6 (99% CI 7.1–11.4) and 13 months (8.7–18.1), $p = 0.03$]. Hammel et al. conducted the LAP07 randomized clinical trial to assess whether CRT improves the OS of patients with LAPC controlled after 4 months of GEM-based induction chemotherapy and to assess the effect of erlotinib on survival [55]. CRT was associated with decreased local progression (32% vs. 46%, $p = 0.03$) and no increase in grade 3–4 toxicity, except for nausea. There was no significant difference in OS with CRT compared with chemotherapy alone. The radiotherapy regimen in this study is 54 Gy/30 fr using 3D-CRT, and chemotherapy

Table 9.3 Randomized controlled trials for locally advanced pancreatic cancer

Study	Year	*N*	RT regimen Dose(Gy)/Fr	I	CT	PFS (M)	MST (M)	*p* value
Moertel et al. [49]	1981	25	60 Gy	–	–		5.7	<0.01
		28	40 Gy	–	5FU		10.6	<0.01
		31	60 Gy	–	5FU		10.1	
GITSG [50]	1988	22	–	–	SMF		8.0	0.02
		21	54 Gy	–	5FU		10.5	
Shinchi et al. [51]	2002	16	–	–	5FU		6.4	0.0009
		15	50.4 Gy	–	5FU		13.2	
Li et al. [52]	2003	16	50.4–61.2 Gy/28–34 fr	–	5FU	2.7	6.7	0.027
		18		–	GEM	7.1	14.5	
Loehrer et al. [53] ECOG	2011	37	–	–	GEM	6.7	9.2	0.017
		34	50.4 Gy/28 fr	–	GEM	6.0	11.1	
Chhauffert et al. [54] FFCD/SFRO	2008	60	–	–	GEM		8.6	0.03
		59	60 Gy/30 fr	–	5FU+CDDP		13.0	
Hammel et al. [55] Lap 07	2020	136	–	GEM/GEM+Erlotinib	–	11.8	16.4	0.83
		133	54 Gy/30 fr	GEM/GEM+Erlotinib	CAP	12.5	15.2	

I, induction therapy; N, number; RT, radiotherapy; CT, chemotherapy; PFS, progression-free survival; MST, median survival time; M, months; 5FU, 5-fluorouracil; GEM, gemcitabine; CDDP, cisplatin; CAP, capecitabine; SMF, streptozotosin+mitomycin C+fluorouracil

was GEM at a dose of 1000 mg/m^2 and erlotinib. It was thought that it was necessary to improve the method of radiotherapy and the type of chemotherapy drug in order to obtain a higher therapeutic effect.

With the rapid progress of radiotherapy technology in the 2000s and the spread of high-precision radiotherapies such as IMRT and SBRT, the dose of surrounding organs can be reduced and more concentrated irradiation can be performed on tumors.

Recently, SBRT has been used as a viable alternative to conventionally fractionated radiotherapy (CFRT) [56–58]. Tchelebi LT et al. have performed a meta-analysis of CFRT versus SBRT for LAPC [59]. For SBRT, the median therapeutic dose was 30 Gy, with the most common regimen being the 30 Gy/5 fr. For CFRT, the dose ranged from 45 to 54 Gy with a fraction of 1.8–2.0 Gy, and in the majority of studies, 50.4 Gy was applied to 28 fractions with GEM. The estimated 2-year OS was 26.9% (95% CI, 20.6–33.6%) for SBRT and 13.7% (95% CI, 8.9–19.3%) for CFRT. The OS for SBRT was statistically significantly higher. Estimated incidence of acute grade 3/4 toxicity was 5.6% (95% CI, 0.0–20.0%) for SBRT, compared to 37.7% (95% CI, 24.0–52.5%) for CFRT. The incidence of toxicity with CFRT was statistically significantly higher. These results suggest that SBRT in LAPC results in a modest improvement in 2-year OS, a reduced incidence of acute grade 3/4 toxicity.

However, the median SBRT total dose was 24 Gy (range: 25–33), delivered in 1–5 fractions [60–64]. Toesca DAS et al. reviewed the treatment characteristics and outcomes of 149 patients who received multi-fraction SBRT for unresectable pancreatic adenocarcinoma [65]. Patients treated with SBRT dose 40 Gy ($n = 51$) had superior progression-free survival (PFS) and OS compared to those who received doses <40 Gy (median PFS: 13 vs. 10 months, HR: 0.62, 95% CI: 0.44–0.88, $p = 0.007$; median OS: 23 vs. 14 months, HR: 0.49, 95% CI: 0.34–0.72, $p = 0.0007$).

It was considered that one of the reasons why effective results could not be obtained was that the irradiation dose was not sufficiently high with the conventional SBRT. Krishnan S et al. compared OS and recurrence-free survival (RFS) between the biologically effective dose (BED)10 > 70 Gy [66] and BED10 ≤ 70 Gy groups in 200 patients with LAPC who received CRT [64]. Patients with BED10 > 70 Gy had better median OS than patients with BED10 ≤ 70 Gy (17.8 months vs. 15.0 months, $p = 0.03$).

Using the adaptive magnetic resonance (MR) image-guided RT technique, Rudra et al. treated 44 inoperable pancreatic cancer patients with different RT schemes including high-dose (BED10 > 70) group or standard-dose groups (BED10 ≤ 70) [67]. The authors reported high-dose group ($n = 24$) had statistically significant improvement in 2-year OS (49% vs. 30%, $p = 0.03$) compared to standard-dose patients ($n = 20$). Patients treated with dose-escalated IGRT demonstrated improved OS.

These techniques such as IGRT suggest opportunities to potentially improve outcomes with dose escalation with RT.

9.4 Particle Therapy

Particle beams, especially heavy particle beams, have come to be expected as effective treatments for pancreatic cancer due to their unique physical and enhanced radiobiological properties.

Durante M et al. show that CRT with protons or carbon ions results in 1-year OS significantly higher than those obtained with other treatments [68]. Further hypofractionation using charged particles may result in improved local control and survival. A comparative clinical trial using the standard X-ray scheme versus the best current standard with carbon ions is crucial and may open new opportunities for this deadly disease.

9.4.1 CIRT in Potentially Resectable Pancreatic Cancer

Shinoto et al. conducted a phase I study to evaluate the efficacy and tolerability of CIRT as a short-term (8 fractions/2 weeks) preoperative treatment [69]. Dose escalation was performed from 30 to 36.8 Gy (relative biological effectiveness (RBE)) in eight fractions by increments of 5 %. Between 2003 and 2010, 26 patients were enrolled. All patients completed the scheduled treatment and no dose-limiting toxicity (DLT) was observed. Twenty-one patients (81%) underwent resection, in resected patients, no local recurrence was observed in the resected cases. The 5-year survival rates for all 26 patients and for those who underwent surgery were 42% and 52%, respectively. Though maximally tolerated dose (MTD) was not reached, 36.8 Gy (RBE) was recommended as standard secondary to excellent local control. Ebner D et al. updated the study to report treatment outcomes in 40 patients [70]. There were no other grade 2 or higher adverse events. Local control for resected patients (32 cases) at 5 years was 92.3%. Overall survival at 5 years in all cases was 40% and in resected cases 49%, respectively.

Standard preoperative CRT is delivered over a period of 5–6 weeks followed by surgery after 4–6 weeks. Preoperative CRT may reduce local recurrence following surgery, but if the tumor does not respond well to CRT, there is a risk of tumor progression during this prolonged treatment. Conversely, preoperative CIRT is delivered over a period of just 2 weeks; the likelihood of tumor progression is very low because of its excellent local control and its short duration. The authors concluded that short-course preoperative CIRT is both tolerable and feasible without intolerable morbidity in cases of resectable pancreatic cancer.

9.4.2 Proton Beam Therapy in Locally Advanced Pancreatic Cancer

In a clinical trial of Proton Beam Therapy (PBT) for LAPC, the Hyogo Ion Beam Medical Center carried out a prospective phase I/II trial of GEM simultaneous

PBT for LAPC (T3–T4) enrolled in 50 patients [71]. The dose of PBT increased from 50 to 67.5 Gy (RBE) and then increased to 70.2 Gy (RBE) in 25–26 fractions. The OS rate for 1 year was 76.8%. Grade 5 or higher gastric ulcer and bleeding were observed in five patients (10%) with grade 5 toxicity. The Florida Proton Therapy Institute reported early outcomes in 11 LAPC patients treated with 59.4 Gy (RBE) in 33 fractions [72]. The 1-year OS rate was 61% and there was no grade 2 or higher gastrointestinal toxicity. The median follow-up was limited to 1 year in both reports, so further research is needed to assess the long-term impact on survival.

9.4.3 CIRT in Locally Advanced Pancreatic Cancer

The management of LAPC is controversial and has been extensively discussed in the last decade. Increasing local control using radiotherapy is expected to influence the survival, but radiosensitivity of the upper abdominal organ limits dose to suboptimal levels for controlling disease. A significant proportion of LAPC patients may not benefit from extensive local treatment, as they develop distant metastasis within a few weeks. CIRT has shown promising results in LAPC.

Shinoto et al. performed a dose-escalation study in the setting of LAPC to determine the MTD of carbon ion radiation therapy (C-ion RT) and GEM [73]. Between 2007 and 2012, 72 patients were treated. CIRT was delivered in 12 fractions over 3 weeks. The initial CIRT dose was 43.2 Gy (RBE), with GEM increased from 400 to 700, then to 1000 mg/m^2. GEM dose was then fixed at 1000 mg/m^2, with CIRT dose escalated to 55.2 Gy (RBE) in 5% increments. DLTs were observed in only three patients: two patients suffered from grade 4 neutropenia and grade 3 cholangitis was observed in one patient. Only one patient treated with 50.4 Gy (RBE) experienced a grade 3 gastric ulcer with hemorrhage. The 1- and 2-year OS rates were 73% and 35%, respectively. In the high-dose group with stage III disease (>45.6 Gy RBE) the 2-year OS was 48%. We concluded that 55.2 Gy (RBE) with full-dose GEM did not exceed the MTD. This study did not conclude an MTD; however, they did not administer a dose greater than 55.2 Gy (RBE) because of the risk of severe late toxicities. A notable finding in this study was that CIRT including the primary tumor and the subclinical lymph nodal areas along with a full dose of GEM was well tolerated by this cohort. This study set the platform for escalating the dose of CIRT while administering a full dose of GEM, which might provide the maximal locoregional and systemic effects essential for managing this deadly disease.

Recently, Kawashiro et al. retrospectively analyzed the efficacy of high-dose CIRT as well as the total dose of GEM in LAPC in a multicenter study [74]. The study included a total of 72 patients with LAPC from 2012 to 2014 at three centers. The prescribed dose of CIRT was 52.8 Gy (RBE) or 55.2 Gy (RBE), both given in 12 fractions, with 1000 mg/m^2 of GEM injected concomitantly on days 1, 8, and 15. Seventy-eight percent of patients received simultaneous chemotherapy. Cumulative local recurrences at 1 and 2 years were 16% and 24%, respectively. The OS rate was

73% at 1 year and 46% at 2 years, with a median OS of 21.5 months. Patients who received 55.2 Gy (RBE) were associated with better OS than 52.8 Gy (RBE) (2-year OS 60% vs. 20%, $p = 0.001$) [75]. With regard to acute toxicity, 26% of patients suffered from grade 3 to 4 hematological toxicity associated with the use of GEM-based chemotherapy. Only one patient (1%) developed a grade 3 duodenal ulcer. This is a much lower rate than IMRT, SBRT, or proton therapy [76, 77]. Compared to other modalities, CIRT has proven to be a safe and viable treatment for LAPC with excellent results.

CIRT is also characterized by the ability to re-irradiate. Hagiwara et al. examined the efficacy and feasibility of re-irradiation using carbon ions for pancreatic cancer that recurs after carbon-ion radiotherapy [78]. Twenty-one patients with recurrent pancreatic cancer who underwent repeat Cion RT between December 2010 and November 2016 at our institute were retrospectively analyzed. Only one patient (4.8%) developed grade 3 acute toxicities and none developed grade 3 late toxicities. The 1-year local control and OS rates were 53.5% and 48.7%, respectively. Repeating CIRT may be a reasonable option with tolerable toxicity for patients with recurrent pancreatic cancers.

9.4.4 Perspective

QST is planning multi-ion radiotherapy as a next-generation treatment. This is a method of irradiating with a combination of oxygen ions and helium ions other than carbon ions, depending on the condition of the tumor and the surrounding normal tissue. This is expected as a more therapeutic method.

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Part III

Anti-cancer Treatments for Cholangiocarcinoma

Chemotherapy for Unresectable Cholangiocarcinoma

10

Takashi Sasaki

Abstract

Systemic treatment is important for patients with unresectable biliary tract cancer. Various treatments using cytotoxic agents, molecular-targeted agents, and immunotherapy have been investigated in this field. For first-line chemotherapy, the combination of gemcitabine plus cisplatin has been established as the global standard of care. In addition, the effects of various regimens such as the combined use of oral fluoropyrimidines have been shown. Furthermore, several regimens that have been shown to be effective in pancreatic cancer are now under investigation for the treatment of biliary tract cancer. However, there has been no standard treatment for second-line chemotherapy. In recent years, several treatments, such as mFOLFOX, ivosidenib, and regorafenib, have demonstrated survival benefits in comparison with best supportive care, meaning that standard treatment may be established in the near future based on these results. Currently, combination therapies with various molecular-targeted drugs and immunotherapy are being investigated in several clinical trials, and it is expected that systemic therapy for advanced biliary tract cancer will become more diverse in the future as it has in other carcinomas.

Keywords

Unresectable · Cholangiocarcinoma · Biliary tract cancer · Chemotherapy Molecular-targeted drug · Immunotherapy

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10.1 Introduction

Biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma, extrahepatic (hilar and distal) cholangiocarcinoma, gallbladder cancer, and ampullary carcinoma. BTC has been regarded as common cancer in Japan, Southeast Asia, South America, and India [1, 2]. While the incidence of gallbladder cancer has been decreasing in recent years, cholangiocarcinoma has been increasing worldwide [3–5]. In Japan, BTC is the sixth leading cause of cancer-related death; approximately 22,000 patients suffer from this cancer and 18,000 patients die from it annually [6]. The age at diagnosis of BTC is increasing significantly, as more than 45% of new diagnoses in Japan occurred in patients over the age of 80.

It is very important to pursue the possibility of surgery, because surgical resection is considered to be the only curative treatment. However, there are many patients who are not candidates for surgery due to cancer progression, old age, and comorbidities, meaning systemic treatment is also important for these unresectable cases. Various treatments using cytotoxic agents, molecular-targeted agents, and immunotherapy have been investigated in this field. Herein, we summarize the systemic chemotherapy (mainly cytotoxic agents) used in the treatment of advanced (unresectable or recurrent) BTC.

10.2 First-Line Chemotherapy

Chemotherapy for BTC has begun to be developed using therapies previously used in the treatment of pancreatic cancer. Gemcitabine (GEM) has long played a central role in this field [7]. GEM + cisplatin (CDDP) is now the standard of care as first-line chemotherapy for advanced BTC, and GEM + oxaliplatin (GEMOX) is considered an alternative to GEM + CDDP therapy. Oral fluoropyrimidines, S-1 and capecitabine, are also important drugs and are commonly used in clinical practice as monotherapy or in combination with GEM. Tables 10.1 and 10.2 show the major clinical trials that have examined the treatments used for advanced BTC.

10.2.1 GEM + CDDP

The ABC-02 study is the phase III study conducted in the United Kingdom that compared GEM + CDDP and GEM alone [8]. Four hundred ten patients with advanced BTC were randomly assigned to GEM + CDDP or GEM alone. Median overall survival (OS) of GEM + CDDP and GEM alone was 11.7 months and 8.1 months (hazard ratio (HR) 0.64, $p < 0.001$), and median progression-free survival (PFS) was 8.0 months and 5.0 months ($p < 0.001$), respectively. The response rate (RR) and disease control rate (DCR) of GEM + CDDP was 26.1% and 81.4%, respectively. Grade 3/4 toxicities of neutropenia (25.3%) and anemia (7.6%) were more frequent in GEM + CDDP than in GEM monotherapy. As a result of this study, GEM + CDDP is now the standard of care for patients with advanced BTC worldwide.

Table 10.1 Phase III studies of first-line chemotherapy for advanced biliary tract cancer.

Authors	Year	Regimen	Study design	Result	N	RR (%)	Median PFS	Median OS
Rao et al. [19]	2005	5FU + CDDP + epirubicin	Superiority	Negative	27	19.2	5.2 M	9.0 M
		5FU + LV + etoposide			27	15.0	7.3 M	12.3 M
Valle et al. [8]	2010	GEM + CDDP	Superiority	Positive	204	26.1	8.0 M	11.7 M
		GEM			206	15.5	5.0 M	8.1 M
Sharma et al. [9]	2010	GEMOX	Superiority	Positive	26	30.7	8.5 M	9.5 M
		5FU + FA			28	14.3	3.5 M	4.6 M
		BSC			27	0	2.8 M	4.5 M
Lee et al. [20]	2012	GEMOX + Erlotinib	Superiority	Negative	135	29.6	5.8 M	9.5 M
		GEMOX			133	15.8	4.2 M	9.5 M
Sharma et al. [10]	2019	GEMOX	Non-inferiority (Superiority)	Negative (Under power)	119	25.2	5.0 M	9.0 M
		GEM + CDDP			124	23.4	4.0 M	8.3 M
Morizane et al. [15]	2019	GEM + S-1	Non-inferiority	Positive	179	29.8	6.8 M	15.1 M
		GEM + CDDP			175	32.4	5.8 M	13.4 M
Sakai et al. [17]	2018	GEM + CDDP + S-1	Superiority	Positive	123	41.5	7.4 M	13.5 M
		GEM + CDDP			123	15.0	5.5 M	12.6 M
Kim et al. [18]	2019	Capecitabine + Oxaliplatin	Non-inferiority	Positive	108	15.7	5.8 M	10.6 M
		GEMOX			114	24.6	5.3 M	10.4 M

N, number; RR, response rate; PFS, progression-free survival; OS, overall survival; M, month; 5FU, 5-fluorouracil; CDDP, cisplatin; LV, leucovorin; GEM, gemcitabine; FA, folinic acid; BSC, best supportive care; GEMOX, gemcitabine + oxaliplatin

The GEM + CDDP regimen included GEM 1000 mg/m^2 and CDDP 25 mg/m^2 administered iv on days 1 and 8 every 3 weeks, and the treatment was repeated up to a maximum of 24 weeks in this study. CDDP increased peripheral neuropathy as the total dose approached 300 mg/m^2. In clinical practice, the treatment period of GEM + CDDP is often decided based on the adverse effects of diminishing renal function and peripheral neuropathy, and there are many cases in which this treatment is repeated for longer than 24 weeks.

10.2.2 GEMOX

One randomized controlled study comparing GEMOX, fluorouracil (FU) + folinic acid (FA), and best supportive care (BSC) was conducted in India [9]. Eighty-one patients with unresectable gallbladder cancer were randomly assigned to one of three arms. The median OSs of GEMOX, FU + FA, BSC were 9.5 months, 4.6

Table 10.2 Randomized phase II studies of first-line chemotherapy for advanced biliary tract cancer

Authors	Year	Regimen	Result	N	RR (%)	Median PFS	Median OS
Kang et al. [21]	2012	S-1 + CDDP	Positive	47	23.8	5.4 M	9.9 M
		GEM + CDDP		49	19.6	5.7 M	10.1 M
Lee et al. [22]	2015	Capecitabine + CDDP	Positive	44	27.3	5.2 M	10.7 M
		GEM + CDDP		49	6.1	3.6 M	8.6 M
Malka et al. [23]	2014	GEMOX + Cetuximab	Negative	76	23.1	6.0 M	11.0 M
		GEMOX		74	29.0	5.3 M	12.4 M
Chen et al. [24]	2015	GEMOX + Cetuximab	Negative	62	27.4	6.7 M	10.6 M
		GEMOX		60	16.7	4.1 M	9.8 M
Leone et al. [25]	2016	GEMOX + Panitumumab	Negative	45	24.4	7.7 M	9.5 M
		GEMOX		44	18.2	5.5 M	9.9 M
Vogel et al. [26]	2018	GEM + CDDP + Panitumumab	Negative	62	45.2	6.5 M	12.8 M
		GEM + CDDP		28	39.3	8.3 M	20.1 M
Valle et al. [27]	2015	GEM + CDDP + Cediranib	Negative	62	44.1	7.7 M	14.1 M
		GEM + CDDP		62	18.5	7.4 M	11.9 M
Moehler et al. [28]	2014	GEM + Sorafenib	Negative	52	14.3	3.0 M	8.4 M
		GEM		50	10.0	4.9 M	11.2 M
Santoro et al. [29]	2015	GEM + Vandetanib	Negative	58	19.3	3.8 M	9.5 M
		GEM		56	13.5	4.9 M	10.2 M
		Vandetanib		59	3.6	3.5 M	7.6 M
Schnizari et al. [30]	2017	FOLFOX4	Positive	25	28.0	5.2 M	13.0 M
		5FU + LV		23	21.7	2.8 M	7.5 M
Markussen et al. [31]	2020	GEMOX + Capecitabine	Negative	47	17.0	5.7 M	8.7 M
		GEM + CDDP		49	16.3	7.3 M	12.0 M
dos Santos et al. [32]	2020	CPT-11 + CDDP	Positive	24	35	5.3 M	11.9 M
		GEM + CDDP		23	31.8	7.8 M	9.8 M

N, number; RR, response rate; PFS, progression-free survival; OS, overall survival; M, month; CDDP, cisplatin; GEM, gemcitabine; GEMOX, gemcitabine + oxaliplatin; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; 5FU, 5-fluorouracil; LV, leucovorin; CPT-11, irinotecan

months, and 4.5 months ($p = 0.039$), and the median PFSs were 8.5 months, 3.5 months, and 2.8 months ($p < 0.001$), respectively. The RR and DCR of GEMOX were 30.8% and 68.7%, respectively. The major grade 3/4 toxicities of GEMOX were myelosuppression (38.5%), transaminitis (15.4%), neurotoxicity (11.5%), and vomiting (7.7%).

Another randomized controlled study comparing GEMOX and GEM + CDDP was also conducted in India [10], in which 243 patients with unresectable gallbladder cancer received at least one dose, and the results were evaluated for safety and efficacy. The median OSs of GEMOX and GEM + CDDP were 9.0 months and 8.3

months (HR 0.78, $p = 0.057$), and the median PFSs were 5.0 months and 4.0 months ($p = 0.047$), respectively. The RR and DCR of GEMOX were 25.2% and 49.6%, respectively. Grade 3/4 thrombocytopenia (24.4%) and peripheral neuropathy (6.7%) were more frequent with GEMOX than with GEM + CDDP, while grade 3/4 nephrotoxicity (0%) was less frequent in GEMOX than in GEM + CDDP. In this study, 108 patients were required in each arm to have an equivalence margin of ± 2 months with a power of 80%. The mean OSs (95% confidence interval [95% CI]) of GEMOX and GEM + CDDP were 11.2 (9.8–12.6) months and 10.4 (9.1–11.7) months. The difference of mean OS was calculated as 0.8 months (95% CI, –1.1–2.7). Therefore, 95% CI exceeded the predefined equivalent margin of 2 months. Although the median OS of GEMOX was marginally longer than that of GEM + CDDP, this study failed to show the equivalence of these two regimens: eight cycles of GEM + CDDP was not equivalent to six cycles of GEMOX, and GEMOX was definitely not inferior to GEM + CDDP. Whether GEMOX is superior to GEM + CDDP can only be answered by an adequately powered study. Although these studies only included unresectable gallbladder cancer, GEMOX is still considered an alternative to GEM + CDDP in patients with advanced BTC.

The regimen of GEMOX was GEM 900 mg/m^2 and oxaliplatin 80 mg/m^2 administered iv on days 1 and 8 every 3 weeks for a maximum of six cycles. GEMOX is a more convenient regimen because it does not require as much hydration as GEM + CDDP.

10.2.3 GEM + S-1

S-1 is an oral fluoropyrimidine derivative mainly used in Asian countries. GEM + S-1 has been widely evaluated in phase II studies and randomized phase II studies in Japan [11–14]. Based on these results, the phase III study (FUGA-BT/JCOG1113) comparing GEM + CDDP and GEM + S-1 was conducted in Japan [15], in which 354 patients with advanced BTC were randomly assigned to either GEM + CDDP or GEM + S-1. The median OSs of GEM + CDDP and GEM + S-1 were 13.4 months and 15.1 months (HR 0.945, $p = 0.046$ for non-inferiority), and the median PFSs were 5.8 months and 6.8 months (HR 0.86), respectively. The RR and DCR of GEM + S-1 were 29.8% and 83.7%, respectively. The major grade 3/4 toxicity of GEM + S-1 was neutropenia (59.9%). Diarrhea (20.9%), oral mucositis (28.8%), maculopapular rash (23.7%), and skin hyperpigmentation (20.3%) were more frequent in GEM + S-1 than in GEM + CDDP. Because this phase III study was conducted as a non-inferiority study of these two regimens, GEM + S-1 is now considered a new standard of care option for patients with advanced BTC.

The regimen of GEM + S-1 included GEM 1000 mg/m^2 administered iv on days 1 and 8 and S-1 administered orally twice daily [60 mg/day for a body surface area [BSA] < 1.25 m^2, 80 mg/day for a BSA between 1.25 and 1.50 m^2, and 100 mg/day for a BSA > 1.50 m^2] on days 1–14. This regimen was repeated every 3 weeks. GEM + S-1 is a more convenient regimen because it does not require hydration and the infusion time of the anticancer drug at an outpatient clinic can be as short as one hour.

10.2.4 GEM + CDDP + S-1

The triplet regimen using GEM, CDDP, and S-1 was also evaluated in Japan [16]. Because the phase II study showed good tumor efficacy, a phase III study (KHBO1401-MITSUBA trial) was conducted in Japan to compare GEM + CDDP + S-1 and GEM + CDDP [17]. Two hundred forty-six patients with advanced BTC were randomized to GEM + CDDP + S-1 or GEM + CDDP. The median OSs of GEM + CDDP + S-1 and GEM + CDDP were 13.5 months and 12.6 months (HR 0.791, $p = 0.046$), and the median PFSs were 7.4 months and 5.5 months (HR 0.748, $p = 0.015$), respectively. The RR and DCR of GEM + CDDP + S-1 was 41.5% and 79.8%, respectively. The major grade 3/4 toxicity of GEM + CDDP + S-1 was neutropenia (39.5%). Diarrhea (24.4%), stomatitis (27.7%), and rash (22.7%) were more frequent in GEM + CDDP + S-1 than in GEM + CDDP. Because this phase III study was conducted to evaluate the superiority of GEM + CDDP + S-1 to GEM + CDDP, this triplet therapy is now considered another new standard first-line chemotherapy for advanced BTC.

The regimen of GEM + CDDP + S-1 included GEM 1000 mg/m^2 and CDDP 25 mg/m^2 administered iv on day 1, while S-1 was administered orally twice daily [80 mg/day for a BSA < 1.25 m^2, 100 mg/day for a BSA between 1.25 and 1.50 m^2, and 120 mg/day for a BSA > 1.50 m^2] on days 1–7. This regimen was repeated every 2 weeks.

10.2.5 XELOX (Capecitabine + Oxaliplatin)

Capecitabine is an oral fluoropyrimidine derivative used worldwide. A phase III study was conducted in South Korea to show the non-inferiority of capecitabine + oxaliplatin (XELOX) against GEMOX [18]. Two hundred twenty-two patients with advanced BTC were randomly assigned to GEMOX or XELOX. The median OSs of XELOX and GEMOX were 10.6 months and 10.4 months ($p = 0.131$), and the median PFSs were 5.8 months and 5.3 months, respectively. The RR and DCR of XELOX were 15.7% and 58.3%, respectively. The major grade 3/4 toxicities of XELOX were thrombocytopenia (9.4%) and neutropenia (3.8%). Because this phase III study was conducted to evaluate the non-inferiority of XELOX to GEMOX, this doublet is considered an alternative first-line chemotherapy for advanced BTC.

The XELOX regimen included capecitabine 1000 mg/m^2 administered orally twice daily on days 1–14 and oxaliplatin 130 mg/m^2 administered iv on day 1. This regimen was repeated every 3 weeks.

10.2.6 Other Randomized Controlled Studies

There were many other randomized controlled studies of first-line chemotherapy for advanced BTC (Tables 10.1 and 10.2). The first randomized phase III study comparing the combination of epirubicin, CDDP and 5FU (ECF) versus 5FU, leucovorin (LV) and etoposide (FELV) was reported from the United Kingdom in 2005 [19].

This study tried to enroll 116 patients, but recruitment was slow, and thus only 54 patients were finally randomized to each treatment arm. According to this phase III study, ECF did not improve OS compared to FELV. Another phase III study evaluated the addition of erlotinib to GEMOX, but this study also did not show significant improvement in PFS [20]. There were many randomized phase II studies reported, and some of them showed superiority [21–31]. Oral fluoropyrimidine derivatives plus CDDP demonstrated the same efficacy as GEM + CDDP [21, 22]. FOLFOX4 demonstrated better tumor efficacy than 5-FU + LV, and the efficacy of FOLFOX4 was comparable to that of GEM + CDDP [30]. In other studies, the addition of molecular-targeted drugs was evaluated for GEM, GEM + CDDP, and GEMOX, but the effect of adding molecular-targeted drugs could not be confirmed in any of the studies [24–29]. The triplet regimen using GEM, oxaliplatin, and capecitabine could also not demonstrate superiority to GEM + CDDP [31]. Irinotecan + CDDP was compared with GEM + CDDP, and comparable efficacy was achieved in a randomized phase II study [32].

10.2.7 Interesting Regimens from Phase II Studies

Several interesting regimens have been evaluated in phase II studies, including drugs and treatment regimens that have been proven to be effective in pancreatic cancer. Nab-paclitaxel is one of the drugs now under investigation for the treatment of advanced BTC. The combination chemotherapy of GEM + nab-paclitaxel was evaluated in a phase II study [33]. Seventy-four patients were treated with this combination chemotherapy; the median PFS was 7.7 months, and the median OS was 12.4 months. Although this phase II study did not meet its primary endpoint, the results indicated that GEM + nab-paclitaxel combination chemotherapy showed a certain degree of efficacy. The triplet therapy of GEM + CDDP + nab-paclitaxel was also evaluated in a phase II study [34], and the RR and DCR were 45% and 84%, respectively. The median PFS and OS of this phase II study were 11.8 months and 19.2 months, respectively, demonstrating the very good efficacy of this triplet therapy, which will be tested in a phase III randomized clinical trial comparing it with GEM + CDDP. FOLFIRINOX is another standard chemotherapy for advanced pancreatic cancer. FOLFIRINOX is also under investigation in a phase II/III study for the treatment of advanced BTC [35]. The triplet therapy of S-1 + irinotecan + oxaliplatin was also evaluated in a phase II study [36]. This combination therapy also showed favorable efficacy outcomes: the RR was 50%, and the median PFS and OS were 6.8 months and 12.5 months, respectively. Moreover, some molecular-targeted agents were also evaluated as first-line chemotherapy in phase II studies [37–40].

10.3 Second-Line Chemotherapy

For a long time now, there has been no standard second-line chemotherapy regimen for the treatment of BTC. In Japan, S-1 monotherapy was widely used in cases refractory to gemcitabine-based first-line chemotherapy [41]. Some randomized

Table 10.3 Randomized studies of recurrent biliary tract cancer

Authors	Year	Regimen	Phase	Line	N	RR (%)	Median PFS	Median OS
Lamarca et al. [45]	2021	mFOLFOX	PIII	2	81	4.9	4.0 M	6.2 M
		Active symptom control			81	–	–	5.3 M
Abou-Alfa et al. [46]	2020	Ivosidenib	PIII	2 or 3	124	2.4	2.7 M	10.8 M
		Best supportive care			61	0	1.4 M	9.7 M
Demols et al. [47]	2020	Regorafenib	rPII	2 or 3	33	0	3.0 M	5.3 M
		Best supportive care			33	0	1.5 M	5.1 M
Cereda et al. [42]	2016	Capecitabine + mitomycin-C	rPII	2	29	3.4	2.3 M	8.1 M
		Capecitabine			28	0	2.1 M	9.5 M
Zheng et al. [43]	2018	Capecitabine + irinotecan	rPII	2	30	13.3	3.7 M	10.1 M
		Irinotecan			30	6.7	2.4 M	7.3 M
Kim et al. [44]	2020	Trametinib	rPII	2	24	8.3	1.4 M	4.3 M
		5FU + LV or Capecitabine			20	10.0	3.3 M	6.6 M

N, number; RR, response rate; PFS, progression-free survival; OS, overall survival; M, month; PIII, phase III study; rPII, randomized phase II study; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; 5FU, 5-fluorouracil; LV; leucovorin

phase II studies have been reported, but these regimens did not become the standard of care for second-line chemotherapy (Table 10.3) [42–44]. Recently, several randomized phase II or phase III studies were reported, and new treatments showed significant improvement in the prognoses versus BSC [45–47]. From these results, it is expected that the standard treatment for second-line chemotherapy will be established in the near future.

10.3.1 mFOLFOX Versus BSC (ABC-06 Study)

The ABC-06 study is a phase III study conducted in the United Kingdom comparing mFOLFOX and active symptom control (BSC) [45]. One hundred sixty-two patients with advanced BTC who were previously treated with GEM + CDDP were randomly assigned to mFOLFOX or active symptom control (BSC). The patients in the placebo arm could receive mFOLFOX when radiographic disease progression was confirmed. The primary endpoint was OS. The median OS of mFOLFOX and active symptom control (BSC) were 6.2 months and 5.3 months (HR 0.69, $p = 0.031$), respectively. In the mFOLFOX group, RR and DCR were 4.9% and 33.3%, and the median PFS was 4.0 months. The benefit of chemotherapy was consistent across the subgroups, including the platinum sensitivity of first-line GEM + CDDP. The major grade 3/4 adverse events were fatigue (18.5%), neutropenia (12.3%), and

catheter-related infection (3.7%). This study is the first prospective phase III study evaluating the benefit of chemotherapy after GEM + CDDP in patients with advanced BTC, and mFOLFOX is now expected to become the standard of care for second-line chemotherapy in this field.

The regimen of mFOLFOX included oxaliplatin 85 mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), and 5FU 400 mg/m^2 (bolus) administered intravenously on day 1, and then 5FU 2400 mg/m^2 administered as a 46-h continuous infusion. The treatment was repeated every 14 days for up to 12 cycles.

10.3.2 Ivosidenib Versus BSC (ClarIDHy)

The ClarIDHy study is a global phase III study comparing ivosidenib and BSC [46]. Ivosidenib is a first-in-class, oral, targeted, small-molecule inhibitor of the mutant IDH1 protein. IDH1 mutations occur in up to 20% of cholangiocarcinoma cases. One hundred eighty-five patients with advanced cholangiocarcinoma who had received 1–2 prior therapies were enrolled in this study. These patients were randomized in a 2:1 ratio of ivosidenib to placebo, and the patients in the placebo arm could receive ivosidenib when radiographic disease progression was confirmed. The primary endpoint was PFS. The median PFS and OS were 2.7 months and 10.8 months with ivosidenib versus 1.4 months and 9.7 months with the placebo, respectively. Ivosidenib significantly improved PFS versus placebo (HR 0.37, $p < 0.001$), and a significant improvement in OS was also confirmed when adjusting for crossover (HR 0.46, $p < 0.001$). The most common grade 3/4 adverse event was ascites (7.4%). This study shows the feasibility and clinical benefit of targeting a molecularly defined subgroup of cholangiocarcinoma and warrants tumor mutation profiling as a new standard of care in this heterogeneous disease.

The ivosidenib regimen was ivosidenib 500 mg orally once daily in continuous 28-day cycles.

10.3.3 Regorafenib Versus BSC (REACHIN)

The REACHIN study is the randomized, double-blind, phase II study comparing regorafenib and BSC that was conducted in Belgium [47]. Regorafenib is a multikinase inhibitor that inhibits angiogenesis through VEGF receptors 1–3 and TIE2; targets oncogenesis through inhibition of the downstream pathways of KIT, RET, RAF1, and BRAF; affects the tumor microenvironment by blocking the activity of the intracellular domains of PDGFR and FGFR; and acts on tumor immunity. Sixty-six patients with advanced BTC who had failed GEM + CDDP-based chemotherapy were randomly assigned 1:1 to regorafenib or BSC. No crossover was allowed. The primary endpoint was PFS. Median PFS was 3.0 months in the regorafenib group and 1.5 months in the BSC group (HR 0.49, $p = 0.004$). Median OS was 5.3 months and 5.1 months, respectively ($p = 0.28$). The major grade 3/4 adverse events were fatigue (18.2%), nausea/vomiting (9.1%), and hand and foot skin reactions (9.1%).

Regorafenib significantly improved PFS in patients with previously treated advanced BTC in the second-line or third-line setting.

The regorafenib regimen was regorafenib 500 mg orally once daily in continuous 28-day cycles.

10.3.4 Other Randomized Controlled Studies

Several other randomized phase II studies have been reported previously. A randomized phase II study comparing capecitabine + mitomycin C combination therapy with capecitabine monotherapy did not show good outcomes in either group [42]. However, in a randomized phase II study comparing capecitabine + irinotecan combination therapy with irinotecan monotherapy, the primary endpoint of median PFS was 3.7 months with capecitabine + irinotecan combination therapy compared with 2.4 months with irinotecan monotherapy ($p = 0.036$) [43]. Moreover, a randomized phase II study comparing the MEK inhibitor trametinib monotherapy with 5FU + LV or capecitabine monotherapy was performed, but trametinib monotherapy was ineffective and was discontinued early [44]. As a result of these previous reports, capecitabine + irinotecan combination therapy is expected to play a role in second-line treatment, although further evaluation is necessary for this combination chemotherapy.

10.3.5 Interesting Regimens from Phase II Studies

There are several interesting regimens that have been evaluated in phase II studies. Various FGFR inhibitors have been investigated, and promising data have been obtained. Pemigatinib is a selective, oral inhibitor of FGFR 1, 2, and 3. One hundred seven patients with FGFR2 fusion or rearrangement were treated with pemigatinib in a phase II study (FIGHT-202) [48]. The RR and DCR were 35.5% and 82.2%, and the median PFS and OS were 6.9 months and 21.1 months, respectively. Based on this phase II study, pemigatinib is now approved by the FDA for use as a second-line treatment option for patients with FGFR2 fusion or other FGFR2 rearrangements. Other FGFR inhibitors such as infigratinib and derazantinib have also demonstrated good antitumor activities in phase II studies for patients with advanced BTC with FGFR genetic alterations (e.g., fusion, mutation, and amplification) [49, 50]. In addition, the results of phase II studies using molecular-targeted agents such as sorafenib, cabozantinib, trametinib, bevacizumab, axitinib, and SPI-1620 have also been reported [51–56], as have some phase II studies evaluating combinations of cytotoxic agents [57, 58].

10.4 Clinical Trials

While there have been various advances in chemotherapy for the treatment of advanced BTC over the last decade, treatment options for this disease remain limited. Previously, randomized controlled trials themselves were rarely conducted, but

Table 10.4 Ongoing clinical trials for advanced biliary tract cancer

Regimen	N	Phase	Trial ID
First-line chemotherapy			
NUC-1031 (Acelarin) + CDDP vs. GEM + CDDP (NuTide:121)	828	PIII	NCT04163900
GEM + CDDP + Pembrolizumab vs. GEM + CDDP (KEYNOTE-966)	788	PIII	NCT04003636
GEM + CDDP + Durvalumab vs. GEM + CDDP (TOPAZ-1)	757	PIII	NCT03875235
Pemigatinib vs. GEM + CDDP (FIGHT-302)	432	PIII	NCT03656536
GEMOX + KN035 vs. GEMOX (KN035-BTC)	390	PIII	NCT03478488
Infigratinib vs. GEM + CDDP (PROOF trial)	384	PIII	NCT03773302
GEM + CDDP + nab-paclitaxel vs. GEM + CDDP (SWOG/S1815)	268	PIII	NCT03768414
Futibatinib vs. GEM + CDDP (FOENIX-CCA3)	216	PIII	NCT04093362
GEM + CDDP + Bintrafusp alfa vs. GEM + CDDP	512	PII/III	NCT04066491
Modified FOLFIRINOX vs. GEM + CDDP (AMEBICA-PRODIGE 38)	316	PII/III	NCT02591030
GEM + CDDP ± Ramucirumab vs. GEM + CDDP ± Merestinib	306	rPII	NCT02711553
GEM + CDDP + CX-4945 vs. GEM + CDDP	124	rPII	NCT02128282
5FU + LV + Nal-IRI vs. GEM + CDDP (NIFE)	92	rPII	NCT03044587
GEM + CDDP + Anlotinib + Sintilimab vs. GEM + CDDP	80	rPII	NCT04300959
GEM + CDDP + CPI-613 vs. GEM + CDDP (BilT-04)	78	rPII	NCT04203160
GEMOX + Regorafenib vs. GEMOX (BREGO)	66	rPII	NCT02386397
GEM + CDDP + Nivolumab vs. Nivolumab + Ipilimumab	64	rPII	NCT03101566
GEM + CDDP + Selumetinib vs. GEM + CDDP	57	rPII	NCT02151084
S-1 + LV + oxaliplatin + GEM vs. GEM + CDDP	46	rPII	NCT03406299
Second-line chemotherapy			
Capecitabine + Varlitinib vs Capecitabine (TreeTopp study)	490	PII/III	NCT03093870
5FU + LV + Nal-IRI vs. 5FU + LV	174	rPII	NCT03524508
S-1 + Resminostat vs. S-1	100	rPII	JapicCTI-183883
Modified FOLFOX vs. modified FOLFIRI	118	rPII	NCT03464968
JPH203 vs. best supportive care	33	rPII	UMIN000034080

N, number; PIII, phase III study; PII, phase II study; rPII, randomized phase II study; CDDP, cisplatin; GEM, gemcitabine; GEMOX, gemcitabine plus oxaliplatin; FOLFIRINOX, 5-fluorouracil + leucovorin + irinotecan + oxaliplatin; 5FU, 5-fluorouracil; LV, leucovorin; Nal-IRI, nano liposomal irinotecan; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFIRI, 5-fluorouracil + leucovorin + irinotecan

now a number of randomized controlled trials are being conducted to validate new treatment options (Table 10.4), and various drugs are being investigated for the treatment of advanced BTC [35, 59–62].

As for first-line chemotherapy, some randomized controlled studies are being conducted to verify the effect of adding a new drug to GEM + CDDP (or GEMOX), and other studies are comparing FGFR inhibitors (pemigatinib, infigratinib,

futibatinib) with GEM + CDDP. In addition, the FOLFIRINOX and NAPOLI regimens (5FU + LV + nanoliposomal irinotecan) used in advanced pancreatic cancer have been evaluated, and immunotherapy has also been evaluated for the treatment of advanced BTC. NUC-1031 (Acelarin) is a prodrug based on an aryloxy phosphoramidite derivative of GEM. NUC-1031 activation is significantly less dependent on deoxycytidine kinase and on nucleoside transporters, and it is resistant to cytidine deaminase-mediated degradation. Therefore, it is expected to have a higher antitumor effect than GEM, and a large randomized phase III study comparing NUC-1031 + CDDP with GEM + CDDP is underway.

To examine second-line chemotherapy options, a large randomized controlled trial called the TreeTopp study is being conducted. However, the press release reported that varlitinib failed to meet the primary endpoints of PFS and RR. This trial was a global, double-blind, randomized two-arm study that enrolled 127 patients who had failed first-line therapy. In the trial, the median PFS was 2.83 months for varlitinib in combination with capecitabine compared to a median PFS of 2.79 in the control arm. In the varlitinib arm, RR was 9.3% compared to 4.8% in the control arm. Further reports are anticipated for detailed results. Efficacies of mFOLFOX, ivosidenib, and regorafenib have been proven as second-line treatments, and it is expected that comparative studies with these drugs will be considered in the future.

There are other unique regimens and other drugs currently being evaluated in phase II studies, such as HER2 inhibitors, PARP inhibitors, and NTRK inhibitors. From these clinical trials, it is expected that an effective treatment method for advanced BTC will be developed in the near future.

10.5 Conclusions

The current status of chemotherapy for advanced BTC is summarized in this chapter. In the last decade, various treatments have appeared in this field. In the future, it is expected that treatment development will proceed by combining various treatments such as molecular-targeted agents and immunotherapy in addition to the conventional treatment with cytotoxic agents. In addition, precision medicine that identifies gene mutations in cancer is expected to progress steadily.

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Adjuvant Chemotherapy for Cholangiocarcinoma

11

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Abstract

Surgical resection is the only curative treatment modality for cholangiocarcinoma; however, patients often develop recurrence because of its malignant nature. Therefore, the development of adjuvant therapy is urgently needed to improve the prognosis of this disease. Several clinical trials have evaluated the efficacy of some regimens as adjuvant chemotherapy, including fluorouracil (5-FU) + mitomycin C, 5-FU + leucovorin, gemcitabine monotherapy, gemcitabine plus oxaliplatin, and capecitabine monotherapy. Although none of these met the primary endpoint, capecitabine monotherapy showed clinically meaningful efficacy in a sensitivity analysis and is considered for use in patients who have high-risk factors for recurrence, such as microscopic residual (R1) and node-positive (N1) disease. In recent years, the development of systemic chemotherapy for advanced cholangiocarcinoma has shown significant survival benefits, such as gemcitabine plus cisplatin and targeted molecular therapy against FGFR2 and IDH1 mutant tumors. Furthermore, immune checkpoint inhibitors have been evaluated as monotherapy or in combination with cytotoxic agents. These regimens are also candidates for testing in future adjuvant therapy clinical trials.

Keywords

Bile duct · Gallbladder · Ampulla · Adjuvant · Gemcitabine · Capecitabine Mutation · Immune therapy

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11.1 Introduction

Surgical resection is the only curative treatment for cholangiocarcinoma; however, the curative resection rates are 68.3% for intrahepatic cholangiocarcinoma, 47.3% for gallbladder cancer, 46.7% for extrahepatic cholangiocarcinoma, and 86.6% for ampulla of Vater cancer [1]. Even in patients who have undergone radical resection, the 5-year overall survival rates are 32.7% for those with intrahepatic cholangiocarcinoma, 41.6% for those with gallbladder cancer, 33.1% for those with extrahepatic cholangiocarcinoma, and 52.8% those with for ampulla of Vater cancer, indicating that this is an intractable cancer with poor prognosis [1]; hence, effective adjuvant therapies must be developed to improve the treatment results.

The efficacy of adjuvant chemotherapy has long been verified in clinical studies comparing surgery alone with those with mitomycin C (MMC) and 5-fluorouracil (5-FU) as adjuvant chemotherapy. Analysis of the overall survival by disease was performed in 158 patients with pancreatic cancer, 118 with cholangiocarcinoma, 112 with gallbladder cancer, and 48 with ampulla of Vater cancer who were enrolled in the study. Per-protocol analyses showed no improvement in the overall survival rates for pancreatic cancer, cholangiocarcinoma, and ampulla of Vater cancer; however, the 5-year overall survival rates for gallbladder cancer was 14% in the resection alone arm and 26% in the MMC and 5-FU combination therapy arm, showing a significantly better outcome [2]. Since then, several randomized controlled studies have been conducted (Table 11.1). In all of the studies conducted, no significant differences were observed in the results of pre-specified analyses of the overall population (intention-to-treat). To date, there is still no standard treatment for cholangiocarcinoma, which is presented below. However, several sub-analyses suggested that adjuvant chemotherapy with capecitabine is a Category 1 treatment, and the use of this treatment in patients with cholangiocarcinoma is recommended in the National Comprehensive Cancer Network Guidelines (Version 5.2020) [3].

Table 11.1 Prospective randomized trials of adjuvant chemotherapy for cholangiocarcinoma

Author	Phase	Experimental arm	Control arm	Primary endpoint	Hazard ratio (95% CI)
Neoptolemos, J. P., et al	III	5-FU+LV or GEM	Surgery alone	OS	0.86 (0.66–1.11)
Edeline, J., et al	III	GEM + L-OHP	Surgery alone	RFS	0.88 (0.62–1.25)
Sharma, A., et al	III	Cape	Surgery alone	OS	0.81 (0.63–1.04)
Ebata T., et al	III	GEM	Surgery alone	OS	1.01 (0.70–1.45)
Ben-Josef, E.	II (single arm)	GEM + Cape followed by Cape + RT	Surgery alone	2 year-OS	65% (53–74%)

5-FU, fluorouracil; LV, folinic acid; OS, overall survival; L-OHP, oxaliplatin; RFS, relapse-free survival; Cape, capecitabine; GEM, gemcitabine; RT, radiotherapy

11.2 Fluorouracil + Leucovorin

Fluorouracil is considered to be the key drug for gastrointestinal cancers, including pancreatic cancer and cholangiocarcinoma. In the ESPAC-3 study, the efficacy of 5-FU + folinic acid (FL) and that of gemcitabine were compared with the efficacy of surgery alone in cancers in the periampullary region, which mainly include duodenum papillary cancer and extrahepatic cholangiocarcinoma [4]. All enrolled patients were randomized in a 1:1:1 ratio into the surgery-alone arm, gemcitabine arm (gemcitabine 1000 mg/m^2 once weekly for 3 consecutive weeks with 1 week rest as 1 cycle for 6 cycles), or FL arm (folinic acid 20 mg/m^2 bolus intravenous injection followed by a bolus intravenous injection of fluorouracil 425 mg/m^2 every 28 days for 5 consecutive days as 1 cycle for 6 cycles). Randomization was performed by stratifying the patients according to country and resection margin (R0 versus R1). The primary endpoint was an improvement in the overall survival, assuming that the 5-year overall survival in the adjuvant chemotherapy arm would be 12% higher than that in the surgery-alone arm (hazard ratio [HR]: 0.68). With a two-sided α of 5% and a power of 80%, the calculated sample size was 430 patients.

By July 2008, 434 patients had been enrolled, with median overall survival values of 35.2 months (95% confidence interval [CI]: 27.2–43.0) in the surgery-alone arm and 43.1 months (95% CI: 34.0–56.0) in the chemotherapy arm, and an HR of 0.86 (95% CI: 0.66–1.11, $p = 0.25$), showing that adjuvant chemotherapy had no effect on prolonging the survival. In a sensitivity analysis with adjustments for important prognostic factors, the HR was 0.75 (95% CI: 0.57–0.98, $p = 0.03$), favoring adjuvant chemotherapy over surgery alone, while the HR for FL versus surgery alone was 0.79 (95% C: 0.58–18, $p = 0.13$), indicating that FL had no significant benefit.

11.3 Gemcitabine + Oxaliplatin

Gemcitabine + oxaliplatin (GEMOX) combination therapy was associated with prolonged overall survival compared with best supportive care (BSC) or FL in a Phase III study on advanced gallbladder cancer [5]. Moreover, the GEMOX regimen is also more convenient than the gemcitabine + cisplatin regimen because it does not require long-time hydration, and the regimen has been used as the standard of care in several randomized controlled studies [6]. Thus, the expectation was that this regimen would also be used as an effective adjuvant chemotherapy. The PRODIGE12-ACCORD18 study was an open-label, randomized, phase III study of adjuvant chemotherapy with gemcitabine plus oxaliplatin versus surgery alone in non-papillary cholangiocarcinoma [7]. Patients were randomized in a 1:1 ratio to the surgery-alone arm or the GEMOX arm (gemcitabine 1000 mg/m^2 on day 1 + oxaliplatin 85 mg/m^2 on day 2, every 2 weeks for 12 cycles). Randomization was performed by stratifying the patients based on the location of primary lesion (intrahepatic versus extrahepatic bile ducts versus gallbladder), resection margin (R0 versus R1), status of lymph node metastases (N0 versus N1 versus NX), and study site.

The primary endpoint was recurrence-free survival (RFS), assuming a median RFS of 18 months in the surgery-alone arm and a median RFS of 30 months in the GEMOX arm (HR: 0.60). With a two-sided α of 5%, a power of 80%, an enrollment period of 5 years, a follow-up period of 2 years, and a lost-to-follow-up rate of 5%, the calculated sample size was 190 patients.

Between July 2009 and February 2014, 196 patients were enrolled. The median RFS values were 18.5 months (95% CI: 12.6–38.2 months) in the surgery-alone arm and 30.4 months (95% CI: 15.4–43.0) in the GEMOX arm, indicating the non-superiority of the GEMOX arm with an HR of 0.88 (95% CI: 0.62–1.25, $p = 0.48$). Similar distant metastasis-free survival rates were also shown: 71% in the surgery-alone arm and 75% in the GEMOX arm. Moreover, a subgroup analysis of the GEMOX arm showed that none of the stratified groups utilized this therapy. These results ruled out the efficacy of GEMOX as adjuvant chemotherapy.

11.4 Capecitabine

Capecitabine is an oral prodrug of fluoropyrimidine and effective adjuvant chemotherapy for colorectal cancer [8] and several types of gastrointestinal cancer such as esophageal cancer, gastric cancer [9], and pancreatic cancer [10]. Thus, capecitabine was also expected to be effective adjuvant chemotherapy for cholangiocarcinoma. The BILCAP study was an open-label, randomized, phase III study comparing the efficacy of capecitabine as adjuvant chemotherapy with that of surgery alone in non-papillary cholangiocarcinoma [11]. The enrolled patients were randomized in a 1:1 ratio into the surgery-alone arm or capecitabine arm (capecitabine 1250 mg/m^2 on days 1–14, with 3 weeks as 1 cycle for 8 cycles). Randomization was performed by stratifying the patients according to study site, location of the primary lesion, resection margin (R0 versus R1), and Eastern Cooperative Oncology Group performance status score (0 versus 1 versus 2). The primary endpoint was an improvement in the overall survival, assuming that the 2-year overall survival in the surgery-alone arm would be 20% and that in the adjuvant capecitabine arm would be 12% (HR: 0.71). With a two-sided α of 5% and a power of 80%, 360 patients were planned to be enrolled in order to detect 270 events. However, the number of events was clearly insufficient as of July 2013, and the independent data monitoring committee recommended the analysis of results when 234 events had been observed. With 234 events, the HR for the expected survival was modified to 0.69.

Between March 2006 and December 2014, 447 patients were enrolled. In the intention-to-treat analysis, the median survival time in the surgery-alone arm was 36.4 months (95% CI: 29.7–44.5), while that in the capecitabine arm was 51.1 months (95% CI: 34.6–59.1), showing the non-superiority in the capecitabine arm with an HR of 0.81 (95% CI: 0.63–1.04, $p = 0.097$). However, in the per-protocol analysis of 430 patients, excluding those who were ineligible at enrollment and those who did not receive capecitabine therapy, the median survival time in the surgery-alone arm (36 months) was superior to that in the capecitabine arm (53 months), with an HR of 0.75, and this result was considered significant (95% CI:

0.58–0.97, $p = 0.028$). A sensitivity analysis adjusted for the presence or absence of lymph node metastases, pathological grade, and sex also showed a superior HR of 0.71 (95% CI: 0.55–0.92, $p = 0.010$) in the capecitabine arm.

Based on these results, adjuvant chemotherapy with capecitabine is not considered as an international standard of care treatment, but it can be used in patients at higher risk of disease recurrence.

11.5 Gemcitabine

Gemcitabine monotherapy was used as the community standard of care treatment for advanced cholangiocarcinoma prior to the ABC-02 study. As adjuvant chemotherapy for pancreatic cancer, gemcitabine significantly prolonged the patients' survival compared with surgery alone [12].

Based on these results, gemcitabine was also expected to be an effective adjuvant chemotherapy for cholangiocarcinoma. In the aforementioned ESPAC-3 study, a comparison between surgery alone and gemcitabine was performed as a secondary endpoint [4]. The prognosis in the gemcitabine arm was significantly prolonged compared with that in the surgery-alone arm, with an HR of 0.70 (95% CI: 0.51–0.97, $p = 0.03$).

The BCAT study was a randomized phase III study that evaluated the efficacy of gemcitabine in patients with hilar cholangiocarcinoma and distal cholangiocarcinoma [13]. The patients were randomized in a 1:1 ratio to the gemcitabine-alone arm (gemcitabine 1000 mg/m^2 administered once weekly for 3 consecutive weeks with 1 week of rest for a total of 18 doses) or surgery-alone arm and were stratified by resection margins (R0 versus R1), status of lymph node metastasis (N0 versus N1), location of the primary lesion (hilar versus distal bile duct), and study site. The primary endpoint was overall survival, assuming that the 5-year overall survival in the surgery-alone arm would be 30% and that the HR in the gemcitabine arm would be 0.85. With a two-sided α of 5%, a power of 80%, an enrollment period of 2 years, and a follow-up period of 5 years, 300 patients were planned to be enrolled to detect 189 events. Enrollment was initiated in September 2007; however, due to the small number of patients enrolled, the enrollment period was extended by 2 years at the interim analysis. Ultimately, 226 patients were enrolled through January 2011, and the results were analyzed with a median observation period of 79.4 months. The median survival time in the surgery-alone arm was 63.8 months, while that in the gemcitabine arm was 62.3 months, with an HR of 1.01 (95% CI: 0.70–1.45, $p = 0.964$), showing no effect on prolonging the prognosis. In this study, no significant differences were observed between the gemcitabine and surgery-alone arms in subgroups such as N1 and R1, which were considered to be at high risk for postoperative recurrence.

Some limitations of gemcitabine monotherapy as adjuvant chemotherapy were pointed out. The efficacy of gemcitabine versus surgery alone in the ESPAC-3 study was a secondary endpoint. Moreover, since the BCAT study was completed using less than the planned number of patients to be enrolled, it was not powered to detect

the observed differences from a statistical point of view; thus, a definitive conclusion has not been reached.

11.6 Gemcitabine + Capecitabine

With regard to the recurrence pattern after surgery, local recurrence was common in patients with extrahepatic cholangiocarcinoma, while distant metastases were common in patients with gallbladder cancer [14]. Thus, this finding suggests the efficacy of radiotherapy or chemoradiotherapy in extrahepatic cholangiocarcinoma [15] and the efficacy of chemotherapy in gallbladder cancer [16]. Therefore, a clinical study on sequential chemoradiotherapy following chemotherapy was conducted in patients with extrahepatic cholangiocarcinoma and gallbladder cancer (Southwest Oncology Group S0809 study) [17]. Patients who had a post-resection pathologic diagnosis of T2–4 or N1 or positive surgical margins (R1) were eligible for the study; all enrolled patients received gemcitabine 1000 mg/m^2 on days 1 and 8 and capecitabine 1500 mg/m^2/day orally on days 1–14 (with each treatment cycle lasting for 3 weeks, with a total of 4 cycles) followed by capecitabine (1330 mg/m^2/day daily) plus radiation therapy (45 Gy to regional lymph nodes, 54 Gy/30 Fr–59.4 Gy/33 Fr to the preoperative tumor bed, or 52.5–55 Gy/25 Fr for intensity-modulated radiation therapy (IMRT)) if recurrence was not observed in imaging assessments. The primary endpoint was 2-year survival rate stratified by resection margin (R0/R1). According to previous studies, the 2-year survival rate of patients after R0 resection was estimated to be 55% and that of patients after R1 resection was estimated to be 38%. The expected values were thus set to 65% and 45%, respectively. A sample size of 35 patients each with R0 or R1 resections led to an estimated 2-year survival rate of ±17%, with an estimated error of ±12% for the entire study.

Between December 2008 and October 2012, 105 patients were enrolled. Of them, 21 patients were deemed ineligible by central review. As the protocol treatment was not initiated in 5 additional patients, only the remaining 79 were analyzed. During a median follow-up of 35 months, 41 patients (52%) died. The 2-year survival rates were 67% (95% CI: 52–78%) in patients who underwent R0 resection and 60% (95% CI: 38–76%) in those who underwent R1 resection; meanwhile, the 2-year survival rate of the overall population was 65% (95% CI: 53–74%). The median overall survival was 34 months in the R0 group and 35 months in the R1 group, and the median overall survival in the entire population was 35 months, demonstrating a favorable overall survival. Local recurrence was observed in 14 patients, and 9 of them experienced a recurrence of distant metastases at the same time—meanwhile, 24 patients only experienced recurrence of distant metastases. No major differences were observed in the overall survival by primary lesion: 68% in cholangiocarcinoma and 56% in gallbladder cancer.

The most frequently reported grade 3 adverse events were neutropenia (35%), hand-foot-skin syndrome (13%), diarrhea (8%), and lymphopenia (8%); meanwhile, the most common grade 4 adverse events were neutropenia (9%), leukopenia (1%), and ventricular tachycardia (1%). Both gemcitabine + capecitabine

combination therapy and capecitabine combination radiotherapy were reported to be feasible, and a phase III study using these regimens is anticipated.

11.7 Meta-analysis

In a meta-analysis of 20 studies on adjuvant therapy, Horgan et al. reported a non-significant trend favoring the adjuvant arm (odds ratio [OR]: 0.74, $p = 0.06$). Adjuvant therapy was particularly effective in patients with positive surgical margins (OR: 0.36, $p = 0.002$) and positive lymph node metastases (OR: 0.49, $p = 0.004$). In addition, chemotherapy tended to be better than radiotherapy alone (OR: 0.39, $p < 0.001$ and OR: 0.98, $p = 0.90$).

More recently, another meta-analysis of 35 studies on adjuvant therapy was reported by Rangarajan et al. [18]. They reported a significant improvement in overall survival compared with surgery alone with a hazard ratio of 0.74 (95% CI, 0.67–0.83, $p < 0.001$). It was also reported that there was a significant benefit for adjuvant chemotherapy in those with R1 (risk ratio [RR], 0.83 with 95% CI, 0.77–0.91; $p < 0.001$) and N1 disease (RR, 0.82 with 95% CI, 0.76–0.89; $p < 0.001$).

Thus, future development of regimens that are proven to be effective adjuvant chemotherapies for cholangiocarcinoma is anticipated, especially for patients with R1 and N1 diseases.

11.8 Ongoing Clinical Trial

Adjuvant chemotherapy is often developed using agents that have shown efficacy against unresectable or recurrent diseases. Gemcitabine + cisplatin combination therapy (GC therapy) is one of the current standard therapies for unresectable cholangiocarcinoma and is expected to be an adjuvant chemotherapy for post-resection cholangiocarcinoma. The ACTICCA-1 study was a randomized phase III trial comparing the efficacy of GC therapy and resection alone in patients with resected cholangiocarcinoma [19]. Cohorts with cholangiocarcinoma and gallbladder cancer were pooled separately, and the status of lymph node metastases and the location of the primary lesion (intrahepatic bile duct versus hilar or extrahepatic bile duct) in the cohort of cholangiocarcinoma patients were used as stratification factors; patients were then randomized in a 1:1 ratio into the GC therapy arm or surgery-alone arm. The treatment used in this trial was similar to that in the Phase III ABC-02 study of GC therapy for unresectable cholangiocarcinoma. The primary endpoint was disease-free survival (DFS). For the cholangiocarcinoma cohort, assuming that the 2-year DFS rates were 40% in the surgery-alone arm and 55% in the GC arm and with a two-sided α of 5% and a power of 80%, the enrollment of 271 patients and a 24-to-28-month observation period were required in order to detect 166 events. For the gallbladder cancer cohort, assuming that the 2-year DFS rates were 35% in the surgery-alone arm and 55% in the GC arm, a total sample size of 154 patients was required to observe 90 events. Enrollment was started in June 2014;

however, BILCAP trial showed an equivocal improvement of overall survival for capecitabine compared to observation in 2017, and ACTTICA-1 trial was amended to set capecitabine alone as the standard arm after that. The results of the trial are anticipated (ClinicalTrials.gov Identifier: NCT02170090).

In addition, the combination of tegafur-gimeracil-oteracil potassium (S-1) is also frequently used as a treatment for unresectable or recurrent cholangiocarcinoma in Japan. Thus, a randomized phase III trial comparing S-1 with resection alone was also conducted in patients with resected cholangiocarcinoma (ASCOT study) [20]. The target population included patients with cholangiocarcinoma, gallbladder cancer, and ampullary cancer who underwent R0–1 resection. S-1 was administered at a dose of 80–120 mg/body/day, according to the body surface area, orally for 28 consecutive days followed by a 14-day rest period as 1 cycle for 4 cycles. The primary endpoint was overall survival, assuming that the 3-year survival rate was 47% in the surgery-alone arm and 57% in the S-1 arm. With a one-sided α of 5%, power of 70%, a 4-year enrollment period, and a 3-year observation period, 350 patients were planned to be enrolled. The study was started in September 2013 and, since enrollment of participants was favorable, the power was changed to 80% in July 2017 to enroll a total of 440 patients. In the BILCAP study, capecitabine, an oral fluorouracil similar to S-1, showed promising results, and the results of this study are also anticipated.

11.9 Future Direction

Regarding the design of the study evaluating the efficacy of adjuvant chemotherapy, overall survival should be the primary endpoint. Systemic chemotherapy has been developed for advanced stage disease, including recurrence after surgery, therefore, neither RFS nor DFS will not be the surrogate endpoints of the true endpoint as overall survival. Another issue of the trial design is the object. Cholangiocarcinoma includes the different types of cancer: intrahepatic, perihilar, and extrahepatic bile duct cancer, gallbladder cancer, and ampullary cancer. In the era of cytotoxic agents, biological, and prognostic similar diseases could be enrolled together: however, the recent studies of molecular profile reveal these diseases are different from each other. In these days, molecular-targeted drugs are being developed as therapies for unresectable/recurrent cholangiocarcinoma mentioned below. In the era of these drugs tested as an adjuvant chemotherapy, cholangiocarcinoma should be divided according to its primary site.

Molecular-targeted drugs and immune checkpoint inhibitors study that have been confirmed to be effective for unresectable/recurrent disease may be used as adjuvant chemotherapy in the future. As molecular-targeted drugs, pemigatinib [21] was effective against intrahepatic cholangiocarcinoma with fibroblast growth factor receptor 2 fusion genes, while ivosidenib was effective against intrahepatic cholangiocarcinoma with isocitrate dehydrogenase 1 gene mutations. If these gene mutations were detected during the postoperative pathological diagnosis, adjuvant chemotherapy with these molecular-targeted drugs may be used as effective

treatments against these mutations. On the contrary, previous clinical studies have been conducted to evaluate the efficacy of erlotinib or cetuximab in patients with advanced cholangiocarcinoma harboring epidermal growth factor receptor gene mutations; however, none of them showed efficacy. In addition, due to the high rate of human epidermal growth factor receptor (HER)-2 gene amplification observed in patients with gallbladder cancer and cholangiocarcinoma, clinical studies have been conducted to evaluate the efficacy of pan-HER inhibitor varlitinib [22] and an antibody against HER2 receptor and topoisomerase I inhibitor deruxtecan conjugate DS8201a (ClinicalTrials.gov Identifier: NCT04482309, UMIN ID: UMIN000036697). If these drugs are effective against unresectable cholangiocarcinoma, they are also expected to be effective as adjuvant chemotherapy agents.

In terms of immunotherapies, nivolumab, an anti-programmed death 1 (PD-1) antibody, has been suggested to be effective in combination with GC therapy, which is a standard treatment for unresectable cholangiocarcinoma and showed efficacy as a single agent [23]. Currently, the anti-PD-1 antibody pembrolizumab (ClinicalTrials.gov Identifier: NCT04003636), anti-programmed death ligand 1 (PD-L1) antibody durvalumab (ClinicalTrials.gov Identifier: NCT03875235), and a transforming growth factor-β trap with anti-PD-L1 activity bintrafusp alfa (ClinicalTrials.gov Identifier: NCT04066491) are being tested in phase III studies in combination with GC therapy, and results are anticipated. Depending on the results, immunotherapy may also be considered adjuvant chemotherapy.

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Neoadjuvant Therapy and Conversion Surgery for Cholangiocarcinoma

12

Yutaka Suzuki and Yoshihiro Sakamoto

Abstract

Survival of patients who undergo curative surgical resection for cholangiocarcinoma remains unsatisfactory, with a reported 5-year survival rate of 33%. An effort to obtain clinical evidence to support adjuvant chemotherapy after curative resection for cholangiocarcinoma has been planned in Japan. Concurrently, a prognostic advantage of neoadjuvant therapy for resectable cholangiocarcinoma is expected. Retrospective studies of neoadjuvant chemotherapy for resectable cholangiocarcinoma suggest that it might improve the survival of patients without decreasing the resection rate. In those studies, neoadjuvant therapy involved the combination of gemcitabine-based chemotherapy and radiation. Presently, several prospective studies on neoadjuvant therapy for cholangiocarcinoma are ongoing. On the other hand, retrospective studies on conversion surgery for initially unresectable locally advanced cholangiocarcinoma have also suggested favorable results, although the definition of "unresectable locally advanced" remains unclear. Reports on conversion surgery in combination with chemotherapy for recurrent cholangiocarcinoma after surgery are scarce, but some long-term survivors after conversion surgery have been reported.

Keywords

Cholangiocarcinoma · Resectable · Unresectable · Adjuvant chemotherapy · Neoadjuvant therapy · Conversion surgery

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12.1 Introduction

Curative surgical resection is the gold standard for the cure of cholangiocarcinoma. However, postoperative recurrence rates remain high, and the long-term prognosis after curative resection remains unsatisfactory. In the Japanese multi-institutional registry of biliary tract cancer between 1998 and 2004, the curative resection rate of all biliary cancers was 72.7% [1], and the 5-year survival rate of cholangiocarcinoma was 33.1%. Considering the current surgical results for cholangiocarcinoma, adjuvant and/or neoadjuvant therapy in addition to curative resection will be required. At present, no clinical evidence of adjuvant and/or neoadjuvant therapy has been described in the Japanese guideline [2] or National Comprehensive Cancer Network (NCCN) guideline [3], and neoadjuvant therapy is sometimes confused with conversion surgery because the resectability of cholangiocarcinoma remains unclear. In this chapter, we summarize the current trends in neoadjuvant therapy for resectable cholangiocarcinoma and conversion surgery for unresectable or recurrent cholangiocarcinoma.

12.2 Neoadjuvant Chemotherapy for Cholangiocarcinoma

12.2.1 Need for Neoadjuvant Chemotherapy

Adjuvant and neoadjuvant therapy for cholangiocarcinoma have not yet been established. For adjuvant therapy, Primrose et al. reported the results of a randomized controlled study of adjuvant chemotherapy with capecitabine (the BILCAP study) [4]. This study found no significant difference in the overall survival rate (OS) between the capecitabine group and observation group, but per-protocol analysis showed that the OS was significantly higher in the capecitabine group than in the observation group [hazard ratio (HR) 0.75; median survival time (MST), 52.7 versus 36.1 months, $p = 0.028$]. Capecitabine is not available for biliary cancers in Japan, so there has been no standard regimen of adjuvant therapy for cholangiocarcinoma.

However, the prognostic advantage of introducing neoadjuvant chemotherapy is expected to improve the survival of patients with resectable cholangiocarcinoma. This may be owing to the low tolerability to adjuvant chemotherapy after curative surgery given that surgeries to treat cholangiocarcinomas, such as extended hepatectomies and pancreaticoduodenectomies, are highly invasive, and only a few patients can afford adequate adjuvant chemotherapy.

12.2.2 Reports on Neoadjuvant Therapy for Cholangiocarcinoma

Reports on neoadjuvant therapy for resectable cholangiocarcinoma are shown in Table 12.1 [5–8]. Kobayashi et al. reported a retrospective study of neoadjuvant combination therapy with gemcitabine and radiation for biliary cancer [7]. The

Table 12.1 Case series of neoadjuvant therapy for resectable cholangiocarcinoma

Author	Year	Diagnosis	No. of pts	Regimens	Resection rate (%)	R0 (%)	Recurrence Rate (%)	Survival of the pts with R0	
								MST (months)	5-year OS (%)
Katayose [5]	2011	Hilar, Ex	11	GEM+RT	90.9	90.9	–	–	–
Kobayashi [6]	2015	Hilar, Ex, GB	25	GEM+RT	100	96.0	24.0	–	74.4
Kobayashi [7]	2017	Hilar, Ex, GB	27	GEM+RT	100	–	18.5	–	85
			79	Surgery alone	100	–	40.5	–	58
Yadav [8]	2019	ICC, Ex	299	NAC: CT+/–RT	100	71.2	–	40.3	42.5
				Adjuvant: CT+/–RT	100	61.6		32.8	31.7

Ex, extrahepatic cholangiocarcinoma; GB, gallbladder; ICC, intrahepatic cholangiocarcinoma; GEM, gemcitabine; RT, radiation therapy; NAC, neoadjuvant chemotherapy; CT, chemotherapy; MST, median survival time; OS, overall survival

3-year recurrence-free survival was significantly higher for the neoadjuvant therapy group than for the surgery alone group (HR 0.32, 78.3% versus 56.8%, $p = 0.026$), and the OS rate adjusted for the inverse probability of treatment weighting was higher in the neoadjuvant therapy group (HR, 0.35; $p = 0.002$). The recurrence rate was significantly lower in the neoadjuvant therapy group than in the surgery alone group (18.5% versus 40.5%, $p = 0.039$). Yadav et al. also used a propensity score-matched analysis to retrospectively compare the long-term outcome of neoadjuvant therapy with that of adjuvant chemotherapy [8]. The OS rate was significantly higher in the neoadjuvant therapy group than in the adjuvant chemotherapy group (HR, 0.78; MST, 40.3 versus 32.8 months; 5-year OS rate 42.5% versus 31.7%; $p = 0.01$). These retrospective results suggest that neoadjuvant therapy potentially could improve the survival rate of patients without decreasing the resection rate.

12.2.3 Prospective Studies of Neoadjuvant Therapy for Cholangiocarcinoma

Katayose et al. conducted a Phase I trial of neoadjuvant chemoradiation combined with gemcitabine and external beam radiation therapy for resectable cholangiocarcinoma [5]. Of the 11 patients who received chemoradiation, 10 (90.9%) underwent curative resection, and one patient did not because of multiple liver metastases. A Phase II trial of neoadjuvant chemoradiation is currently ongoing (NACRAC study, UMIN000001754) [9]. In these reports, gemcitabine with radiation therapy was expected to be optimal for neoadjuvant therapy for cholangiocarcinoma. However, the question of whether or not the combination of gemcitabine plus radiation is optimal for cholangiocarcinoma remains.

In Japan, standard regimens of chemotherapy for biliary cancer involve gemcitabine/cisplatin (GC) and gemcitabine/S-1(GS). However, these standard regimens might be underpowered when they are used for neoadjuvant chemotherapy because the response rates of GC and GS have been reported to be <40% (GC, 19.5–27.8% [10–12]; GS, 20–6.4% [13–15]).

In this context, the Kansai Hepato-Biliary Oncology (KHBO) Group conducted a Phase I trial of chemotherapy with gemcitabine/cisplatin/S-1 (GCS) for advanced biliary tract cancer and obtained favorable response rates (22–50%) [16, 17]. A Phase II trial of neoadjuvant chemotherapy with GCS for resectable cholangiocarcinoma with lymph node metastasis diagnosed by fluorodeoxyglucose–positron-emission tomographty (FDG-PET) was performed (KHBO1201, UMIN000009831). This study was completed in 2019, but the results are to be reported in the near future.

Several clinical trials on neoadjuvant therapy for resectable cholangiocarcinoma, including a feasibility study of neoadjuvant GC versus adjuvant S-1 (UMIN000021206), neoadjuvant GC/radiation (UMIN20964), and Phase I/II study for S-1/cisplatin/radiation (UMIN000009028), are currently ongoing.

12.2.4 Patient Selection for Neoadjuvant Therapy for Cholangiocarcinoma

Appropriate patient selection is important for effective induction of neoadjuvant therapy for resectable cholangiocarcinoma because early stage cancer patients may not be candidates for neoadjuvant therapy. To determine the optimal indication, poor prognostic factors for survival after surgical resection must be identified. Lymph node metastasis [18–26], preoperative serum carbohydrate antigen 19-9 (CA19-9) [20, 27], preoperative serum C-reactive protein level [26], perineural invasion [18, 28], vascular invasion [19, 21, 26, 29], status of surgical margins [20, 22, 30], tumor size [22, 26], and tumor differentiation [22] are reported prognostic factors. Of these factors, perineural invasion, vascular invasion, status of surgical margins, and tumor differentiation cannot be proved before surgery, but nodal metastasis may be diagnosed preoperatively by using imaging modalities [31]. To select patients with advanced cancer, the KHBO study group used FDG-PET to preoperatively diagnose nodal metastasis, and neoadjuvant therapy was administered in patients with PET-positive nodal metastasis.

12.3 Conversion Surgery for Cholangiocarcinoma

12.3.1 Definition of Resectability for Cholangiocarcinoma

Systemic chemotherapy is the first-choice treatment for unresectable cholangiocarcinoma. However, the definition of resectability for cholangiocarcinoma remains unclear; that is, there is a wide variety of surgical indications for advanced cholangiocarcinoma. In the Japanese guideline, cholangiocarcinoma with metastasis to the liver, lung, bone, peritoneum, or distant lymph nodes is considered to be a contraindication for surgery [2]. On the other hand, there is no obvious consensus on unresectable factors regarding local extensions to the vascular structures. In the NCCN guideline, cholangiocarcinomas with invasion to the main portal vein or bilateral portal branches, the common hepatic artery, the second-order biliary branches, and the second-order unilateral biliary branch with contralateral portal vein or hepatic artery invasion are defined as unresectable [3]. However, several research institutions have reported the feasibility of extensive hepatectomy combined resection of the portal vein and hepatic artery and subsequent favorable survivals of patients undergoing curative resection [32–35]; thus, it may be difficult to simply unify the surgical indications for locally advanced cholangiocarcinoma.

12.3.2 Reports on Conversion Surgery for Locally Advanced Cholangiocarcinoma

Considering this ambiguous definition of resectability, conversion surgery for cholangiocarcinoma can be defined as rescue surgery for patients with initially

Table 12.2 Case series of conversion surgery for locally advanced unresectable cholangiocarcinoma

Author	Year	Diagnosis	No. of pts	Regimens	Resection rate (%)	R0 (%)	Survival of the pts with R0	
							MST (months)	5-year OS (%)
McMasters [36]	1997	Ex	9[a]	5-FU + RT	100	100	22.2	–
Kato [37]	2013	GB, Ex, ICC	22	GEM	36.4	18.2	19.3	45%
Kato [38]	2015	GB, Ex, ICC	24	GEM	37.5	16.7	17.9	32.0% (2-year)
			39	GEM + CDDP	25.6	18.0		
Rayer [39]	2015	ICC	45	5-FU base GEM base	22.2	22.2	–	60% (3-year)
Konstantinidis [40]	2016	ICC	78	GEM+HAI	3.8	3.8	30.8	–
			26	GEM	7.7	7.7	18.4	–
Jung [44]	2017	Hilar	12[a]	5-FU base +RT GEM base +RT	100	83.3	32.9	–
Le Roy [45]	2017	ICC	74	GEM base	52.7	41.9	24.1	24%

GB, gallbladder; Ex, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; RT, radiation; 5-FU, 5-fluorouracil; GEM, gemcitabine; CDDP, cisplatin; HAI, hepatic arterial infusion chemotherapy; MST, median survival time, OS; overall survival

[a]Patients who underwent surgery only

unresectable cancer who have achieved downstaging by induction of systemic chemotherapy. However, there are only a few promising regimens for unresectable cholangiocarcinoma. Currently, GC and GS are widely used as standard regimens for unresectable cholangiocarcinoma, as described previously.

Reports on conversion surgery for locally advanced unresectable cholangiocarcinoma are shown in Table 12.2 [36–45]. McMasters et al. first reported a series of nine patients with extrahepatic cholangiocarcinoma who underwent conversion surgery after chemoradiation in 1997 [36]. Since 2013, gemcitabine-based regimens have been used with or without radiation and/or cisplatin for locally advanced cholangiocarcinoma. Although the resection rate and R0 resection rate remained low (resection rate, 3.8–64.3%; R0 rate, 3.8–22.2%, respectively), the survival rate of patients who underwent R0 conversion surgery was reported to be equivalent to that of resectable cholangiocarcinoma (MST, 17.9–50.1 months).

Kato et al. reported the outcomes of conversion surgery after downsizing chemotherapy with gemcitabine for locally advanced cholangiocarcinoma [37]. The MST after downsizing chemotherapy was significantly higher for surgical patients than for patients with chemotherapy alone (19.3 months versus 7.5 months, respectively; $p = 0.032$). The 5-year OS rate of surgical patients after downsizing chemotherapy for locally unresectable cholangiocarcinoma was equivalent to that of surgical patients for resectable cholangiocarcinoma (40.8% versus 45.0%, respectively). Kato et al. also studied the survivals of patients undergoing conversion surgery after chemotherapy and chemotherapy alone for locally advanced initially unresectable

cholangiocarcinoma [38]. They found that the survival after conversion surgery was significantly higher than after chemotherapy alone (MST 17.9 versus 12.4 months; 2-year OS 32.0% versus 0%, respectively; $p = 0.038$). Le Roy et al. compared the outcomes of patients undergoing conversion surgery after chemotherapy, chemotherapy alone for locally advanced intrahepatic cholangiocarcinoma (ICC), and surgery for resectable ICC [45]. The survival rate was significantly lower for patients in the chemotherapy alone group than for patients in the conversion surgery group (HR, 3.80; MST, 7.8 versus 24.1 months; 5-year OS, 3% versus 24%, respectively; $p < 0.001$). No difference in survival was found between patients who underwent surgery alone for resectable cancer and patients who underwent conversion surgery for locally advanced cancer (HR, 1.14; MST, 25.7 versus 24.1 months, 5-year OS, 27% versus 25%, respectively; $p = 0.6$).

12.3.3 Reports on Conversion Surgery for Cholangiocarcinoma with Distant Metastasis or Recurrent Cholangiocarcinoma

There are only a few reports on conversion surgery for cholangiocarcinoma with distant metastasis and several case series (Table 12.3) [47–50], and the resection rates are not as high as those of locally advanced unresectable cholangiocarcinoma. Morise et al. reported an experience of systemic chemotherapy using S-1 and cisplatin for cholangiocarcinoma with distant metastasis in eight patients [48]. Consequently, only two (25%) of eight patients underwent surgical resection, but the MST was longer for the two patients who underwent surgery than for the six non-surgical patients (45.5 versus 9.5 months, respectively).

There are even fewer reports on adjuvant surgery after chemotherapy for recurrent cholangiocarcinoma than on conversion surgery for cholangiocarcinoma with distant metastasis. Song et al. reported surgical resection for recurrent biliary cancers, including intrahepatic-, perihilar-, and extrahepatic cholangiocarcinoma [51]. The recurrences were located in the liver, locoregional except liver, lung, pleura, abdominal wall, chest wall, and/or peritoneum. The R0 resection rate of these patients was 92.6%. The OS rate was significantly higher for the surgery group than for the non-resection group by multivariate analysis (MST, 18.9 versus 7.7 months, respectively; $p = 0.025$). Noji et al. compared the surgical outcomes for recurrent extrahepatic cholangiocarcinoma and gallbladder cancer in comparison with those of palliative therapy [52]. The 5-year survival rate was significantly higher for the resection group than for the palliative group (23.5% versus 0%, respectively; $p < 0.01$).

12.3.4 Conversion Hepatectomy for Liver Metastasis of Distal Bile Duct Cancer

We experienced a case of conversion hepatectomy for liver metastasis of distal bile duct cancer after chemotherapy using GC. This patient underwent pancreatoduodenectomy for distal bile duct cancer (Fig. 12.1a). Forty months after surgery, the serum level of CA19-9 increased to 38.9 IU/L, but no recurrent lesion was found on

Table 12.3 Cases of conversion surgery for cholangiocarcinoma with synchronous distant metastasis

Author	Year	Diagnosis	Metastasis	Regimens	Duration of preoperative chemotherapy (months)	Response	Surgical procedure	Recurrence	Prognosis (months)
Slupski [47]	2007	ICC	Lung	5-FU, CDDP IFN, Dox	8	PR	RH	(–)	Alive (29)
Morise [48]	2009	ICC	Lung, LN	S-1, CDDP	14	PR	PD	(–)	Alive (45)
		ICC	Lung	S-1, CDDP	4	SD	–	(+)	Alive (46)
Oshiro [49]	2013	Ex	Liver	GEM	18	CR	PD	(–)	Alive (5Y)
Adachi [50]	2019	Ex	Liver	GEM, CDDP	7	PR	PD	(–)	Alive (19)

ICC, intrahepatic cholangiocarcinoma; Ex, extrahepatic cholangiocarcinoma; LN; lymph node; 5-FU, 5-fluorouracil; GEM, gemcitabine; CDDP, cisplatin; IFN, interferon; Dox, doxorubicin; CR, complete response; PR, partial response; SD, stable disease; RH; right hepatectomy; PD; pancreaticoduodenectomy

imaging studies. Fifty-six months after surgery, the CA19-9 level increased to 348.5 IU/L, and a 21-mm diameter metastatic lesion was found in segment 6 of the liver (Fig. 12.1b). The patient underwent systemic chemotherapy using GC, and after 14 cycles of chemotherapy, the serum CA19-9 level decreased to 198.4 IU/L,

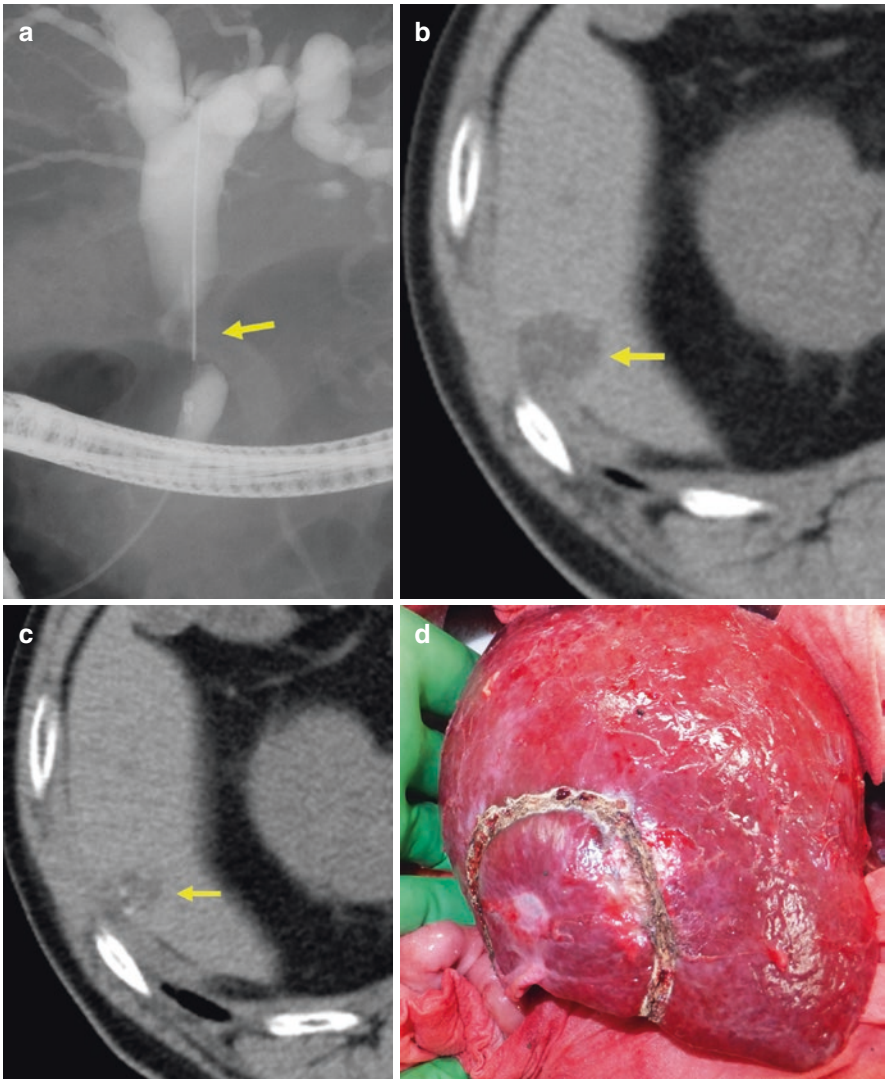

Fig. 12.1 Conversion hepatectomy for liver metastasis of extrahepatic cholangiocarcinoma after chemotherapy. (**a**) An endoscopic retrograde cholangiography showed a defect (arrow) in the distal bile duct, which was diagnosed as a distal bile duct cancer. (**b**) Fifty-six months after surgery, a 21-mm diameter metastatic liver tumor was found in segment 6. (**c**) The size of the metastatic tumor decreased to 15 mm in diameter after chemotherapy. (**d**) Intraoperative appearance of the metastatic tumor

and the tumor size decreased to 15 mm in diameter (Fig. 12.1c). Given that the metastatic tumor showed a partial response to chemotherapy, we performed partial resection of segment 6 of the liver to eradicate the liver metastasis (Fig. 12.1d). The patient was doing well 54 months after conversion hepatectomy without any sign of recurrence.

As shown in these reports, conversion surgery for locally advanced and metastatic cholangiocarcinoma can potentially improve the prognosis of patients with initially unresectable cholangiocarcinoma. However, there have not been enough prospective randomized trials to make a confident conclusion about the efficacy of conversion surgery.

12.4 Conclusion

Clinical evidence or a consensus on adjuvant or neoadjuvant therapy for cholangiocarcinoma in combination with curative resection remains to be established. Several prospective clinical trials on neoadjuvant therapy for resectable cholangiocarcinoma are ongoing. It may be difficult to specify unified indications for resectability of locally advanced cholangiocarcinoma and subsequent conversion surgery. However, several reports have shown the prognostic advantage of conversion surgery for cholangiocarcinoma compared with that of palliative therapy.

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Radiotherapy for Cholangiocarcinoma

13

Kazuki Terashima

Abstract

Radiotherapy, which has evolved from conventional radiotherapy to stereotactic body radiotherapy (SBRT), intensity-modulated radiotherapy (IMRT), and particle therapy (PT), is a treatment option that can be performed in the adjuvant, neoadjuvant, and definitive setting for intrahepatic cholangiocarcinoma (IHCC) and extrahepatic cholangiocarcinoma (EHCC). Radical radiotherapy for IHCC was previously difficult, but definitive SBRT or PT has recently become the primary modality for the radical treatment of unresectable IHCC. Similarly, the main modality for EHCC has changed from highly invasive intraluminal brachytherapy and intraoperable radiotherapy to these advanced radiation techniques. Adjuvant IMRT has been used for resected EHCC, neoadjuvant IMRT or SBRT before transplantation for EHCC, and definitive IMRT or PT for unresectable EHCC. These therapies are assumed to be favorable for improving the survival and quality of life of patients with cholangiocarcinoma, which has a distinctive characteristic of the tumor being surrounded by the liver, gastrointestinal tract, and important vessels such as the hepatic artery and portal vein. However, the indication for radiotherapy should be considered deliberately because radiation-induced liver disease (liver failure), biliary injury (bleeding and stenosis), and gastrointestinal radiation mucositis (ulcer, bleeding, and stenosis) can be fatal.

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Keywords

Cholangiocarcinoma · Radiotherapy · Three-dimensional radiotherapy · Stereotactic body radiotherapy · Intensity-modulated radiotherapy · Particle therapy · Proton therapy · Carbon-ion therapy · Radiation-induced liver disease

13.1 Introduction

Radiotherapy (RT) is widely used as a palliative treatment modality to improve the prognosis and symptoms (e.g., cancer pain) in advanced stage cancer and to prevent nerve palsy. The development of more sophisticated RT planning and delivery techniques such as three-dimensional conformal radiotherapy (3D-CRT) and stereotactic body radiotherapy (SBRT) has expanded the use of RT for the radical treatment of various malignancies. These techniques have made it possible to safely increase the RT dose to the tumor while limiting the dose to the surrounding normal tissues that are sensitive to RT. In addition, particle therapy (PT) using charged particles such as protons and carbon ions, which have different physical properties from photons, has also advanced.

Cholangiocarcinoma is classified into intrahepatic cholangiocarcinoma (IHCC), perihilar (or hilar) cholangiocarcinoma (PHCC), and distal cholangiocarcinoma according to the main site of the tumor. PHCC and distal cholangiocarcinoma are collectively referred to as extrahepatic cholangiocarcinoma (EHCC) in this document. Although liver transplantation or surgical resection is the only curative treatment modality, RT has been used for unresectable tumors as a palliative therapy for improving survival and preventing jaundice and stent occlusion because IHCC is often too large for hepatic resection. Further, EHCC often cannot be radically resected due to the intrahepatic bile duct and major arterial invasion. RT has often been added to surgical resection as neoadjuvant or adjuvant therapy because microscopic or macroscopic residuals sometimes remain even after resection. In recent years, curative doses have been delivered as definitive RT using advanced external body radiotherapy (EBRT) techniques such as SBRT, intensity-modulated radiotherapy (IMRT), and PT.

13.2 Techniques for External Body Radiotherapy

13.2.1 3D-CRT and SBRT

For accurate EBRT, the dose distributions are three-dimensionally calculated using CT image data, especially for intricate tumors surrounded by radiosensitive organs such as the liver and gastrointestinal tract. In SBRT, short-course irradiation with 4 to 10 fractions with accurate body fixation and respiratory synchronization or

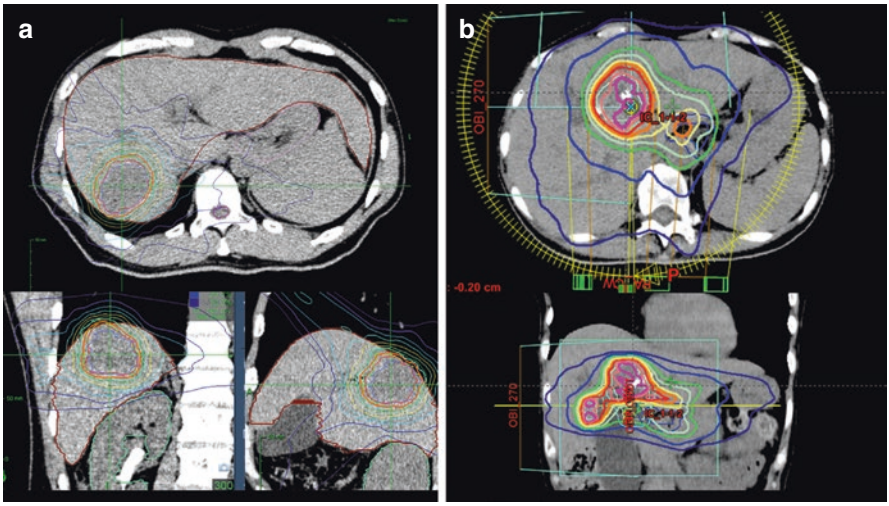

Fig. 13.1 Dose distributions in photon radiotherapy. (**a**) Stereotactic body radiation for intrahepatic cholangiocarcinoma at a dose of 60 Gy in 8 fractions with dynamic fiducial marker tracking with CyberKnife™. (**b**) Intensity-modulated radiotherapy for perihilar cholangiocarcinoma at a dose of 57 Gy in 20 fractions (Courtesy of Dr. Mayahara, Kobe Minimally invasive Cancer Center)

fiducial marker tracking in addition to 3D-CRT technique is used to enhance the therapeutic effect (Fig. 13.1a).

13.2.2 IMRT

This is a method of forming a dose gradient inside the irradiation region and a dose distribution suitable for a complicated shape such as a convex and concave. It is considered particularly useful for EHCC with a non-spherical shape invasion. The total dose and dose fractions are often similar to those of 3D-CRT (Fig. 13.1b).

13.2.3 PT

Charged particles derived clinically using proton beams or carbon-ion beams are accelerated by particle accelerators such as synchrotrons and cyclotrons. These beams have a physical property called Bragg's peak, which stops abruptly at a certain depth from the body surface, in contrast to photons that pass through the body. Utilizing this property enables irradiation with a very dose-intensive and complicated shape while avoiding exposure to important normal organs. In addition, the carbon-ion beam has a sharper Bragg's peak and a higher relative biological effectiveness than the proton beam. Therefore, it is expected to be useful for tumors close to normal organs and radioresistant tumors (Fig. 13.2).

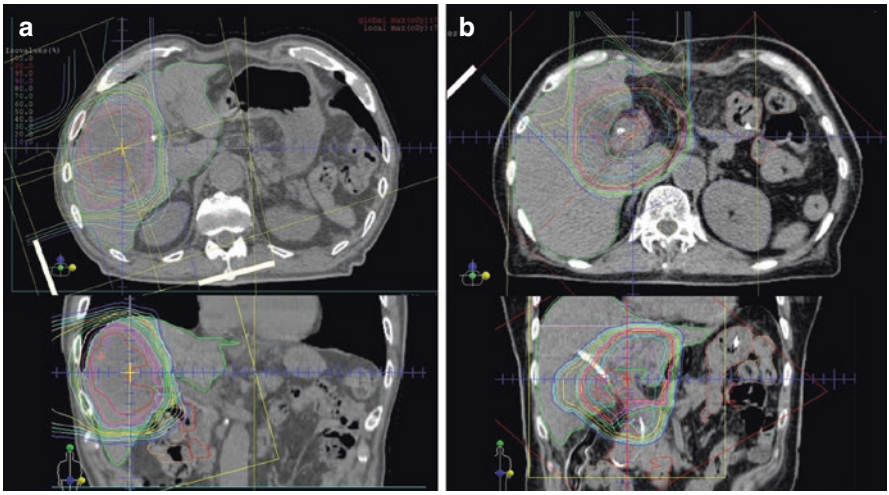

Fig. 13.2 Dose distributions in particle therapy. (**a**) Proton therapy for intrahepatic cholangiocarcinoma at a total dose of 70.2 Gy in 26 fractions. (**b**) Carbon-ion therapy for perihilar cholangiocarcinoma at a dose of 70.2 Gy in 26 fractions with a surgical spacer in the omentum

13.3 RT for Cholangiocarcinoma

13.3.1 IHCC

13.3.1.1 Adjuvant Radiotherapy

Adjuvant radiotherapy (ART) is expected to be effective for microscopic invasion and lymph node metastases after surgical resection. A retrospective analysis evaluated 5368 patients with IHCC diagnosed between 1973 and 2003, using the Surveillance, Epidemiology, and End Results database. The addition of RT yielded better overall survival outcomes: surgery and ART vs. surgery alone (hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.70–0.96) [1]. Similarly, a single institutional retrospective study of 90 patients with lymph node metastases demonstrated significant advantages of ART over non-ART (median overall survival (OS): 19.1 vs. 9.5 months, $p = 0.011$) [2]. Moreover, in a retrospective study of 2897 patients with resected IHCC between 1998 and 2013 from the National Cancer Database, ART showed a trend for improved OS in R1/R2 patients with negative lymph nodes [3].

However, contrasting findings on the survival benefit of ART have also been reported. Tran Cao et al. evaluated 2323 resected IHCC patients from the National Cancer Database between 2004 and 2012. They found no survival advantage even with the addition of either adjuvant chemotherapy or adjuvant chemoradiotherapy (CRT) regardless of the surgical margin status [4]. Similarly, a meta-analysis reported in 2020 failed to confirm the benefit of ART. Meanwhile, adjuvant chemotherapy and transcatheter arterial chemoembolization showed survival benefits [5].

Based on these conflicting findings, the indication for ART is controversial. However, ART with chemotherapy may be performed in cases with lymph node metastasis because lymph node metastasis generally has high radiosensitivity. Further, RT with modern techniques such as IMRT or PT can deliver radical doses to these regions.

13.3.1.2 Neoadjuvant Radiotherapy

Neoadjuvant radiotherapy (NART) has been used as an adjunct therapy before liver transplantation of IHCC. However, unlike PHCC, the therapeutic benefit of NART before transplantation is still unclear to date [6]. Neoadjuvant CRT has the potential for downstaging unresectable IHCC. A retrospective study reported that five of the seven patients with unresectable IHCC could undergo resection after CRT (50 Gy in 25 fractions using IMRT concurrent with S-1), and four patients were confirmed to have achieved R0 [7]. However, RT-related liver injury has been considered to inhibit safe liver resection, and the indication of NART for IHCC should be carefully considered.

13.3.1.3 Definitive RT

Definitive RT is an important therapeutic option for unresectable IHCC due to local tumor progression or poor general condition. Four prospective single-arm studies have been reported. In a prospective study of 128 patients with unresectable liver tumors, including 46 IHCC patients treated with 3D-CRT (median RT dose of 60.75 Gy with a conventional fractional dose of 1.5 Gy) with concurrent hepatic arterial floxuridine, the median OS was 13.3 months. The common severe complications were gastrointestinal ulceration and bleeding (5%), radiation-induced liver disease (RILD) (4%), and catheter-related problems (3%) [8]. In a study of 41 patients with unresectable primary liver cancer, including 10 IHCC patients treated with SBRT (median dose of 36 Gy in 6 fractions), the median OS was 15 months, and two patients with IHCC developed progression from Child-Pugh (CP) A classification to B within 3 months after SBRT. However, no patient developed RILD [9]. Similarly, a study using SBRT (55 Gy in 5 fractions) for 26 patients with unresectable liver cancer, including 12 patients with IHCC, reported a median OS of 13.2 months for IHCC patients. Further, 9 of all 26 patients showed a decline in CP score of more than 2 points, and 2 patients died from hepatic failure [10]. A recent multi-institutional prospective study of proton beam therapy (67.5 Gy equivalent in 15 fractions) for 83 patients with unresectable primary liver cancer, including 39 IHCC reported a median OS of 22.5 months for IHCC patients. A total of 3.6% of patients showed worsening CP score, and 7.7% of the IHCC patients developed severe radiation-related toxicities [11].

Two retrospective studies have reported the efficacy of SBRT using CyberKnife™ with real-time fiducial marker tracking. The median OS was 17 and 16 months for 31 patients treated at 30 Gy in 3 fractions and for 28 patients treated at 36–54 Gy in 3–5 fractions, respectively, with good local control without severe liver toxicity [12, 13]. Tao et al. evaluated the benefit of using 3D-CRT combined with IMRT with photon or proton therapy for 79 patients with unresectable

IHCC. The median OS from diagnosis for all patients, the high-dose RT group (biologic equivalent dose >80.5 Gy), and the low-dose RT group were 30, 50.4, and 23 months, respectively [14]. A high-dose proton therapy for 37 patients at a median prescribed dose of 72.6 GyE in 22 fractions achieved a favorable median OS of 25 months in 25 patients with curative coverage (the planning target volume covered all detected macroscopic tumors, including positive lymph nodes) [15]. In addition, photon IMRT or proton therapy for 66 patients yielded a median OS from diagnosis of 25 months. Proton therapy tends to improve OS ($p = 0.05$) in the multivariate analysis, although no difference in toxicity between them was observed [16]. In addition, in a multi-institutional retrospective study of 56 patients, including 27 IHCC and 29 PHCC patients treated with carbon-ion therapy with the most commonly prescribed dose at 76 Gy equivalent in 20 fractions, the median OS of the IHCC patients was 23.8 months. One patient developed classic RILD and died of liver failure, and one patient developed grade 3 treatment-related bile duct stenosis [17].

As an alternative for EBRT, radioembolization (RE), in which microspheres bound to the β-emitter Yttrium-90 are injected through a catheter into the tumor arteries using an angiography technique, has been used for hypervascular tumors. RE achieves a median OS of 16 months (range, 9.3–22 months). However, patients with hypovascular tumors are not eligible for RE [18].

In summary, the median OS from RT has improved with newer techniques such as high-dose SBRT and IMRT, proton therapy, and carbon-ion therapy. The OS of 23–25 months is considerably better than that of chemotherapy (e.g., 16.7 months for liver-only cholangiocarcinoma treated with gemcitabine with/without cisplatin in the post hoc analysis [19]) and of transarterial chemoembolization (TACE) (e.g., 13 months in a meta-analysis [20]). However, the risk of RILD should be considered when planning RT, with consideration that a higher irradiation dose and volume to the liver are correlated with RILD. In addition, the doses to other organs at risks such as the gastrointestinal tract, lung, kidney, and skin should also be reduced to the lowest possible according to the limitations for each organ.

Concurrent chemotherapy and RT have been used in the definitive treatment for IHCC. Many anti-cancer drugs have been shown to be sensitizers for RT, and CRT may be useful in improving the therapeutic effect. However, the indications should be carefully considered because CRT can also cause exacerbations of both radiation-induced and chemotherapy-induced toxicities.

13.3.2 Extrahepatic Cholangiocarcinoma

13.3.2.1 Adjuvant Radiotherapy

Several studies in the 1990s indicated that ART has no survival benefit for resected EHCC. In a randomized study comparing patients with and without ART therapy for patients with resectable PHCC, ART had no effect on survival (median OS, 18.4 vs. 20.1 months) and quality of life [21]. Two recent retrospective studies also negated the effect of ART [22, 23].

Meanwhile, since the 2000s, most studies on resectable EHCC indicated the survival benefit of ART with concurrent systemic chemotherapy. The SWOG S0809 prospective trial evaluated the tolerability and efficacy of adjuvant chemotherapy with 4 cycles of capecitabine and gemcitabine followed by IMRT (45 Gy to regional lymphatics; 54–59.4 Gy to the tumor bed) concurrent with capecitabine for 69 patients with resected EHCC and gallbladder carcinoma. There was no significant difference in OS between R0 and R1 patients (median OS: 35, 34, and 35 months for the overall population, R0 patients, and R1 patients, respectively). This indicated the effectiveness of RT for suppressing local recurrence after resection. Similarly, adjuvant IMRT (50.4–54 Gy) with concurrent 5-fluorouracil (5-FU) or capecitabine chemotherapy was associated with improved OS (HR 0.37, $p = 0.004$) for both margin-negative and -positive resections [24]. A meta-analysis of EHCC and gallbladder cancer, including 21 clinical trials, found a higher 5-year OS rate in the ART group than in the no ART group (odds ratio (OR) = 0.63; 95% CI = 0.50–0.81, $p = 0.0002$).

Intraoperative radiotherapy (IORT) can provide intensive irradiation to the tumor by avoiding the gastrointestinal tract during surgery. Todoroki et al. suggested the survival benefit of intraoperative and postoperative RT for locally advanced hilar tumors (5-year OS: 39.2% vs. 13.5%, $p = 0.01$) [25]. In contrast, Nakano et al. reported that IORT has no therapeutic benefit for EHCC, including ampullary cancers [26]. The indication for IORT has recently decreased due to the extremely complicated procedure and the progress of EBRT technology.

SBRT cannot be used for ART because the high risk of gastrointestinal toxicities such as ulcer, hemorrhage, and perforation is unavoidable in hypofractional high-dose irradiation for the hepatic hilar area, which is adjacent to the biliary jejunal anastomosis, duodenum, and stomach. Accordingly, there are no reports on SBRT for the adjuvant treatment of cholangiocarcinoma.

In summary, ART with concurrent chemotherapy is expected to improve the survival of resected EHCC patients, especially those with positive surgical margins or positive lymph nodes. The clinical target volume should preferably include both the tumor bed and regional lymph node area. The radiation dose is 50.4 Gy to 54 Gy in conventional fractions with a small amount of boost irradiation if margin positive. IMRT with concurrent chemotherapy (5-FU, capecitabine, or gemcitabine) is used to reduce the irradiation to organs at risks, such as the duodenum and stomach.

13.3.2.2 Neoadjuvant Radiotherapy

NART for EHCC has been mainly used before liver transplantation. Liver transplantation alone is inadequate for improving survival, with a 5-year OS rate of 23% [27]. Thus, neoadjuvant CRT was added before liver transplantation to control tumor growth while waiting for transplantation and to prevent local regional recurrence after transplantation. A multi-institutional retrospective analysis evaluated neoadjuvant CRT therapy with EBRT combined with intravenous 5-FU and/or intraluminal brachytherapy (ILBT) for 287 patients. Treatment involved the insertion of a radiation source directly into the biliary tract through a stent and/or maintenance chemotherapy (oral capecitabine) followed by liver transplantation. The results showed favorable treatment efficacy with a 5-year OS rate of 53% [28].

The other purposes of NART are to downstage unresectable EHCC to a resectable status and to increase the rate of negative resection margins. For unresectable EHCC, the possibility of CRT for downstaging unresectable locally advanced PHCC was suggested in a protocol for NART (50 Gy in 25 fractions using IMRT mainly concurrent with S-1) [7].

For resectable EHCC, some retrospective studies reported that NART (50.4–54 Gy in conventional fractions with 5-FU based chemotherapy) has no superior survival benefit to resection only [29]. In contrast, a retrospective study supported the benefit of NART in 27 EHCC patients treated with RT (50–60 Gy at daily 2 Gy) concurrent with full-dose gemcitabine (1000 mg/m^2). The patients treated with neoadjuvant CRT showed significantly higher recurrence-free survival and OS rates than those who did not receive the treatment [30]. These findings supported that compared with chemotherapy alone, the advantage of neoadjuvant CRT is that it can be administered without dose reduction, unlike in postoperative conditions.

13.3.2.3 Definitive RT

Definitive RT with or without concurrent chemotherapy is a treatment option for locally advanced unresectable EHCC, although prospective evidence is yet to be obtained. From the 1990s to the early 2000s, several retrospective studies indicated the benefit of combining EBRT with ILBT. The OS ranged from 9 months to 14 months (median, 12 months). Then, early studies in the 2000s indicated the benefit of adding ILBT to EBRT [31]. However, later studies in the 2010s found no such benefit [32]. A multi-institutional retrospective study concluded that the additional ILBT does not yield better OS compared to EBRT alone [33]. These studies included conventional EBRT (e.g., two-dimensional RT) and 3D-CRT because of their long-term enrollment period. Meanwhile, a retrospective study using 3D-CRT (45–50.4 Gy at 1.8 Gy per fraction with 5.4–9.0 Gy boost) concurrent with a 5-FU-based regimen or gemcitabine plus cisplatin demonstrated an acceptable OS of 16.5 months with no acute severe toxicity [34].

In SBRT, two retrospective studies for PHCC have been conducted. SBRT at a total dose of 30 Gy in 3 fractions concurrent with gemcitabine yielded a good median OS of 35.5 months without severe complications. However, it should be noted that only ten patients were included in this study [35]. Conversely, at a relatively high dose of 45 Gy in 3 fractions for 26 PHCC and 1 IHCC patient, the median OS was 10.6 months, with 9% of these patients experiencing severe gastrointestinal ulcers [36]. These results indicate that 15 Gy per fraction may be too high for the hilum.

In PT, a retrospective study evaluated 28 patients, including 10 with recurrent tumors, 6 with unresectable IHCC, and 12 with unresectable EHCC, treated with proton therapy at a median dose of 68.2 Gy (2.0–3.2 Gy daily equivalents). The median OS of the overall population was 12 months, and severe late gastrointestinal complications were observed in 25% of the patients [37]. However, a retrospective multi-institutional study of 29 patients with PHCC who underwent carbon-ion therapy reported a median OS of 12.6 months without severe complications [17].

With respect to biliary stent patency, many studies have demonstrated the effectiveness of increasing stent patency and prolonging the time to occlusion for improving the quality of life of patients with poor prognosis.

To summarize, although RT might be effective in improving prognosis and preventing stent occlusion compared to best supportive care, the suitable RT modality still needs to be clarified. Novel adjuvant modalities such as transcatheter arterial fiducial marker placement instead of percutaneous puncture, especially in the hilar region, and a surgical spacer to separate the gastrointestinal tract from the tumor have been developed for a more accurate irradiation.

13.4 RT Toxicity

13.4.1 Radiation-Induced Liver Disease

RILD is a significant limiting factor in RT for liver malignancy because there is no effective treatment for hepatic dysfunction leading to hepatic failure. RILD has two types. Classic RILD is an anicteric ascites without tumor progression that occurs within 2 weeks to 4 months after irradiation. Meanwhile, non-classic RILD is an elevation of liver transaminases more than five times the upper limit of normal level or worsening of CP score of 2 points within 4 months after irradiation.

Best supportive care, including medications (e.g., diuretics and ursodeoxycholic acid) and fluid management, is generally the only treatment for RILD. Meanwhile, amifostine, low molecular weight heparin, and pentoxifylline were found to be effective for preventing hepatic damage from RT. RILD has a high mortality rate, ranging from 50% to 76%. Therefore, the indications for RT for IHCC should be considered carefully, and the irradiation dose to the liver should be reduced as much as possible.

13.4.2 Biliary Tracts

Biliary stenosis, obstruction, bleeding, cholangitis, and cholecystitis are observed in the late phase from 3 months to a few years after RT. Among these late events, biliary stenosis and cholangitis are frequently observed in cholangiocarcinoma, and percutaneous or endoscopic biliary drainage is often required to treat the stenosis.

13.4.3 Gastrointestinal Tracts

Gastric and duodenal mucositis, ulcer, hemorrhage, and perforation due to irradiation of the stomach and duodenal are observed in the acute and late phases, especially for EHCC. Because bleeding and perforation can be fatal, long-term therapy with various anti-ulcer medications is recommended. In addition, hemostasis via argon plasma mucosal coagulation and partial gastrectomy are usually effective for severe hemorrhage and perforation.

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Part IV

New Treatment for Pancreatic Cancer and Cholangiocarcinoma

Precision Medicine for Pancreatic Cancer and Cholangiocarcinoma

14

Chigusa Morizane

Abstract

Next-generation sequencing techniques, commercially available since 2006, have enabled cost- and time-effective sequencing of tumor DNA. Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, used as maintenance therapy following platinum-based chemotherapy, has been shown to improve progression-free survival in patients with metastatic pancreatic cancer and a germline *BRCA1/2* mutation. *KRAS* mutations are predominant in pancreatic cancer. Although effective targeted therapy remains to be established, *KRAS* G12C inhibitors and the combined inhibition of MEK and autophagy are candidates for future treatment strategies. Regarding *KRAS* wild-type, *BRAF*-activating alterations, microsatellite instability, and kinase fusion genes, especially *NRG1* fusion genes, are important genetic abnormalities of high interest as treatment targets.

Biliary tract cancer is an umbrella term that encompasses carcinoma of the extrahepatic bile ducts, carcinoma of the gallbladder, ampullary carcinoma, and intrahepatic cholangiocarcinoma, all of which are characterized by wide genomic variation associated with the different primary organs affected. For example, in intrahepatic cholangiocarcinoma, *FGFR2* rearrangement and *IDH1* mutation are important actionable driver genes successfully targeted in clinical trials. *BRAF*, *HER2/neu*, *BRCA1/2,* and overexpression of *c-MET* genes are among the other candidate targets.

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Pancreatic cancer · Biliary tract cancer · Precision medicine · Next generation sequencing · *KRAS* · *BRCA2* · *FGFR2* fusion · *IDH1*

14.1 Introduction

Following the completion of the Human Genome Project in 2003, research in oncology has progressively focused on the sequencing of cancer genomes, aiming to elucidate the genetic basis of oncogenesis and identify actionable alterations. Next-generation sequencing (NGS) techniques, commercially available since 2006, have enabled cost- and time-effective sequencing of tumor DNA. Comprehensive genomic profiling (CGP) with NGS technique use has become part of standard practice. CGP has advanced personalized precision medicine, improved the understanding of disease biology, and offered novel approaches to targeted therapy.

Tumor-agnostic therapies emerged in the era of precision medicine, revolutionizing the approach to cancer treatment. Tumor-agnostic therapies target specific genomic anomalies or molecular features of the tumor, independently of its site of origin. Two targets have been identified, and three drugs have already received regulatory approval and entered clinical practice, creating a precedent for tumor-agnostic therapies in precision medicine. Pembrolizumab, an anti-programmed cell death-1 monoclonal antibody, has been approved for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with microsatellite instability-high (MSI-H) or deficient DNA mismatch repair (dMMR). Meanwhile, larotrectinib and entrectinib, administered orally, are potent, and selective inhibitors of tropomyosin receptor kinases, approved for use in unresectable or metastatic solid tumors with neurotrophic tropomyosin receptor kinase (NTRK)-fusion proteins in adult and pediatric populations. Although promising, tumor-agnostic treatment is not applicable to all targets, and further research is required, including studies into specialized treatments for specific genetic targets in each cancer subtype. This chapter aims to provide an overview of precision medicine in pancreatic cancer and cholangiocarcinoma.

14.2 Precision Medicine for Pancreatic Cancer

At the time of diagnosis, pancreatic ductal adenocarcinoma (PDAC) tends to present as an advanced disease with poor patient prognosis and limited survival. Gemcitabine + Nab-paclitaxel and FOLFIRINOX are the standard first-line treatments for advanced PDAC, improving overall survival compared to that achieved with gemcitabine alone. Although erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, was approved for pancreatic cancer, precision medicine for pancreatic cancer has been lacking momentum.

However, recent reports are promising. The "Know Your Tumor Project" initiative undertaken by the Pancreatic Cancer Patient Association in the United States reported that 26% of patients with pancreatic cancer had actionable genetic alterations, suggesting targeted therapies could prolong survival. Additionally, findings from an international phase III trial of homologous recombination deficiency (HRD), poly (ADP-ribose) polymerase (PARP) inhibitors in germline *BRCA*-mutated PDAC have been reported. As a tumor-agnostic targets for precision medicine in clinical practice, MSI-high/dMMR detection rate is only 0.7–0.8% [1, 2] and *NTRK1-3* fusion gene detection rate is only 0.56% [3] in PDAC. In addition, a recent report has suggested that the response rate to pembrolizumab in MSI-high/dMMR PDAC was somewhat lower than that in cancers from the other primary site [4].

14.2.1 Genetic Landscape of Pancreatic Ductal Adenocarcinoma (Fig. 14.1)

KRAS, *CDKN2A*, *TP53*, and *SMAD4* have been recognized as the "Big 4" major driver genes in pancreatic carcinogenesis. The proto-oncogene *KRAS* is mutated in more than 95% of PDAC cases. The prevalent subtypes of *KRAS* mutation in PDAC are *KRAS* G12D, G12V, and G12R.

In *KRAS* wild-type PDAC, which accounts for <5% of all cases, *BRAF* mutations, and MSI, and kinase fusion genes, including *NRG1*-fusion, have been reported at a relatively high incidence [5]. Among histological subtypes of pancreatic cancer, MSI-H/dMMR has been reported to be associated with medullary and mucinous/colloid histology or Intraductal Papillary Mucinous Neoplasm (IPMN)-derived carcinomas [6]. *BRAF/RAF1* fusion and *BRCA1/2* mutations have been frequently reported in acinar cell carcinomas [7].

Resected PDAC that underwent whole genome sequence has been categorized into four subtypes based on the patterns of structural variation (variation in chromosomal structure); this categorization may have clinical utility and includes a "stable" (≤50 structural variants; 20% of all samples), "locally rearranged" (a significant focal event on 1 or 2 chromosomes; 30% of all samples), "scattered" (moderate range of chromosomal damage, 50–200 structural variants; 36% of all samples), and an "unstable" (up to 558 structural variants) subtype.

While most PDAC cases occur sporadically, PDAC associated with hereditary syndromes or familial PDAC (FPC), defined as an individual with two or more first-degree relatives diagnosed with PDAC [8], accounts for approximately 10% of cases. Hereditary cancer syndromes associated with increased risk of PDAC include Peutz–Jeghers syndrome, hereditary pancreatitis, familial atypical multiple mole melanoma, familial adenomatous polyposis, Lynch syndrome, and hereditary breast and ovarian cancer syndrome. A number of genes, including *BRCA1/2* [9], *PALB2* [10], and *ATM* [11], have been associated with the increased risk of FPC; among them, *BRCA2* mutations are most prevalent, with an estimated 5% of PDAC patients harboring this germline mutation.

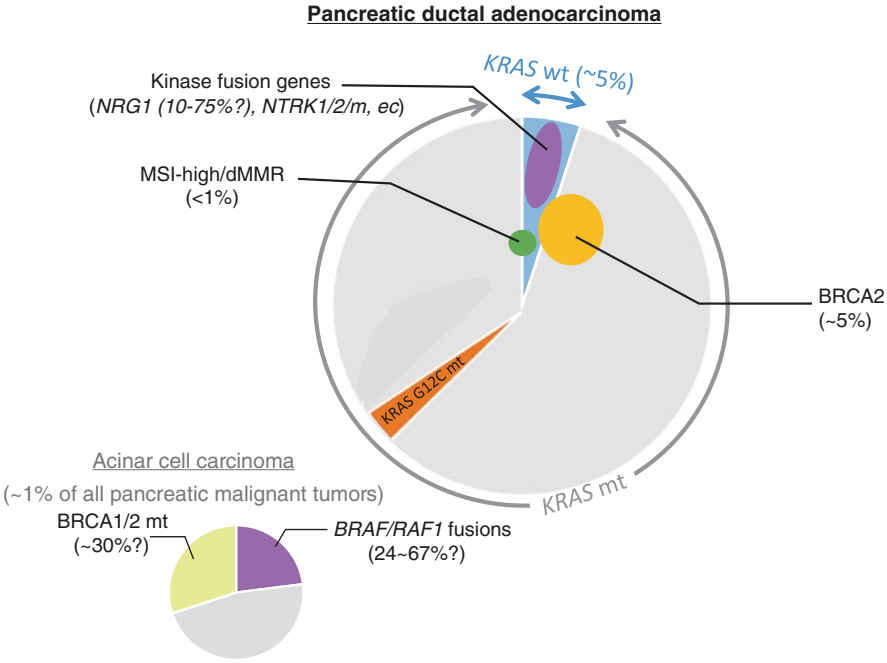

Fig. 14.1 Targetable genetic alterations of Pancreatic cancer

14.2.2 Pancreatic Ductal Adenocarcinoma Harboring Germline *BRCA1/2* Mutation

Mutations of the DNA repair-associated genes, such as *BRCA1/2*, *PALB2*, and *ATM* are considered the most common "highly actionable" alterations in PDAC. In patients with these gene mutations, PARP inhibitors have been reported to exert anti-tumor effects by inducing cell death via synthetic lethality. Findings from the international, phase III POLO (Pancreas cancer Olaparib Ongoing) trial have shown that treatment with PARP inhibitor olaparib may significantly reduce the risk of disease progression in patients with a germline *BRCA1/2* mutation and metastatic pancreatic cancer, and disease that had not progressed during the first-line platinum-based chemotherapy [12]. Patients were randomized to receive olaparib or placebo. Progression-free survival (PFS), the primary endpoint, was significantly prolonged in the olaparib group compared to the placebo group (median PFS: 7.4 months vs. 3.8 months, hazard ratio [HR] = 0.53, 95% confidence interval [CI], 0.35 to 0.82, $p = 0.004$).

Moreover, other PARP inhibitors such as veliparib and rucaparib are being examined in clinical trials for pancreatic cancer [13, 14]. Next-generation sequencing of FPC genome has identified candidate susceptibility genes such as *PALB2* and *ATM*, which participate in homologous recombination repair; further investigations are currently ongoing. Meanwhile, non-*BRCA* homologous recombination

repair-deficient PDAC remains unexplored and is the next focus of the related precision medicine research.

14.2.3 Pancreatic Ductal Adenocarcinoma Harboring *KRAS* Mutation

Although *KRAS* mutations are predominant in pancreatic cancer, no effective therapeutic agent targeting *KRAS* mutations has been established to date despite development efforts [15]. A recent report has suggested that autophagy inhibitor chloroquine combined with the genetic or pharmacological inhibition of specific autophagy regulators synergistically enhanced the inhibition of the RAS-RAF-MEK-ERK pathway, mediating anti-tumor activity in *KRAS*-driven PDAC [16, 17]. A recent report has presented a patient with PDAC treated with the combination of trametinib and hydroxychloroquine, which resulted in a partial, but nonetheless striking disease response [17]. Phase I clinical trials of trametinib and hydroxychloroquine (NCT03825289) and binimetinib and hydroxychloroquine (NCT04132505) in patients with PDAC are ongoing.

Moreover, several candidate inhibitors of the *KRAS* G12C mutant protein have been reported. Among them, a phase I study of sotorasib in solid tumors, in particular, in a non-small cell lung cancer cohort has produced promising results [18]. Although the prevalence of *the KRAS* G12C subtype is estimated at ~4% [19], these promising results of lung cancer are exciting and will provide hope for PDAC treatments.

14.2.4 Pancreatic Ductal Adenocarcinoma of *KRAS* Wild-Type

A large, multicenter, non-randomized trial of 581 PDAC patients, which is a part of the so-called "Know Your Tumor" initiative [20], has recently reported that wild-type *KRAS* tumors accounted for 8% of PDAC cases in this cohort; meanwhile, a significant proportion (24%) of these tumors had alterations in other MAPK pathway effectors, including *BRAF*-activating alterations. This cohort is a good candidate for approaches to MAPK pathway targeting, including BRAF/MEK inhibitor. Another genetic alteration enriched in *KRAS* wild-type PDAC is MSI/dMMR. A recent study has demonstrated that MSI-high/dMMR PDAC harbors *KRAS* mutations less frequently than conventional PDAC. These findings suggest the importance of testing the MSI status of *KRAS* wild-type PDAC cases to identify the small subset of this population most likely to benefit from pembrolizumab treatment.

Another promising treatment targets in *KRAS* wild-type PDAC are kinase fusion genes, which include *ALK, BRAF, FGFR2, RAF, RET, MET, NTRK1, ERBB4*, and *FGFR3*, reported to be putative driver alterations [5]. In this context, kinase inhibitors are candidate targets that raise interesting clinical questions. Recently, several studies have reported neuregulin 1 (*NRG1*) fusion genes in several cancer types, including lung cancer and *KRAS* wild-type PDAC. NRG1 is a ligand for ERBB3,

which leads to its heterodimerization with ERBB2. *NRG1* gene fusions are generally in-frame and generate fusion proteins that maintain the extracellular EGF domain of NRG1 and the transmembrane domain of the rearrangement partner. Thus, the EGF domain of the fusion protein can constitutively bind to its partner and activate signaling through MAPK, PI3K-AKT, and NF-kB, increasing the rate of tumor proliferation and the likelihood of tumor survival. In heavily pretreated patients with PDAC carrying *NRG1* fusion, treated subsequently with afatinib, an irreversible ERBB1-4 inhibitor, a significant and rapid disease response has been demonstrated [21, 22].

14.3 Precision Medicine for Biliary Tract Cancer

Biliary tract cancer (BTC), extrahepatic cholangiocarcinoma (ECC), carcinoma of the gall bladder (GBC), ampullary carcinoma, and intrahepatic cholangiocarcinoma (ICC) are characterized by wide geographic variation in incidence, with few cases reported in Europe and North America, and a relatively high disease rate in Latin America and Asia, including Japan. BTC malignancies represent a group of different diseases that affect individuals of distinct demographic, clinical, and molecular characteristics. BTC etiology is typically associated with liver fluke infection, hepatitis B and C, primary sclerosing cholangitis, pancreaticobiliary maljunction, and exposure to chemicals such as 1,2-dichloropropane and dichloromethane. However, in most cases, BTC is sporadic, with no related risk factors identifiable in Europe, North America, and Japan. BTC is often diagnosed at an advanced stage and associated with a poor patient prognosis. Combination chemotherapy with gemcitabine + cisplatin (GC) is the first-line treatment for advanced BTC with a significant but modest survival advantage over monotherapy. Two randomized phase III studies have recently reported non-inferiority of gemcitabine and S-1 to GC alone (FUGA-BT, JCOG1113) and superiority of gemcitabine + cisplatin+ S-1 to GC alone (MITSUBA, KHBO1401) for advanced BTC. These regimens may be considered suitable as first-line treatment in Japanese patients. Regarding second-line chemotherapy, results from a randomized study have shown a survival benefit associated with fluorouracil, leucovorin, and oxaliplatin (modified FOLFOX regimen). Concurrently, clinical trials investigating targeted therapies for unselected BTC have failed to demonstrate clinical benefit. Recent studies into the molecular characteristics of BTC have revealed complex biological heterogeneity within these tumors, identifying some targetable genomic aberrations. NGS has enabled rapid mutational analysis of multiple genes in human cancers, and driver genetic alterations have been reported in BTC. In April 2020, the Food and Drug Administration approved pemigatinib, a selective fibroblast growth factor receptor (FGFR) inhibitor, for patients with BTC with an *FGFR2* fusion or rearrangement and who had received prior treatment. Moreover, a randomized trial involving ivosidenib has identified shown prolonged PFS compared with those receiving placebo in patients with BTC and *IDH1* mutations.

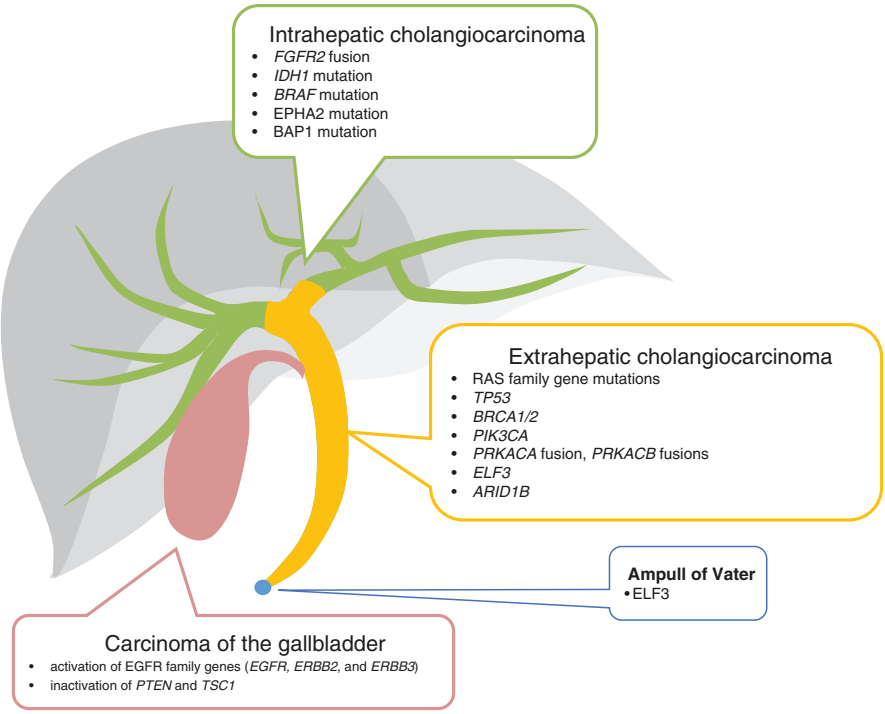

Fig. 14.2 Genetic alterations of biliary tract carcinomas

14.3.1 Genetic Landscape of Biliary Tract Cancer (Fig. 14.2)

BTC is genomically diverse; recent studies have reported some characteristic gene abnormalities associated with BTC. In ICC research, gene expression profiles, high-density single-nucleotide polymorphism arrays, and mutation analyses using formalin-fixed samples from patients identified two biological classes of this disease [23]. The first class, the inflammation class (38% of ICC cases), has been characterized by activation of inflammatory signaling pathways, overexpression of cytokines, and STAT3 activation. In contrast, the proliferation class (62% of ICC cases) has been characterized by activation of oncogenic signaling pathways and associated with shorter survival compared with inflammation class. Nakamura et al. reported findings from whole-exome and transcriptome sequencing of a large BTC cohort (260 cases, including 145 ICC, 86 ECC, and 29 GBC) of Japanese patients. Alterations in the kinase-RAS module were the most frequently identified molecular event, observed in 51.9% of cases. *FGFR1* and *FGFR2* alterations occurred exclusively in ICC, whereas activation of EGFR family genes (*EGFR*, *ERBB2*, and *ERBB3*) was relatively frequent in GBC. *EPHA2* mutations occurred relatively frequent in ICC. RAS family gene mutations were frequent in ICC and ECC, and inactivation of *PTEN* and *TSC1* was frequent in GBC. *FGFR2* and *ALK* fusions and

ERBB2, RAS gene family, *BRAF*, and *NF1* mutations occurred in a mutually exclusive manner. Alterations to the TP53 and RB cell cycle modules occurred in 33.9% and 11.7% of cases, respectively, and were more frequent in GBC than in the other diseases.

14.3.2 Biliary Tract Cancer Harboring *FGFR2* Rearrangement

FGFR2 gene rearrangement has been identified as a novel oncogenic and druggable target in a number of cancers. FGFR activity modulates distinct downstream pathways, including RAS/MAPK and PI3K/AKT. Recent genomic analysis has revealed the presence of *FGFR2* fusion genes in 11–14% of ICC cases [24–26]. In addition, ICC with *FGFR2* fusion has been associated with female predilection, younger age at onset, and improved overall survival [25, 27]. Recently, a Japanese multi-institutional prospective observational (PRELUDE) study has examined the frequency of *FGFR*2 rearrangement with fluorescent in situ hybridization and RNA sequencing, alongside other clinicopathological characteristics of BTC. In this study, among patients with advanced/recurrent ICC, the frequency of *FGFR2* rearrangement-positive cases was 7.4%, which was lower than previously reported in studies of surgically resected cases. *FGFR2* rearrangement-positivity has been associated with younger age ($\leq$ 65 years) and a history of viral hepatitis. In addition, this study has revealed that 3.6% of patients with perihilar cholangiocarcinomas had *FGFR2* rearrangements [28].

FGFR2 rearrangements are good candidates for therapeutic targets in ICC as well as in perihilar cholangiocarcinomas; various FGFR2 inhibitors are currently in clinical development with encouraging preliminary results. Table 14.1 summarized the results of phase II clinical trials of various FGFR2 inhibitors. The objective response rate is approximately 30%. On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib for the treatment of adult patients with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with an *FGFR2* fusion or other rearrangements. The Agency has also approved the FoundationOne® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection. At the time of writing, randomized phase III studies of infigratinib (NCT03773302), pemigatinib (NCT03656536), and futibatinib (NCT04093362) in patients with chemo-naive advanced cholangiocarcinoma with *FGFR2* fusion or other rearrangement are underway, with control arms that involve GC therapy. While FGFR2 inhibitors have shown promising results in the treatment of advanced BTC, acquired resistance remains a challenge that needs to be addressed. Goyal et al. have demonstrated that patients who responded to infigratinib developed an *FGFR2* V564F mutation and polyclonal *FGFR2* mutations during disease progression. Futibatinib, a third-generation irreversible pan-FGFR inhibitor, has since been shown to be active against multiple mutations conferring resistance to infigratinib [29].

Table 14.1 Results of phase II studies of FGFR inhibitors for advanced cholangiocarcinoma with FGFR gene alterations

	Population	*n*	Objective response rate (%)		Progression-free survival (months)		Overall survival (months)	Refs.
Erdafitinib	*FGFR2* fusion	8	50	60	5.59	12.35		[42]
	FGFR2 mutation	3						
	FGFR3 fusion	1						
	FGFR3 mutation	2						
Pemigatinib	*FGFR2* fusions or rearrangements	107	35.5		6.9		21.1	[43]
	Other *FGF/FGFR* alterations,	20	0		2.1		6.7	
	No *FGF/FGFR* alterations	20	0		1.7		4	
Infigratinib	*FGFR2* fusions	48	14.8	18.8	5.8			[44]
	FGFR2 mutation	8						
	FGFR2 amplification	3						
Futibatinib	*FGFR2* fusions or rearrangements	103	37.3		7.2			[45]

14.3.3 Biliary Tract Cancer Harboring *IDH1* Mutation

Isocitrate dehydrogenase 1 (*IDH1)* encodes the enzyme isocitrate dehydrogenase, which is involved in the citric acid cycle and other metabolic processes. When mutated, *IDH* increases the production of an oncometabolite, 2-hydroxyglutarate (2HG), which alters the epigenetic programming of cells, thereby promoting cancer. Alterations in *IDH1* genes are often identified in ICC, brain tumors, and acute nonlymphocytic leukemias and are thought to be the key drivers of tumorigenesis. *IDH1* mutations have been reported in 7–36% of ICC cases [26, 30–34]. In a recent phase III study with oral ivosidenib, which is a selective, potent inhibitor of mutant *IDH1*, patients with advanced cholangiocarcinoma with an *IDH1* mutation showed improved PFS compared to patients treated with placebo. The median PFS was 2.7 months in 124 patients treated with ivosidenib compared to 1.4 months in the 61 patients receiving placebo (HR = 0.37 [95% CI, 0.2. to 0.54], $P < 0.001$) [29].

14.3.4 Biliary Tract Cancer with *HER2/neu* Gene Amplification or Overexpression

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family, associated with tyrosine kinase activity. Dimerization of the receptor results in the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiates a variety of signaling pathways leading to cell proliferation and tumorigenesis. *The HER2/neu* gene is thought to be the key driver of tumorigenesis in several solid tumors, including breast cancer and gastric cancer. In those cancer types, several clinical trials have indicated that HER2-targeted therapy prolongs patient survival. *HER2/neu* gene amplification or overexpression are seen in approximately 5–25% of ECC and 16–17% of GBC cases. Preliminary data from the MyPathway trial, a multi-basket study in solid tumors harboring relevant genetic alterations, indicated that pertuzumab plus trastuzumab was active in *HER2/neu* gene amplified/overexpressed/mutated metastatic BTC. This report included data from 11 BTC patients with *HER2/neu* gene alteration (amplified/overexpressed, $n = 8$; mutated, $n = 3$). At the median follow-up of 4.2 months, 4 and 3 patients presented with partial response and stable disease, respectively [35]. In addition, a phase II trial of trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody-drug conjugate, in HER2-positive (immunohistochemistry/in situ hybridization status: 3+/any or 2+/+) BTC is currently underway in Japan (JMA-IIA00423, HERB trial).

14.3.5 *BRAF* Mutation

RAS and RAF proteins are involved in MAPK signaling. BRAF is a member of the serine-threonine kinase RAF family, which includes RAF-1/CRAF, ARAF, and

BRAF. In normal cells, BRAF functions as a mitotic signal transporter in the RAS/RAF/ MEK1/2/ERK1/2/MAPK pathway. This pathway plays a pivotal role in regulating embryogenesis, cell proliferation, differentiation, migration, and survival. In the last decade, a high frequency of *BRAF* point mutations has been identified in melanoma and other human cancers. *BRAF* mutations have been detected in many types of cancer, including melanoma, colorectal cancer, thyroid cancer, non-small cell lung cancer, and hairy cell leukemia. *BRAF V600* mutations are present in approximately 40% of metastatic melanoma tumors. BRAF and MEK inhibitors have been shown to improve overall survival and PFS among patients with metastatic melanoma. In colorectal cancer, a combination therapy consisting of BRAF, EGFR (and MEK) inhibitors has recently been shown to be a promising second-line or third-line alternative treatment [36].

In a study with a biomarker-unselected population, the MEK inhibitor selumetinib has been shown to have limited clinical value in patients with advanced BTC [37]. The *BRAF* V600E mutation is relatively rare, with prevalence estimated at 5–7% in BTC. Preliminary results from the BTC cohort of the ROAR basket study of patients with 33 *BRAF* V600E mutation who had failed previous systemic chemotherapy and were treated with BRAF inhibitor (dabrafenib) and MEK inhibitor (trametinib) demonstrated an objective response rate of 42%, median PFS of 7.2 months, and overall survival of 11.3 months [38].

14.3.6 Other Genomic Alterations and Targeted Therapy

Mutations of the *BRCA1/2, ATM*, *PIK3CA,* and overexpression of c-MET genes are among the other interesting targets. *BRCA* mutations are found in 3.6–5.2% of BTC cases [39], and some reports indicate that homologous recombination-related gene alterations are identified in 28.9–63.5% of newly diagnosed BTC patients [40, 41]. Following several trials assessing PARP inhibitors in breast cancer and ovarian cancer, recent studies have tested the role of PARP inhibitors in patients affected by HRD gastrointestinal malignancies, with the pivotal POLO trial for pancreatic cancer. A phase II study of olaparib, a PARP inhibitor, is ongoing for metastatic BTC with aberrant DNA repair gene mutations.

14.4 Conclusions and Future Perspectives

Recent advances in molecular profiling of PDAC and BTC may enable the prediction of response to particular therapeutic agents in individual patients. To improve outcomes of patients affected by these diseases, a thorough understanding of tumor characteristics and patient molecular stratification are required. Precision medicine will likely involve molecular targeting of oncogenic signaling pathways, DNA damage response or epigenetic modifiers, immunotherapy, and cytotoxic agents, or the combination of thereof.

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Immunotherapy for Pancreatic Cancer and Cholangiocarcinoma

15

Makoto Ueno

Abstract

The administration of immune checkpoint inhibitors (ICIs) that can block immune checkpoints (for example, CTLA-4 or PD-1 engagement on lymphocytes) has been shown to lead to tumor regression in patients with various cancers. Moreover, synergistic combinations of immunotherapy modalities provide important opportunities to improve responses and outcomes for patients. However, the evidence for them in pancreatic and biliary tract cancer is limited. Recently, some early phase studies were reported. Most studies showed modest efficacies, and further studies, especially with ICI combination therapies, are needed.

Keywords

Immunotherapy · Immune checkpoint inhibitor · CTLA-4 · PD-1 · PD-L1 Pancreatic cancer · Biliary tract cancer

15.1 Introduction

There are three major categories of effective immunotherapies for the treatment of patients with cancer: nonspecific stimulation of the immune system, active immunization using cancer vaccines, and adoptive cell transfer immunotherapy [1]. Use of a nonspecific immunotherapy approach, such as the administration of immune checkpoint inhibitors (ICIs) that can block immune checkpoints (for example, cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1)

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engagement on lymphocytes), has also been shown to lead to tumor regression in patients with melanoma [2]. ICIs are revolutionizing the treatment of patients with cancer. Moreover, synergistic combinations of immunotherapy modalities represent an important opportunity to improve responses and outcomes for patients. However, ICIs alone are not sufficient for pancreatic and biliary tract cancer. Herein, we introduce the current status and future perspective of ICIs and their use in combination with other targets.

15.2 Types of ICIs

Immune checkpoints play a key role in maintaining immune homeostasis. Immune checkpoint mechanisms are often activated to suppress an antitumor immune response that has led to tumor progression. Since the initiation of the first clinical trial for the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab in 2000 and the anti-PD-1 mAb nivolumab in 2006, several mAbs targeting CTLA-4, PD-1, or programmed cell death protein ligand 1 (PD-L1) have been shown to be efficacious in various types of cancers [3]. Ipilimumab is an anti-CTLA-4 mAB that improves overall survival (OS) in patients with advanced melanoma [4]. Nivolumab and pembrolizumab are human mAb against PD-1 that inhibit the binding of PD-L1 to PD-1 and therefore enhance the immune response to tumors. They have been shown to have antitumor activity in a wide range of tumors, including metastatic melanoma, squamous non-small-cell lung cancer, and renal cell carcinoma [5].

15.3 Mechanism of ICIs

T cells are activated by the primary signal from the recognition of tumor antigens *via* the T cell receptor (TCR) and the secondary signal generated by the binding of CD28 to B7 molecules (CD80/CD86) on dendritic cells, and the activated T cells attack the tumor. Tregs suppresses dendritic cells *via* CTLA-4, and CTLA-4 on activated T cells binds to CD80/86, which suppresses T cell activation [6].

PD-1 is expressed on activated T cells, B cells, and myeloid cells. The engagement of PD-1 by its ligand, PD-L1, leads to the transmission of suppressive signals into T cells and the induction of peripheral immune tolerance [7]. PD-L1 is aberrantly expressed in various tumors, allowing them to escape from host immune surveillance.

Administration of anti-CTLA-4 mAb and anti-PD-1/PD-L1 mAb can abrogate these inhibitory mechanisms and restore the ability of T cells to attack tumors [8].

15.4 Biomarker of ICIs

Recently, an increasing number of predictive biomarkers, such as tumor mutation burden (TMB), PD-L1, and mismatch repair defect (dMMR)/microsatellite instability (MSI), have been used in immunotherapy research.

TMB refers to the total number of substitution and insertion/deletion mutations per megabase in the exon coding region of the gene being evaluated in the tumor cell genome [9]. Interest in TMB has increased, as tumors with higher TMB can be more responsive to ICI therapies, which may be due to their increased inherent immunogenicity [10]. PD-L1 can be expressed not only by tumor cells but also by immune cells, including myeloid cells and lymphocytes. PD-L1 status is recognized as a predictive marker of response to ICIs in some tumor types (notably, non-small cell lung cancer) [11]. High microsatellite instability (MSI-H) is an important biomarker for predicting the effect of ICIs on advanced solid tumors. MSI-H is detected in various cancers [12], but its frequency varies by cancer type and stage and the frequency in pancreatic and biliary tract cancer remains at a small percentage [13]. Immune-related adverse events (irAEs) are common during ICI treatment and reported to be associated with good survival [14].

15.5 Tumor Microenvironment

ICIs have revolutionized the treatment of cancers that are naturally immunogenic by enabling the infiltration of T cells into the tumor microenvironment (TME). Tumors possessing complex immunosuppressive TMEs, such as pancreatic cancers, present unique therapeutic obstacles, as response rates to ICIs remain low [15]. In contrast to many other solid tumors, intratumoral effector T cells are rare in pancreatic cancer, which is associated with a massive infiltration of immunosuppressive leukocytes into the TME. Moreover, the development of pancreatic cancer is associated with a strong desmoplastic reaction consisting of multiple cell types, molecular factors, and extracellular matrix. The resulting extensive stroma is just a passive barrier for the immune system [16].

Improved efficacy of both anti-PD-1 and anti-CTLA-4 was achieved by inducing tumor-infiltrating lymphocytes (TILs) [17] and reprogramming immunosuppressive tumor-associated macrophages (TAMs) [18].

Recently, it has been noted that a series of 7 steps, the Cancer-Immunity Cycle (release of cancer cell antigens, cancer antigen presentation by dendritic cells, priming and activation by T cells, trafficking of T cells to tumors by cytotoxic T lymphocytes (CTLs), infiltration of T cells into tumors, recognition of cancer cells by T cells, and killing of cancer cells), is needed to ensure an effective immune response [19]. For this reason, ICI combination therapies have been examined in a variety of cancers, such as hepatocellular carcinoma [20].

15.6 ICIs in Pancreatic Cancer

Pancreatic cancer is unique from an immunological perspective. First, intratumoral effector T cells are rare [21]. The development of pancreatic cancer is associated with a strong desmoplastic reaction that consists of multiple cell types, molecular factors, and extracellular matrix [16]. This dense desmoplastic stromal reaction is

one of the hallmarks of pancreatic cancer and plays a pivotal role in promoting angiogenesis and evasion of immune cells [21, 22]. In the area of ICIs, both CTLA-4 and PD-L1 inhibitors were investigated in patients with locally advanced or metastatic pancreatic cancer in two clinical trials. The clinical outcomes were disappointing, although only small number of patients were treated in both trials [23, 24].

15.6.1 Anti-PD-L1 Antibody

15.6.1.1 BMS-936559

Programmed cell death protein 1, a T cell co-inhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host's immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. Antibody-mediated blockade of PD-L1 (BMS-936559) induced durable tumor regression (objective response rate (ORR) of 6–17%) and prolonged stabilization of disease (rates of 12–41% at 24 weeks) in patients with advanced cancers, including non-small-cell lung cancer, melanoma, and renal cell cancer. In this trial, 14 patients with pancreatic cancer were included, but there was no response [23].

15.6.2 Anti-CTLA-4 Antibody

15.6.2.1 Ipilimumab

Ipilimumab can mediate immunologic tumor regression in other histologies. A phase II trial evaluated the efficacy of ipilimumab for advanced pancreatic cancer. The subjects were adults with locally advanced or metastatic pancreatic cancer with measurable disease, good performance status, and minimal comorbidities. Ipilimumab was administered intravenously (3.0 mg/kg every 3 weeks; 4 doses/course) for a maximum of 2 courses. Twenty-seven subjects were enrolled (20 with metastatic disease and 7 with locally advanced disease). Three subjects experienced ≥ grade 3 irAEs (colitis, 1; encephalitis, 1; hypophysitis, 1). There were no responders according to the response evaluation criteria in solid tumors criteria [24].

15.6.3 Anti-PD-L1 Antibody Plus Anti-CTLA-4 Antibody

15.6.3.1 Durvalumab Plus Tremelimumab

In a randomized phase 2 study of durvalumab plus tremelimumab and durvalumab monotherapy, the ORR was 0% for patients receiving the monotherapy. The ORR was 3.1% for patients receiving the anti-PD-L antibody plus tremelimumab therapy, and it did not proceed to an additional cohort [25].

15.6.4 Combination with a Cytotoxic Agent

15.6.4.1 Nivolumab

FOLFIRINOX and gemcitabine plus nab-paclitaxel are the standard of care. Regarding immune-oncology (IO) with cytotoxic combination therapy in lung cancer, IO with these combination regimens is desirable. An open-label, phase I trial of nivolumab plus *nab*-paclitaxel and gemcitabine in patients with locally advanced/metastatic pancreatic cancer has been reported. The safety profile of nivolumab plus *nab*-paclitaxel and gemcitabine at standard doses in advanced pancreatic cancer was manageable, with no unexpected safety signals. However, the median progression-free survival (PFS) and OS were 5.5 and 9.9 months, respectively. The ORR was 18%. The median PFS and OS were 5.5 and 9.7 months for PD-L1 <5% and 6.8 and 11.6 months for PD-L1 ≥5%, respectively. Unfortunately, the efficacy was not as good as expected [26].

15.6.4.2 Durvalumab with Tremelimumab

The randomized phase II study was conducted to assess the efficacy and safety of durvalumab with tremelimumab plus *nab*-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer. The study randomized 180 patients in a 2:1 ratio. The primary endpoint is OS; secondary endpoints include PFS, safety, and ORR. There was no significant difference in OS (hazard ratio (HR) = 0.94, 90% confidence interval (CI) 0.71–1.25, $p = 0.72$). The median OS was 9.8 months and 8.8 months. ORR was not significantly different, 30.3% versus 23.0%, respectively. The addition of dual ICIs to *nab*-paclitaxel and gemcitabine did not result in a significant improvement [27].

15.6.5 Combination with Radiation

Combination of an ICI with radiation is known to promote the immune cycle [19], and synergistic effects are expected. A phase I study to evaluate the safety of an ICI with stereotactic body radiation therapy (SBRT) in patients with metastatic pancreatic cancer has been reported. The combination of the ICI and SBRT has an acceptable safety profile and has shown a modest treatment benefit in patients with metastatic pancreatic cancer [28].

15.6.6 Ongoing Trials

Noteworthy ongoing trials for pancreatic cancer are shown in Table 15.1.

Table 15.1 Noteworthy ongoing trials for pancreatic cancer

Drug	Target	Line	Phase	Trial number
Pembrolizumab/Lenvatinib	PD-1	2	2	NCT03797326
Nivolumab/ipilimumab/radiation	PD-1 CTLA-4	1	2	NCT04361162
Durvalumab/radiation	PD-L1	Neoadjuvant	2	NCT03572400

PD-1 programmed cell death protein 1, *PD-L1* programmed cell death protein ligand 1, *CTLA-4* cytotoxic T lymphocyte antigen 4

15.7 ICIs in Biliary Tract Cancer

Compared with pancreatic cancer, more trials are conducted of IO monotherapies and IO combination therapies; however, positive results have not been shown without obvious reasons.

15.7.1 Anti-PD-1 Antibody

15.7.1.1 Pembrolizumab

Data from patients with advanced biliary tract cancer receiving pembrolizumab in the KEYNOTE-158 (phase 2) and KEYNOTE-028 (phase 1b) studies have been reported. PD-L1-positive tumors were required for eligibility in KEYNOTE-028 only. The primary efficacy endpoint was the ORR. KEYNOTE-158 enrolled 104 patients, and KEYNOTE-028 enrolled 24 patients. In KEYNOTE-158, the ORR was 5.8%, and the median duration of response (DOR) was not reached (range, 6.2–26.6 months). Median OS and PFS were 7.4 and 2.0 months. Among PD-L1-expressers ($n = 61$) and PD-L1-nonexpressers ($n = 34$), the ORRs were 6.6% and 2.9%, respectively. In KEYNOTE-028, the ORR was 13.0%, and the median DOR was not reached (range, 21.5–53.2+ months). Median OS and PFS were 5.7 and 1.8 months [29].

15.7.1.2 Nivolumab

A multicenter, open-label, phase 1 trial of nivolumab has been conducted in Japan. Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens received nivolumab monotherapy (240 mg every 2 weeks) in the monotherapy cohort. The median OS for the monotherapy cohort was 5.2 months, and the median PFS was 1.4 months; 3.3% of the patients had an objective response. The efficacy of nivolumab was limited [30].

A multicenter phase 2 study of nivolumab, in which 54 patients with histologically confirmed biliary tract cancer and disease progression while undergoing treatment with at least 1 line but no more than 3 lines of systemic therapy, has also been conducted. An independent central review found an ORR of 11%, including 1 unconfirmed partial response, with a disease control rate (DCR) of 50%. Among the intention-to-treat population, the median PFS was 3.7 months, and the median OS was 14.2 months. PD-L1 expression in tumors was associated with prolonged PFS (HR, 0.23; 95% CI, 0.10–0.51; $P < 0.001$).

15.7.2 Dual Checkpoint Inhibition

15.7.2.1 Nivolumab Plus Ipilimumab

CA209-538 (NCT02923934) is a multicenter phase 2 study conducted in Australia. Dosing corresponded to the “Nivo3/Ipi1” regimen, in which nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg are administered every 3 weeks for a total of 4

doses, followed by nivolumab monotherapy every 2 weeks. The ORR in the biliary tract cancer subgroup analysis was 23%, and the DCR was 44%. The median PFS and OS were 2.9 and 5.7 months, respectively [31]. The ORR was better, but the DCR was not so good.

15.7.3 Combination with a Cytotoxic Agent

15.7.3.1 Nivolumab

An open-label, phase 1 trial evaluated the clinical efficacy of nivolumab in combination with the standard of care, the combination chemotherapy of gemcitabine and cisplatin (GemCis), as the first-line treatment in Japanese patients. The median OS was 15.4 months, and the median PFS was 4.2 months; 37% of patients had an objective response. The response rate seemed to be higher than previous GemCis results [30].

15.7.3.2 Durvalumab with and Without Tremelimumab

Combinations of GemCis and the anti-PD-L1 antibody durvalumab with and without the anti-CTLA-4 antibody tremelimumab were presented at ASCO 2020. The combinations yielded very promising efficacy, with a DCR of 100%, a median PFS of 11.0 months, and a median OS of 18.1 months in the durvalumab arm and a DCR of 98%, a median PFS of 11.9 months, and a median OS of 20.7 months in the durvalumab/tremelimumab arm in combination with GemCis, respectively. PD-L1 expression prior to treatment was not associated with immunotherapy efficacy.

15.7.4 Antiangiogenic Therapy

15.7.4.1 Ramucirumab

Antiangiogenic therapies targeting vascular endothelial growth factor receptor (VEGFR) or VEGF receptor-2 (VEGFR2) have been shown to increase T cell trafficking into tumors and to reduce immunosuppressive cytokines and regulatory T cells. VEGFR-directed therapies may thus help to overcome resistance to ICIs [32]. The safety and efficacy of the IgG1 VEGFR-2 antagonist ramucirumab with the IgG4 PD-1 antagonist pembrolizumab were examined in biomarker-unselected patients with previously treated advanced or metastatic biliary tract cancer [33].

15.7.4.2 Lenvatinib

Lenvatinib plus pembrolizumab has demonstrated a relatively high antitumor response in several solid tumors. In a Chinese biliary tract cancer cohort, the ORR was 25%, and the DCR was 78.1%. As a non-first-line therapeutic regimen, the median PFS was 4.9 months, and the median OS was 11.0 months [34].

Table 15.2 Noteworthy ongoing trials for biliary tract cancer

Drug	Target	Line	Phase	Trial number
Pembrolizumab/GemCis (KN-966)	PD-1	1	3	NCT04003636
Durvalumab/GemCis (TOPAZ-1)	PD-L1	1	3	NCT03875235
Bintrafusp alfa/GemCis	TGF-β, PD-L1	1	2/3	NCT04066491
KN 035/GEM oxaliplatin	PD-L1	1	3	NCT03478488

PD-1 programmed cell death protein 1, *PD-L1* programmed cell death protein ligand 1, *TGF-β* the transforming growth factor β, *GemCis* the combination chemotherapy of gemcitabine and cisplatin, *GEM* gemcitabine

15.7.5 Transforming Growth Factor β (TGF-β)

15.7.5.1 TGF-β Plus PD-L1

Bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the transforming growth factor βRII (TGF-βRII) receptor fused to a human IgG1 antibody blocking PD-L1, has shown clinical efficacy. In a phase I, open-label trial expansion cohort, the ORR was 20%. The median PFS and OS were 2.5 months and 12.7 months, respectively [35].

15.7.6 Ongoing Trials

Noteworthy ongoing trials for biliary tract cancer are shown in Table 15.2.

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Treatment Approach for Pancreatic Cancer with Peritoneal Dissemination

16

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Abstract

The median survival time (MST) of patients with pancreatic ductal adenocarcinoma with distant organ metastasis is poor, at less than 12 months, even with modern chemotherapy regimens. The MST of patients with peritoneal dissemination ranges from 6 weeks to 3 months because of poor performance status due to various symptoms. The diagnostic performance of imaging studies has limitations because it is difficult to detect small peritoneal nodules and perform cytological examination. Therefore, staging laparoscopy is mandatory for the accurate diagnosis of occult peritoneal dissemination.

Recent studies have revealed that the MST of patients who received systemic chemotherapy varied from 4 to 13 months. Results of a phase II study of systemic and intraperitoneal chemotherapy demonstrated an MST of 15–16 months and a conversion surgery rate of 17%–24%, which represent a strong potential to improve quality of life and overall survival. Currently, a phase III trial to investigate the clinical efficacy of systemic and intraperitoneal chemotherapy is ongoing (jRCTs051180199). Since a lack of evidence remains regarding the natural history, definitive diagnosis, and appropriate treatment, sustainable efforts are warranted to support patients with pancreatic ductal adenocarcinoma with peritoneal dissemination who have poor quality of life and a high risk of death.

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16.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) continues to have a dismal prognosis, with a 5-year survival rate of <10%, even in the modern era [1, 2]. The median survival time (MST) of patients with distant organ metastasis is poor, at less than 12 months, even after administration of modern chemotherapy regimens, such as FOLFIRINOX [3] and gemcitabine+nab-paclitaxel [4]. Among patients receiving those regimens, the MST of patients with peritoneal dissemination is extremely poor, reported as 6 weeks in a population-based study in the Netherlands by Thomassen et al. [5], 3 months in a population-based study in the Netherlands by Mackay et al. [6], and 7 weeks in a series of 73 patients with malignant ascites in Japan by Takahara et al. [7].

Peritoneal dissemination can be defined as macroscopic (presence of a nodule or omental cake) or microscopic (positive ascitic fluid for peritoneal washing cytology) disease.

The population-based study from the Netherlands [5] carried out between 1995 and 2009 revealed that patients diagnosed with peritoneal dissemination represented 9.1% of the total of 2924 patients with a condition diagnosed as nonendocrine pancreatic cancer. In some patients, the peritoneal cavity was the only metastatic site (3.9% of total), whereas 152 patients (5.2%) also presented with metastases at other locations. Updated data showed that between 2005 and 2015, peritoneal dissemination was diagnosed in 7.7% of 19,098 patients with PDAC, and the MST in patients with peritoneal dissemination was 3.4 months for tumors in the pancreatic head, 2.3 months for tumors in the pancreatic body, and 2.2 months for tumors in the pancreatic tail [6].

Peritoneal dissemination in PDAC is associated with a variety of conditions, such as positive peritoneal washing cytology in resectable PDAC, massive ascites, obstructive ileus, or urethral obstruction due to peritoneal nodules and formation of omental cake. Patients with peritoneal dissemination generally have numerous symptoms, such as abdominal fullness, appetite loss, abdominal pain, constipation, and oliguria. The presence of these symptoms leads to poor performance status, which in turn deprives the patients of the opportunity to receive systemic chemotherapy.

In this chapter, we review the diagnostic and treatment approaches in patients with macroscopic and microscopic peritoneal dissemination to clarify the current status of this disease entity in the real world.

16.2 Diagnostic Approach to Peritoneal Dissemination

A systematic review and meta-analysis revealed that computed tomography (CT) should be preferred to magnetic resonance imaging for detecting peritoneal metastases [8]. However, staging laparoscopy diagnosed peritoneal dissemination in 7%–19% of patients with locally advanced PDAC defined using contrast-enhanced multi-detector row CT [9, 10]. Those authors suggested that the diagnostic performance of CT had limitations because it is difficult to detect small peritoneal nodules and perform cytological examinations. Ta et al. [11] reported in a meta-analysis that with staging laparoscopy, occult peritoneal dissemination was found in 19% of 367 patients with PDAC. Karabicak et al. [9] reported that staging laparoscopy diagnosed peritoneal dissemination consisting of positive cytology (no peritoneal nodules) in 23% and peritoneal nodules in 19% of 110 patients with radiographically defined unresectable locally advanced PDAC. They suggested that PDAC located in the pancreas body-tail and tumor size >42 mm were risk factors for peritoneal dissemination, and 65.4% of patients with these factors had peritoneal dissemination. Clark et al. [12] also reported that staging laparoscopy upstaged 58 of 202 patients with unresectable locally advanced PDAC (29%) to stage IV, which consisted of microscopic peritoneal dissemination in 20% (n = 41), macroscopic peritoneal dissemination in 3% (n = 5), and hepatic metastases in 13% (n = 26). Takadate et al. [13] revealed the presence of microscopic peritoneal dissemination during staging laparoscopy in 24% (n = 10) of patients with resectable disease (n = 42), 22% (n = 11) of patients with the borderline resectable disease (n = 49), and 38% (n = 21) of patients with unresectable locally advanced disease (n = 55). Moreover, staging laparoscopy showed the presence of macroscopic peritoneal dissemination during staging laparoscopy in 0% of patients with resectable disease, 6% (n = 3) of patients with borderline resectable disease, and 11% (n = 6) of patients with unresectable locally advanced disease. Thus, the proportion of patients with peritoneal dissemination increased according to PDAC resectability status, and staging laparoscopy is mandatory for more accurate diagnosis.

16.3 Treatment Approach for Peritoneal Dissemination

Patients with peritoneal dissemination display a variety of symptoms, and their stages may range from microscopic peritoneal dissemination to massive ascites, multiple sites of macroscopic peritoneal dissemination, or development of omental cake. Important goals of treatment should be to control developing ascites and to improve survival in patients with PDAC with peritoneal dissemination who have poor quality of life and a dismal prognosis.

16.3.1 Systemic Chemotherapy

Use of FOLFIRINOX [3], gemcitabine+nab-paclitaxel [4], gemcitabine [14], S-1 [15] or gemcitabine+erlotinib [16] has been recommended in patients with metastatic PDAC. Takahara et al. [7] investigated the clinical role of systemic chemotherapy in patients with malignant ascites (microscopic peritoneal dissemination). Overall survival (OS) was significantly longer in 21 patients (performance status 0–2) receiving chemotherapy than in 35 patients receiving best supportive care alone (124 vs. 50 days, $p < 0.01$). In a multivariate analysis, chemotherapy was a significant independent prognostic factor, in addition to performance status, CRP, and small amount of malignant ascites. Bonnet et al. [17] reported the clinical course of 48 patients with PDAC with peritoneal dissemination combined with liver (62.5%) and lung (31.3%) metastases diagnosed using CT or integrated positron emission tomography. The MST in 36 patients who received FOLFIRINOX treatment was favorable, at 13.2 months.

Using staging laparoscopy of 67 patients who had radiographically defined unresectable locally advanced PDAC, we found microscopic peritoneal dissemination in 16 patients (24%), macroscopical peritoneal dissemination in 13 patients (19%), liver metastasis in 10 patients (15%), and locally advanced disease in 28 patients (42%) [18]. Development of ascites within 1 year after initial treatment was found most frequently in patients with macroscopic peritoneal dissemination (11 of 13 patients, 85%), which was higher than in the other three groups. The duration of gemcitabine or S-1 based chemotherapy and proportion of second-line chemotherapy in patients with macroscopic peritoneal dissemination was shorter than in the other groups. The MST was 13 months in patients with microscopic peritoneal dissemination, 11 months in patients with locally advanced disease, and 7 months in patients with macroscopic peritoneal dissemination or liver metastasis.

Recent studies revealed that MST varied from 4 to 13 months according to the status of peritoneal dissemination and seemed to be prolonged in patients with good performance status who received systemic chemotherapy [7, 17, 18]. In particular, FOLFIRINOX can be expected to be effective, even in patients with peritoneal dissemination.

16.3.2 Systemic and Intraperitoneal Chemotherapy

Pharmacokinetic studies revealed that anticancer drugs administered systemically do not necessarily enter the peritoneal cavity. Compared with systemic chemotherapy, intraperitoneal (i.p.) chemotherapy appears to be advantageous for the treatment of peritoneal dissemination due to a high drug concentration in the peritoneal cavity to directly contact tumor nodules. Results of clinical studies of i.p. paclitaxel (PTX) in patients with ovarian cancer [19, 20] and gastric cancer [21, 22, 23] with peritoneal dissemination have been favorable. Kamei et al. [24] demonstrated that the i.p. administration of PTX nanoparticles in mice resulted in high accumulation in disseminated nodules, presumably due to its superior penetrating activity directly

into malignant tissue. Most notably, Ishigami et al. [25] conducted a phase III study of weekly intravenous (i.v.) and i.p. PTX plus S-1 compared with S-1 plus cisplatin in gastric cancer with peritoneal dissemination. This trial, unfortunately, failed to show the statistical superiority of i.p. PTX plus systemic chemotherapy owing to a crucial imbalance in the high amount of ascites in the experimental group and the crossover use of i.p. therapy in the control group. However, an exploratory analysis suggested possible clinical benefits of i.p. PTX for gastric cancer based on a sensitivity analysis adjusted for baseline ascites and in the per-protocol set that excluded patients with post-protocol treatment violations. Moreover, the patients who received i.p. chemotherapy showed a high proportion (78%) of negative conversion on peritoneal cytology. The investigators stated that considering the results of these analyses, the efficacy of the i.p. regimen seemed underestimated by the primary analysis as a result of the unexpected imbalance in the amount of ascites and the crossover from systemic chemotherapy to i.p. chemotherapy.

Thus, i.p. chemotherapy using PTX is considered an ideal therapeutic approach for peritoneal dissemination from the viewpoint of drug delivery. In the area of PDAC with peritoneal dissemination, several clinical studies have been conducted since 2016 in Japan to investigate a clinical role of i.p. chemotherapy, as shown in Table 16.1.

Takahara et al. [26] first reported the clinical effectiveness of combination chemotherapy consisting of i.v. and i.p. PTX with S-1 in 35 gemcitabine-refractory patients with PDAC with malignant ascites. The regimen showed a median OS of 4.8 months, a median progression free survival (PFS) of 2.8 months, a response rate of 8% and a disease control rate of 69%. Malignant ascites had disappeared or decreased in 69% of patients, including complete resolution in 15% and a negative change in cytological status in 31% of patients. The major grade 3/4 adverse events included neutropenia (34%), anemia (31%), nausea (9%), and catheter-related infections (6%).

We conducted a retrospective study to compare OS in patients with macroscopic and microscopic peritoneal dissemination without other distant organ metastases who received systemic chemotherapy ($n = 29$) or S-1 combined with i.v. and i.p. PTX chemotherapy ($n = 20$) [27]. The OS, response rate, ascites development rate, and conversion surgery rate in the i.p. group were significantly better than those in the systemic chemotherapy group. Implementation of the S-1 + i.v./i.p. PTX regimen was closely associated with improved OS and quality of life in patients with PDAC with peritoneal dissemination.

Moreover, a multicenter phase II study of S-1 combined with i.v. and i.p. PTX chemotherapy was conducted in 33 patients with macroscopic and microscopic peritoneal dissemination without other distant organ metastases [28]. The MST and the 1-year survival rate were 16.3 months and 62%, respectively. The response rate and disease control rate were 36% and 82%, respectively. Surprisingly, eight patients (24%) underwent conversion surgery after confirmation of no macroscopic and microscopic peritoneal dissemination on staging laparoscopy, and their OS was significantly higher than that of non-surgical patients. Grade 3/4 hematologic toxicities occurred in 42% of patients, and non-hematologic adverse events occurred in 18%.

Table 16.1 Summary of articles on the clinical role of intraperitoneal chemotherapy with paclitaxel

Authors	Study period	Number of patients	Study design	Entry criteria	Systemic chemotherapy	OS/PFS (months)	Response rate (%)	Negative conversion rate of peritoneal cytology (%)	Conversion surgery rate (%)
Takahara [26]	2011–14	35	Pros cohort	Gem-refractory malignant ascites	S-1 + PTX	4.8/2.8	8	31	NA
Satoi [27]	2007–14	IP 20 vs. sCTx 29	Retro	PM alone	S-1 + PTX vs. sCTx	20/13.5 vs. 10/6.8	45 vs. 28	90	30 vs. 7
Satoi [28]	2012–15	33	Phase II	PM alone	S-1 + PTX	16.3/NA	36	55	24
Takahara [29]	NA	12	Phase I	Chemo-naïve PM[a]	Gem+nab-PTX	NA/5.4	25	67	8.3 (1/12)
Yamada [30]	2016–18	50	Phase I/II	PM alone	Gem+nab-PTX	14.5/NA	49	39	17

OS overall survival, *PFS* progression free survival, *Pros* prospective, *Gem* Gemcitabine, *PTX* paclitaxel, *NA* not available, *IP* intraperitoneal chemotherapy, *sCTx* systemic chemotherapy, *Retro* retrospective, *PM* peritoneal dissemination

[a]Irrespective of the primary and extraperitoneal tumor status

Complications related to the peritoneal access device presented as infection of the i.p. catheter in one patient and dislocation of the device in two patients.

Very recently, results of two-phase I trials of gemcitabine+nab-PTX combined with i.p. PTX were published from Japan [29, 30]. Takahara et al. [29] recommended gemcitabine doses of 1000 mg/m^2, nab-PTX doses of 125 mg/m^2, and i.p. PTX doses of 30 mg/m^2 in chemo-naïve patients with peritoneal dissemination, irrespective of the primary and extraperitoneal tumor status. Yamada et al. [30] also recommended gemcitabine doses of 800 mg/m^2, nab-PTX doses of 75 mg/m^2, and i.p. PTX of doses 20 mg/m^2 in patients with peritoneal dissemination alone without other distant organ metastases. The difference in the recommended doses between the two studies may be explained by a difference in age [29, 56 (42–74), 30, 69 (47–79)]. The subsequent phase II study by Yamada et al. 2020 [30] revealed a favorable MST of 14.5 months with a response rate of 49%, a negative conversion rate of peritoneal cytology of 39%, and a conversion surgery rate of 17% in 46 patients. Grade 3–4 hematological and non-hematological toxicities developed in 76% and 15% of patients, respectively. Peritoneal port trouble was found in 30% of patients (grade 3/4, one patient).

Taken together, these findings suggest that i.p. PTX regimens can provide promising clinical efficacy with acceptable tolerability. The specific events associated with i.p. chemotherapy were peritoneal port trouble, such as dislocation, infection, and leakage out of the peritoneal port, which ranged from 6% to 30% in total, but severe events were rare.

In summary, systemic and i.p. chemotherapy have the potential to improve quality of life and overall survival in patients with PDAC with peritoneal dissemination and without other distant organ metastases. Limited treatment effects may be expected in patients with massive ascites, poor performance status, or other distant organ metastases.

Currently, a multicenter phase III trial to investigate the clinical efficacy of S-1 + i.v./i.p. PTX relative to gemcitabine+nab-PTX is ongoing (jRCTs051180199; https://jrct.niph.go.jp/). It is important to note that the use of i.p. chemotherapy and PTX is currently off-label in Japan.

16.3.3 Hyperthermic Intraperitoneal Chemotherapy

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has been successfully implemented in selected patients with peritoneal dissemination from colon cancer, pseudomyxoma peritonei, gastric cancer, and ovarian cancer at specialized centers in Western countries [31, 32]. Case series only exist in patients with PDAC with peritoneal dissemination [33, 34, 35]. Farma et al. [33] reported peri-operative morbidity in 56% and mortality in 5.6%, and Tentes et al. [34] reported mortality in two of eight patients. Thus, evidence is still lacking for the use of cytoreductive surgery and HIPEC in PDAC.

16.3.4 Pressurized Intraperitoneal Aerosol Chemotherapy

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been proposed as a novel minimally invasive treatment for patients with peritoneal dissemination. PIPAC can provide easier repeat application, lower morbidity, and better quality of life relative to HIPEC. Intraperitoneal administration of the drug has pharmacokinetic advantages, such as higher intra-tumoral concentrations and less systemic toxicity. Pressurized vaporization can provide better distribution and penetration of the drug, relative to i.p. chemotherapy. Grass et al. [36] reviewed 16 preclinical studies and 13 clinical studies (none of which was a randomized trial). Preclinical data suggested better distribution and higher tissue concentrations of chemotherapy agents with PIPAC compared with conventional intraperitoneal chemotherapy by lavage. The investigators concluded that PIPAC was feasible, safe, and well tolerated. Moreover, a systematic review by Alyami et al. [37] revealed that PIPAC provided an objective clinical response rate of 62%–88% in patients with ovarian cancer (MST of 11–14 months), 50%–91% in patients with gastric cancer (MST of 8–15 months), 71%–86% in patients with colorectal cancer (MST of 16 months), and 67%–75% (MST of 27 months) in patients with peritoneal mesothelioma. Conclusively, PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, the investigators noted that its use in further indications needed to be validated by prospective studies. Some retrospective case series of patients with PDAC with peritoneal dissemination have been published [38, 39, 40, 41]. They reported that PIPAC was feasible and safe, and the MST ranged from 9.2 to 14.0 months. Although a lack of evidence remains in this area, several prospective studies are ongoing in Europe. Reliable results should be available within the next 5–10 years.

16.3.5 Future Perspectives

Patients with peritoneal dissemination have a dismal prognosis and poor quality of life due to massive ascites, obstructive ileus, or urethral obstruction due to peritoneal nodules and formation of omental cake. Evidence of actual morbidity is lacking because there are no definite diagnostic criteria. Since selective use of staging laparoscopy during the diagnostic process is mandatory for accurate diagnosis, a diagnostic algorithm should be established for peritoneal dissemination. Although systemic chemotherapy, such as FOLFIRINOX, may prolong survival in the limited number of patients with good performance status, it is not good enough, especially for controlling the development of ascites. Results of a phase II study of systemic and i.p. chemotherapy revealed an MST of 15–16 months and a conversion surgery rate of 17%–24%, which represent a strong potential to improve quality of life and overall survival in patients with PDAC with peritoneal dissemination without other distant organ metastases. Currently, a multicenter phase III trial to investigate the clinical efficacy of S-1 + i.v./i.p. PTX relative to gemcitabine+nab-PTX is ongoing (jRCTs051180199; https://jrct.niph.go.jp/). Moreover, encouraging survival data

and acceptable feasibility and safety with the use of PIPAC have been reported in patients with colorectal, gastric, and ovarian cancers. A well-designed clinical trial of PIPAC is greatly expected even in patients with PDAC in the near future.

We should be aware of the presence of various subsets in this population, ranging from occult disease to massive ascites with multiple peritoneal nodules that is easily diagnosed with CT. When clinical trials are conducted, the target population of patients with peritoneal dissemination should be clarified.

Since a lack of evidence remains regarding the natural history, definitive diagnosis, and appropriate treatment, sustainable efforts are warranted to support patients with PDAC with peritoneal dissemination who have a poor quality of life and a high risk of death. Currently, a clinical practice guideline for peritoneal malignancy is in preparation for publication in Japan.

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Treatment Strategies for Frail and Elderly Patients with Pancreatic Cancer

17

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Abstract

The risk of cancer increases with age, and the need of cancer treatments are dramatically increasing in the super-aged society. Comprehensive Geriatric Assessment is an approach that provides comprehensive medical care by evaluating in detail the physical, mental, and social functions of patients. It is also important to make an intervention plan and follow-up over the long term. The NCCN guidelines for older adults indicate an approach to decision-making based on life expectancy, the ability of decision-making, and patients' goals. As pancreatic cancer increases with age, we should consider the process of decision-making for vulnerable and elderly patients.

Keywords

Elderly · Frail · Comprehensive geriatric assessment · Functional status Comorbidity · Polypharmacy · Cognition · Nutrition · Decision-making

17.1 Introduction

More than 50% of patients newly diagnosed with cancer are 65 years and older. Age is a risk factor for cancer, and physiologic changes with aging imply reduced life expectancy and limited tolerance to cancer treatment. Although the number of elderly patients is increasing with aging society, there is less evidence of the standard treatment for older patients with cancer. For patients with low-performance status (PS) or vulnerabilities, who are ineligible for a clinical trial, there is few

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evidence for standard treatment [1]. As elderly patients are under-represented in clinical trials of cancer treatment, few evidence-based information is contributed for treatments of elderly patients [2]. Furthermore, there is heterogeneity in the aging process, and it is complex to decide cancer treatment for elderly patients.

17.2 Geriatric Assessment

Comprehensive Geriatric Assessment (CGA) is an approach that provides comprehensive medical care by evaluating in detail the physical, mental, and social functions of patients that affect cancer prognosis in older patients [3]. CGA includes evaluation of physical function, comorbidities, medications, nutritional status, cognitive function, mood, social support, and geriatric syndrome (falls, delirium, incontinence, osteoporosis, etc.) [3, 4]. In addition, it is important to make an intervention plan and follow-up over the long term [3]. This approach has been established in the field of geriatrics and has been shown to improve clinical outcomes by addressing identified problems, including reduced mortality, maintenance of physical function, and reduced readmission rates.

On the other hand, in the oncology setting, there is no specialized intervention or evaluation over time, and the research and development goals emphasized the prediction of adverse events and the decision of treatment policy [3].

CGA is also recommended in the field of oncology setting [3–5]. It is thought that by implementing geriatric assessment (GA), it is possible to discover issues specific to the elderly that are difficult to grasp in daily medical care, pick up patients who need palliative treatment, and predict adverse events and prognosis due to cancer treatment [3].

17.2.1 Functional Status

In cancer treatment, the PS scale (The Karnofsky Performance Status, ECOG Performance Status) is widely used for the evaluation of physical function. PS is a prognostic factor for cancer, but the presence of comorbidities often makes it difficult to assess PS, and it is considered unreliable in the elderly [6]. It has also been reported that the attending physician has not fully evaluated the factors that affect the functioning of the elderly [7].

On the other hand, Activity of Daily Living (ADL) and Instrumental Activity of Daily Living (IADL) are used to measure functional status, which are evaluation methods based on patient reports [8, 9]. Gait speed and Time up and Go (TUG) which are evaluation methods for measuring actual movements. ADL assesses the ability to put on and take off clothes, excrete, eat, go to bed, and get up from a chair without assistance. IADL evaluates basic activities for living an independent social life, such as shopping, housework, laundry, money management, movement, telephone, and medication management. Evaluation of functional status has been reported to be associated with the tolerability and prognosis of chemotherapy in elderly cancer patients [10, 11].

17.2.2 Comorbidities

Comorbidities increase with age, and it leads to increased complications of cancer treatment. Therefore, the severity and treatment status of comorbidities affect the therapeutic effect and adverse reactions of elderly cancer patients [12, 13]. Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale (CIRS) are performed to estimate the risks of comorbidities [14, 15]. In a study of elderly patients with advanced non-small cell lung cancer, increased comorbidity scale of CCI was associated with shorter survival [16].

17.2.3 Polypharmacy

As the number of comorbidities increases, so does the amount of oral medication. In carrying out systemic chemotherapy, drug interactions with concomitant drugs may diminish the therapeutic effect or exacerbate adverse events. Polypharmacy means not only a large number of drugs taken but also a condition that leads to problems such as the increased risk of adverse drug reactions, incorrect medication and decreased drug adherence. Elderly people are at high risk because they often have medical conditions requiring pharmacotherapy [17].

It has been reported that adverse events increase with the use of more than one drug, and polypharmacy is suspected in the multidrug combination of five drugs [18].

17.2.4 Cognition

Patients with cognitive impairment are increases with age, and a comprehensive multidisciplinary approach is important for proper care [19]. The Blessed Dementia Rating Scale [20], MMSE [21], Mini-Cog [22] are studied as a screening tool.

17.2.5 Nutrition

Malnutrition or poor nutritional status is an increased risk of severe hematologic toxicities, increased risk of mortality after chemotherapy [23]. Weight loss is sometimes observed in elderly patients, and a marker for poor nutritional status.

17.2.6 Geriatric Assessment Tools

While we could use many GA tools for assessment, the Expert Panel recommends IADLs for function, validated tools for comorbidity, a question for falls, the Geriatric Depression Scale (GDS) to screen for depression, the Mini-Cog or the Blessed Orientation-Memory-Concentration (BOMC) test to screen for cognitive impairment, and weight loss for assessment of nutrition [4]. G8/VES-13 is originally used

Table 17.1 Domains and scales of geriatric assessments

Domain	Measures	
Physical functions	Performance status	
	Karnofsky self-reported performance rating scale	
	(number of falls in recent 6 months)	
	Timed Up and Go	
	ADL: Ability of Daily Living	MOS-ADL
		Barthel Index
	IADL: Instrumental Ability of Daily Living	FAI: Frenchay Activities Index
Comorbidity	OARS Comorbidity Scale	
	CCI: Charleson Comorbidity Index	
Cognition	Mini-Cog	
	MMSE: Mini Mental State Examination	
	BONC Test	
	Hasegawa Dementia Scale	
	FAB: Fullerton Advanced Balance Scale	
Mood (Psychological)	GDI: Geriatric Depression Scale	
	PHQ: Patient Health Questionnaire	
Nutrition	BMI: Body Mass Index	
Polypharmacy	(Number of Medications)	
Social Functioning and Social Support	MOS Social Support Survey	
	G8 Geriatric Assessment	
Prognosis Expectation	VES-13	
	EQ-5D	

as screening tools for identifying elderly patients who need more comprehensive geriatric assessments and takes 5 minutes to perform [24]. The G8 is composed of eight items from a more comprehensive nutritional measure, the Mini Nutritional Assessment (MNA) [25]. The VES-13 is demonstrated excellent predictive abilities for functional decline in patients with breast cancer [26]. The Expert Panel also recommends G8 or VES-13 could help to predict mortality [4]. Table 17.1 shows geriatric assessment tools.

17.3 Approach to Cancer Treatment for Elderly

As a way of thinking about medical treatment for elderly and vulnerable cancer patients, it is important to consider not only the disease called “cancer” but also the physical, mental, and social vulnerabilities of the patients. The NCCN guidelines indicate an approach to decision-making in the older adult with cancer to provide appropriate treatments and care [5]. It is based on the idea of advancing medical care while always considering the balance between treatment risks and benefits. Furthermore, the flow is recommended to refer NCCN guidelines for the treatment of cancer by the site after establishing assessment of patient’s goals and objectives with regard to his/her cancer diagnosis.

17.3.1 Estimate Life Expectancy and Use It as a Reference for Determining Whether or Not Treatment Is Possible

The NCCN guidelines recommend estimating life expectancy to determine treatment availability. If the patient dies of another disease before the onset of cancer symptoms, it can be suggested to choose follow-up or palliative care without aggressive cancer treatment.

In the United States, ePrognosis (Lee Schonberg Index) is published on the Web based on epidemiological data. This is a simple tool that allows you to estimate the life expectancy of a patient. Enter 15 items such as age, gender, body mass index (BMI), health status, lung disease, cancer history, congestive heart failure, diabetes, smoking history, ability to walk, abilities of money management/bathing/carrying. This predicts the risk of death in 10 years.

17.3.2 Evaluate Decision-Making Ability

In order for appropriate informed consent to be established, it is a prerequisite that the patient has the ability to appropriately judge the content of the explanation from the medical staff.

(A) **Understanding**: A patient can understand the diagnosis and treatment plan explained by the doctor.
(B) **Recognition**: A patient can recognize the current situation (medical situation, cause of illness, needs to treatment) as oneself.
(C) **Logical thinking**: A patient can logically compare the risks and benefits of treatment options proposed by doctors.
(D) **Expression of choice**: A patient can express his choice of cancer treatment by words or other means.

After checking these four items, if it is judged that the decision-making ability is insufficient, we devise appropriate support for the decision-making ability. We can communicate with patients considering in terms of spending a lot of time to explain, using illustrations, attending family and friends, reducing anxiety by psychological support, encouraging contemplation and delaying decisions.

17.3.3 Grasp the Patient's Wishes and Values for Treatment

We should confirm the consistency with the treatment content provided by the medical staff. If the patient is even in good general condition to receive cancer treatment, but does not want intensive treatment, we offer other treatment options.

17.3.4 Evaluate the Risk Using the Elderly Function Evaluation

If problems such as functional deterioration are identified, necessary support interventions will be performed. Propose appropriate treatment methods based on risk assessment.

17.4 Treatment of Elderly Patients with Pancreatic Cancer

Generally, the aims of cancer treatment are prolonged survival and palliation of symptoms. Patients who are fit or feasible for curative treatment can choose surgery, radiation therapy, systemic chemotherapy, and targeted therapies.

Pancreatic cancer frequently occurs in the elderly, and the number of elderly pancreatic cancer patients is increasing rapidly in the face of a super-aged society. Since standard treatment for patients with advanced pancreatic cancer was conducted as a clinical trial in non-elderly patients, there is little evidence for elderly patients with pancreatic cancer, and standard treatment has not been established.

17.4.1 Surgery

As chronologic age alone should not be a determinant for surgical treatment decisions, with adequate perioperative risk stratification, functional assessment, and oncologic prognostication, elderly patients with cancer can do as well as their younger counterparts [27].

Preoperative assessment of cancer in the elderly (incorporates fatigue, IADL, PS, American Society of Anesthesiologist (ASA) grade) represents a valuable tool in enhancing the decision process concerning the candidacy of elderly cancer patients for surgical intervention and can reduce inappropriate age-related inequity in access to surgical intervention [28]. The American College of Surgeons (ACS) Geriatric Surgery Verification (GSV) Program presents 32 new surgical standards designed to systematically improve surgical care and outcomes for elderly patients [29].

17.4.2 Radiation Therapy

Radiation therapy is generally offered for elderly patients in the curative or palliative setting [30]. Stereotactic body radiation therapy (SBRT) has good local control for locally advanced pancreatic cancer with minimal toxicity [31, 32] and is also feasible in elderly patients [33]. International Society of Geriatric Oncology (SIOG) task force reported elderly patients with unresectable pancreatic cancer could undergo SBRT with the expectation of local control and at low toxicity [34].

17.4.3 Systemic Chemotherapy for Unresectable Pancreatic Cancer

A randomized study was conducted with the primary endpoint as a clinical symptom improvement effect (pain, functional impairment, and weight loss) for advanced pancreatic cancer and demonstrated gemcitabine monotherapy is more effective than 5-fluorouracil (5-FU) [35]. Gemcitabine monotherapy has mild adverse events and is well tolerated in the elderly, gemcitabine monotherapy is considered the standard treatment in the elderly.

A phase III randomized controlled trial of FOLFIRINOX shows this combination regimen is an effective first-line treatment option for patients with metastatic pancreatic cancer [36]. As the eligibility criteria in this trial are 75 years or younger and ECOG PS 0-1, the tolerability and efficacy in elderly and poor PS patients are unclear.

In addition, nab-paclitaxel plus gemcitabine (GnP) significantly improved survival and response rate compared to gemcitabine monotherapy [37]. There was no age limit for eligibility criteria in this study, and the GnP therapy group included cases between the ages of 27 and 86 (median: 63 years). Therefore, GnP therapy may be performed for elderly people in consideration of their general condition. However, it is controversial whether GnP therapy should be considered the standard treatment for the elderly with pancreatic cancer. A subgroup analysis of this study indicates the hazard ratio is unfavorable in GnP for the elderly aged 65 and over (hazard ratio 0.81 versus 0.65). Furthermore, the elderly patient who was receiving GnP experienced functional decline.

GnP is reported to be feasible with appropriate dose adjustments and attention to adverse events for elderly patients [38] and showed acceptable toxicities and effectiveness in a multicenter retrospective study [39].

As elderly people are more diverse than non-elderly people, clinical trials for non-elderly patients in good general condition demonstrate little information on the treatment of elderly patients with cancer.

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Part V

Endoscopic Management of Pancreatic Cancer and Cholangiocarcinoma

Endoscopic Diagnosis of Pancreatic Cancer and Cholangiocarcinoma

18

Hideyuki Shiomi, Ryota Nakano, Hassan Atalla, and Yuzo Kodama

Abstract

Early detection and appropriate diagnosis are important for improving the prognosis of pancreatic cancer and cholangiocarcinoma. Endoscopic ultrasonography (EUS) is useful for early detection because it can identify small pancreatic masses that cannot be visualized by other modalities due to its high resolution. In addition, EUS-guided fine needle aspiration (EUS-FNA) has high diagnostic ability and safety, making it indispensable for the definitive diagnosis and evaluation of pancreatic cancer staging. Recently, pancreatic carcinoma in situ with a good prognosis has been reported in Japan. Serial pancreatic juice aspiration cytological examination (SPACE) using endoscopic retrograde cholangiopancreatography (ERCP) is useful for its diagnosis. On the other hand, ERCP is the mainstay for the endoscopic diagnosis of cholangiocarcinoma, but EUS, including intraductal ultrasound (IDUS), plays an essential role in clinical practice. IDUS is excellent not only for detecting bile duct malignancy but also for evaluating Bismuth-type hilar lesions. Cholangioscopy-guided tissue acquisition was superior to ERCP modalities for tissue sampling. Recently, cholangioscopy using easier to maneuver peroral single-operator cholangioscopy has been per-

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formed frequently and is useful for establishing a definitive diagnosis of cholangiocarcinoma. Thus, the endoscope plays an important role in diagnosing pancreatobiliary malignancy, and we need to use different endoscopic modality in a complementary manner depending on the situation.

Keywords

Pancreatic cancer · Cholangiocarcinoma · Endoscopic diagnosis · Endoscopic ultrasonography (EUS) · Endoscopic retrograde cholangiopancreatography (ERCP) · EUS-guided fine needle aspiration (EUS-FNA) · Serial pancreatic juice aspiration cytological examination (SPACE) · Chlangioscopy · Early detection

18.1 Endoscopic Diagnosis of Pancreatic Cancer

18.1.1 Background

Pancreatic cancer has a poor prognosis, with a 5-year survival rate of 8–9%, which is the lowest of all cancers. The reason for this is that early detection is challenging, and at the time of diagnosis, it is already an unresectable advanced cancer. If pancreatic cancer can be detected at an early stage (i.e., less than 2.0 cm), the prognosis is relatively good. Therefore, accurate early diagnosis is crucial for improving the prognosis of pancreatic cancer. With recent advances in endoscopic equipment and technology, endoscopy has become indispensable for the diagnosis and treatment of pancreatobiliary diseases. Among them, endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) play a significant role in the early detection of pancreatic cancer.

EUS is an ultrasound (US) technique in which the tip of the endoscope is equipped with a high-frequency transducer. To observe pancreatic lesions in real-time through the gastrointestinal tract, it is possible to obtain high spatial resolution and high image resolution without being affected by gastrointestinal gas artifacts. Therefore, EUS is extremely useful for detecting small pancreatic tumors. Furthermore, EUS-related procedures such as contrast-enhanced EUS (CE-EUS), EUS elastography, and EUS-guided fine needle aspiration (EUS-FNA) enable a more accurate diagnosis.

The established usefulness of EUS-FNA for pancreatic masses has reduced the chances of performing diagnostic ERCP with a risk for post-ERCP pancreatitis (PEP). However, recently, there have been increasing reports of pancreatic carcinoma in situ with no mass and only pancreatic duct stenosis from Japan. Serial pancreatic juice aspiration cytological examination (SPACE) using ERCP is useful for diagnosis, and the need for ERCP has been reconfirmed.

Thus, it is important to use EUS and ERCP for the diagnosis of pancreatic cancer. In the first section, we introduce the role of the two modalities in the clinical practice of pancreatic cancer.

18.1.2 Endoscopic Ultrasound (EUS)

18.1.2.1 Type of EUS

There are two types of EUS, radial, and convex types, depending on the distally attached ultrasonic probe. The radial EUS image was visualized 360° perpendicular to the scope axis. The pancreatic duct can be visualized on the long axis. It has the advantage that changes in the pancreatic duct diameter are easy to detect. However, it is sometimes difficult to visualize the transitional part from the pancreatic head to the pancreatic body (pancreatic neck) and visualize the end of the pancreatic tail. On the other hand, the convex EUS image is visualized parallel to the scope axis. It has the advantage that it is easy to understand the relationship between the lesion and the blood vessel because the blood vessel easily aligns with the axis of the scope. In addition, the pancreatic neck can be visualized. The major difference between the two types is that radials, in contrast to the convex type, does not allow fine needle aspiration (FNA). It is essential to understand the characteristics, advantages, and disadvantages of the radial and convex types and use them appropriately according to the situation.

18.1.2.2 Detection of Pancreatic Cancer

EUS is considered the most sensitive diagnostic imaging modality for detecting solid pancreatic lesions. Summarizing 12 previously published reports, the sensitivity of EUS for the detection of pancreatic cancer was 98%, which was superior to that of US (72.5%), computed tomography (CT; 74%), and magnetic resonance imaging (MRI; 83%) [1–13]. Thus, EUS is particularly useful in detecting small pancreatic lesions due to its high resolution. In recent years, the usefulness of multidetector-row CT (MDCT) in diagnosing pancreatic cancer has been reported [14]. However, when detecting pancreatic cancer of ≤20 mm, the detection rate of MDCT decreased to 50%, while EUS had a high detection rate of more than 90% [15, 16]. Several reports have shown that EUS can detect pancreatic cancer that was not identified on other modalities. Krishna et al. reported that the sensitivity of EUS for detecting pancreatic malignancy when MDCT findings were indeterminate was 85%, with a specificity of 58% [17]. Therefore, EUS should be performed in patients suspected of having pancreatic cancer even if MDCT does not detect a mass.

Recently, the results of Japanese pancreatic cancer registries showed that even for pancreatic cancer ≤20 mm, there was a difference in the 5-year survival rate between < 10 mm and 10–20 mm (80.4% versus 50%, respectively) [18]. Kamada et al. reported that the detection rates of US, contrast-enhanced CT, and EUS for pancreatic cancer of <10 mm were 30%, 30%, and 100%, respectively [1]. Based on the above, EUS plays a crucial role in detecting small pancreatic cancer.

EUS images of pancreatic cancer are visualized as a well-circumscribed hypoechoic mass with irregular margins. It may also be accompanied by dilation of the pancreatic duct distal to the mass, dilation of the surrounding branch duct, and retention of cysts. It is sometimes difficult to distinguish between benign mass-forming pancreatitis and pancreatic cancer. Contrast-enhanced EUS, which will be described later, is useful for the differential diagnosis; pancreatic cancer is

visualized as a hypovascular pattern, and mass-forming pancreatitis is visualized as a homogenous isovascular pattern [19].

18.1.2.3 Differential Diagnosis of Solid Pancreatic Mass

Contrast-Enhanced EUS (CE-EUS)

CE-EUS can image the blood vessel flowing into the lesion in real-time and obtain a clear contrast with the surrounding pancreatic parenchyma. CE-EUS has been reported to be useful for the differential diagnosis of pancreatic tumors because it enables qualitative diagnosis of tumors and detailed blood flow evaluation. In Japan, Sonazoid®, a second-generation low-sound pressure system intravenous contrast agent, is widely used. This contrast agent consists of gas-filled microbubbles of approximately 2–5 μL in diameter, encapsulated by a phospholipid or lipid shell. In principle, EUS can detect the secondary harmonic component generated from the contrast agent, so that an ultrasonic contrast agent can be directly captured as a signal, and a contrast image can be obtained.

The mass is evaluated as hyperenhancement, isoenhancement, hypoenhancement, or nonenhancement, depending on how much the mass contrasts with the surrounding pancreatic parenchyma. Pancreatic cancer mainly shows a hypoenhancement pattern, mass-forming pancreatitis shows an isoenhancement pattern, and endocrine tumors show a hyperenhancement pattern. Kitano et al. [16] reported that the sensitivity and specificity of pancreatic cancer showing hypoenhancement patterns were 95% and 89%, respectively, in 277 patients with pancreatic tumors. On the other hand, in the same study, the sensitivity and specificity of endocrine tumors showing hypervascular pattern were 79% and 99%, respectively. The sensitivity and specificity of tumorigenic pancreatitis showing an isovascular pattern were 78% and 95%, respectively. Furthermore, in the meta-analysis, the sensitivity and specificity of CE-EUS for pancreatic cancer were 93% and 80%, respectively, showing promising results [20]. Interestingly, regarding small lesions of < 2 cm, MDCT had a sensitivity of 70.6% and a specificity of 91.9%, whereas CE-EUS had a sensitivity of 91.2% and a specificity of 94.4%. CE-EUS was significantly superior to MDCT [16].

T staging and N staging are important factors in deciding on the course of treatment for pancreatic cancer. In T staging, it is essential to diagnose the presence or absence of infiltration of pancreatic cancer into the surrounding blood vessels. Imazu et al. [21] reported that the diagnostic rate of T staging was significantly improved by adding CE-EUS (92%) compared to EUS alone (69%). In addition, they described that contrast enhancement was particularly useful in determining portal vein infiltration because the portal vein wall could be visualized more clearly. CE-EUS has also been reported to be useful in diagnosing N staging [22].

Elastography (EG)

US elastography is a technique for imaging or quantifying tissue elasticity. An image of strain, which has a negative correlation with tissue elasticity, is called strain elastography (strain-EG). Strain-EG is originally a qualitative examination

that is evaluated by color pattern, but quantitative tissue elasticity diagnosis such as strain ratio and histogram analysis is possible by processing the image. Giovannini et al. [23] classified the EUS-EG color patterns into five categories and evaluated the ability to distinguish between benign and malignant pancreatic masses. As a result, the sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic masses were 92.3% and 80.0%, respectively, compared to 92.3% and 68.9%, respectively, for the conventional B-mode images. They concluded that EUS elastography is superior to conventional B-mode imaging and appears to distinguish benign from malignant pancreatic masses with high sensitivity, specificity, and accuracy. Although this color pattern evaluation is visual and easy to understand, the interpretation tends to be subjective. Therefore, it should be recognized that the results obtained will be less objective.

There is a strain ratio (SR) that semi-quantitatively analyzes the image information of the EUS-EG. SR can be evaluated objectively, and its usefulness has been reported. Iglesias-Garcia et al. [24] evaluated the ability to distinguish between benign and malignant pancreatic masses using SR and reported that the diagnostic ability was high, with a sensitivity of 91.2%, a specificity of 91.0%, and an accuracy rate of 91.1%.

CE-EUS and EUS elastography may provide additional information on the diagnosis of pancreatic cancer, in addition to the yield from EUS-FNA. CE-EUS helps to identify EUS-FNA targets and reduces the need to repeat FNA [16]. The specificity of EUS-FNA may be improved when used in combination with EUS elastography [25]. If the pancreatic mass with negative EUS-FNA findings is a hypovascular mass with CE-EUS or a hard mass with EUS elastography, repeating EUS-FNA is recommended.

18.1.2.4 Definitive Diagnosis of Pancreatic Cancer

EUS-FNA

Pathological diagnosis is essential for diagnosing pancreatic cancer and in deciding on courses of treatment for pancreatic cancer. EUS-FNA is a technique for collecting tissue under the guidance of EUS, and Villmann et al. [26] reported the clinical application of EUS-FNA for pancreatic lesions in 1992. EUS-FNA is widely performed for the pathological diagnosis and staging of solid pancreatic masses owing to its high diagnostic ability and safety. A meta-analysis of EUS-FNA in pancreatic tumors reported that the sensitivity of EUS-FNA was 85–89%, and the specificity was 96–99% [27]. In addition, the diagnostic ability of EUS-FNA for lymph node swelling is also high, with a sensitivity of 86.8% and a specificity of 95.8% [28].

Factors that influence the diagnosis of EUS-FNA are classified into three factors: patient factors, procedural factors, and other factors.

Patient factors include size, characterization, location, and background pancreatic parenchyma. Regarding the size of the pancreatic masses, it was reported that the diagnostic ability of EUS-FNA was lower for smaller lesions. The accuracy rate was 93.4% for lesions > 20 mm, 83.5% for 10 mm to 20 mm, and 82.5% for <10 mm [29].

Procedural factors include the needle's diameter and shape, puncture, and suction method. Generally, the thicker the needle, the larger the sample collected; however, the maneuverability deteriorates. On the other hand, the thinner the needle, the better the operability, but the smaller the amount of sample collected. Therefore, a thick needle is selected when many tissues, such as for immunostaining and genetic testing, are required. A thinner needle is selected for puncture from the duodenum, where the scope's curvature becomes strong. In recent years, needles for the histological examination have been developed for an endoscopic ultrasound-guided fine needle biopsy (EUS-FNB), and their usefulness has been reported. The shape of these needles' tips has been devised, such as the franceen shape and other shapes with side holes and core traps. Recent reports indicated that EUS-FNB has a significantly lower number of punctures and a higher diagnosis rate than EUS-FNA [30].

Recently, cancer genomic medicine using next generation sequencing (NGS) has become widespread. In a report comparing the success of NGS between FNA needles and FNB needles, FNB needles could collect samples that were significantly more suitable for NGS than FNA needles (90.9% versus 66.9%, $p = 0.02$) [31].

Regarding the puncture, various measures have been taken to improve the accuracy rate of EUS-FNA. For example, the Door knocking method, in which a tissue sample is taken into the needle by hitting the needle strongly against the mass, is useful for a hard tumor with significant fibrosis. The fanning technique has also been reported, in which tissue is collected from different parts of the tumor by moving the needle in a fan shape and can be diagnosed with a small number of punctures [32].

As for the suction pressure, applying negative pressure using a 20 ml syringe is common. In addition, the high negative pressure method using a 50 ml pressure-resistant syringe [33], slow-pull method using the capillary phenomenon by slowly pulling the stylet [34], the wet-suction method in which the inside of the needle is filled with saline [35], and the non-suction method are available. However, there is no consensus on the best suction method among them, and it is important to change the suction method according to the mass characteristics.

Other factors include processing of the sample collected and additional genetic testing. It has been reported that rapid on-site examination (ROSE) in the presence of a pathologist or cytotechnologist not only improves the accuracy rate of EUS-FNA, it also reduces complications with the decrease in the number of punctures [36]. Nevertheless, Iwashita et al. recommend macroscopically identified white tissue of more than 4 mm in the sample collected by EUS-FNA to improve the accuracy rate if ROSE is not available (macroscopic on-site quality evaluation: MOSE) [37]. By combining EUS-FNA with K-ras mutation, the diagnostic ability of EUS-FNA can be increased. In a meta-analysis by Fuccio et al., adding K-ras mutations to inconclusive EUS-FNA cases reduced false-negative rates by 55% and increased diagnostic sensitivity by 8.1% [38].

The main complications include bleeding, pancreatitis, and perforation. According to a systematic review by Wang et al. [39], the frequency of EUS-FNA complications in the pancreas was 1.03%, of which pancreatitis was 0.44%, bleeding was 0.10%, and perforation was 0.01%. In solid pancreatic tumors, the overall complication rate is reported to be 0.82%, which is lower for pancreatitis (0.35%),

bleeding (0.07%), and perforation (0.01%). Thus, EUS-FNA is regarded as a very safe procedure. However, it should be noted that EUS-FNA related complications for pancreatic cystic lesions are slightly higher at 2.8%.

Recently, there have been some case reports of needle tract seeding (NTS) by EUS-FNA. The frequency is unknown, but in a retrospective multicenter study by Yane et al. [40], NTS was found in 3.4% (6/176) of patients who underwent EUS-FNA before pancreatic tail resection; there was no significant difference in prognosis between the EUS-FNA group and the non-EUS-FNA group (48 months versus 43.9 months, $P = 0.392$), but it was reported that the frequency was not negligible. Gao et al. [41] summarized 33 cases extracted from previous reports; among them, there were 28 cases of NTS in EUS-FNA/FNB for pancreatic cancer, all of which were tumors of the pancreas' body and tail. The NTS site was found on the stomach wall (particularly the posterior wall) in all cases, and the median size was 25 mm (range: 4–50 mm). Most were localized in the submucosa and exhibited the morphology of submucosal tumors. Although the detection strategy and treatment for NTS have not been clarified, surgical resection is possible by early detection, and some cases have a good prognosis. It is important to follow up with NTS in mind after surgery carefully. The factors of NTS are considered to be associated with the number of punctures, size and shape of the needle, and tumor characteristics. However, it is unclear which factor is involved due to few reports. Therefore, it is important to avoid unnecessary EUS-FNA or reduce the number of punctures of the pancreatic body and tail tumors that do not include the puncture route in the surgical resection area [42]. FNB needles have been reported to have better diagnostic rates with a smaller number of punctures than FNA needles, and choosing FNB needles may be one way to avoid NTS.

18.1.3 Case Presentation (Fig. 18.1)

A 70-year-old male visited our hospital with an elevated tumor marker (CA19-9 level: 109 U/mL). Abdominal contrast-enhanced CT revealed no dilation of the pancreatic duct and no tumorous lesions (Fig. 18.1a). EUS showed a hypoechoic lesion with a diameter of 10 mm at the pancreatic body (Fig. 18.1b). CE-EUS showed a hypovascular pattern (Fig. 18.1c), and EUS-EG showed a dominant blue pattern with heterogeneity (Fig. 18.1d). We suspected pancreatic cancer based on these findings and subsequently performed EUS-FNA (Fig. 18.1e). Pathological findings revealed pancreatic adenocarcinoma (Fig. 18.1f). The patient underwent distal pancreatectomy and was diagnosed with pancreatic cancer (pT1b, pN0, pM0, pStage IA; UICC 8th edition).

18.1.4 Endoscopic Retrograde Cholangiopancreatography (ERCP)

In the clinical practice of pancreatic cancer, ERCP is considered as a therapeutic modality (biliary drainage) mainly for obstructive jaundice and cholangitis due to

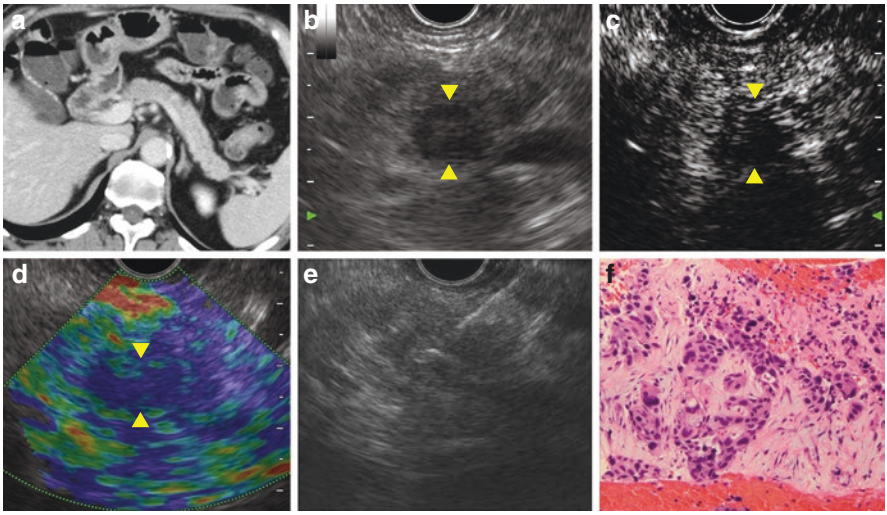

Fig. 18.1 (**a**) CE-CT revealed no dilation of the pancreatic duct and no tumorous lesions. (**b**) EUS showed a hypoechoic lesion with a diameter of 10 mm at the pancreatic body (yellow arrowhead). (**c**) CE-EUS showed a hypovascular pattern (yellow arrowhead). (**d**) EUS-EG showed a dominant blue pattern with heterogeneous (yellow arrowhead). (**e**) EUS-FNA was performed for a hypoechoic lesion in the pancreatic body. (**f**) Pathological findings revealed adenocarcinoma

the spread of EUS-FNA. In some small pancreatic cancers with a tumor diameter <10 mm, it may be challenging to identify the mass even with EUS, and EUS-FNA is not indicated in such cases. Furthermore, in cases such as carcinoma in situ of the pancreas that presents only with pancreatic duct stenosis, a definitive pathological diagnosis can be obtained only by pancreatic juice cytology using ERCP. The usefulness of preoperative ERCP cytology for early diagnosed pancreatic cancer cases, such as Stage 0–1, has been reported in Japan. In addition, continuous cytology with endoscopic nasopancreatic drainage (ENPD) tube placement (SPACE) is useful for diagnosing patients with smaller pancreatic cancer [43, 44]. The advantages of SPACE are that a sufficient amount of pancreatic juice can be obtained and that multiple pancreatic juice cytology can be performed, which can be expected to maximize the diagnostic yield. The sensitivity of SPACE at Stage 0 was 70–100%, and the smaller the tumor diameter, the better [45]. In addition, in the case of localized pancreatic duct stenosis without mass lesions, the sensitivity was 82%, the specificity was 100%, and the accuracy rate was 95%. If early pancreatic cancer is suspected in patients with pancreatic duct stenosis whose mass cannot be visualized by EUS, ERCP cytology and SPACE should be actively performed.

18.1.5 Case Presentation (Fig. 18.2)

A 60-year female visited our hospital with mild upper abdominal pain. CE-CT revealed dilatation of the pancreatic duct in the body and tail of the pancreas, but no tumorous lesions were detected (Fig. 18.2a). EUS showed dilatation of the main

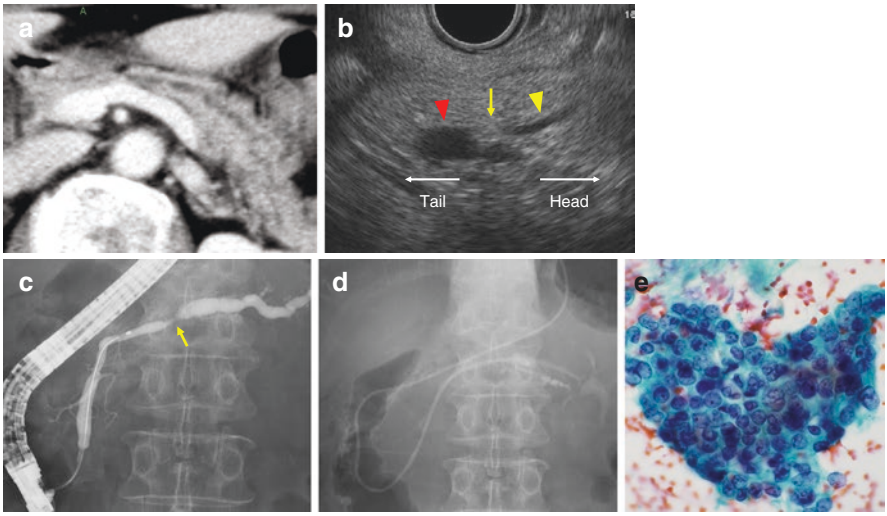

Fig. 18.2 (**a**) CE-CT revealed dilatation of the pancreatic duct in the body and the tail of the pancreas, but no tumorous lesions were detected. (**b**) EUS showed dilatation of the main pancreatic duct in the pancreatic body and tail (red arrowhead). Stenosis (yellow arrow) was suspected on the proximal side of the dilated part of the main pancreatic duct. There were no mass regions consistent with stenosis of the main pancreatic duct. (yellow arrowhead: normal diameter of the main pancreatic duct on the head side of the stenosis). (**c**) ERP revealed focal stenosis (yellow arrow) with distal dilation of the pancreatic duct in the tail of the pancreas. (**d**) SPACE was performed using an endoscopic nasopancreatic drainage tube. (**e**) Malignant findings were obtained by SPACE

pancreatic duct in the pancreatic body and tail. Stenosis was suspected on the proximal side of the dilated part of the main pancreatic duct. At the site where the caliber of the pancreatic duct changed, there were no mass regions (Fig. 18.2b). ERP revealed focal stenosis with distal dilation of the pancreatic duct in the tail of the pancreas (Fig. 18.2c). SPACE was performed (Fig. 18.2d), and malignant findings were obtained (Fig. 18.2e). Thus, laparoscopic distal pancreatectomy was performed. High-grade pancreatic intraepithelial neoplasm (PanIN) was observed in the resected specimen, consistent with stenosis of the main pancreatic duct. Finally, the patient was diagnosed with pancreatic carcinoma in situ (pTis, pN0, pStage 0; UICC 8th edition).

18.2 Endoscopic Diagnosis of Cholangiocarcinoma

18.2.1 Background

Cholangiocarcinoma (CC) is an uncommon gastrointestinal malignancy originating from the epithelial lining of the biliary tract. CC accounts for approximately 3% of all gastrointestinal malignancies [46]. Nevertheless, CC is the most common malignant tumor of the biliary tract and is the second most common primary hepatic cancer [47]. Incidence varies worldwide, with the highest known rates in Southeast Asia and much

lower rates in the Western world [48] with relatively higher rates among the elderly with a male predominance [49]. The clinical course, localization, and histological analysis of CC usually represent challenging issues for diagnosis and management.

Although surgery and liver transplantation are the main curative options for CC, at the time of diagnosis, most patients have advanced stages at diagnosis with unresectable disease, resulting in a poor prognosis with low 5-year overall survival [50]. Approximately 30% of patients considered resectable on the initial imaging are shown to be unresectable on surgical exploration [51].

Anatomically, CC is usually categorized into intrahepatic (iCC), distal (dCC), or perihilar (pCC) subtypes. The latter can be further classified based on the involvement pattern of biliary ducts, according to the Bismuth-Corlette classification, into four different types. pCC represents about 50–60%, dCC 40%, and iCC < 10% of CC cases [52]. iCC incidence appears to be increasing in Western countries [53]. This increase may be explained to some extent by the progress in diagnostic procedures; however, the rise of viral hepatitis and fatty liver disease may have largely impacted this rising incidence [54].

CCs are grouped morphologically into either mass-forming, periductal-infiltrating, or intraductal-growing subtypes [55]. Histologically, most CCs are adenocarcinomas (90%). Other variants include papillary adenocarcinoma, squamous cell carcinoma, signet-ring type, intestinal-type adenocarcinoma, and undifferentiated carcinoma [56].

Although the definite etiology is not clearly understood, several risk factors for CC are well-described, including cholangitis, particularly primary sclerosing cholangitis (PSC), inflammatory bowel disease (both ulcerative colitis and Crohn's disease), parasitic infections, choledochal cysts, hepatolithiasis, choledocholithiasis, hepatitis C and B viral infections, liver cirrhosis regardless of the cause, toxic agents such as thorotrast, diabetes, obesity, heavy alcohol use, and smoking [57].

Despite the advances in cross-sectional imaging techniques, the diagnosis and differentiation of malignant bile duct strictures remain challenging. Endoscopic approaches are often required for definitive histological diagnosis in addition to precise local staging and resectability assessment in early-stage disease when radiological features are uncertain.

Endoscopic evaluation includes various procedures such as endoscopic retrograde cholangiography (ERC), endoscopic ultrasound (EUS), intraductal ultrasound (IDUS), direct cholangioscopy, and probe-based confocal laser endomicroscopy (pCLE).

18.2.2 Endoscopic Retrograde Cholangiography and Associated Procedures

Traditionally, ERC has been the first-line procedure for suspected CC, allowing complete evaluation of the extrahepatic biliary tree, better understanding of site and length of biliary strictures, and providing cytological and/or histological diagnosis upon which management strategies can be planned.

Bile aspiration is an affordable, easy, old-fashion ERC-assisted technique for obtaining cytological analysis using a catheter at the level of the bile duct stricture to aspirate 10–15 mL of bile [58]. However, it has low sensitivity for the detection of malignancy, ranging from 6 to 32% [59]. On the other hand, another novel approach for early detection of CC depends on bile analysis for tumor proteins "proteomics" with the concept that carcinoma takes place at the biliary epithelium and tumor-related proteins can be detectable in bile. In a comparative study, bile proteomic analysis discriminated benign conditions (choledocholithiasis and PSC) from CC with high accuracy [60].

ERC-assisted biliary brushing for cytology remains the most commonly used method for histological diagnosis of CC at the time of ERC. Despite being an easy, straightforward, and highly specific technique depending on a wire-guided cytology brush directed into the biliary stricture, its sensitivity for the diagnosis of potentially malignant strictures has been unsatisfactory, ranging from 30 to 57% [59]. New generations of cytobrushes with increased length, size, and bristle stiffness were investigated with the aim of increasing ERC-based tissue yield, but the results were disappointing [61]. Similarly, many modifications of the cytobrushing technique have been tried to increase its sensitivity. For instance, dilatation of the stricture before and after brushing was studied, but with poor results [62]. On the other hand, obtaining successive brush specimens has been shown to increase tissue yield [62, 63]. In a recent prospective study, the sensitivity of biliary cytobrushing was reported to have increased to 84.3% when combined with biliary aspiration before and after the brushing technique [64]. Furthermore, advanced cytological techniques such as fluorescence in situ hybridization (FISH) [65] and flow cytometry have improved sensitivity when combined with conventional biliary cytology [66]. FISH depends on the use of fluorescence-labeled probes to detect chromosomal abnormalities in the form of aneuploidy or polyploidy in cells obtained via routine biliary brushings. Benign strictures have been predictively differentiated from malignant ones in PSC patients by optimizing the performance of FISH testing of multiple specimens of the biliary tract [67]. However, these advanced techniques are not usually available or widely approved.

ERC-assisted endobiliary forceps are assumed to provide deeper tissue samples with increased diagnostic sensitivity. Its sensitivity to detect malignant bile duct strictures was shown to be higher, ranging from 43 to 81% [68]. However, a recent meta-analysis showed that this increase was only demonstrated when biopsy was combined with brushing, with almost the same pooled sensitivity for both of them (45% for brushing versus 48% for endobiliary forceps) [69]. Nevertheless, this technique is more challenging with a risk of major bleeding [70] and perforation [71] and thus requires a high degree of experience to perform safely.

18.2.3 Endoscopic Ultrasound

Although magnetic resonance cholangiopancreatography (MRCP) is the primary non-invasive tool for pancreaticobiliary systems, EUS has a comparable impact on

the management of CC. EUS provides a detailed examination of the extrahepatic biliary tree and surrounding structures, making it a valuable tool for the diagnosis and accurate staging of extrahepatic CC with a lower complication rate when compared to ERCP [72]. Moreover, EUS evaluates associated portal lymphadenopathy [56] with a high degree of accuracy using non-invasive real-time EUS elastography. In addition, EUS-FNA has been more accurate than CT and positron emission tomography (PET)-CT for the evaluation of regional lymph node metastasis [73] which in turn has largely influenced the selection of different management lines [74].

In a large study by Mohamadnejad et al., EUS has succeeded in detecting malignancy in 100% of dCC cases in addition to the higher sensitivity of EUS-FNA in dCC than in pCC (81% versus 59%, respectively) [75]. However, another study has investigated the potential role of EUS-FNA as a first-line treatment for patients with suspected pCC and revealed a higher sensitivity (79%) with 82% accuracy [76]. Moreover, the sensitivity for CC detection in patients with negative brush cytology was improved using EUS-FNA, as reported in a study by DeWitt et al. [77]. This emphasizes the important role of EUS in the early diagnosis of both dCC and pCC, particularly if other procedures were inconclusive. There is a large concern about the risk of tumor seeding through EUS-FNA, which in one study has reached 83% versus 8% in patients without prior EUS-FNA sampling [78]. Some centers may discourage transplantation for those patients who are at risk of peritoneal metastasis [65]. Hence, the benefits of EUS-FNA of primary tumors must be weighed against the risk of tumor dissemination.

18.2.4 Intraductal Ultrasound

ERC-assisted wire-guided small-diameter high-frequency (20 MHz) probes are introduced intraductal for better evaluation of biliary stricture and for obtaining fine details [79]. Malignancy criteria by IDUS include a hypoechoic mass with irregular margins invading surrounding tissues, bile duct wall interruption, and asymmetrical wall thickening. In addition, loss of the hyperechoic line between the tumor and nearby vessel is considered as vascular invasion [80]. IDUS was reported to be more accurate than endobiliary forceps biopsy and cytology in detecting bile duct malignancy [81]. IDUS was shown to be more accurate than standard EUS for T staging of malignant biliary strictures (IDUS 77.7%; EUS, 54.1%) but not for N staging (IDUS 62%; EUS, 62.5%) [82]. When IDUS was combined with cholangioscopy, the accuracy for evaluation of Bismuth-type hilar lesions was 95–100% [83]. However, in patients with PSC, IDUS has failed to differentiate between inflammatory and malignant strictures [84], which in turn requires an aggressive workup including cholangioscopy and tissue acquiring techniques. Currently, the substantial progress in the cholangioscopy system has limited the role of IDUS in the evaluation of ductal CC, which is now less frequently performed in many centers.

18.2.5 Cholangioscopy

The lumen of the bile duct can be directly visualized using cholangioscopy accompanied by targeted biopsies with relative endoscopic efficiency for the discrimination of suspicious malignant lesions. Cholangioscopic criteria highly suggestive of malignancy include dilated and tortuous vessels, intraductal nodules and masses, and infiltrative or ulcerated strictures [85]. Cholangioscopy-guided tissue acquisition appears to be superior to ERCP modalities for tissue sampling, with an overall success rate of up to 90% [86–88].

With the rapidly growing progress in cholangioscopy systems, the current generation of digital single-operator cholangioscopy (SOC) (SpyGlass DS; Boston Scientific, Marlborough, MA) has been the most frequently used diagnostic tool for indeterminate biliary strictures, and the easier to maneuver properties have widened their use even beyond tertiary centers [65]. In a single-center study, SOC showed a high sensitivity and specificity (88% and 94%, respectively) for definitive diagnosis in patients with indeterminate biliary lesions [89]. Nonetheless, in a recent meta-analysis, the pooled sensitivity and specificity for detection of CC using SOC were 66.2% (95% confidence interval (CI), 59.7–72.3%) and 97% (95.0% CI, 94.0–99.0%), respectively, and that for biliary strictures with negative prior brushings and biopsies were 74.7% (95% CI, 63.3–84.0%) and 93.3% (95% CI, 85.1–97.8%), respectively [90].

In the case of PSC, studies are conflicting about the role of cholangioscopy in differentiating ductal strictures, either benign or malignant. While a study by Awadallah et al. has shown unsatisfactory results for the discrimination of bile duct malignancy using cholangioscopy [91], Tischendorf et al. revealed that transpapillary cholangioscopy has higher sensitivity and specificity (92% and 93%, respectively) for malignant stricture discrimination in patients with PSC [92]. However, the technique is usually challenging with an increased risk of cholangitis, especially in patients with PSC [93].

18.2.6 Chromocholangioscopy and Narrow Band Imaging

Chromocholangioscopy depends on the same principle as standard chromoendoscopy for discriminating dysplastic lesions along the gastrointestinal tract. It enhances visualization through selective dye uptake and highlights alterations in the mucosal surface pattern of the bile ducts [94].

Few studies have investigated the role of chromocholangioscopy. A study by Maetani et al. differentiated benign from malignant biliary epithelium depending on the degree of methylene blue uptake; malignant tissue showed null uptake, while normal and dysplastic epithelium showed higher degrees (90% and 69%, respectively) [95]. In another study by Hoffman et al., after 55 patients underwent chromocholoscopy, normal epithelium was homogenously stained, while inflammatory

and dysplastic lesions showed heterogeneous dark staining and benign strictures, such as post-liver transplant and PSC, were weakly stained [96]. On the other hand, the accuracy of chromocholangioscopy was affected by staining of the mucin and exudates overlying the biliary lesion with the biliary epithelium hiding beneath them [97].

Narrow band imaging (NBI) depends on filtering the white light into blue and green colors with different wavelengths, resulting in enhancement of vascular and surface patterns of the biliary mucosa. In a prospective multicentric study, NBI improved the cholangioscopy ability to distinguish malignant from benign lesions in 34 of 38 patients with indeterminate biliary lesions [98]. In another study, compared to white light cholangioscopy, NBI was significantly better for vascular and surface patterns of biliary lesions [99].

18.2.7 Confocal Laser Endomicroscopy

Probe-based confocal laser endomicroscopy (pCLE) is a novel imaging technique that provides a microscopic view of the surface epithelium and up to 250 μm of the lamina propria in real-time [100]. For biliary imaging, a confocal miniprobe is either passed within a carrying catheter through the channel of the ERCP or through the instrument channel of a cholangioscope. Intravenous fluorescein contrast is used to highlight the vasculature and extracellular matrix of examined tissues sparing the nuclei that appear dark. Low-power lasers illuminate tissues and detect the reflected fluorescent light, providing real-time images for evaluation and incorporating dynamic information such as blood flow, contrast uptake, and leakage [94, 101]. This technology seems to be useful in differentiating neoplastic from benign biliary strictures. Using a combination of specific pCLE criteria highlighting malignancy (including thick white bands (>20 mm), thick dark bands (>40 mm), dark clumps or epithelial structures) have succeeded in discriminating malignant strictures with high sensitivity (97%) but with low specificity (33%) owing to false-positive cases with inflammation related mainly to prior stent placement [102]. Hence, pCLE can considerably increase the sensitivity of detection of malignant biliary lesions and appears to be a promising diagnostic method.

18.2.8 Case Presentation (Figs. 18.3 and 18.4)

A 72-year-male visited our hospital with obstructive jaundice. MRCP revealed a common bile duct stricture (Fig. 18.3a). ERC revealed stenosis with upstream dilatation of the common bile duct, and IDUS showed bile duct wall interruption and asymmetrical wall thickening consistent with stenosis (Fig. 18.3b, c). Thus, cholangiocarcinoma was suspected; subsequently, brush cytology (Fig. 18.3d) and biopsy were performed under fluoroscopy (Fig. 18.3e). Finally, a plastic stent was placed into the common bile duct (Fig. 18.3f). However, no malignant findings were observed. We decided to perform cholangioscopy using a digital single-operator

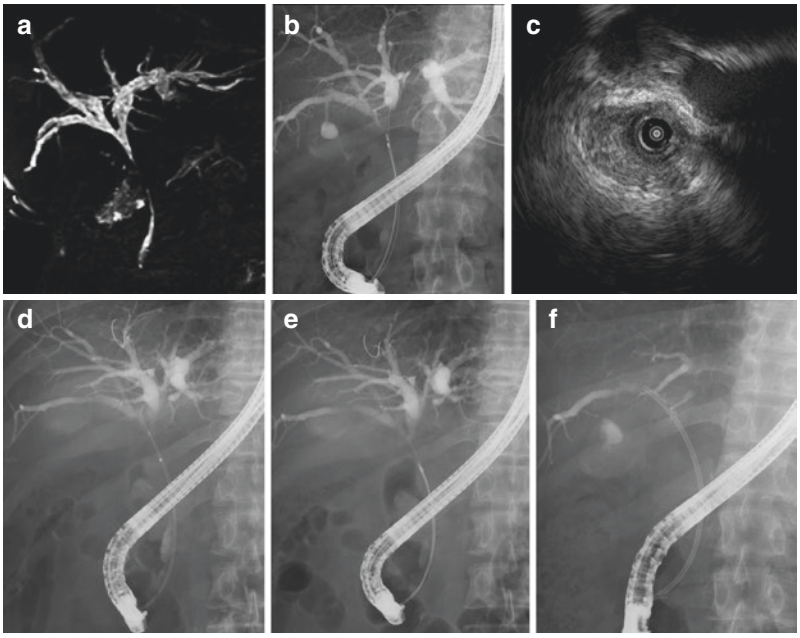

Fig. 18.3 (**a**) MRCP revealed common bile duct stricture. (**b**) ERC revealed stenosis with upstream dilatation of the common bile duct. (**c**) IDUS image showed bile duct wall interruption and asymmetrical wall thickening consistent with stenosis. (**d**) Brush cytology was performed for stenosis of the common bile duct. (**e**) Biopsy was performed under fluoroscopy. (**f**) A plastic stent was placed into the common bile duct

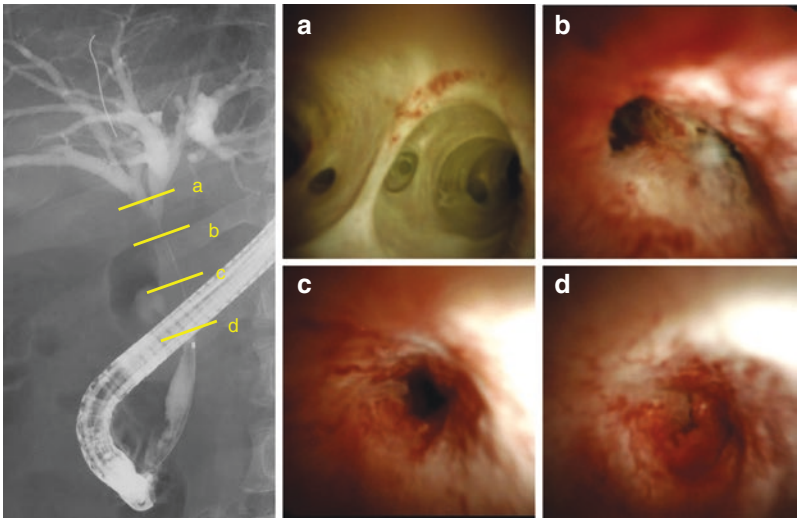

Fig. 18.4 (**a**) Cholangioscopic image showed the normal mucosa at the hilar portion. (**b–d**) Cholangioscopic images showed irregularly dilated and tortuous vessels, irregular mucosa, and lumen narrowing, and easy bleeding

cholangioscopy (SpyGlass DS). The cholangioscopic images showed that the most suspicious malignancy was irregularly dilated and tortuous vessels, irregular mucosa, and lumen narrowing, and easy bleeding (Fig. 18.4b, c, d). Targeted biopsies were performed for stenosis under direct vision. A diagnosis of cholangiocarcinoma could be made with a biopsy sample.

18.2.9 Conclusion

EUS- and ERCP-related procedures have become essential modalities in detecting, providing a definitive diagnosis of, and deciding upon courses of treatment for pancreaticobiliary carcinoma. Although EUS plays a central role in detecting and diagnosing pancreatic cancer, ERCP should be actively performed for pancreatic duct stenosis in which a mass cannot be visualized by EUS. In the diagnosis of cholangiocarcinoma, cytology, and biopsy under ERCP have limitations, but the advent of SOC will facilitate cholangioscopy and improve the diagnostic ability. To reduce deaths from pancreatobiliary carcinoma, new promising diagnostic methods are expected in the future.

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Preoperative Biliary Drainage for Pancreatic Cancer and Cholangiocarcinoma

19

Kei Saito

Abstract

Routine preoperative biliary drainage (PBD) for malignant distal biliary obstruction is not recommended in cases undergoing upfront surgery due to the lack of advantage in PBD. However, PBD is still performed in clinical practice because early surgery is not always possible and biliary drainage is necessary in cases with concomitant cholangitis or in cases undergoing neoadjuvant chemo(radiation) therapy (NAC). While a self-expandable metallic stent (SEMS) appears to provide better stent patency than a plastic stent (PS), there are still some concerns about the use of SEMS as PBD because of possible inflammation along the bile duct.

Hilar cholangiocarcinoma (HCCA) often invades the common hepatic duct and the confluence of the left and right hepatic ducts. The growth of tumors in porta hepatis can easily cause obstructive jaundice. PBD can relieve obstruction, reduce symptoms of cholangitis, and correct severe malnutrition. Techniques of PBD include endoscopic biliary drainage (EBD) and percutaneous transhepatic biliary drainage (PTBD). EBD was often associated with stent occlusion and retrograde infection of the bile duct. Bacterial contamination caused by EBD may induce preoperative cholangitis, which is considered to be an independent risk factor in surgical resection. On the other hand, PTBD is associated with tumor-seeding metastasis.

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19.1 PBD for Malignant Distal Biliary Obstruction in Patients with Pancreatic Cancer

Pancreatic cancer (PC), especially in the head of the pancreas, is often complicated by obstructive jaundice. While endoscopic metal stent placement is the standard of care in cases with malignant biliary obstruction (MBO) due to unresectable PC [1–3], routine preoperative biliary drainage (PBD) is not recommended in cases undergoing upfront surgery due to the lack of advantage in PBD [4]. However, early surgery is not always possible and biliary drainage is necessary in cases with concomitant cholangitis or in cases undergoing neoadjuvant chemo(radiation) therapy (NAC) [5].

NAC is increasingly utilized in cases with borderline resectable PC (BR-PC) as well as resectable PC (R-PC) because survival after upfront surgery is still suboptimal due to the high incidence of early recurrence and the low completion rate of adjuvant chemotherapy after invasive pancreatic resection [6, 7]. Although self-expandable metallic stents (SEMS) appear to be superior to plastic stents (PS) in terms of stent patency in the neoadjuvant setting, there were no significant differences in the cost-effectiveness between PS and SEMS in a small randomized controlled trial (RCT) [8]. Clinical outcomes of PBD might vary by the settings, i.e., stage (R-PC vs. BR-PC), duration of NAC, and so on, but clinical data are still lacking.

19.2 Was PBD Associated with an Increased Rate of Postoperative Wound Infection?

Sohn et al. identified in a multivariate analysis that PBD was an independent risk factor for the development of postoperative wound infections [9], although only 36% of the utilized stents were placed via endoscopic retrograde cholangiopancreatography (ERCP). On the contrary, Martignoni et al. demonstrated that the overall postoperative morbidity and mortality were unaffected by the presence of preoperative jaundice and could not identify it as an independent risk factor [10]. They were able to show an increased incidence of postoperative bleeding requiring reoperation in severely jaundiced patients (bilirubin >100 mol/L). In another retrospective analysis, Matteo et al. reported that severely jaundiced (bilirubin >75 mol/L) was a risk factor of postoperative complication. Furthermore, Coates et al. reported an increase in blood loss in stented patients and most interestingly an unaffected rate of wound infections in preoperatively drained patients after application of an intensified

perioperative antibiotics treatment regimen [11]. The randomized controlled trial by van der Gaag et al. [4] further supports the unfavorable effects of PBD on postoperative outcomes. Here, patients were either assigned to operative intervention within 1 week from the presentation or received 4–6 weeks of biliary decompression by endoscopic stenting of the common bile duct, resulting in operative intervention within 1.2 or 5.2 weeks, respectively. In the PBD-receiving treatment arm, 47% of the patients developed drainage-related complications after an average time of 13 weeks in contrast to 2% in the early surgery group, while operation-related complications were observed in 74% and 37% of the patients, respectively. The incidence of perioperative death was found to be unaffected by PBD.

19.3 Which Is Better, SEMS or PS?

While SEMS appears to provide better stent patency than PS both in resectable and unresectable MBO, there are still some concerns about the use of SEMS as PBD because of possible inflammation along the bile duct. However, the use of SEMS was reportedly not associated with overall postoperative complications, hospital stay, or mortality [5, 12] despite a higher wound infection rate and longer operation time. In our prospective study, there were no postoperative mortality and three morbidities were observed in two patients (10.5%), which suggested that partially covered SEMS (PCSEMS) did not adversely affect surgical outcomes [13]. In general, the use of PBD is associated with postoperative infectious complications and in a previous study, the rate of wound infection was significantly higher in SEMS: 31.0% in SEMS, 12.8% in PS, and 6.2% in non-stented group ($P < 0.001$) [5]. The effects of PBD on postoperative complications are clinically important since the introduction of adjuvant chemotherapy is essential even after R0 resection of PC [14]. Thus, the effects of the stent type on postoperative infections, the introduction of adjuvant chemotherapy, and overall survival, should be further evaluated.

19.4 Which Is Better, FCSEMS, PCSEMS, or UCSEMS for PBD in Patients with Distal MBO?

Although a recent Japanese RCT demonstrated that PCSEMS showed better stent patency than uncovered SEMS (UCSEMS) in unresectable distal MBO [2], conflicting data have been reported on the comparison of covered and uncovered SEMS [15, 16]. While covered SEMS prevents tumor ingrowth, it is associated with stent migration. Few data are available on covered versus uncovered SEMS in the neoadjuvant setting. Only one international RCT showed non-inferiority of PCSEMS to UCSEMS in cases undergoing NAC for PC but further investigations are necessary [17].

In unresectable MBO, previously, it reported that fully covered SEMS (FCSEMS) and PCSEMS were comparable in safety and effectiveness including stent migration (14% in FCSEMS and 8% in PCSEMS) [18, 19]. While FCSEMS allows easy

stent removal at surgical resection, PCSEMS theoretically decreases the chance of stent migration even after tumor shrinkage by NAC, especially when a longer (>6 months) duration of NAC is expected [19]. It is still unclear whether either FCSEMS or PCSEMS is preferable as PBD in the neoadjuvant setting.

19.5 PBD in Patients Undergoing NAC

In patients undergoing NAC for PC, recurrent biliary obstruction (RBO) can cause delay or discontinuation of NAC and affect treatment outcomes. The reported rates of RBO were 15–35% when SEMS was used as PBD [8, 20, 21]. There is no consensus on the indication, regimen, and duration of NAC for PC. Therefore, the resection rate and time to surgery after NAC depend on the tumor status and each institution's protocol. If patients with potentially resectable PC are enrolled, then, the duration of NAC can be short with a high surgical resection rate. Meanwhile, if patients with locally advanced PC are included, the duration of NAC can be long and the conversion rate to palliation will be high, which can affect the rate of RBO and time to RBO (TRBO). The addition of radiation might also affect outcomes of PBD during NAC; the rates of RBO were 75.0 and 16.7% in patients undergoing chemoradiation therapy and chemotherapy alone in our previous trial [13], though the number of cases was small. Two possible reasons for the high RBO rate in chemoradiation therapy are considered. First, the duration and severity of neutropenia might increase by adding radiation therapy to chemotherapy. Second, radiation can cause some inflammation and edema in the duodenum. It was reported that RBO would increase in cases with duodenal invasion [22]. It is possible that radiation would increase duodenobiliary reflux and subsequent cholangitis and RBO. Kubota et al. reported that the median TRBO was longer in PCSEMS (97 days vs. 55 days in PCSEMS and PS groups) but that the re-intervention rate was still as high as 23.5% in PCSEMS during the 3-months period of neoadjuvant chemoradiation therapy [21]. Since there is no consensus on the indication (R-PC and/or BR-PC), regimen, and duration of NAC, inter-study comparison is difficult and only a prospective RCT can clarify appropriate stent selection during NAC.

19.6 Complication of PBD

Post-ERCP pancreatitis was a common complication and severe pancreatitis can delay surgery and the introduction of NAC as well as potentially interfere with surgical procedures due to the peripancreatic inflammation. SEMS with high axial force and non-pancreatic cancer were independent risk factors for pancreatitis after SEMS placement [23]. There have been no data supporting routine endoscopic sphincterotomy (EST) prior to SEMS placement for the prevention of pancreatitis in unresectable MBO [24, 25]. An earlier stage of PC might be associated with a relatively higher incidence of pancreatitis because pancreatic duct obstruction with

upstream pancreatic atrophy is more often seen in advanced PC and the necessity of EST prior to PBD should further be clarified in the early stage of PC.

It was reported that tumor involvement in the orifice of the cystic duct (OCD) was a risk factor for cholecystitis [26]. In the previous study of SEMS as PBD without NAC, the rate of cholecystitis was 8% [27]. Previous studies showed no significant differences in the rate of cholecystitis between uncovered and covered SEMS for unresectable and borderline resectable PC [26, 28]. Since cholecystitis can delay surgery or NAC, it is further to be explored how we can reduce the risk of cholecystitis.

19.7 The Role of Endoscopic Ultrasound/ Ultrasonography-Guided Biliary Drainage for PBD

Adverse event rates related to ERCP-assisted transpapillary stenting range from 28 to 36% [29, 30]. Acute pancreatitis is the most common adverse event for those undergoing the procedure, with reported rates between 2 and 18% [29–31]. Transmural stent placement under endoscopic ultrasound (EUS) guidance has emerged as an alternative procedure to percutaneous transhepatic biliary drainage (PTBD) after the failure of ERCP [32, 33]. Some theoretical advantages of EUS-guided biliary drainage (EUS-BD) over endoscopic biliary drainage (EBD) include avoidance of traumatic papillary manipulation that can lead to acute pancreatitis [29]. Woo et al. showed that technical and clinical success rates were not different from EUS-BD to EBD for the primary palliation in patients with distal MBO [34]. But, evidence of EUS-BD for PBD in patients with distal MBO has not been shown [35].

19.8 PBD for Hilar Cholangiocarcinoma

Surgery is the key treatment for HCCA. Liver resection with jaundice has always been considered a potentially dangerous procedure, due to the higher risk of bleeding, sepsis, and liver failure [36]. However, the use of PBD in jaundice patients remains a controversial topic in the management of HCCA. In fact, it is considered that PBD is a procedure that is not exempt from risks (cholangitis, extended preoperative hospital stay, failure to improve the nutritional state, increased postoperative complications). Recently, some meta-analyses that investigated the efficacy of PBD in patients with hilar MBO, revealed conflicting results: Celotti et al. showed that PBD was associated with increased postoperative infective complications in patients with HCCA [36], while Moole et al. showed significantly less major adverse events in the PBD group, in patients with HCCA or PC [37]. Thus, there were not standard recommendation, the use of PBD for HCCA has been widely adopted, especially in case of advanced malnutrition, cholangitis, or prolonged delay in surgery. Recently, the role of PBD for hilar MBO is not just a procedure for jaundice resolution [38, 39]. Additionally, cholangiography with its adjunct procedure is an important diagnostic procedure for the evaluation of disease extension and/or pathological

confirmation. Resectability can be determined based on cholangiogram with mapping biopsies, and biliary drainage is mandatory after cholangiography to prevent post-procedure cholangitis.

19.9 What Is the Appropriate Drainage Method?

Techniques of PBD include EBD and PTBD. EBD is an internal drainage procedure via endoscopic biliary stenting (EBS) or endoscopic nasobiliary drainage (ENBD) and has the advantage of low trauma, but it seems to induce procedure-related complications more easily. Previous studies have shown that PTBD had a lower incidence of PBD-related complications than EBD [40]. Chen et al. showed that PTBD had a lower risk of drainage-related complications than EBD (odds ratio [OR], 2.73; 95% confidence interval [CI], 1.52–4.91; $P < 0.05$) [40]. Meanwhile, the incidence of cholangitis in the PTBD group was higher than that in the EBD group in the RCT [41]. In the PTBD procedure, catheters are punctured into the bile duct from the portal vein, which may easily cause the internal fistula of the portal vein and bile duct, and the drainage time will also be prolonged. Tang et al. showed that PTBD should be performed as an initial method of biliary drainage in terms of reducing the incidence of procedure-related cholangitis, pancreatitis, and improving the rates of palliative relief of cholestasis [42]. The risk of EBD is the induction of pancreatitis; however, in recent studies, the severity of pancreatitis did not affect the subsequent surgery. Additionally, according to Kawashima et al., a large number of patients with Bismuth-type III/IV did not affect the technical success rate of ENBD, 80% of which were effective after successful insertion into the future residual liver (FRL) [43]. EBD is considered as a kind of intracavitary drainage, which will not cause bile overflow in theory. The catheter of PTBD is placed freely through the abdominal cavity or chest cavity, so bile containing exfoliated cancer cells may overflow. Thus, PTBD is considered to be a risk factor for seeding metastasis [44]. Wiggers et al. performed computed tomography (CT) or magnetic resonance imaging (MRI) based on the tumor marker levels or physical examination, which may underestimate the recurrence [45]. The total recurrence rate showed a significant difference in favor of EBD. The 5-year overall survival rate in several studies also confirmed that the prognosis of PTBD was indeed worse than that of EBD.

PBD aims to relieve biliary obstruction and ensure the recovery of preoperative liver function. However, due to inadequate preoperative drainage, patients will not benefit from PBD when the volume of FRL is greater than 50% [46, 47]. EBD dredges the left and right hepatic ducts to achieve total biliary drainage (TBD), while PTBD uses a catheter to achieve selective biliary drainage (SBD). This means that PTBD could regulate the drainage of different liver segments according to the surgical plan. De Palma et al. evaluated the drainage effect of SBD and TBD in unresectable HCCA, they found that SBD is better than TBD in promoting hypertrophy of FRL [48]. Whether it is the same in resectable HCCA needs to be confirmed. In another retrospective cohort study, no increased risk of cholangitis was found in patients with SBD [49]. Studies above showed the advantages of SBD,

which may indirectly explain why PTBD is more popular in the past decade. There is a greater need to design prospective randomized controlled studies to obtain high-level evidence-based medical proof. PTBD is a reasonable choice for PBD, and EBD should only be used as preoperative drainage for HCCA by more experienced physicians. Moreover, it is worth noting that, whether EBD or PTBD, accurate SBD should be the trend.

19.10 Which Is the Appropriate EBD, Stent Placement Above the Papilla, Stent Placement Across the Pallia or ENBD?

ENBD is advantageous because it reduces the rate of reflux cholangitis in patients who have to endure it for 2 weeks over due to NAC or portal vein embolization (PVE). NAC followed by surgical resection in patients with HCCA may be promising for R0 resection. NAC for at least 3 months is essential for safe control of biliary infection and jaundice. Liver resection is challenging and places patients at risk of postoperative liver insufficiency. This risk is largely dependent on the volume and function of the FLR. PVE before major hepatectomy allows resection and inadequate FLR with good long survival. It needs to be 2–4 weeks after PVE. ENBD for FLR is generally recommended as PBD for hilar MBO in Japan, but prolonged ENBD placement causes discomfort, and EBS is often used in cases that cannot tolerate ENBD placement. In Japanese multicenter retrospective analysis, the advantage of ENBD over EBS as the initial PBD for resectable hilar MBO was not demonstrated [50]. EBS is an internal drainage procedure via PS and SEMS. Endoscopic SEMS placement is not suitable for surgery in patients with HCCA because the surgical margin attached with them obscures identification. PS placement above the papilla is promising because it can reduce cholangitis reflux (Fig. 19.1). Kubota et al showed that PS placement above the pallia should be

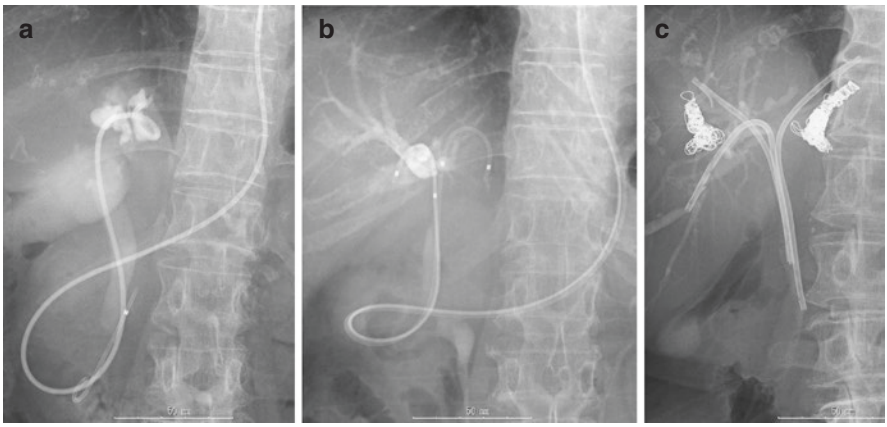

Fig. 19.1 PBD for malignant hilar biliary obstruction. (**a**) ENBD in the left hepatic duct. (**b**) ENBD in the left and right hepatic duct. (**c**) Plastic stent placement above the pallia

considered for the relief of the cost for patients with initially unresectable locally advanced Klatskin tumor [51]. The role of stent placement above the pallia should be further evaluated in the future.

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ERCP for Malignant Biliary Obstruction for Unresectable Pancreatic Cancer and Cholangiocarcinoma

20

Yousuke Nakai and Hirofumi Kogure

Abstract

Transpapillary biliary drainage by ERCP is the standard of care for both distal and hilar malignant biliary obstruction due to unresectable pancreatobiliary cancer. Although metal stents are preferred over plastic stents because of longer stent patency, various factors should be taken into consideration for biliary drainage; type of stents, biliary drainage area in hilar obstruction, risk of adverse events, presence of gastric outlet obstruction, prognosis. In general, covered metal stents are recommended in distal malignant biliary obstruction and bilateral uncovered metal stents above the papilla in hilar malignant biliary obstruction. Given the improved prognosis by the development of chemotherapy, drainage methods should be based on the long-term management, not the first intervention alone. New approaches such as intraductal ablation, functioning stents, and endoscopic ultrasonography-guided biliary drainage also need further investigation.

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Keywords

ERCP · Malignant biliary obstruction · Metal stents · Plastic stents · Recurrent biliary obstruction · Stents

20.1 Introduction

Endoscopic biliary stenting is the current standard of care for palliation of malignant biliary obstruction (MBO) and pancreatobiliary cancer is one of the most common causes of MBO. Surgical bypass of choledochojejunostomy was often performed as palliative surgery for MBO with relatively high rates of morbidity and mortality, and percutaneous transhepatic biliary drainage (PTBD), and later, endoscopic transpapillary biliary drainage was introduced as less invasive procedures. In 1987, Speer et al. [1] conducted a randomized controlled trial of endoscopic and percutaneous biliary drainage and showed higher resolution of jaundice and less mortality in endoscopic biliary drainage. Then, in 1994, Smith et al. [2] confirmed less mortality and morbidity in endoscopic biliary stent placement than in surgical bypass.

The type of biliary drainage is selected based on the location (distal vs. hilar), disease stage (resectable vs. unresectable), and the nature of biliary strictures (intrinsic vs. extrinsic). The type of biliary stents is either plastic or metal, and metal stents are either covered or uncovered, which is selected based on various factors such as resectability, location, and prognosis. We focus on unresectable MBO due to pancreatobiliary cancer in this chapter.

20.2 Distal Malignant Biliary Obstruction

Although distal MBO is often used in clinical practice, the definition of distal MBO varies among investigators, i.e., distal third, distal half, or intrapancreatic bile duct. However, when a single stent can drain the entire biliary system, we can clinically assume it as distal MBO [3].

Metal stents with a large diameter are often selected over plastic stents because of longer stent patency since the pivotal randomized controlled trial by Davids et al. [4] demonstrated longer stent patency in metal stents. In a meta-analysis [5], metal stents are associated with less stent occlusion with an odds ratio (OR) of 0.36 in distal MBO. Although the cost of metal stents is higher than that of plastic stents, in a cost-effective analysis, metal stents are preferred if the life expectancy is over 6 months because of less stent occlusion [6]. Given the improved prognosis by the advancement of chemotherapy, most patients can survive 6 months and are likely to benefit from metal stent placement. There are two types of metal stents, covered and uncovered. Covered metal stents were developed since the tumor can occlude the stent lumen by ingrowth through the mesh of uncovered metal stents. Some

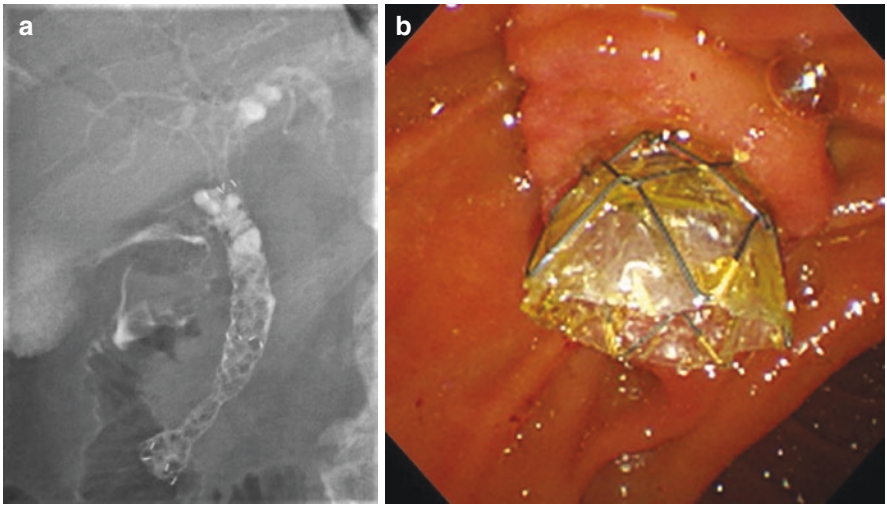

Fig. 20.1 A fully-covered metal stent for distal malignant biliary obstruction due to pancreatic cancer. (**a**) Fluoroscopic image. (**b**) Endoscopic image

randomized controlled trials showed the superiority of covered metal stents in stent patency [7, 8] but meta-analyses of covered versus uncovered metal stents showed conflicting data [9, 10]. While covered metal stents (Fig. 20.1) can prevent tumor ingrowth, they are prone to stent migration and sludge formation. Two meta-analyses of similar randomized controlled trials showed different conclusions due to the lack of a standard definition of stent outcomes [9, 10] and we proposed the standardization of stent outcomes using Tokyo Criteria 2014 [11]. In a recent meta-analysis [12] of 11 randomized controlled trials involving 1272 patients, the risk reduction of stent failure was 32% but the difference was not statistically significant. Tumor ingrowth was significantly decreased by covered metal stents (OR 0.21) but stent migration (OR 5.11) and sludge formation (OR 2.46) were more common with covered metal stents. Of note, the rates of procedure-related adverse events including cholecystitis and pancreatitis were similar in covered and uncovered metal stents.

Apart from stent patency of the first biliary drainage, reinterventions for recurrent biliary obstruction are similarly important. Due to the recent advancement of chemotherapy, not a few patients receiving metal stents experience recurrent biliary obstruction and need reinterventions. At the time of reintervention for covered metal stents, there are three options; balloon sweep for sludge within the occluded stent, stent-in-stent, and stent exchange. We reported removal and exchange of covered metal stents was a better approach than balloon sweep within the occluded stent since the presence of biofilm in the first stent can lead to early recurrent biliary obstruction [13]. Stent patency was 176 days in stent exchange, 57 days in stent-in-stent with plastic stents, and 46 days in balloon sweep alone. On the other hand, stent-in-stent by a new covered metal stent is the best approach for tumor ingrowth

of uncovered metal stents [14]. Stent patency of stent-in-stent was 220 days in covered metal stents, 141 days in uncovered metal stents, and 58 days in plastic stents.

In summary, covered metal stents show equal or better stent patency in distal MBO and there are no solid data supporting uncovered metal stents can reduce stent-related adverse events such as pancreatitis and cholecystitis. Removal and exchange of covered metal stents are technically possible and provide longer stent patency as second-line biliary drainage. Therefore, we recommend covered metal stents in patients who receive systemic chemotherapy.

20.3 Hilar Malignant Biliary Obstruction

Management of hilar MBO is more complex with various treatment options: Bilateral vs. unilateral drainage, metal vs. plastic stent, above or across the papilla, stent-in-stent vs. side-by-stent in cases with bilateral metal stent placement.

In resectable hilar MBO, drainage in future remnant liver alone is the principle but in unresectable hilar MBO, there are some treatment options for drainage area. In some retrospective studies [15, 16], >50% (or 33% in preserved liver function) of the liver volume drainage would lead to effective drainage as well as survival. Patency of the portal vein is also important since portal vein occlusion can eventually lead to liver atrophy, and the drainage area should be based on both the liver volume and portal vein flow. Technically, pre-procedure drainage planning is important based on computed tomography (CT) and/or magnetic resonance cholangiopancreatography (MRCP) [17] and selective guidewire insertion without contrast injection is recommended during ERCP.

To drain >50% of the liver volume, bilateral biliary drainage is often necessary. Lee et al. [18] recently conducted a randomized controlled trial comparing bilateral vs. unilateral biliary drainage using a metal stent and demonstrated bilateral biliary drainage was associated with longer stent patency (252 days vs. 139 days in the bilateral and unilateral drainage group).

As for the types of stents, two randomized controlled trials revealed uncovered metal stents provide longer stent patency than plastic stents [19, 20]. However, bilateral stent placement is still technically challenging for non-experts, and reinterventions after the recurrent biliary obstruction is sometimes technically impossible in some cases. Thus, some endoscopists still prefer plastic stents for complex hilar MBO because of easy reinterventions. Recently, the use of covered metal stents with a small diameter (6 mm) was also reported as a treatment option for non-complex hilar MBO [21, 22] and stent exchange is also technically possible in most patients. However, it is unclear whether covered metal stents provide longer stent patency than plastic stents or not, and cost benefits should be evaluated between plastic stents and covered metal stents.

For bilateral metal stent placement, two techniques are available; stent-in-stent and side-by-side stent placement. While stent-in-stent has been technically difficult, recent "large-cell" type metal stents allow relatively easy stent insertion (Fig. 20.2) [23]. Side-by-side stent placement is relatively easy once two guidewires are placed

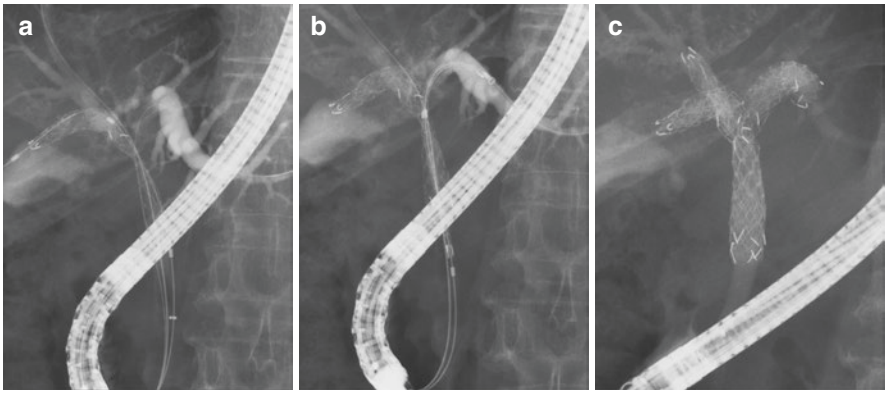

Fig. 20.2 Stent-in-stent for hilar malignant biliary obstruction. Three uncovered "large cell" metal stents were placed in a stent-in-stent fashion. (**a**) First stent deployment to the right posterior branch after three guidewire placement to the left, right anterior, and posterior branches. (**b**) Second stent deployment to the left branch. (**c**) Final stent deployment to the right anterior branch

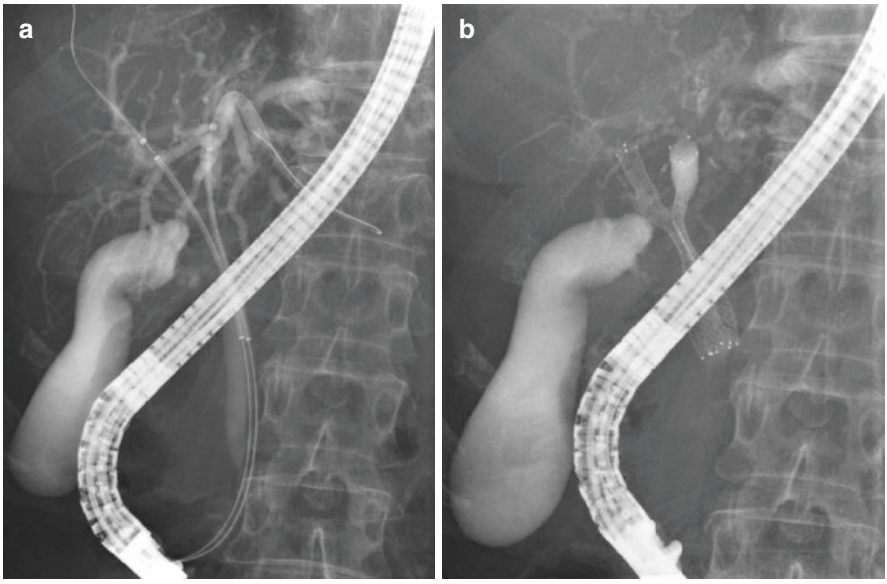

Fig. 20.3 Side-by-side for hilar malignant biliary obstruction. (**a**) Two 6-Fr stent delivery systems were advanced into the left and right bile duct simultaneously. (**b**) Two uncovered metal stents were simultaneously deployed in a side-by-side fashion

in both lobes. The recent development of metal stents with a small (<6 Fr) delivery system allows simultaneous side-by-side stent placement, too (Fig. 20.3) [24]. There has been controversy on the selection of these two techniques but a recent randomized controlled trial [25] demonstrated no significant differences between stent-in-stent and side-by-side techniques by experts. The disadvantage of

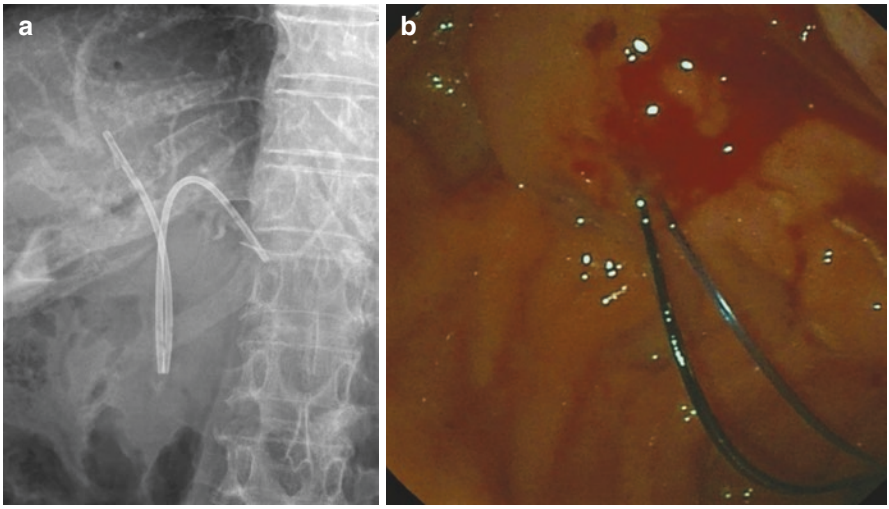

Fig. 20.4 Two "inside stent" placements above the papilla for hilar malignant biliary obstruction. (**a**) Fluoroscopic image. (**b**) Endoscopic image. Threads for stent retrieval were placed across the papilla

side-by-side stenting is overexpansion of the bile duct by placing two or more metal stents placed in the common bile duct. Historically, it was reported the overexpansion of the common bile duct caused portal vein thrombosis but the rate of thrombosis by side-by-side technique using recently available metal stents is unknown. A combined stent-in-stent and side-by-side technique is also reported for multi-branch stent placement using dedicated stents, too [26, 27]. Therefore, the selection of techniques for multiple stent placement can be selected by local expertise.

Another treatment option is stent placement across the papilla or above the papilla, so-called "inside-stent" (Fig. 20.4). The concept of "above-the-papilla" stent placement is to preserve the Oddi's function and to prevent duodenobiliary reflux because duodenobiliary reflux in hilar MBO can lead to cholangitis or liver abscess in the undrained biliary system. In cases with metal stent placement, a retrospective comparative study of side-by-side stents across and above the papilla stents was reported [28]. Early adverse events, mainly pancreatitis, were more common in the across-the-papilla group; 11.7% vs. 1.9% ($p = 0.04$) but stent occlusion rate and stent patency were comparable between the two groups. We also compared stent-in-stent above the papilla and side-by-side across the papilla retrospectively and reported higher rates of adverse events in the across-the-papilla group (46% vs. 23%, $p = 0.09$) [29]. Therefore, in hilar MBO, above-the-papilla stent placement is recommended to reduce adverse events, especially pancreatitis. However, technical success of reinterventions was reportedly higher in across-the-papilla stenting in one retrospective study [30], and long-term outcomes between above and across the papilla stent placement need further investigation. Plastic stent placement above the papilla was also reported from Japan [31–33], where inside stents with retrieval threads are commercially available. In one retrospective comparative study [31],

stent patency of inside stents (142 days) was longer than conventional plastic stents across the papilla (32 days) and similar to metal stents (150 days). Although promising data of "inside stent" were reported, prospective randomized controlled trials are mandatory to confirm its role in hilar MBO. Since the removal of inside stents can be technically difficult as compared to conventional plastic stents across the papilla, the advantage of longer stent patency should be proven to introduce this inside stent widely into clinical practice.

In summary, bilateral metal stent placement, either by stent-in-stent or side-by-side technique, is currently the standard of care where expertise is available. However, reinterventions after bilateral metal stent placement are technically demanding and it should be further elucidated whether plastic stents, especially inside stents, have a role in the management of hilar MBO. Finally, endoscopic ultrasonography-guided biliary drainage (EUS-BD) for hilar MBO [34, 35] should be investigated in the future.

20.4 Combined Malignant Biliary Obstruction and Gastric Outlet Obstruction

MBO is often complicated by gastric outlet obstruction (GOO), and about 60–70% of patients can develop MBO and GOO in advanced pancreatic cancer [36]. Although endoscopic stenting is performed for GOO similarly to MBO, management of combined MBO and GOO is often technically challenging. Even if double endoscopic stenting is technically possible for MBO and GOO, recurrent stent occlusion or cholangitis by duodenobiliary reflux is often observed [37, 38].

Antireflux metal stent (ARMS) or EUS-BD can be an alternative technique in this situation [39]. We previously reported promising data of ARMS for reintervention after recurrent biliary obstruction [40], but conflicting data are reported on ARMS as a first-line treatment. Although one Korean pilot randomized controlled trial [41] demonstrated longer stent patency in ARMS than in conventional covered metal stents(407 days vs. 220 days, $p = 0.013$), our Japanese multicenter randomized controlled trial [42] failed to demonstrate significant differences in time to recurrent biliary obstruction (251 days in ARMS and 351 days in conventional covered metal stents, $p = 0.11$). Since various types of ARMS are now available and the ideal design of antireflux valves is still unclear, more preclinical and clinical data are necessary to confirm the role of ARMS. On the other hand, increasing data are reported on EUS-BD, and in cases with an indwelling duodenal stent, EUS-guided hepaticogastrostomy may be preferred over EUS-guided choledochoduodenostomy [43].

20.5 Risk Factors for Adverse Events

Adverse events other than stent occlusion can occur after stent placement such as pancreatitis, cholecystitis, and migration. Adverse events after biliary stent placement can lead to discontinuation of chemotherapy and impair the quality of life.

Stent characteristics can affect clinical outcomes and we previously reported two stent-related forces, axial force and radial force [44] to characterize various metal stents. An axial force is defined as the force to recover to a straight position after bending and is measured using the dedicated machine. For example, WATCH-study [45] was a historical comparative study of two covered metal stents: One is a partially-covered stainless Wallstent (Boston Scientific, Natick, Massachusetts, USA) and the other is a new partially-covered nitinol WallFlex stent (Boston Scientific). The new WallFlex stent has a higher radial force and lower axial force and reduced early recurrent biliary obstruction, especially stent migration.

Pancreatitis can occur after ERCP alone but transpapillary metal stent placement is known as a risk factor for post-ERCP pancreatitis. Risk factor analysis revealed nonpancreatic cancer and metal stents with high axial force were associated with pancreatitis after metal stent placement [46] and endoscopic sphincterotomy cannot prevent post-ERCP pancreatitis. Cholecystitis is also one of the common adverse events after stent placement and tumor involvement in the cystic duct is a risk factor for cholecystitis [47]. Although it is believed that covered metal stents are risk factors for pancreatitis and cholecystitis, our previous studies did not reveal the use of covered metal stents as a risk factor [46, 47]. Stent migration also necessitates reintervention if symptomatic, and is almost exclusively seen in covered metal stents. Chemotherapy, stents with low axial force, and duodenal invasion were associated with early stent migration in our retrospective analysis [48]. Thus, to prevent these stent-related adverse events, risk factors should be fully evaluated and stents with low axial force and high radial force should be selected.

20.6 Future Perspective

While biliary stent placement is a palliative treatment for obstructive jaundice, attempts have been made to add antitumor effects to biliary stents such as drug-eluting stents and radioactive stents. Although no randomized controlled trials have demonstrated the superiority of those new stents over conventional stents, the development of these drug-eluting or radioactive stents may further improve stent patency and survival in pancreatobiliary cancers. In addition to biliary stents, intraductal ablation for MBO is also increasingly reported [49] but a large-scale randomized controlled trial is warranted to establish its role in the management of MBO. Finally, the role of EUS-BD is expanding from salvage procedure after failed ERCP to primary biliary drainage for unresectable MBO. Prospective randomized controlled trials have shown non-inferiority of EUS-BD to ERCP-BD for distal MBO [50] but it is still controversial whether EUS-BD will replace all ERCP-BD in the future or not.

In summary, ERCP-based management of MBO in pancreatobiliary cancers has been established as the standard of care but there still remains the need for improvement in various aspects. There still remains room for the development of better stents based on characterization by axial force and radial force as well as stents with a special function.

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Interventional EUS for Pancreatic Cancer and Cholangiocarcinoma

21

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Abstract

In the management of patients with pancreatic cancer and cholangiocarcinoma, various issues other than antitumor therapy will develop: obstructive jaundice due to the tumor invasion to the bile duct or the biliojejunal anastomotic stricture after pancreatoduodenectomy; recurrent pancreatitis or pancreatic pain due to the pancreatojejunal anastomotic stricture after pancreatoduodenectomy; cholecystitis due to the placement of biliary self-expandable metal stents; postoperative pancreatic fistulas with or without peripancreatic fluid collections, and severe abdominal pains due to the tumor invasion to the celiac plexus. Traditionally, endoscopic transpapillary or percutaneous approaches were applied for the treatment of such problems; however, they have many limitations in the success and the quality of life of patients. To date, endoscopic ultrasound (EUS)-guided interventions have emerged to resolve these issues as minimally invasive therapies. In this chapter, EUS-guided interventional procedures in the management of pancreatic cancer and cholangiocarcinoma will be described.

Keywords

Endoscopic ultrasound · Biliary drainage · Choledochoduodenostomy · Hepaticogastrostomy · Hepaticoduodenostomy · Rendezvous · Pancreatic duct drainage · Gallbladder drainage · Postoperative pancreatic fistula · Celiac plexus neurolysis · Celiac ganglion neurolysis

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21.1 Introduction

Endoscopic ultrasound (EUS) was developed in the late 1970s for the observation of extraenteric organs. In 1992, EUS-guided pancreatic pseudocyst drainage [1] and fine-needle aspiration (FNA) [2] were reported. Thereafter, a number of interventional EUS procedures have developed: drainage procedures for the bile duct, pancreatic duct, gallbladder, and peripancreatic fluid collections (PFCs); the celiac plexus block or neurosis for the control of the abdominal pain; antitumor therapies of pancreatic neoplasms such as the ethanol injection and radiofrequency ablation; creations of gastroenteric anastomosis such as gastrojejunostomy for the malignant gastric outlet obstruction, and gastro-gastrostomy for endoscopic procedures in patients with Roux-en-Y gastric bypass; the intravascular coil deployment for gastric varices. In this chapter, EUS-guided drainage procedures and celiac plexus neurosis are described with relevance to the management of pancreatic cancer and cholangiocarcinoma.

21.2 Required Equipment for Interventional EUS Procedures: Echoendoscope, Processor, and Accessories

A curved linear array (convex) type of echoendoscope with a large accessory channel (3.7 mm or more) can be used for interventional EUS [3]. Usage of an oblique-viewing echoendoscope is the mainstream, whereas a forward-viewing echoendoscope is also useful for some kinds of interventional EUS procedures, such as choledochoduodenostomy, pancreatic duct drainage, and PFC drainage [4, 5]. An ultrasound processor should have a function of Doppler mode for allowing intervening vessels to be avoided during the needle puncture. EUS-guided drainage procedures start with the puncture of objectives with an FNA needle followed by the contrast injection and insertion of a guidewire. As usual, the sizes of a needle and guidewire are 19-gauge and 0.025-inch, respectively, whereas the combination of a 22-gauge needle and 0.018-inch guidewire can be used for the non-dilated bile duct/main pancreatic duct. For the precise seeking of the biliary tree and reliable exchange of devices, guidewires with the hydrophilic tip and stiff shaft are recommended. The next step is tract dilation. There are three kinds of dilators: bougie dilators, balloon dilators, and diathermic dilators [3]. Bougie dilators are most safe, but the size of the created hole is the smallest. Balloon dilators can make the largest hole, but the overdilation of the tract can lead to the leak of the biliopancreatic or gastrointestinal juice. Diathermic dilators have the strongest power to create a hole; otherwise, the hemorrhage from surrounding arteries due to burning effects is worried. So far, diathermic dilators are considered to be alternatives in cases in which other dilation methods fail [3]. Finally, stents are deployed. Types of stents include plastic stents, self-expandable metal stents (SEMSs), and lumen-apposing metal stents (LAMSs) [6]. Plastic stents are less expensive and easy to be placed but have some potential risks: the stent clogging due to the small caliber (7 Fr as usual) and the leak of the biliopancreatic or gastrointestinal juice due to the lack of the self-expanding

property [3, 7]. Single- or double-pigtail type plastic stents are usually used to prevent stent migration. In SEMSs, uncovered types are not suitable because the biliopancreatic or gastrointestinal juice could leak through the mesh between the targeted organs and gastrointestinal wall, so that covered SEMSs are used. Covered SEMSs could prevent the leak by sealing the fistula due to the self-expanding property. Since migration is the major limitation of covered SEMSs, various anti-migration properties have been developed, such as uncovered ends, flared ends, and flaps [6, 8, 9]. LAMSs are the most reliable devices with regard to making a tight anastomosis with the strong power of attracting both face-to-face lumens and large flared ends [10]. LAMSs facilitate additional endoscopic procedures via the created large anastomosis, such as endoscopic necrosectomy for the walled-off necrosis after necrotizing pancreatitis [11] and the extraction of gallstones for calculous cholecystitis [12].

21.3 EUS-Guided Biliary Drainage (EUS-BD)

Both pancreatic cancer and cholangiocarcinoma can cause malignant biliary obstruction (MBO). Pancreatic head cancer (occasionally pancreatic body cancer) can cause distal MBO and cholangiocarcinoma can cause both distal and hilar MBO. The biliary drainage should be done primarily via endoscopic transpapillary cholangiopancreatography (ERCP) [3, 13]; however, the biliary access is sometimes impossible due to the failed biliary cannulation, the duodenal invasion of the tumor, or the surgically altered anatomy. Moreover, in cases with hilar MBO, adequate biliary drainage is often difficult even after the successful biliary cannulation especially in Bismuth type 3 or 4 [14, 15]. EUS-guided biliary drainage (EUS-BD) has recently emerged as an alternative to transpapillary drainage [16–24]. EUS-BD includes transmural drainage, antegrade stenting, and rendezvous. The transmural drainage includes EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS), and EUS-guided hepaticoduodenostomy (EUS-HDS).

The selection of methods of EUS-BD should be decided based on not only the site of the biliary obstruction and the accessibility to the ampulla but also the resectability of the tumor [3, 13, 25, 26]. The transmural drainage is not suitable for the preoperative biliary drainage (PBD) in potentially resectable tumors, because the influence of the created fistula on surgical procedures is still unknown. Thus, the antegrade stenting or rendezvous can be used for the PBD basically [3]. On the other hand, any method is acceptable for palliative drainage in unresectable tumors. A proposed algorithm for EUS-BD in MBO is noted in Fig. 21.1.

21.3.1 EUS-Guided Transmural Biliary Drainage

EUS-guided transmural biliary drainage is the method that makes a fistula between the bile duct and the gastrointestinal lumen. Although a recently published

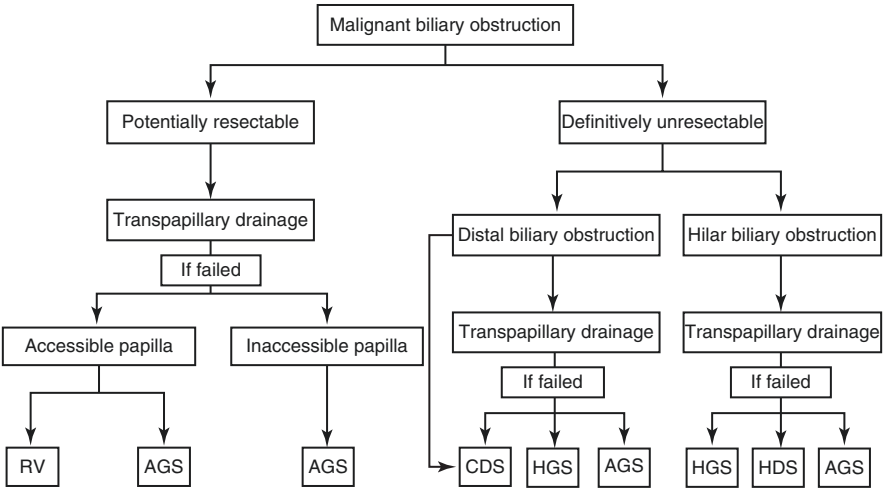

Fig. 21.1 A proposed algorithm for EUS-guided biliary drainage (EUS-BD) in malignant biliary obstruction. *RV* rendezvous, *AGS* antegrade stenting, *CDS* choledochoduodenostomy, *HGS* hepaticogastrostomy, *HDS* hepaticoduodenostomy

systematic review and meta-analysis demonstrated that EUS-guided transmural biliary drainage could show similar efficacy and safety when compared with ERCP for the primary drainage of distal MBO [27], the indication of the transmural biliary drainage is considered to be the alternative to the failed ERCP in principle, at present.

21.3.1.1 EUS-Guided Choledochoduodenostomy (EUS-CDS) (Fig. 21.2)

EUS-CDS is the method of making a fistula between the duodenal bulb and the extrahepatic bile duct (EHBD) for distal MBO and was firstly reported by Giovannini et al. [28]. An echoendoscope is advanced into the duodenal bulb with a pushed (long) scope position; subsequently, the dilated EHBD is punctured by a 19-gauge needle, and a 0.025-inch guidewire is inserted and placed in the intrahepatic bile duct (IHBD). After the tract dilation, stents are placed across the choledochoduodenal fistula [3, 29]. Although plastic stents were used initially [30–32], covered SEMSs [5, 16, 33, 34] or LAMSs [35–39] are currently used preferably to reduce the bile leak and create larger fistulas [3, 6].

The conventional indications for EUS-CDS are unresectable distal MBO after failed ERCP. However, two randomized controlled trials (RCTs) comparing primary EUS-CDS with ERCP for distal MBO were published in 2018 demonstrating the similar success rate, adverse events rate, and stent patency [40, 41]. Given these results and the technical easiness, the application of EUS-CDS to the primary drainage [5, 29] is likely to be acceptable.

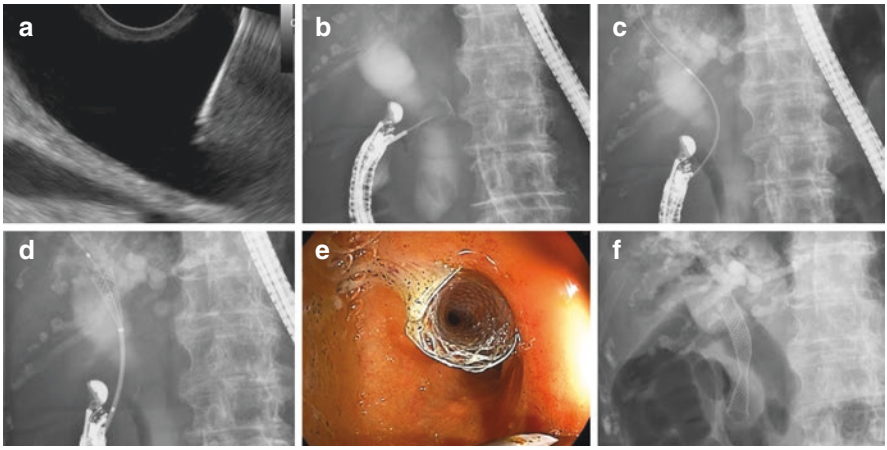

Fig. 21.2 EUS-guided choledochoduodenostomy (EUS-CDS). (**a**) Puncture of the common bile duct under EUS guidance. (**b**) Cholangiogram on fluoroscopy. (**c**) Tract dilation with a diathermic dilator under fluoroscopic guidance. (**d**) A partially covered self-expandable metal stent deployment under fluoroscopic guidance. (**e**) Endoscopic view after the stent placement. (**f**) Fluoroscopy after the stent placement

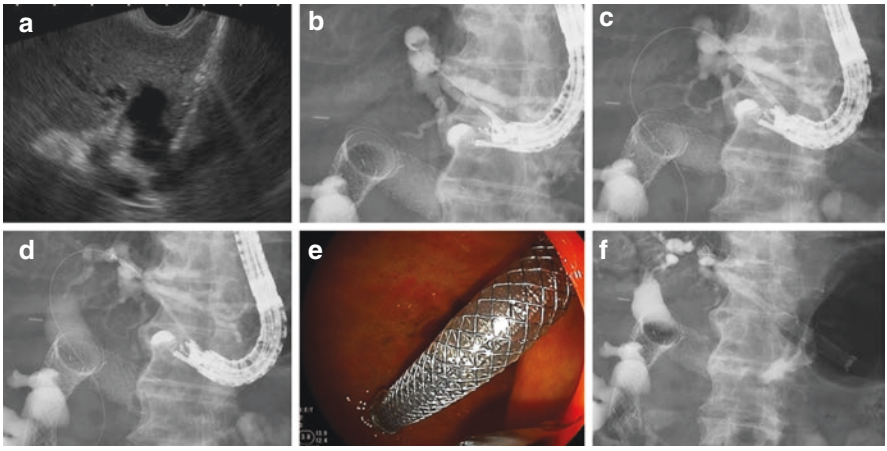

Fig. 21.3 EUS-guided hepaticogastrostomy (EUS-HGS). (**a**) Puncture of the left intrahepatic bile duct (B3) under EUS guidance. (**b**) Cholangiogram on fluoroscopy. (**c**) Tract dilation with a balloon catheter under fluoroscopic guidance. (**d**) Delivery system of a partially covered self-expandable metal stent insertion under fluoroscopic guidance. (**e**) Endoscopic view after the stent placement. (**f**) Fluoroscopy after the stent placement

21.3.1.2 EUS-Guided Hepaticogastrostomy (EUS-HGS) (Fig. 21.3)

EUS-HGS is the method of making a fistula between the stomach and the left IHBD for distal or hilar MBO. In 2003, Burmester et al. [42] and Giovannini et al. [43] reported EUS-HGS first. Since the puncture of the B2 has a potential

risk of mediastinitis owing to the trans-esophageal puncture, B3 is preferable over B2 to be punctured [3]. EUS-HGS is a more complicated procedure than EUS-CDS regarding technical issues and adverse events. First, the puncture of an inadequately dilated bile duct is technically challenging. Second, the portal vein or hepatic artery in the Glisson's sheath could be accidentally punctured resulting in bleeding or pseudoaneurysm [44]. Third, the migration of the distal end (gastric side) of the stent into the abdominal cavity could easily occur due to the large peristaltic movements of the stomach, and it causes a fatal adverse event [45]. To prevent the migration and subsequent bile leak, covered SEMSs with a long length (10 cm or more) or anchoring flap/fin are preferable [3, 8, 9, 46].

EUS-HGS has more various indications than EUS-CDS. The most major indication is distal MBO combined with the duodenal invasion [47–51]. ERCP via the mesh of an indwelled duodenal stent covering the ampulla is extremely difficult. Even if the ampulla is not covered by the duodenal stent, transpapillary-placed stents in the presence of a duodenal stent are likely to be occluded by the food impaction or biliary sludge due to the decreased duodenal flow, and transmural drainage might have better patency [52]. Other indications include MBO with the surgically altered anatomy as an alternative to device-assisted enteroscope-guided ERCP (DAE-ERCP) [51], and hilar MBO requiring the drainage of the left hepatic lobe with the failed transpapillary drainage [14].

One RCT comparing primary EUS-guided transmural drainage (HGS or CDS) with ERCP for unresectable MBO including patients with the duodenal obstruction or surgically altered anatomy showed similar efficacy and the lower rate of adverse events and a higher rate of stent patency in the EUS-guided transmural drainage group [53]. The better stent patency could be attributed to the avoidance of the tumor ingrowth or hemorrhage with transmural stenting bypassing the obstruction site. However, the appropriateness of primary EUS-HGS has been conflicting due to a lack of evidence around the direct comparison with ERCP.

According to a recent systematic review and meta-analysis, EUS-CDS and EUS-HGS have equal efficacy and safety. Rates of technical success, clinical success, and adverse events were 94.1%, 88.5%, 18.6% in EUS-CDS and 93.7%, 84.5%, 18.8% in EUS-HGS, respectively [54]. The main adverse events of EUS-CDS/HGS were the bile leak, stent migration, bleeding, perforation, and peritonitis.

21.3.1.3 EUS-Guided Hepaticoduodenostomy (EUS-HDS) (Fig. 21.4)

EUS-HDS is the method of making a fistula between the duodenal bulb and the right IHBD for hilar MBO. In EUS-HDS, the right posterior branch of the bile duct is punctured from the duodenal bulb with a pushed (long) scope position. Therefore, patients with surgically altered anatomy or duodenal invasion are contraindications, unlike EUS-HGS. EUS-HDS is just the drainage method of the right hepatic lobe in which the transpapillary access fails. Evidence of EUS-HDS is extremely limited [55, 56].

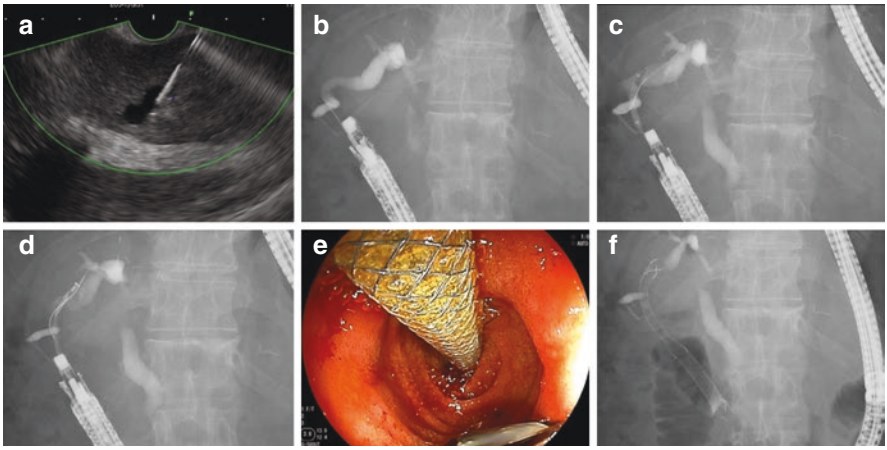

Fig. 21.4 EUS-guided hepaticodeodenostomy (EUS-HDS). (**a**) Puncture of the right intrahepatic bile duct (B6) under EUS guidance. (**b**) Cholangiogram on fluoroscopy. (**c**) Tract dilation with a balloon catheter under fluoroscopic guidance. (**d**) A partially covered self-expandable metal stent deployment under fluoroscopic guidance. (**e**) Endoscopic view after the stent placement. (**f**) Fluoroscopy after the stent placement

21.3.2 EUS-Guided Antegrade Stenting (EUS-AGS)

EUS-AGS is a technique to deploy stents across the stricture in the antegrade fashion via the HGS route [3, 57, 58]. It was firstly reported by Nguyen-Tang et al. [59]. Because of the physiological bile flow and the unnecessity of creating the fistula, EUS-AGS could be used for PBD. Usually, uncovered SEMSs with slim delivery systems, which do not require the tract dilation prior to the stent insertion, are used [57, 58, 60]. Since uncovered SEMSs could be occluded by the tumor ingrowth, keeping the bilio-enteric fistula is desirable for re-intervention. That is, for the palliative drainage, EUS-AGS is usually performed as a combination with EUS-HGS [60], not as alone. In distal MBO, whether additional EUS-AGS to EUS-HGS contribute to prolonging the time to recurrent biliary obstruction or not are unknown. In hilar MBO, EUS-AGS from the left IHBD to right IHBD to connect both ducts, which should be performed with EUS-HGS for biliary drainage, is useful for the bilateral drainage [14]. The technical success rate of EUS-AGS was reported as 83% [3].

21.3.3 EUS-Guided Rendezvous (EUS-RV)

EUS-RV is a rescue technique for the failed biliary cannulation in ERCP, which was firstly reported by Mallery et al. [61]. After the puncture of the bile duct, a guidewire is inserted into the bile duct and subsequently manipulated to pass the stricture

and the sphincter of Oddi. After the placement of the guidewire in the duodenum, an echoendoscope is exchanged to a duodenoscope keeping the guidewire left in place. Finally, the transpapillary biliary cannulation is attempted with the help of the EUS-placed guidewire [62, 63].

In EUS-RV, there are four approach routes: the puncture of the distal EHBD from the duodenal second part with a stretched (short) scope position, the puncture of the proximal EHBD from the duodenal bulb with a pushed (long) scope position, the puncture of the left IHBD from the stomach with a short scope position, and the puncture of the right IHBD from the duodenal bulb with a long scope position [25, 62–64]. The puncture of the distal EHBD from the duodenal second part is likely to be the best approach route because the maneuverability of the guidewire is favorable due to the short distance between the puncture site and the papilla, and the favorable direction of the needle [25, 65–67].

The indication for EUS-RV is potentially resectable MBO, whereas EUS-guided transmural biliary drainage is preferable for definitively unresectable MBO due to its simple and short-time procedure. Rates of technical success and adverse events of EUS-RV were reported as 82% and 13%, respectively, in a review article [68].

21.4 EUS-Guided Pancreatic Duct Drainage (EUS-PD)

EUS-PD is a salvage technique for failed ERCP in symptomatic strictures of the main pancreatic duct or pancreatojejunal anastomosis after pancreatoduodenectomy. Francois et al. [69] and Bataille et al. [70] firstly reported about EUS-PD in 2002. Pancreatic head cancer often causes the main pancreatic duct stricture; however, pancreatic duct drainage is rarely needed unlike chronic pancreatitis [71, 72]. Thus, in the area of pancreatobiliary malignancy, EUS-PD is mainly performed for the relief of abdominal pain or recurrent pancreatitis due to the pancreatojejunal anastomosis stricture after pancreatoduodenectomy. In this setting, distinguishing whether the cause of the stricture is the recurrence of cancer or inflammation is crucial to patient management. Since DAE-ERCP allows the direct visualization of the anastomotic site, it is better than EUS-PD in patients in whom definitive cancer recurrence is not detected on other imaging modalities. EUS-PD should be applied when DAE-ERCP fails or the recurrence of the cancer is incontrovertible.

There are two methods for EUS-PD, such as rendezvous (RV) [70, 73] and transmural drainage [69, 74]. The latter includes antegrade stenting and pancreaticogastrostomy [75–81]. In cases with an accessible papilla or anastomosis, EUS-RV can be selected. Generally, the main pancreatic duct is punctured from the stomach at first. After the injection of a contrast agent to obtain a pancreatogram, a guidewire is inserted into the pancreatic duct. If the passage of the guidewire through the stricture is successful, EUS-RV or antegrade stenting can be attempted. In EUS-RV, an echoendoscope is exchanged to a duodenoscope alongside the guidewire, and the pancreatic duct cannulation via the papilla or anastomosis with the help of the EUS-placed guidewire is performed. In antegrade stenting, the tract and stricture site are

dilated by dilation devices like EUS-BD, followed by the insertion of a plastic stent across the stricture. When the guidewire or dilator cannot pass the stricture, the stent is placed with the tip in the upstream pancreatic duct as pancreatogastrectomy.

In a recent review article, rates of technical success and adverse events of EUS-PD were 78.7% and 21.8%, respectively. The technical success rate of EUS-RV was lower than that of transmural drainage due to the difficulty in the guidewire passage through the stricture [75].

21.5 EUS-Guided Gallbladder Drainage (EUS-GBD)

EUS-GBD is a procedure to drain the gallbladder for the relief of the symptoms of acute cholecystitis, which was firstly introduced in 2007 [82–84]. Major causes of acute cholecystitis in the field of biliopancreatic malignancy are the blockage of the orifice of the cystic duct (OCD) by biliary SEMSs or the direct tumor invasion. Acute cholecystitis can occur in around 5–7% after the placement of biliary SEMS [85, 86]. Tumor invasion to the OCD [85] and the high axial force of the SEMS [86, 87] are likely to be associated with the incidence of cholecystitis, so that not only covered SEMSs but also uncovered SEMSs could be a risk of cholecystitis. Percutaneous transhepatic gallbladder drainage (PTGBD) is the standard therapy for acute cholecystitis in patients unfit for urgent surgical cholecystectomy [88]. However, it is unsuitable for nonsurgical candidates, even for elective surgery, because permanent external drainage is required. The percutaneous external drainage tube placement often causes various adverse events, such as sustained pain, tube clogging, tube migration, and tube fracture [89]. Recent meta-analyses [90, 91] and an RCT [92] comparing EUS-GBD with PTGBD showed that technical and clinical success rates were similar but procedural and long-term adverse events rates were higher with PTGBD. Therefore, internal drainage with EUS-GBD is the ideal method for palliative drainage in nonsurgical candidates [7]. Another indication of EUS-GBD is the biliary drainage for distal MBO after the failed transpapillary or EUS-guided biliary drainage, in which the OCD is patent [93, 94].

In EUS-GBD, basic methods are similar to those of EUS-BD: the puncture of the gallbladder from the duodenal bulb or gastric antrum, the guidewire insertion into the gallbladder lumen, the tract dilation, and the stent deployment. Although various kinds of stents can be used for EUS-GBD, LAMSs are the most frequently reported stents owing to the lumen-apposing feature for prohibiting the bile leak and stent migration, and the large diameter to allow sufficient drainage. Moreover, a LAMS with an electrocautery tip (HOT AXIOS™; Boston Scientific Corp, Natick, MA, USA), with which all procedural steps can be done in a single pass, is recently developed [95]. HOT AXIOS™ is expected to reduce the risk of the bile leak, shorten the procedural time, and enable fluoroless and contrast-free procedures [96].

Although LAMSs have many advantages, long-term safety has not been established. The long-term indwelling of LAMSs could induce serious delayed adverse events, such as the buried stent, hemorrhage, food influx, and pyloric ring obstruction [97–100]. Therefore, in patients whose predicted prognosis is over several

months, LAMSs had better be removed or exchanged for plastic stents within 3 months [99, 101, 102]. Even though LAMSs are considered to be ideal devices, the superiority of LAMSs over other stents has not been verified [103]; favorable results have been demonstrated regardless of the stent type [104, 105]. According to the recent meta-analysis including 557 patients (14 studies) who underwent EUS-GBD with various stent types, overall pooled rates of technical success, clinical success, and adverse events were 95.3%, 96.7%, and 12.4%, respectively. Adverse events included bleeding (4.3%), perforation (3.7%), bile leak (2.9%), stent migration (2.7%), and stent occlusion (2.6%). The most advantage of LAMSs is the large fistula which allows direct cholecystoscopy with a standard endoscope to perform extraction of gallstones in calculous cholecystitis [106–108]; however, it is unnecessary in the field of biliopancreatic malignancy. In addition, LAMSs are expensive and not commercially available for EUS-GBD in many countries. The best drainage device in this field should be further investigated.

21.6 EUS-Guided Therapy for Postoperative Pancreatic Fistulas

A postoperative pancreatic fistula (POPF), which represents a failure of healing (sealing) of a pancreatic-enteric anastomosis or a parenchymal leak not causally related to an anastomosis [109], is a major cause of morbidity after pancreatectomy and can occur in up to 30% of patients following partial pancreatic resections [110]. Traditionally, POPFs have been managed by the percutaneous or operative drainage; however, endoscopic therapies developed recently.

POPFs with evident PFCs can be relatively easily treated by EUS-guided PFC drainage [111–115], which was firstly reported by Grimm et al. in 1992 as a treatment of pancreatic pseudocysts secondary to acute pancreatitis [1]. Techniques of EUS-guided PFC drainage were similar to those of EUS-GBD. When most of the contents of a PFC are liquid materials, plastic stents are usually used; however, LAMSs are preferable in a PFC which contains rich necrotic tissues in order to facilitate endoscopic necrosectomy [116, 117]. POPFs without definite PFCs include internal pancreatic fistulas (IPFs) and external pancreatic fistulas (EPFs): the former surface in the form of pancreatic ascites or pancreatic pleural effusions, the latter are created surgically or by a percutaneous catheter, respectively. In these cases, a transpapillary bridging therapy with a drainage tube placement across the disruption point is needed. However, DAE-ERCP in the early postoperative phase is difficult and complete disruption (disconnection) of the MPD is hard to be restored. Endoscopic approaches for cases with failed transpapillary therapies are really complicated and challenging. In EPFs, rendezvous techniques that combined endoscopic and percutaneous procedures could be performed to internalize EPFs: in the "outside-in" method, after the puncture into the stomach lumen from the existing percutaneous drainage fistula under the fluoroscopic guidance alone, a guidewire delivered through the needle is captured endoscopically; subsequently, the tract dilation and plastic stents insertion are performed; in the "inside-out" method, after

the EUS-guided puncture to create a fistula to the percutaneous drainage catheter, a guidewire is inserted into the cavity then grasped via the percutaneous route; subsequently, the tract dilation and plastic stents insertion are performed [118–121]. In IPFs, EUS-PD into the upstream duct of the leakage point is needed [111]. Technical and clinical success rates of endoscopic treatments of POPF are likely to be 90–100% and 79–100%, respectively [122].

21.7 EUS-Guided Celiac Plexus Neurolysis and Celiac Ganglion Neurolysis (EUS-CPN and CGN)

Most patients with pancreatic cancer suffer from abdominal pain, which represents a major issue in the management of this population. In patients with failed response to narcotic analgesics due to the inadequate effect or adverse event such as nausea, constipation, and sleepiness, celiac plexus neurolysis (CPN) was performed under the guidance of fluoroscopy or computed tomography (CT) until the 1990s. Although those posterior percutaneous techniques showed a high success rate of pain relief, it was worried that severe adverse events such as lower extremity paresthesia might occur [123]. In the mid-1990s, EUS-guided CPN developed as the safer approach under the real-time visualization on the EUS image [124, 125]. The celiac plexus itself cannot be seen on ultrasound but can be targeted based on its expected anatomical position in relation to the position of the celiac trunk [126]. EUS-CPN is divided into two methods, such as the central method and the bilateral method. A 19-gauge or 22-gauge needle is passed through the gastric wall, and advanced to just adjacent to the anterosuperior aspect of the celiac trunk takeoff in the central method, while the needle is advanced through both sides of the celiac trunk to the level of the base of the origin of the superior mesenteric artery in the bilateral method. After an aspiration test to rule out vessel penetration, 2–3 mL of 0.25–0.75% bupivacaine is injected followed by 10–20 mL of absolute alcohol. The bilateral method is more difficult but more effective than the central method as it may allow a larger number of ganglia to be damaged. Sahai et al. reported that the mean reduction rate of pain scores in the bilateral method (70.4%) was significantly higher than that in the central method (45.9%) in the prospective study [127]. In a meta-analysis and systematic review reported by Puli et al., 80.1% of patients with pancreatic cancer showed pain relief by EUS-CPN. The bilateral method showed a significantly higher proportion of patients with pain relief (84.5%) than the central method (46.0%) [128].

EUS-CPN does not attempt injections directly into celiac ganglia. After the recognition that celiac ganglia can be visualized most frequently between the aorta and the left adrenal gland by EUS, Levy et al. firstly reported EUS-guided direct celiac ganglia neurolysis (EUS-CGN) in the retrospective study [129]. In this study, pain relief was obtained in 94% (16/17) of patients with pancreatic cancer. Doi et al. reported in the RCT that the EUS–CGN group demonstrated a significantly higher positive response rate (73.5%) than the EUS-CPN group using the central method (45.4%) without the difference in adverse events or the duration of the pain relief.

Alvarez-Sanchez et al. reported in the review article that adverse events occurred in 21% of 661 EUS-CPN/CGN procedures. Most of the adverse events were minor and spontaneously resolved within 48 h, related to the blockage of sympathetic efferent activity such as transient diarrhea (10%) and hypotension (5%). Major adverse events were observed in only 0.2% of cases, including organ ischemia, abscess, and paraplegia [130].

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Novel Endoscopic Focal Therapy for Pancreatic Cancer and Cholangiocarcinoma

22

Takeshi Ogura

Abstract

Despite attempts at local treatment for pancreatic cancer (PC) and cholangiocarcinoma (CCA), prolonged survival might remain limited because PC and CCA are considered systemic diseases. However, recently, endoscopic therapeutic modalities such as endoscopic ultrasound (EUS) or digital single-operator cholangioscopy (DSOCS) have emerged, and local endoscopic treatment has thus gained significant interest as an innovative technique to treat PC and CCA. If tumor size can be decreased by local endoscopic treatment, several effects might be expected, such as the resolution of bile duct obstruction leading to a biliary stenting-free situation and pain relief. To date, various local endoscopic treatment techniques such as EUS-guided fine-needle injection, brachytherapy, and tumor ablation for PC, and photodynamic treatment, radiofrequency ablation under endoscopic retrograde cholangiopancreatography for CCA. In this chapter, a novel local endoscopic treatment for PC and CCA using EUS and DSOCS is described with a review of the literature.

Keywords

Pancreatic cancer · Cholangiocarcinoma · Endoscopic retrograde cholangiopancreatography · Endoscopic ultrasound · Focal therapy

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Table 22.1 Major techniques of endoscopic local therapy for pancreatic cancer and cholangiocarcinoma

Pancreatic cancer		
	EUS-guided fine-needle injection	
	EUS-guided brachytherapy	
	EUS-guided tumor ablation	Radiofrequency ablation High-intensity-focused ultrasound Cryothermal ablation Photodynamic treatment Neodymium-doped yttrium aluminum garnet laser ablation
Cholangiocarcinoma		
	ERCP-guided photodynamic treatment	
	ERCP-guided radiofrequency ablation	

22.1 Background

The incidence of pancreatic cancer (PC) has increased over recent decades [1]. The poor prognosis of PC is well known, with a survival rate of <10% [2], despite developments in systemic chemotherapy [3, 4]. Cholangiocarcinoma (CCA) is uncommon compared with PC but is known as an aggressive malignancy of biliary epithelial cells [5]. In unresectable cases, the median overall survival in CCA patients is 3–6 months [6]. Early diagnosis of PC and CCA is thus extremely important, and surgical resection should be performed to obtain curative treatment. On the other hand, systemic chemotherapy now plays a core role in advanced-stage PC and CCA patients. Despite attempts at local treatment for PC and CCA, prolonged survival might remain limited because PC and CCA are considered systemic diseases. However, because endoscopic therapeutic modalities such as endoscopic ultrasound (EUS) or digital single-operator cholangioscopy (DSOCS) have emerged, local endoscopic treatment has gained significant interest as an innovative technique to treat PC and CCA. If tumor size can be decreased by local endoscopic treatment, several effects might be expected, such as the resolution of bile duct obstruction leading to a biliary stenting-free situation and pain relief. In addition, prolonged survival may be obtained by this technique when combined with systemic chemotherapy.

In this chapter, a novel local endoscopic treatment for PC and CCA using EUS and DSOCS is described with a review of the literature (Table 22.1).

22.2 Local Endoscopic Treatment for Pancreatic Cancer

PC is characterized as a hypovascular tumor and histologically shows dense stroma, so improving the effectiveness of systemic chemotherapy remains challenging. On the other hand, local endoscopic treatment has the potential to minimize systemic

exposures and to increase local concentrations of antitumor agents or physical treatment effects. Local endoscopic treatment can be divided into two main techniques: EUS-guided fine-needle injection of antitumor agents; and tumor direct ablation. Local endoscopic treatments might have benefits because direct antitumor effects might be obtained by tumor ablation and injection of antitumor agents [7].

22.2.1 EUS-Guided Fine-Needle Injection

After PC is identified under EUS guidance, several materials are directly injected into the tumor through the fine needle. Compared with transvenous or transarterial injections, materials can be directly injected within the tumor, so material effects might be improved. In addition, the adverse event rate seems likely to be reduced, because systemic effects should be minimized [8]. Various antitumor agents have been reported [9–15].

A phase I/II trial examining intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in 21 patients with unresectable PC has been reported [11]. In that study, partial regression was observed in two patients, and minor response in two patients. Eleven patients displayed progressive disease or withdrew from the study due to treatment toxicity. Given those results, achieving clinical efficacy with EUS-guided fine-needle injection remains challenging.

Nishimura et al. recently conducted a clinical trial of EUS-guided fine-needle injection using STNM01, a synthetic double-stranded RNA oligonucleotide that selectively inhibits expression of carbohydrate sulfotransferase 15 (CHST15) [13]. CHST15 is known to promote tumor growth and invasion factors. In this study, a total of 16 mL of STNM01 (250 nM) was injected into the tumor. The safety of this technique was evaluated first, and local expression of CHST15 was histologically evaluated by overall survival (OS). No adverse events were seen in any patients. Mean tumor diameter decreased from 30.7 mm to 29.3 mm by 4 weeks after treatment. Serum levels of soluble CD44 variant 6 (sCD44v6) decreased significantly from 98.1 ng/ml to 83.2 ng/ml. In EUS-guided fine-needle aspiration specimens, CHST15 was highly expressed at baseline, with two patients showing large reductions of CHST15 by week 4. Mean OS for these two patients was 15 months, compared to 5.7 months for the other four patients. They concluded that EUS-guided fine-needle injection of oligonucleotide STNM01 was technically safe for PC patients, and reductions in CHST15 and sCD44v6 could contribute to the prediction of tumor progression and OS.

As noted above, various materials have been attempted, and this novel concept might be expected. However, certain clinical evidence is still lacking. Prospective randomized controlled trials in a large patient cohort are warranted.

22.2.2 EUS-Guided Brachytherapy

Radiation combined with systemic chemotherapy for locally advanced PC now plays an important role in preoperative down-staging [14]. In addition, reducing

tumor volume might benefit patients with cancer pain. However, the pancreas is situated deep in the abdominal cavity, and PC, which histologically comprises adenocarcinoma cells, is relatively insensitive to radiation compared with other histological cancer types such as squamous cell carcinoma. Brachytherapy, as a form of radiotherapy in which radioactive seeds, microparticles, or liquids are directly placed within the tumor, might thus be ideal for PC to obtain effective irradiation. Traditionally, this technique has been indicated for other cancers, such as those of the prostate, cervix, lung, or head [15–17]. The benefits of brachytherapy are the delivery of a much greater dose of radiation to the tumor and relatively low toxicity for other organs compared with external radiotherapy because brachytherapy does not need to penetrate normal tissues existing between the radiation source and target tumor.

Compared with computed tomography (CT)- or transabdominal ultrasonography-guided approaches, EUS-guided approaches using radionuclides such as phosphorus 32, iodine, and gold might offer several advantages in brachytherapy by providing clear real-time imaging. EUS-guided brachytherapy has thus emerged [18–20]. One recent clinical trial of EUS-guided brachytherapy using novel ^{32}P microparticles (P-32) is now underway [7, 18, 21]. P-32 is an experimental technique intended for use in brachytherapy that carries the radioactive β-emitter P-32 inside inactive silicon particles. The PC is punctured using a 22-G fine needle, and the microparticles are inserted into the PC through a needle. A total of nine patients with locally advanced PC have been enrolled. P-32 was successfully inserted into the tumor in all patients without any adverse events. The local disease control rate was 88%, with partial response or stable disease observed in seven of the nine patients. Median tumor volume in week 16 was −9% (range, +61 to −80%). Although the results represent preliminary data, the authors concluded that EUS-guided brachytherapy using P-32 combined with standard chemotherapy is technically feasible and showed an acceptable safety profile in patients with unresectable, locally advanced PC.

EUS-guided brachytherapy might be clinically impactful and technically feasible, but further evaluation in a prospective, randomized study is needed to verify the benefits of this technique.

22.2.3 EUS-Guided Tumor Ablation

Another technique for local endoscopic treatment of PC is tumor ablation. This treatment can be divided into several techniques based on the application of different types of electrical and thermal energy. To date, various kinds of EUS-guided tumor ablation have been reported, such as radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), cryothermal ablation, photodynamic treatment (PDT), and neodymium-doped yttrium aluminum garnet (YAG) laser ablation.

After the first report of EUS-guided RFA by Goldberg et al. [22], the technique has now matured and is now being applied to patients with pancreatic neuroendocrine tumors and pancreatic cystic lesions, especially in cases unsuited to surgical

resection [23]. This technique has recently also been attempted for patients with advanced PC. Among cases of local PC treatment under EUS guidance, EUS-guided RFA has been evaluated the most in clinical trials. After RFA procedures, inflammatory responses such as natural killer cells, dendritic cells, and T lymphocytes have been observed within the RFA site. In addition, according to an investigation of immune reactions in blood samples of patients with locally advanced PC [24], $CD4^+$ and $CD8^+$ increased significantly between days 3 and 30, suggesting the activation of adaptive immune responses. Effector memory T cells (T_{EM}), which play a crucial role in immediate memory response, were also increased. RFA might thus have roles to play not only at local sites but also in systemic responses to patients with locally advanced PC. Naturally, this result from a pilot study should be verified in a prospective, large-scale study. To date, several devices for EUS-guided RFA, such as the Habib™ EUS-RFA electrode (EMcision Ltd, London, UK) and EUSRA RF electrode (STARmed; Koyang, South Korea) have become available [25]. Scopelliti et al. evaluated the technical safety and feasibility of EUS-RFA using STARmed devices for patients with unresectable PC with non-metastatic tumors [26]. In this study, 10 patients were enrolled after neoadjuvant chemotherapy. Technical success was obtained for all patients with no major adverse events, although self-limiting abdominal pain ($n = 2$), increased serum amylase levels ($n = 2$), and peripancreatic effusion ($n = 2$) were observed and successfully treated by conservative treatment. Partial response with reduction in PC size was observed in five patients, and stable disease in five patients. According to that preliminary study, EUS-RFA might be safe and feasible, although a prospective, randomized trial of a large cohort with long-term follow-up is needed.

HIFU is another novel local endoscopic treatment technique, utilizing thermal denaturation caused by ultrasonography leading to tumor necrosis. Zhu et al. retrospectively investigated HIFU for advanced PC [27]. Among 83 patients who underwent HIFU and evaluation of disease control, the complete response rate was 3.6% (3/83), and the partial response rate was 79.5% (66/83). In addition, pain reduction was observed in 74 patients. Overall survival rates at 1 and 2 years were 41.5% and 9.6%, respectively. They, therefore, concluded that HIFU can alleviate cancer-related pain and prolong overall survival. As noted above, HIFU might be a promising treatment modality. To obtain greater treatment effects and to prevent adverse events such as organ injury, devices for EUS-guided HIFU have increasingly been developed (Fig. 22.1) [28, 29]. A clinical study is needed to determine whether EUS-guided HIFU represents a valid alternative treatment.

To prevent thermal injury, which might, in turn, lead to biliary or duodenal stricture and vessel injury, cryothermal ablation has been developed [30, 31]. Cryothermal ablation is a hybrid bipolar method combining the thermal injury of RFA with the cooling effects of cryogenic gases. As a preliminary study, Carrara et al. evaluated EUS-guided cryothermal ablation in the porcine pancreas [30]. Ablation was attempted for 14 pigs with an energy output of 16 W and a simultaneous cryogenic effect, with CO_2 at 650 psi applied for 120–900 s. They reported that the procedure was clearly visible in real time under EUS guidance with no mortality events. After 5 years, Arcidiacono et al. conducted the first feasibility study of

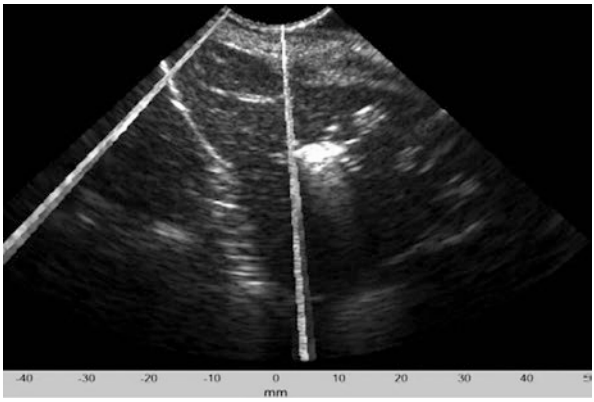

Fig. 22.1 Endoscopic ultrasound-guided high-intensity-focused ultrasound image

EUS-guided cryothermal ablation for 22 patients with local PC [31]. In that study, EUS-guided cryothermal ablation was successfully performed in 16 patients (72.8%), although 6 patients showed technical failure due to stiffness of the intestinal wall and tumor. Severe adverse events were not observed, although minor early adverse events such as minor bleeding (n = 1), increased amylase levels (n = 3), or abdominal pain (n = 3) and late adverse events mainly associated with tumor progressions such as jaundice (n = 2) and duodenal obstruction (n = 1) were observed. EUS-guided cryothermal ablation might be technically feasible, but long-term results from a large-scale clinical trial are needed to evaluate the clinical significance.

PDT has been widely performed for various malignant tumors to obtain selective tissue necrosis or apoptosis. Regarding EUS-guided PDT, a limited approach, especially for the pancreatic head, is one limitation due to the stiffness of the catheter. Recently, a flexible laser-light catheter has been developed for experimental use. Choi et al. evaluated EUS-guided PDT using this device for patients with locally advanced pancreaticobiliary malignancies [32]. In that study, six patients (caudate lobe of the liver, n = 2; far distal bile duct, n = 1; tail of the pancreas, n = 1) were enrolled. Technical success was obtained in all patients with no treatment-related adverse events. Stable disease was observed in all four patients, with a median follow-up of 5 months. According to that preliminary study, EUS-guided PDT might be feasible, but only one PC patient was included in the study. More recently, DeWitt et al. conducted a phase I study of EUS-guided PDT for locally advanced PC [33]. Twelve patients with PC were enrolled, including 8 patients with pancreatic head and/or neck lesions (mean tumor diameter, 45.2 mm). Increased volume and tumor necrosis were observed in 6 of 12 patients (50%) after EUS-guided PDT. Mean overall increases in volume and necrosis were 10 ± 26 cm^3 (P = 0.20) and 18 ± 22% (P = 0.016), respectively. During follow-up (median, 10.5 months), median progression-free survival (PFS) and OS were 2.6 months and 11.5 months, respectively. In addition, adverse events associated with EUS-guided PDT were not seen in any patients. EUS-guided PDT might thus represent a useful treatment technique, although further study is needed.

Compared with the above laser-based treatment techniques, YAG offers several potential benefits, such as the high rate of necrosis associated with a well-defined ablation area and a short application time. Di Matteo et al. recently evaluated the feasibility of EUS-guided YAG for unresectable PC [34]. Among nine patients with stage IIb–III PC who underwent EUS-guided YAG, the ablation area, as demonstrated by 24-h CT, ranged from 0.4 cm^3 (for the lower power setting, 2 W/800 J) to a maximum of 6.4 cm^3 (for 4 W/1000 J). All procedures were successfully performed without any adverse events.

Finally, various techniques regarding EUS-guided tumor ablation have been reported, and these techniques might be feasible and effective as local treatments for PC. However, stronger evidence based on strict, large-scale, randomized clinical trials remains lacking. Further study is needed.

22.3 Local Endoscopic Treatment for Cholangiocarcinoma

Compared with PC, CCA is usually associated with obstructive jaundice. In addition, an EUS-guided approach, such as fine-needle aspiration, is not a common diagnostic method. Therefore, an intraductal approach might be reasonable in CCA patients. As a local endoscopic treatment technique for CCA, PDT, and RFA under endoscopic retrograde cholangiopancreatography (ERCP) have been mainly attempted according to previous studies. Because of the improvement of DSOCS, PDT can be easily attempted under direct visualization, and the effectiveness of RFA can also be observed. To undergo continuous chemotherapy, stent patency or the resolution of bile duct obstruction is very important. Therefore, volume reduction by endoscopic local treatment may make sense.

22.3.1 Photodynamic Treatment

PDT plays a role by creating free-radical-associated tumor cell destruction caused by porfimer enrichment in CCA cells. To date, various clinical trials have been published [35–39]. Ortner et al. conducted a randomized, prospective study of PDT for CCA patients [35]. In this study setting, patients underwent stenting with or without PDT, and all patients did not generally undergo systemic chemotherapy. Although patients' characteristics such as Bismuth types or tumor staging were not significantly different between the groups, median survival was significantly longer in the stent with PDT group (493 days, 95% confidence interval [CI] 276–710 days) than in the stent alone group (98 days, 95% CI 87–107 days; $P < 0.001$). In addition, nonfatal adverse events were not observed with PDT. Kahaleh et al. also conducted a comparison study between stenting alone and stenting with PDT treatment for CCA patients [36]. In this study, 19 patients underwent stenting with PDT, and 29 patients also underwent stenting alone. OS was significantly longer in the stent with PDT group (16.2 months) than in the stent alone group (7.4 months; $P < 0.004$). Although the mortality rate was not significantly different at 12 months, the PDT

with stent group had lower mortality than the stent alone group. Adverse events of PDT, such as skin phototoxicity requiring topical therapy, were observed in three patients. Therefore, according to these studies, PDT for CCA might be feasible and safe, and it has the potential benefit of obtaining longer survival. Recently, an evaluation of the combination therapy of PDT with systemic chemotherapy has been reported as a randomized, phase II trial [38]. Of 43 patients, 21 underwent PDT plus S-1, and 22 underwent PDT alone. The 1-year survival rate was significantly longer in the PDT plus S-1 group than in the PDT alone group (76.2% vs. 32%, $P = 0.003$), and OS was also longer in the PDT plus S-1 group (median 17 months, 95% CI: 12.6–21.4 months, vs. 8 months, 95% CI: 6–10 months, $P = 0.005$; hazard ratio [HR], 0.36, 95% CI: 0.17–0.75). In addition, PFS was longer in the PDT plus S-1 group than in the PDT alone group (median 10 months [95% CI: 4.1–16] vs. 2 months [95% CI: 0.4–3.5], $P = 0.009$; HR for progression 0.39, 95% CI: 0.19–0.83). Therefore, they concluded that PDT plus S-1 was feasible and associated with a significant improvement of OS and PFS. Given these findings, PDT seems promising. On the other hand, according to a more recent randomized trial, negative results have been noted [39]. In this randomized trial, 92 patients were divided into two groups, the PDT with stent group ($n = 46$) and the stent alone group ($n = 46$). Regarding adverse events, no significant differences in grade 3–4 toxicities were observed between the two groups, since grade 3–4 was not observed. However, after a median follow-up of 8.4 months, OS (median 6.2 vs. 9.8 months; HR 1.56, 95% CI 1.00 to 2.43, $P = 0.048$) and PFS (median 3.4 vs. 4.3 months, HR 1.43, 95% CI 0.93 to 2.18, $P = 0.10$) were worse in patients who underwent PDT than in the stent alone group. Based on these results, they concluded that PDT was associated with a worse outcome, and, therefore, PDT cannot be recommended for CCA patients. In addition, some guidelines also do not recommend PDT [40]. In conclusion, PDT under ERCP might be technically feasible and safe. However, clinical outcomes, such as OS, are still unclear. Therefore, further evaluation comparing it to other treatment techniques is needed in larger studies.

22.3.2 Intraductal RFA Treatment

Since RFA for biliary tumors was first reported by Steel et al. [41], many studies of intraductal RFA have been reported [42–50]. In a relatively large-scale study, Dolak et al. evaluated the clinical outcomes of 84 consecutive applications [43]. Median stent patency after the last electively carried out intraductal RFA was 170 days (95% CI 63–277 days) and was plastic stenting (218 vs. 115 days). In addition, the median survival time was 10.6 months (95% CI 6.9–14.4 months) from the time of the first RFA in each patient and 17.9 months (95% CI 10.3–25.6 months) from the time of initial diagnosis. They concluded that this result was much better than the survival rates documented for untreated patients. In a more recent meta-analysis of intraductal RFA including nine studies with a total of 505 patients [44], the pooled weight mean difference of stent patency was 50.6 days (95% CI 32.83–68.4 days), which was better for patients who underwent intraductal RFA. In addition, a pooled

survival analysis using the reconstructed Kaplan–Meier method showed improved survival in patients who underwent intraductal RFA (HR 1.395; 95% CI 1.145–1.7; $P < 0.001$). Therefore, according to this meta-analysis, RFA might be safe and associated with improved stent patency and longer survival. Recently, Yang et al. conducted a randomized trial comparing stent deployment after intraductal RFA ($n = 32$) and stent deployment alone ($n = 33$) for patients with extrahepatic CCA [46]. In this study, plastic stent patency was significantly longer in the stent deployment after the intraductal RFA group (6.8 months; 95% CI 3.6–8.2) than in the stent deployment alone group (6.8 months; 2.4–6.5; $P = 0.02$). Although the preoperative Karnofsky performance status (KPS) score was not significantly different between the two groups (82.9 ± 9.3 vs. 79.9 ± 7.8, $P = 0.28$), the KPS score was significantly higher in the stent deployment after the intraductal RFA group than in the stent deployment alone group at 1 month (86.1 ± 6.8 vs. 72.4 ± 8.2, $P = 0.02$), 3 months (71.4 ± 7.1 vs. 60.3 ± 5.4, $P = 0.04$), 6 months (61.4 ± 7.1 vs. 48.2 ± 6.2, $P = 0.03$), and 9 months (58.2 ± 11.5 vs. 22.5 ± 8.9, $P < 0.001$). In addition, the mean OS was significantly longer in the stent deployment after the intraductal RFA group than in the stent deployment alone group (13.2 ± 0.6 vs. 8.3 ± 0.5, $P < 0.001$). Moreover, intraductal RFA was a major protective factor affecting OS (HR 0.182, 95% CI 0.08–0.322; $P < 0.001$) on multivariate analysis using Cox regression analysis. Intraductal RFA might thus be a useful treatment option based on these reports. Theoretically, intraductal RFA might play two roles for tumor reduction and preventing tumor ingrowth after uncovered metal stent deployment [47]. Therefore, patients can receive continuous chemotherapy, which might prolong overall survival.

Though intraductal RFA itself might result in tumor reduction, the theory that combination treatment with systemic chemotherapy might prolong survival is well accepted. However, many previous studies have been conducted for patients who were unsuitable for systemic chemotherapy. Recently, Yang et al. evaluated the clinical efficacy and safety of intraductal RFA combined with S-1 for the treatment of CCA in a randomized trial [50]. In this study, a total of 75 patients were enrolled and divided into the intraductal RFA with the S-1 group ($n = 37$) and the intraductal RFA alone group ($n = 38$). Stent patency was significantly longer for intraductal RFA with S-1 than for intraductal RFA alone (6.6 ± 1.5 vs. 5.6 ± 0.1 months, $P = 0.014$). In addition, the median OS was significantly longer in the intraductal RFA with the S-1 group (16.0 months) than in the intraductal RFA alone group (11.9 months; $P < 0.001$). The incidence of procedure-related adverse events was not significantly different between the two groups (8.1% vs. 10.5%). Therefore, they concluded that intraductal RFA combined with S-1 is associated with longer survival and stent patency. However, in this study, S-1 was used as systemic chemotherapy. Since the standard chemotherapy regimen is cisplatin with gemcitabine, further trials are needed.

As noted above, intraductal RFA might obtain longer survival, pain relief, and prolonged stent patency, but severe adverse events such as bile duct perforation or bleeding can occur. In fact, with the transhepatic approach, bile duct perforation has been reported as a fatal adverse event [48]. In addition, Tal et al. reported biliary bleeding cases after intraductal RFA [49]. Two of these patients died from

hemorrhagic shock, although bleeding was successfully treated in one patient using immediate self-expandable metal stent (SEMS) placement. If cholangioscopic findings of malignant stricture are not seen, bile duct perforation may easily occur with RFA. Furthermore, RFA for a bile duct with no cholangioscopic findings of malignant stricture can injure the vessel around the bile duct wall, and severe bleeding may occur. To overcome these issues, preoperative evaluation using intraductal ultrasound, EUS, or cholangioscopy is needed. We evaluated the safety of intraductal RFA by DSOCS before/after intraductal RFA [47]. After cholangiography is performed (Fig. 22.2a), DSOCS is first inserted into the stricture site, and whether a tumor is present within the bile duct is evaluated (Fig. 22.2b). Then, intraductal RFA is attempted under fluoroscopic guidance, and the effect of this treatment is evaluated under fluoroscopic and DSOCS guidance (Fig. 22.2c). Although intraductal RFA was safely attempted in our study, patients whose stent patency was extremely short were seen (42, 68, and 82 days). These patients underwent uncovered SEMS placement before intraductal RFA. The reason for the extremely short patency might be one of the characteristics of RFA, such as it is unlikely to affect tumorous tissue outside the metal stent. Therefore, intraductal RFA as re-intervention after metal stent deployment should be evaluated by further studies.

More recently, RFA probe devices have been improved to attempt RFA with greater safety. Lee et al. reported a clinical study of a new intraductal RFA device [45]. In this study, a new intraductal RFA catheter (ELRA™, STARmed, Goyang, Korea) was used. The bipolar electrodes at the terminal portion of the catheter are stainless steel rings (3 or 6 mm in width and 18 or 33 mm in length) (Fig. 22.3a). This new intraductal RFA catheter system operates in continuous mode and temperature mode (Fig. 22.3b). Temperature mode enables continuous maintenance of the chosen electrode temperature during RFA, and thus excessive heating can be avoided. They performed intraductal RFA for 30 patients with malignant distal biliary obstruction (CCA, $n = 19$; PC, $n = 9$; gallbladder cancer, $n = 2$). Intraductal RFA was successfully performed in all patients. Adverse events were observed in three patients. Mild pancreatitis occurred in two patients and was successfully treated by conservative management. Acute cholangitis was observed in one patient and was

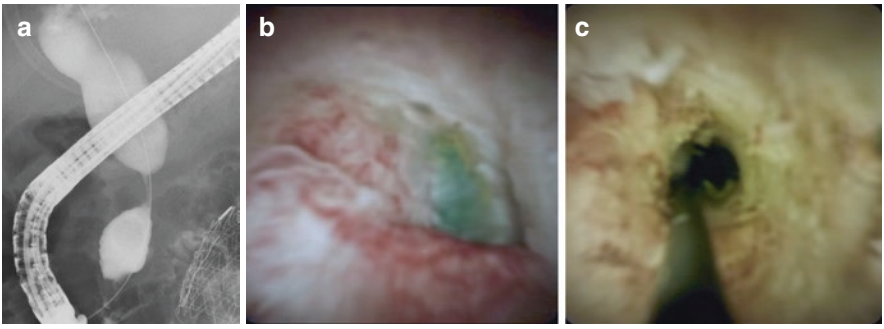

Fig. 22.2 (**a**) Lower bile duct stenosis is observed on cholangiography. (**b**) Tumor can be observed within the bile duct on cholangioscopy. (**c**) After radiofrequency ablation, tumor has disappeared (cholangioscopic imaging)

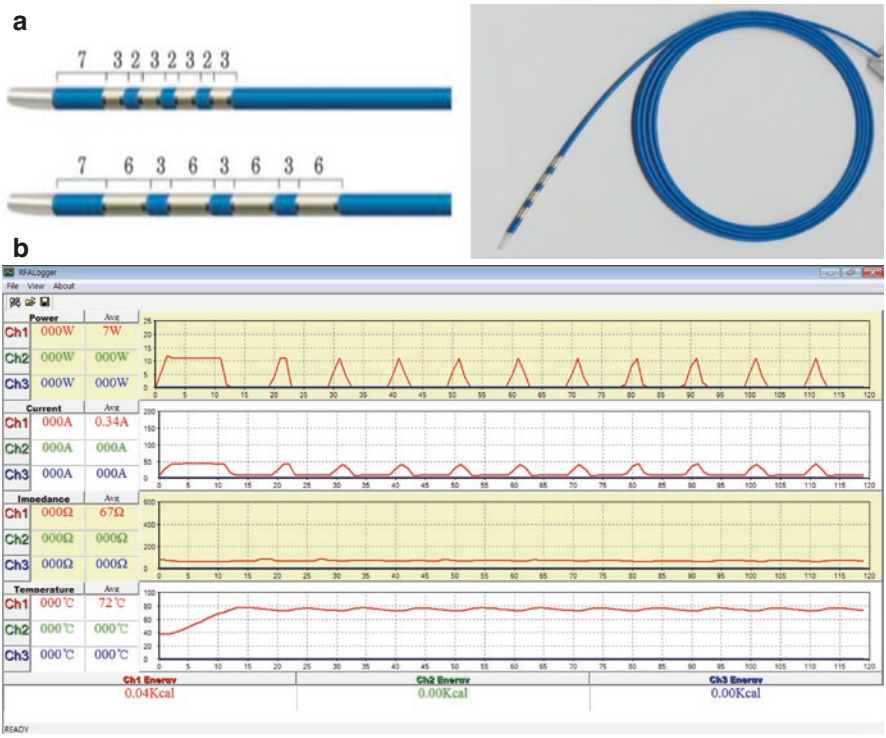

Fig. 22.3 (**a**) The bipolar electrodes at the terminal portion of the catheter are stainless steel rings (3 or 6 mm in width and 18 or 33 mm in length). (**b**) When tip temperature will reach presetting temperature (75 °C, 80 °C), RFA automatically turns off for minimizing complications

also successfully treated conservatively. As noted, hemobilia or bile duct perforation was not seen in any patients during follow-up (median 208 days, range 24–688 days). An automatic temperature-controlled intraductal RFA catheter was safely applied, although further prospective studies with comparison to a conventional RFA probe are needed.

Finally, intraductal RFA is mainly reported as a local treatment for CCA. This treatment might help obtain longer stent patency or pain relief because of its local tumor reduction effect. In addition, according to previous studies, longer survival might also be obtained, although a prospective, randomized, larger-scale study is needed.

22.4 Conclusion

Endoscopic focal treatment for PC or CCA is technically feasible and relatively safe. In addition, good results have been reported, especially in CCA patients. However, advanced pancreatobiliary cancer should be systematically treated to prolong survival because these cancers are well recognized to be a systemic disease. Therefore, not only improvement of devices but also definitive regimens of

combination treatment with systemic chemotherapy are needed, although several effects such as longer stent patency or pain relief are expected in focal endoscopic treatment.

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23

Endoscopic Management of Gastrointestinal Obstruction from Pancreatic Cancer and Cholangiocarcinoma

Naminatsu Takahara and Yousuke Nakai

Abstract

Advanced or recurrent pancreaticobiliary cancer often develops gastrointestinal obstruction including gastric outlet obstruction (GOO) and afferent loop obstruction (ALO). GOO is characterized by mechanical gastroduodenal obstruction secondary to advanced or recurrent tumor, presenting with an insufficient oral intake, intractable vomiting, and severe malnutrition. ALO is one of the postoperative complications caused by tumor recurrence involved in the afferent loop and causes several symptoms including acute cholangitis and epigastric pain, abdominal distention. For anatomical reasons, the gastrointestinal obstruction secondary to pancreaticobiliary cancer is often complicated by biliary obstruction and it further compromises the chance of antitumor therapy and impairs patients' quality of life and survival as well.

Currently, palliation for GOO is primarily based on surgical gastrojejunostomy and endoscopic gastroduodenal stent placement. Several studies have shown that endoscopic stenting has the advantage of a rapid clinical recovery with a short hospital stay, at the cost of a higher stent dysfunction rate and a subsequent need for frequent re-interventions. As for ALO, endoscopic stenting using balloon-assisted endoscope has also become an alternative to conventional

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surgical bypass or percutaneous transhepatic biliary drainage. Recently, a novel therapeutic option has emerged from the field of interventional endoscopic ultrasound (EUS), EUS-guided gastroenterostomy using a lumen-apposing metal stent provides promising results for GOO and ALO. This new procedure may ideally encompass the minimal invasiveness of an endoscopic procedure and the long-lasting effect of the surgical gastrojejunostomy.

In this chapter, we described technical aspects and clinical outcomes of the above-mentioned therapeutic approach and discussed the current management of GOO and ALO secondary to pancreaticobiliary cancer.

Keywords

Pancreatic cancer · Biliary tract cancer · Gastric outlet obstruction · Afferent loop obstruction · Endoscopic gastroduodenal stent placement, EUS-guided gastroenterostomy

Abbreviations

GOO	Gastric outlet obstruction
ALO	Afferent loop obstruction
SEMS	Self-expandable metal stent
LAMS	Lumen-apposing metal stent
PTBD	Percutaneous transhepatic biliary drainage
EUS	Endoscopic ultrasound
QoL	Quality of life

23.1 Malignant Gastric Outlet Obstruction (GOO)

The major clinical entity of gastrointestinal obstruction in pancreaticobiliary cancer is gastric outlet obstruction (GOO) and its incidence is reportedly approximately 20% in pancreatic cancer [1]. Malignant GOO often occurs at the late stage of the disease and therefore is associated with limited survival of 3–4 months, regardless of primary cancer [2]. The mechanical gastroduodenal obstruction by tumor invasion leads to the failed or delayed outflow of gastric contents from the stomach to jejunum, resulting in severe malnutrition and dehydration due to poor oral intake and vomiting (Fig. 23.1). Furthermore, for anatomical reasons, GOO is frequently concomitant with biliary obstruction especially in patients with pancreaticobiliary cancer, unlike gastric cancer. Combined GOO and biliary obstruction is classified according to its location and sequence (Table 23.1). Since there are several treatment options, it is crucial to make an optimal strategy for GOO with special consideration for biliary obstruction in these patients.

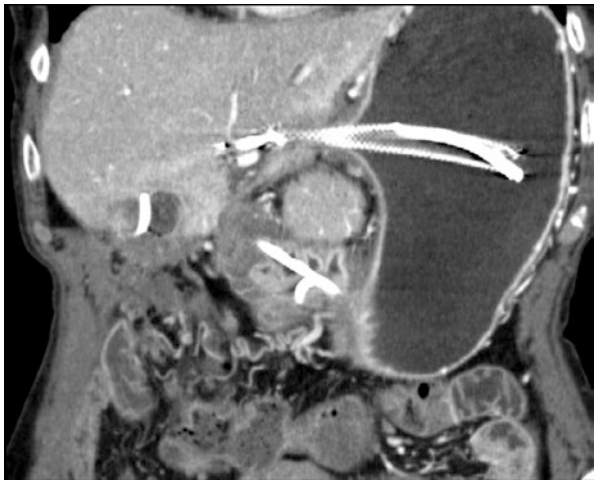

Fig. 23.1 Computed tomography scan appearance of malignant gastric outlet obstruction secondary to pancreatic cancer previously indwelled transmural biliary stents

Table 23.1 Classification of combined GOO and MBO

According to the anatomical location	
Type 1	GOO occurs at the level of the duodenal bulb or upper duodenal genu, but without the involvement of the papilla
Type 2	GOO affects the second part of the duodenum, with the involvement of the papilla.
Type 3	GOO involves the third part of the duodenum, distal to and without the involvement of the papilla.
According to the sequence of obstruction	
Group 1	MBO first, followed by GOO
Group 2	MBO and GOO simultaneously
Group 3	GOO first, followed by MBO

GOO gastric outlet obstruction, *MBO* malignant biliary obstruction

23.1.1 Surgical Gastrojejunostomy Versus Endoscopic Gastroduodenal Stent Placement

The classic treatment for patients with malignant GOO was to undergo surgical gastrojejunostomy, often with a combined biliary bypass. In the current era, this surgery is usually performed laparoscopically given the less invasiveness of this approach over open surgery [3]. However, patients with advanced cancer and GOO are not always candidates even for palliative surgery. Therefore, endoscopic self-expandable metal stent (SEMS) placement was introduced as a less invasive alternative to surgical gastrojejunostomy [4–6], and numerous studies to date have demonstrated its efficacy and safety for palliation of malignant GOO [7–9].

Since the introduction of endoscopic gastroduodenal stenting, there has been vigorous debate on stenting versus surgery for palliation of malignant GOO, and many published studies have tried to address this question definitively but have failed in conflicting results [10–15]. In a recent meta-analysis comparing

endoscopic stenting with surgical gastrojejunostomy including a total of 2354 patients with malignant GOO, endoscopic stenting contributed to a rapid symptom relief such as shorter time to resume oral intake and hospital stay (mean differences of −5 days and −10 days, $p < 0.001$, respectively), whereas surgical gastrojejunostomy provided better long-term outcomes including patency and survival (mean difference of 43 days, $p = 0.006$) [16]. Thus, in clinical practice, despite no large-scale prospective randomized controlled trial (RCT), treatment is usually selected based on the patient's prognosis and performance status. In short, patients with a long life expectancy are likely to undergo surgery while more compromised patients with a short life expectancy might be best treated via stents. This is becoming an important issue because the advancement of chemotherapy has led to improved survival in many cancers including pancreaticobiliary cancer.

23.1.2 Indication for Endoscopic Gastroduodenal Stent Placement

GOO can frequently occur as a preterminal manifestation in a substantial portion of patients with pancreatobiliary cancers, and thus is associated with poor general condition. In a prospective study of consecutive patients with malignant GOO undergoing endoscopic stent placement, one-third of patients had a performance status of 3 or 4 [17]. Since endoscopic stent placement is less invasive compared to surgery, its application can be expanded to a larger proportion of patients suffering from GOO. However, especially in patients with extremely poor general condition, it may be necessary to consider an inherent risk rather than a potential benefit from the procedure because even mild adverse events may result in fatal in such cases.

The goals of stent placement are to relieve symptoms related to gastrointestinal obstruction, to allow the patient to resume an oral intake, and to improve the patient's quality of life. Therefore, it is not indicated for patients who are asymptomatic or are tolerating a normal diet. Another contraindication to stent placement is the presence of multiple small bowel obstructions since treatment of the proximal stricture is unlikely to provide symptom relief. Previously, peritoneal carcinomatosis had been considered as a risk factor for incomplete palliation following stent placement given the potential risk of multiple strictures and reduced bowel movement. However, despite this anecdotal assumption, recent data suggested that a gastroduodenal stent can work even in such patients. Actually, a retrospective study of 215 patients with malignant GOO undergoing stent placement revealed that treatment outcomes were similar between with and without peritoneal carcinomatosis, regarding clinical success (81% vs. 84%), need for re-intervention (18% vs. 27%), and major complications (4% for both groups) [18].

23.1.3 Endoscopic Procedure of Gastroduodenal Stent Placement

From the early 1990s, self-expandable metal stent (SEMS) placement had been introduced for GOO based on clinical experience in the field of malignant esophageal obstructions [4–6]. Conventionally, these SEMS had been deployed an over-the-wire technique exclusively under fluoroscopic assistance. However, due to the anatomical difficulties in GOO contrary to the esophageal obstructions, it was technically challenging and hard for patients. With the development of dedicated SEMS with a slim delivery system and the therapeutic endoscope with a large working channel, SEMS can be placed using the through-the-scope technique which enables the procedure much easier even in long and tortuous gastroduodenal strictures, and recent studies demonstrated a high technical success rate of 95–100% [19–22].

Generally, endoscopic SEMS placement consists of the following three steps: (1) scope insertion followed by guidewire passage through the stricture, (2) definition of the stricture, and (3) SEMS placement (as shown in Fig. 23.2). Under conscious sedation, the procedure was performed using a therapeutic endoscope equipped with a 3.2- or 3.7-mm working channel. The stricture is negotiated using a 0.025- or 0.035-inch guidewire and ERCP catheter under endoscopic and fluoroscopic guidance. A hydrophilic guidewire and a sphincterotome may be helpful to pass the tight and angulated strictures. Subsequently, a catheter is advanced through the guidewire, and a sufficient contrast medium is injected to define the location and length

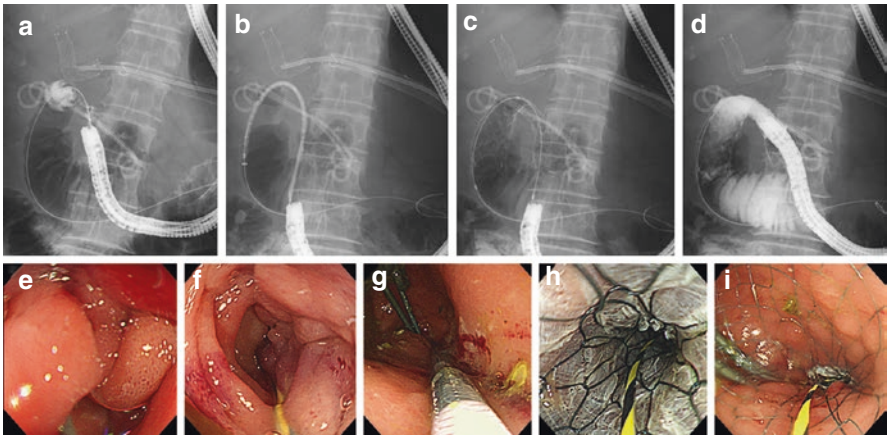

Fig. 23.2 Endoscopic self-expandable metal stent placement for gastric outlet obstruction. The stricture is defined in detail by endoscopic and fluoroscopic view (**a**, **e**). Subsequently, the stent delivery system is inserted along the guidewire through the working channel of the endoscope (**b**, **f**, **g**) and is successfully released across the stricture both on endoscopic and fluoroscopic guidance (**c**, **d**, **h**, **i**)

of the stricture. SEMS length is determined to cover the stricture long enough to prevent tumor ingrowth/overgrowth and to avoid kinking at both ends, with taking a foreshortening ratio of each type of the SEMS into account. Finally, the stent delivery system is inserted along the guidewire through the working channel of the endoscope and released across the stricture both on endoscopic and fluoroscopic guidance. At this step, it is critical to maintain an optimal posture to recognize the stricture in a long axis, which is a key to deploy SEMS appropriate position. A contrast medium was flushed to evaluate luminal recanalization after the SEMS placement. Oral intake can be restarted after no dislocation and sufficient expansion of the SEMS are verified by abdominal radiography.

23.1.4 Efficacy of SEMS

The efficacy of SEMS has been evaluated through several endpoints including technical/clinical success, duration of stent patency/oral intake, survival and quality of life (QoL), etc. Technical success is universally defined as adequate SEMS placement across the stricture. Clinical success is generally defined as the relief of obstructive symptoms or the improvement of oral intake. Adler et al. developed Gastric Outlet Obstruction Scoring System (GOOSS) aimed to objectively quantify the ability of oral intake; GOOSS assigns a score of 0 in case of no oral intake, 1 for only liquids, 2 for soft solids, and 3 for low-residues or full diet, and is currently the most accepted score to measure the clinical improvement after treatment for GOO [7]. However, high heterogeneity exists among published studies on the definition of clinical success. One systematic review revealed that only 40% of studies used GOOSS to evaluate the efficacy of SEMS on malignant GOO [23].

In a recent pooled analysis of endoscopic SEMS placement including more than 1200 GOO participants from 19 prospective studies published between 2009 and 2015, the overall technical success rate was 97.3% and clinical success rate (applied the definition in the original article) was 85.7%. The median stent patency and overall survival ranged from 68 to 98 days and 49–183 days, respectively. When the majority ($\geq$ 50%) of the study sample included patients with pancreatic cancer, the median overall survival ranged from 49 to 106 days [24]. Moreover, a large-scale retrospective study demonstrated that endoscopic SEMS placement was similarly safe and effective in patients with pancreatic cancer comparing to those with non-pancreatic cancer [2]. As for the QoL, despite lack of reliable data, endoscopic SEMS placement may contribute to improve or maintain a physical and psychological status for a particular period after the procedure [13, 25, 26]. These results suggest that endoscopic SEMS placement is a valid treatment option for the palliation of malignant GOO secondary to pancreaticobiliary cancer as well.

Several studies investigated potential factors of clinical failure or stent dysfunction, in order to optimize the outcome of patients with malignant GOO undergoing stent placement. A poor performance status (Karnofsky performance status <50 or Eastern Cooperative Oncology Group performance status $\geq$3) have been identified as a prognostic factor of clinical failure and/or stent dysfunction [27, 28], while the impact of chemotherapy on stent outcomes have been reported with variable results

[29, 30]. It is predominantly reported that chemotherapy is significantly associated with improved stent patency but one study concluded that it did not vary according to whether patients received chemotherapy or not in patients with pancreaticobiliary cancer [31]. With regard to peritoneal carcinomatosis, retrospective studies found that ascites caused by peritoneal carcinomatosis were associated with clinical failure [28, 32]. Moreover, the distal location of GOO and the number of strictures (i.e., ≥3) are also associated with poor outcomes in retrospective studies [27, 33].

23.1.5 Safety of SEMS

According to the above-mentioned pooled analysis, adverse events (AEs) related to SEMS placement can be observed in up to 60% of patients, depending on the definition adopted in the various studies [24]. The American Society for Gastrointestinal Endoscopy advocated that adverse events should be defined as any event that precludes completion of the planned procedure and/or resulted in admission to hospital, prolongation of existing hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation [34]. Moreover, they recommended to classify AEs into three groups depending on the timing of onset: pre-, intra-, and post-procedural AEs (early; up to 14 days, and late; any time after 14 days).

Major early AEs related to gastroduodenal SEMS include bleeding, perforation, stent migration/displacement, cholangitis, and pancreatitis, and late AEs are usually related to stent dysfunction secondary to migration or occlusion by food impaction and/or tumor ingrowth/overgrowth. In recent meta-analyses, stent dysfunction was observed in 19.6% including stent re-occlusion by tumor ingrowth or overgrowth in 12.6% and stent migration in 4.3%, with an overall bleeding and perforation rate of 4.1% and 1.2%, respectively [24]. In pancreaticobiliary cancers, malignant GOO is frequently concomitant with biliary obstruction as a result of tumor involvement. The mechanical compression of the ampulla by SEMS may cause cholangitis or pancreatitis with the incidence of 0–2.5% [35–37] and 3–4% [38–40], respectively. Given the efficacy of endoscopic ultrasound-guided biliary drainage in patients with an indwelling gastroduodenal SEMS, concern with cholangitis might be minimal in current clinical practice, but attention should be paid to avoid SEMS-related pancreatitis [41].

As stated above, a stent may occlude due to tumor ingrowth or overgrowth as well as food impaction. Stent occlusion leads to symptom recurrence related to GOO and often needs endoscopic re-intervention that, although feasible and effective [42, 43], may impair patients' QoL and increase costs for the health system, representing one of the main disadvantages of this approach [44]. In order to reduce the risk of stent occlusion, several studies have investigated the possible role of covered SEMS in the setting of malignant GOO [37, 39, 45, 46].

23.1.6 Comparison Between Covered and Uncovered SEMS

Generally, covered SEMS is newly developed to improve patency by preventing tumor ingrowth which is the major cause of dysfunction in uncovered SEMS, but is

prone to migration [47]. Numerous studies reported the safety and efficacy of SEMS for malignant GOO so far, however, both covered and uncovered SEMSs have inherent advantages and disadvantages.

Actually, a meta-analysis demonstrated that covered SEMS had a lower obstruction risk (risk ratio [RR], 0.42; 95% confidence interval [CI], 0.24–0.73, $P = 0.002$) with a higher migration risk (RR, 3.48; 95% CI, 2.16–5.62, $P < 0.001$) [48]. On the other hand, no significant difference was shown in technical success rate, clinical success rate, post-stenting dysphagia score, stent patency, overall AEs and re-intervention rate between covered and uncovered SEMS. Interestingly, another meta-analysis highlighted a trend toward a lower occlusion risk in covered SEMS (RR, 0.44; 95% CI, 0.28–0.68). However, the higher risk of migration in covered SEMS (RR, 4.28; 95% CI, 2.89–6.34) should be noted, together with no significant difference in stent dysfunction between covered and uncovered SEMS (RR, 1.02; 95% CI, 0.79–1.32) [49]. A more recent systematic review including 1741 patients from 7 randomized controlled trials and 9 observational studies identified that covered SEMS was associated with longer stent patency (RR, 0.68; 95% CI, 0.48–0.96) despite a higher rate of migration (RR, 4.28; 95% CI, 2.79–6.57). There were no differences in terms of clinical/technical success, survival, incidence of AEs, re-intervention rate, dysfunction rate, and GOOSS rate ≥ 2 after SEMS placement between groups [47]. To summarize, outcomes of covered and uncovered SEMS were comparable, although the lower dysfunction rate of covered SEMS observed in the analysis of randomized trials deserves further investigation.

Several technical modifications or precautions (e.g., stent clipping or suturing, anti-migratory design) have been proposed to overcome the migration risk without decreasing the possible advantages of the lower occlusion in covered SEMS [39, 50, 51]. Despite these attractive alternatives, there remain safety concerns in covered SEMS regarding an increased risk of perforation due to stent migration as well as cholangitis and pancreatitis secondary to the compression/occlusion of the ampulla [6, 40]. Therefore, uncovered SEMS might be preferred especially in cases with GOO around the ampulla if transpapillary biliary drainage is likely to be required.

23.1.7 EUS-Guided Gastroenterostomy (EUS-GE)

The progress of interventional EUS opened the door of a new field of minimally invasive endoscopic procedures. This technique enables to create a trans-luminal anastomosis and to achieve an internal drainage of the bile duct, gallbladder, and peripancreatic fluid collections even in patients unfit for surgery or after failed ERCP. With the development of a dedicated metal stent for trans-luminal interventions, an innovative technique named EUS-guided gastroenterostomy (EUS-GE) has emerged as a novel therapeutic option for GOO [52]. Indeed, lumen-apposing metal stents (LAMS), specifically designed for interventional EUS procedures, are fully covered “dumbbell”-shaped short stent with wide anti-migratory flanges which can fix the two lumens each other. The first report of EUS-GE with LAMS (AXIOS stent; Boston Scientific, Marlborough, MA, United

States) was described in 2012 [52]. In the subsequent years, three different techniques have been described to perform EUS-GE with LAMS: (1) Direct EUS-GE; (2) Assisted EUS-GE, performed using accessory devices for small bowel loop distension; and (3) EUS-guided double balloon-occluded gastrojejunostomy bypass (EPASS) [53–55].

Direct EUS-GE requires several steps to complete as follows: (1) identification and puncturing the small bowel with a fine-needle aspiration needle under EUS guidance, (2) guidewire insertion and contrast injection to small bowel followed by tract dilation, and (3) stent deployment. The major concern in this technique is technical difficulty in the correct puncturing of the small bowel which is often collapsed and mobile. Furthermore, several device exchanges can increase the risk of leakage, perforation, and unsuccessful stent deployment. To address these limitations, assisted EUS-GE and EPASS techniques are designed to distend and fix the small bowel. Moreover, the LAMS delivery system has further evolved with the addition of an electrocautery tip (HOT-AXIOS, Boston Scientific Corp., Marlborough, MA, United States) which allows a single-step access to the small bowel distal to the obstruction, without the need for multiple device exchanges [53–55].

Since the stent is deployed away from the tumor in EUS-GE unlike in conventional gastroduodenal stenting, EUS-GE may theoretically contribute to reducing the chances of stent dysfunction due to tumor ingrowth or overgrowth. Recently, EUS-GE has been compared with laparoscopic GE and enteral stenting. In a recent multicenter study, EUS-GE was equally efficacious with fewer adverse events as compared to laparoscopic GE [56]. Similar conclusions were drawn in another study, where both the modalities were equal with respect to clinical success (>90%), adverse events, and recurrence of obstruction [57]. Moreover, EUS-GE was associated with fewer symptom recurrences and requirements for re-intervention [58]. Taken together, these data support EUS-GE should be an attractive option for a patient with malignant GOO though several safety and technical concerns are yet to be elucidated. Further studies are warranted to standardize and generalize this procedure.

23.2 Malignant Afferent Loop Obstruction (ALO)

Unfortunately, tumor recurrence after radical surgery is inevitable in a substantial portion of patients with pancreaticobiliary cancer. Actually, malignant afferent loop obstruction (ALO) secondary to tumor recurrence is not an uncommon postoperative complication in these patients, with an estimated incidence of 13% [59]. ALO is characterized by several symptoms including acute cholangitis and epigastric pain, abdominal distention, etc. which depend on the obstruction sites of the afferent loop and the surgical procedures as well.

Conventionally, ALO had been managed by surgical bypass or percutaneous transhepatic biliary drainage (PTBD) [60]. Since patients with recurrent cancer are often unfit for surgical bypass, PTBD (and subsequent enteral stenting via PTBD route) is widely accepted as a current mainstay of treatment option [61]. However,

there are still several limitations in PTBD; technically challenging procedure with high mortality and morbidity and also a limited indication for dilated bile duct [62]. In addition, permanent external drainage may be required when enteral stent placement for afferent loop obstruction failed, which seriously impairs patients' QoL. The recent development of a short-type balloon-assisted endoscope with a 3.2-mm working channel enables to put a SEMS for ALO by the through-the-scope technique [63]. Sasaki et al. proposed a clear-cut treatment strategy based on a novel classification for three types of malignant ALO according to the relationship between the obstruction site and the bilio/pancreaticoenteric anastomosis [64]. Type 1: The obstruction is located distal to the bilioenteric anastomosis. Thus, decompression of distended afferent loop and concomitant cholestasis may be achieved by simply inserting an enteral stent at the obstruction site. Type 2: The obstruction is involved at the bilioenteric anastomosis. Therefore, in this type, double stenting is required to achieve both decompressions of blind loop and biliary drainage. Since the bilioenteric anastomosis is involved in tumor recurrence, it is difficult to detect the anastomosis and cannulate the bile duct endoscopically. A combination of PTBD or endoscopic ultrasound (EUS)-guided biliary drainage is sometimes required. Type 3: The obstruction is located between the bilioenteric and pancreaticoenteric anastomosis. The decompression of afferent loop obstruction can be achieved by inserting an enteral stent at the obstruction site, but it requires more attention to perforation because of the short-segmented blind loop.Moreover, an enteral stent needs to be deployed at the obstruction so as not to cover the bilioenteric anastomosis.

More recently, there are several reports of EUS-guided intervention for malignant ALO, especially in cases with a failed balloon-assisted endoscopic procedure. There were two approaches of EUS-guided intervention; one is EUS-guided hepaticogastrostomy [65] and the other is EUS-guided gastrojejunostomy using a LAMS [66]. Although these may become a standard of care for malignant ALO in the near future, further studies are warranted to maximize and generalize the clinical efficacy of these novel approaches.

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Development of Biliary Self-Expandable Metal Stents for Pancreatic Cancer and Cholangiocarcinoma

24

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Abstract

The axial force and the radial force are important parameters of metal stents. An axial force is the strength that acts to return a self-expandable metal stent placed in a bent position to a straight position, and radial force is the strength with which the stent expands a bile-duct stricture in the centrifugal direction. In general, stents with weak axial force and strong radial force are considered ideal. Four types of stents are used to treat pancreatobiliary diseases: (1) distal bile-duct stenosis, (2) hilar bile-duct stenosis, (3) pancreatic pseudocyst, and (4) endoscopic ultrasound-guided hepaticogastrostomy. (1) Distal biliary obstruction is the most common indication, for which many types of stents are available. (2) Stent-in-stent and side-by-side placement of dedicated metal stents are used for hilar biliary obstruction. (3) Lumen-apposing metal stents, with a large-diameter lumen, are used for pancreatic pseudocyst and for endoscopic necrosectomy. (4) Stents dedicated to EUS-guided hepaticogastrostomy have also been developed and some have features that prevent their migration into the peritoneal cavity.

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Keywords

Self-expandable metal stent (SEMS) · Uncovered stent · Covered stent · Laser-cut type · Braided type · Axial force · Radial force · Stent-in-stent (SIS) · Side-by-side (SBS) · Lumen apposing metal stent (LAMS)

24.1 Birth of the Stent

The father of the stent is Charles Thomas Stent (1807–1885), an English dentist notable for his advances in the field of denture-making [1]. He improved conventional materials for making dental impressions and introduced a new dental compound with excellent stability and plasticity. The compound was made by mixing conventional natural latex with stearine, a glyceride of stearic, palmitic, and oleic acids derived from animal fat. In the early 1900s, his material was used for plastic surgery of the face, and later became known worldwide as a "stent."

So how did "stent" come into use for pancreatobiliary diseases? It was about 50 years later that stents became widely known. In 1975, Nagai et al. reported the use of an endoscopic nasobiliary drainage tube for obstructive jaundice [2], and in 1979, Soehendra et al. reported a new drainage method using plastic stents [3, 4]. Various improvements were subsequently made, resulting in the plastic stents in use today [5]. Since Carrasco et al. reported a study using dogs in 1985 [6], such stents have found various clinical applications. Yoshioka et al. [7] and Irving et al. [8] developed metal stents for the percutaneous route and reported their effectiveness. The development of metal stents that can be endoscopically deployed is also progressing. Huibregste et al. reported a pilot study of a Wall stent. This was developed into the Wallflex stent (Boston Scientific Corporation, MA), first marketed in 1989 [9].

24.2 Evolution of Metal Stents

At first, metal stents for the bile duct were uncovered. Uncovered stents have a significantly prolonged patency compared with plastic stents, raising the issue of early restenosis due to tumor ingrowth [10]. Covered stents, which have a silicon membrane, were developed to prevent early restenosis due to tumor ingrowth. Self-made covered stents were used prior to the availability of commercially covered stents in Japan. Boston Scientific Corporation marketed covered stents because the randomized control trial by Isayama et al. revealed them to be advantageous [11]. Compared with uncovered stents, covered stents reduce tumor ingrowth and significantly prolong stent patency but are prone to slippage and migration [12]. To prevent migration, covered stents of a dumbbell shape or with a flange at both ends have been created [13]. Stents with attached flaps to prevent migration have also been developed. Backflow of food residue into the bile ducts is also a problem with metal stents and can cause stent obstruction. One ComVi stent has a 7-mm-longer cover

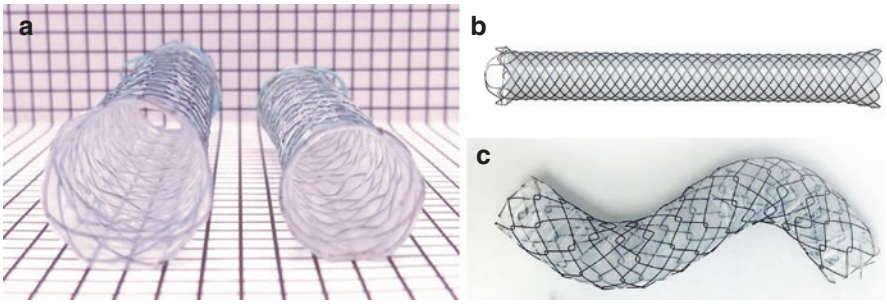

Fig. 24.1 (**a**) Covered SEMS 12 mm in diameter (left; Niti-S SUPREMO12) and 10-mm-diameter stent (right; Niti-S SUPREMO). The picture was provided by Century Medical, Inc., Tokyo Japan. (**b**) Wallflex stent, a typical cross-knitted stent. The picture was provided by Boston Scientific Corporation. (**c**) Niti-S ComVi stent, a typical hook-knitted stent. The picture was provided by Century Medical, Inc.

on the duodenal side, which acts as a check valve to prevent the backflow of food [14]. Other manufacturers have also marketed anti-reflux biliary metal stents [15]. Niti-S developed, at our request, a 12-mm-diameter stent (Niti-S SUPREMO12, Taewoong Medical, Gyeonggi-do, Korea) (Fig. 24.1a) [16], which may prolong patency.

24.3 Structures and Mechanical Properties of Self-Expandable Metal Stents

Metal stents are classified into braided and laser-cut types. Braided-type stents are formed by knitting several wires, and laser-cut type stents are cut from a metal tube using a laser. Generally speaking, the laser-cut type has the advantage of smaller delivery and less shortening. Braided stents can have a variety of characteristics, depending on the size and weaving of the wire. Cross knitting and hook knitting are combined to manufacture braided stents. The expansion force is proportional to the amount of cross knitting and inversely proportional to the amount of hook knitting, which also reduces the axial force [17]. Among stents currently in use, the Wallflex (Boston Scientific Corporation; Fig. 24.1b) stent is a typical cross-knitted stent, and the Niti-S ComVi stent (Taewoong Medical; Fig. 24.1c) is a typical hook-knitted stent.

The axial force and radial force are important parameters of metal stents [18, 19]. The axial force acts to return a self-expandable metal stent (SEMS) placed in a bent position in the bile duct to a straight position and contributes to the conformability of the bile duct. Isayama et al. measured the axial force and radial force of biliary stents and classified the stents into three groups [18]. Strong axial force may increase stent migration [20] or cause bile-duct kinking. SEMSs with high axial force increase the risk of acute cholecystitis [21] and acute pancreatitis

[22]. Recent works have focused not only on the strength of the axial force but also on the angle at which the force is no longer applied to return to the straight position; this is termed the "Axial force zero border" [23]. When SEMSs are placed in a bent bile duct, the larger the angle of the axial force zero border, the weaker the pressure applied to the bile duct, possibly reducing the complication rate.

The radial force is the strength with which the stent expands the stricture of the bile duct in the centrifugal direction. The greater the radial force, the better the patency because the lumen is kept expanded. However, because excessive dilation places pressure on the blood vessels around the bile ducts, leading to the formation of blood clots and obstruction of the cystic and pancreatic ducts, resulting in cholecystitis and pancreatitis, the optimal dilation is critical [16].

The shortening rate refers to the rate of contraction of a metal stent when fully expanded from the state of the stent being narrowed. Because stent length is that when fully expanded, the length in delivery is accommodated longer by the described stent length times the shortening ratio (delivery length = described length (1 + shortening ratio)) [24]. Cross-knitting generally has the highest shortening rate, followed by hook knitting and laser-cut knitting. Stents with higher shortening rates are more difficult to place in the desired location and may become shorter than expected due to stricture expansion. It seems to be a shortcut to get used to the metal stent to use it from the stent in which the shortening rate is low for the beginner of metal stents.

24.4 Development of Metal Stents for Specific Applications

24.4.1 Extrahepatic Biliary Obstruction

The most frequent use of metal stents is in the treatment of distal bile-duct stricture, for which covered stents are typically used because of their (1) long patency, (2) equivalent complications, and (3) greater removability compared to uncovered stents [25, 26]. Recent advances in the treatment of cholangiocarcinoma and pancreatic cancer have improved the prognosis of patients with malignant bile-duct stricture, and bile-duct patency for >1 year can be required. Therefore, stents require a sufficient patency duration and must facilitate reintervention when occluded. In this regard, covered stents are superior to uncovered stents.

However, covered stents more readily migrate than uncovered stents [12]. Several approaches have been used to overcome this issue. A stent with flaps to prevent migration, a stent with larger flanges on both sides (Fig. 24.2a), and the aforementioned stent of large (12 mm) diameter (Fig. 24.2b) can prevent migration [16]. However, large-bore metal stents have a risk of retrograde cholangitis due to reflux of intestinal fluid and food into the bile ducts. Biliary stents with a counterflow prevention valve on the duodenum side prevent counterflow to the bile duct

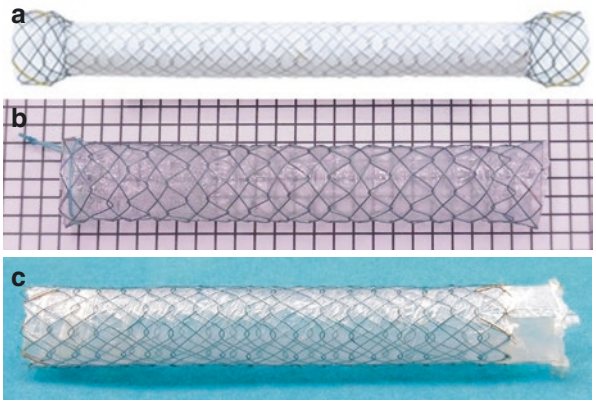

Fig. 24.2 (**a**) HILZO stent, which has large flanges at both ends to prevent stent migration. The picture was provided by ZEON Medical Inc., Tokyo Japan. (**b**) Twelve-millimeter-diameter stent (Niti-S SUPREMO12). The picture was provided by Century Medical Inc. (**c**) Niti-S Long-covered ComVi stent, whose longer cover on the duodenal side acts as a check valve to prevent backflow of food. The picture was provided by Century Medical, Inc.

(Niti-S Long-covered ComVi stent, Taewoong Medical; Fig. 24.2c). It is unclear whether preventing reflux prolongs stent patency [14].

24.4.2 Hilar Biliary Obstruction

It is necessary to drain multiple branches simultaneously when treating hilar biliary obstruction, which is a challenging problem. Plastic stents are often used for drainage of hilar biliary obstruction, but those of small stent diameter can require frequent replacement, typically at 2–3-month intervals.

Stent-in-stent (SIS) and side-by-side (SBS) placement of metal stents can be divided into two types [27]. SIS placement involves placing a stent over multiple branches of the bile duct through an uncovered stent mesh. Although this method has excellent initial drainage efficiency, it is difficult to perform re-intervention when the stent is occluded because it cannot be removed [28]. As described above, only uncovered stents are used for this method. The Niti-S Large cell D-type stent (Taewoong Medical) with a large mesh gap (Fig. 24.3a) [29] and the BONASTENT M-hilar (Standard Sci-Tech Inc., Seoul, South Korea) with a moving cell in the center (Fig. 24.3b) are used for this procedure. These stents, designed specifically for hilar biliary obstruction, have large open cells at the hepatic hilum to facilitate insertion of a second metal stent during the initial SIS procedure and additional metal or plastic stents during re-intervention. Laser-cut stents can also be used because of their large cell size and ability to break the bridge using an expansion balloon. In the SBS method, multiple thin (6 mm) metal stents are placed side by side [30, 31]. This method is fundamentally identical to the insertion of multiple plastic stents. Both covered and uncovered stents can be used for this procedure.

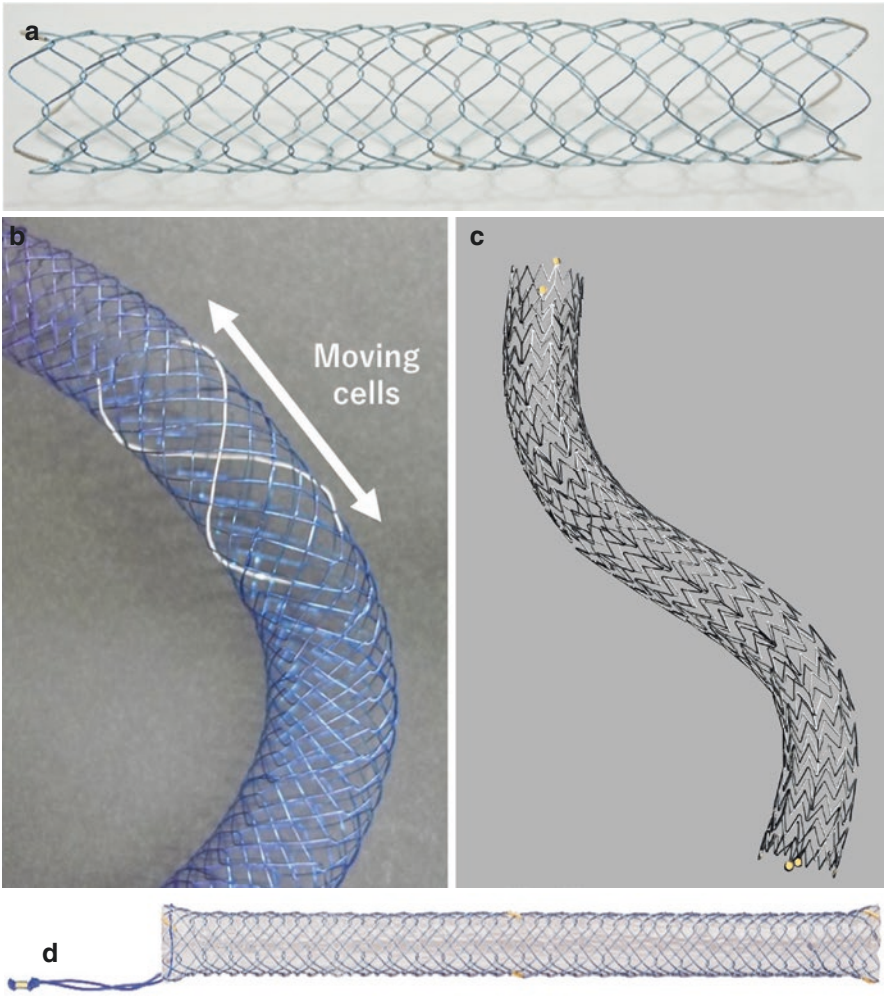

Fig. 24.3 (**a**) Niti-S Large cell D-type stent, which has large mesh gaps to facilitate the insertion of a second metal stent during SIS. The picture was provided by Century Medical, Inc. (**b**) BONASTENT M-hilar stent, which has moving cells in the center for SIS. The picture was provided by Medico's Hirata Inc., Osaka Japan. (**c**) Zilver635 stent, an uncovered laser-cut stent with thin delivery that enables simultaneous placement of two stents for the SBS method. The picture was provided by Cook Medical Inc. (**d**) HANARO 6-mm-diameter covered stent for SBS across the papilla. The picture was provided by Boston Scientific Corporation

Laser-cut uncovered stents have a thin delivery system ($\leq$ 6 Fr, Fig. 24.3c), and so can be placed through the device channel in two tubes simultaneously, reducing the procedure time [32]. A covered stent facilitates re-intervention because it can be removed when obstructed or a complication occurs. However, the covered stent can block the side branch and cause branched cholangitis. Stents have been

developed that allow entry of bile through small holes in the cover to avoid blocking bile flow from biliary branches. Uncovered laser-cut stents with a delivery of 6 Fr or less include, for instance, the Zilver 635 (Cook Medical, IN), Bilerush (Piolax Medical Devices, Kanagawa, Japan), and Epic (Boston Scientific Corporation), which are placed above the papilla to be implanted in the bile duct. The Hanaro (M.I. Tech, Gyeonggi-do, South Korea, Fig. 24.3d) and Niti-S S-type (Taewoong Medical) covered stents of 6 mm diameter are placed across the papilla so that the lower end emerges in the duodenal lumen.

24.4.3 Pancreatic Pseudocyst

Endoscopic drainage of pancreatic pseudocysts caused by pancreatic duct disruption and walled-off necrosis (WON) associated with acute pancreatitis is the first-line treatment.

In the past, plastic stents were placed under endoscopic ultrasonography through the gastrointestinal (GI) tract to drain the contents of the cyst. However, because the drainage efficiency of narrow-bore plastic stents was poor, surgical removal of necrotic material was occasionally necessary [33]. Now, pancreatic pseudocysts and WON are treated using dedicated metal stents that create large fistulas between the walls of the GI tract and the cyst [34].

These dedicated devices are dumbbell-shaped stents termed lumen-apposing metal stents (LAMSs), which have large flanges at both ends (Fig. 24.4a). Those flanges sandwich and crimp the wall of the GI tract and cyst, and the lumen of the stent secures the large fistula. An energizing electrode is installed at the tip of the

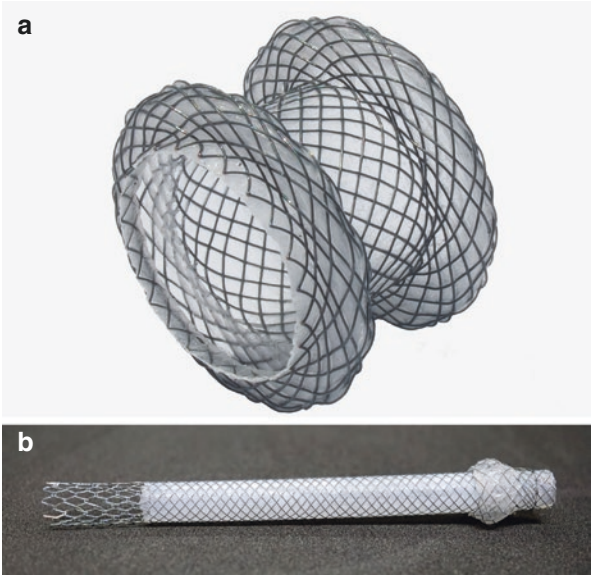

Fig. 24.4 (**a**) AXIOS stent, which has large flanges at both ends for draining pancreatic pseudocysts and walled-off necrosis. The picture was provided by Boston Scientific Corporation. (**b**) Spring Stopper stent, which has an uncovered portion on the bile-duct side and a large stopper on the stomach side for EUS-HGS. The picture was provided by Century Medical, Inc.

delivery endoscope, with which the dedicated stent is placed; neither a puncture needle nor a guidewire is required (Hot Axios, Boston Scientific Corporation). The stent diameter is up to 20 mm and the endoscope can be inserted into the cyst through the stent, and endoscopic necrosectomy is possible. Since the development of this stent, the need for surgical necrosectomy has markedly decreased [35].

Pancreatic-head and distal-bile-duct cancer invade the duodenum, leading to duodenal stricture. Endoscopic bypass using LAMS has recently been used for gastric outlet obstruction. It is possible to create a fistula similar to surgical bypass by the detainment of LAMS from the stomach to the third portion of the duodenum and the proximal jejunum [36].

Acute cholecystitis due to cystic duct invasion and obstruction by stent placement is often experienced in pancreatic cancer and cholangiocarcinoma. In endoscopic gallbladder drainage, a plastic stent is placed through the papilla or the GI tract under endoscopic ultrasonography, and the gallbladder content is drained. Recently, drainage of acute cholecystitis using LAMS via the GI tract has been attempted [37]. The advantages of LAMS are its superior drainage efficiency, attributable to its large diameter, and that cholecystolithiasis causing cholecystitis can be treated simultaneously [38]. This stent of new shape will find various uses in a variety of sizes and shapes.

24.4.4 EUS-Guided Hepaticogastrostomy

Bile duct obstruction is often associated with pancreatic or biliary cancer, and we commonly experience difficulty in drainage of bile through the papilla or duodenum due to cancer invasion. In such cases, percutaneous transhepatic biliary drainage was generally used in the past, but now transgastric drainage is performed under endoscopic ultrasonography. This method, involving puncture and drainage of intrahepatic bile ducts through the stomach under endoscopic ultrasonography, is called EUS-guided hepaticogastrostomy (EUS-HGS). In the early days of this procedure, transpapillary stents were used, but we experienced stent troubles that were unexpected for a transpapillary procedure [39].

The most serious problem with transpapillary stents for EUS-HGS is stent migration [40]. Although the metal stent is placed from the intrahepatic bile duct over the stomach, a covered stent is needed to prevent bile leakage into the peritoneal cavity. To prevent stent migration, metal stents are placed in the stomach for >5 cm [41]. Nevertheless, gastric peristalsis causes the stent to enter the abdominal cavity, resulting in biliary peritonitis [42]. Several stents for EUS-HGS have been developed recently; the bile-duct side of such stents is uncovered for a few centimeters and so the stent mesh bites into the bile duct wall; also, there is a large stopper on the stomach side, which catches in the stomach wall to prevent entry to the peritoneal cavity (Spring Stopper Stent, Taewoong Medical; Fig. 24.4b). In our experience, there is a 10% risk of migration with conventional stents, even if caution is used to prevent migration. However, we have not experienced any case in which the stent had almost migrated since the advent of dedicated stents.

EUS-guided choledochoduodenostomy (EUS-CDS), which drains the common bile duct from the duodenum, is a common alternative to EUS-HGS. A covered stent for the distal bile duct is typically used in this procedure [43], but drainage using LAMS has also been reported [44].

24.5 Stents Under Development for Malignant Biliary Obstruction

Not only conventional cytotoxic anticancer drugs but also molecular-targeted drugs and immunotherapies have been developed for pancreatic cancer and cholangiocarcinoma, and the prognosis of patients has improved. As a result, metal stents need to remain open for longer, and various means of prolonging stent patency have been studied. The formation of sludge and biofilm associated with stent obstruction involves the growth of microorganisms in the bile ducts, and the environment around the metal stent is prone to such growth. Therefore, antibacterial stents that suppress sludge and biofilm formation have been studied [45]. Also, the incorporation of anticancer drugs to stents can reportedly prevent stent blockage due to tumor growth [46].

Since their first clinical application for biliary strictures in the 1980s, metal stents have evolved steadily. Specialized metal stents such as LAMS and stents for EUS-HGS have been created for novel techniques, such as EUS-guided drainage. New technologies are under development, for which we must create metal stents based on past experience. Also, the development of stents for unresolved problems is needed. In particular, stent treatment for hilar biliary obstruction has merits and demerits and no satisfactory therapy has been developed. A stent for treating hilar biliary obstruction must (1) drain multiple biliary branches and be easy to deploy, (2) not obstruct the flow of the collateral, and (3) facilitate reintervention. The development of metallic stents that meet these requirements is an urgent need.

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