12 Management of Resectable and Borderline Resectable Disease: Medical Oncology

Sunyoung Lee and Milind Javle

Introduction

Pancreatic ductal adenocarcinoma (PDAC) commonly presents at an advanced, unresectable disease stage. This year, an estimated 57,600 adults in the USA will be diagnosed with PDAC and 47,050 deaths will result [1]. Only 10% are detected at an early, surgically resectable disease. Their 5-year survival with current therapies is suboptimal at 30–40% [2]. Therefore, multimodality approaches that include neoadjuvant and post-operative adjuvant chemotherapy are critical options to consider along with surgical resection. The advent of high-resolution imaging has outlined definitions such as "resectable," "borderline resectable," and "locally advanced unresectable" PDAC phenotypes. These definitions and their management need to be individualized and will be discussed in the following sections.

Definition of Resectability

At the current time, modern imaging including contrast-enhanced, pancreas-protocol computerized tomography (CT) scan of the abdomen, thoracic imaging, detailed history and physical, tumor markers such as CA 19-9 level are adequate for preoperative evaluation. The role of endoscopic ultrasound for staging is limited. Multi-detector CT scan with protocols optimized for pancreatic imaging provides a detailed assessment of tumor approximation to superior mesenteric artery (SMA), the superior mesenteric vein (SMV) and SMV–portal vein confluence (SMV-PV), the celiac artery, and the hepatic artery [3]. CT imaging is also valuable to detect extra-pancreatic tumor dissemination and congenital arterial or venous variants. Resectable PDAC includes no abutment of SMA, celiac or hepatic artery, and ≤50° narrowing of SMV or SMV-PV (Fig. 12.1).

Adjuvant Therapy

PDAC is considered a systemic disease, even at an early resectable stage. This may explain why surgery as initial therapy for pancreatic cancer does not result in a cure for the majority of patients. There has not been any remarkable improvement in survival after resection over the past three decades. However, surgical morbidity and mortality have improved dramatically over the past decade and in high-volume centers, the perioperative mortality associated with pancreaticoduodenectomy is 1% [4]. A retrospective review of the National Cancer Data Base (2004–2014) included 5279 PDAC patients who had surgery alone and 4537 who received adjuvant

S. Lee · M. Javle (✉)
Department of Gastrointestinal Oncology, MD Anderson Cancer Center, Houston, TX, USA
e-mail: mjavle@mdanderson.org

M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_12

chemotherapy [5]. The primary surgical approach was Whipple procedure in 61% of pts. Adjuvant chemotherapy was associated with improved overall survival irrespective of disease stage when compared with those undergoing surgery alone (median overall survival for surgery alone was 14 months vs. 21 months, for those receiving adjuvant chemotherapy; $p < 0.001$). Although these figures support the use of adjuvant chemotherapy, these data suggest that in the real-world setting, the clinical impact of surgery and adjuvant therapy has been modest over the past three decades. Phase III adjuvant trials for PDAC are depicted in Table 12.1. As suggested here, we may have reached a plateau in terms of overall survival improvement with adjuvant chemotherapy for PDAC. Two recent adjuvant studies, the adjuvant nab-paclitaxel trial for PDAC (APACT) study with gemcitabine and nab-paclitaxel and PRODIGE trial with FOLFIRINOX are exceptions in this regard and suggest that better patient selection as a result of improved diagnostic staging may be accounting for the better survival figures in these two recent trials.

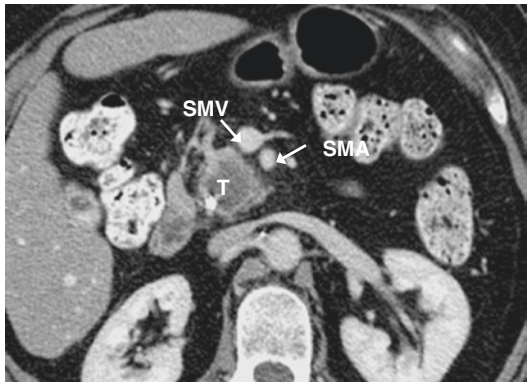

Fig. 12.1 Resectable pancreatic cancer

The APACT trial randomized 866 patients after resection to gemcitabine alone or gemcitabine with nab-paclitaxel [6]. The primary study endpoint was independent reviewer assessed progression-free survival (IR-PFS) and 866 patients were randomized. Median IR-assessed PFS was 19.4 months with the combination vs. 18.8 months with gemcitabine alone (HR, 0.88; $p = 0.1824$). Investigator-assessed PFS was 16.6 months vs. 13.7 months (HR, 0.82; $p = 0.0168$) in the study and control arms, respectively. Overall survival was 40.5 months vs. 36.2 months (HR, 0.82; 0.680—$p = 0.045$) in the study and control arms, respectively. This study although negative for its primary endpoint demonstrated that IR-PFS is not an appropriate endpoint in adjuvant PDAC as progression is often diagnosed on clinical grounds by treating clinician (such as by rising tumor markers or by increasing cancer related symptoms).

Conversely, the PRODIGE trial yielded a clinically and statistically meaningful improvement with modified-FOLFIRINOX chemotherapy as

Table 12.1 Phase III clinical trials of adjuvant therapy in pancreatic adenocarcinoma

Trial	Patients (*n*)	Treatment regimen	Median survival (*p* value)
GITSG [9]	43	Observation vs. chemoradiation	11 vs. 20 months (0.03)
RTOG 9704 [10]	538	Gemcitabine + chemoradiation vs. 5-fluorouracil + chemoradiation	17.1 vs. 18 months (0.12)
CONKO-001 [11]	354	Observation vs. gemcitabine	20 vs. 22.8 months (0.01)
ESPAC-1 [12]	289	Observation vs. chemotherapy vs. radiation	15.5 vs. 20.1 months (0.009)
ESPAC-3 [13]	1088	Fluorouracil vs. gemcitabine	23 vs. 23.6 months (0.39)
ESPAC-4 [14]	732	Gemcitabine + capecitabine vs. gemcitabine	28 vs. 25 months (0.032)
PRODIGE [7]	493	FOLFIRINOX vs. gemcitabine	51 vs. 35 months (0.003)
APACT [6]	866	Gemcitabine + nab-paclitaxel vs. gemcitabine	40.5 vs 36.2 months (0.045)

compared with gemcitabine in a phase III trial of 493 PDAC patients in France [7, 8]. The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group (H.R. 0.58; $p < 0.001$). The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (H.R 0.64; $p = 0.003$). This regimen is now considered as the standard of care as adjuvant therapy for PDAC patients with Eastern Co-operative Oncology Group (ECOG) performance status 0–1. In the above two trials, improved survival is noted both in the study and control arms as compared with historical controls. This improvement may also be on account of better patient selection for surgery, improved imaging techniques, and enhanced post-operative care.

Borderline Resectable PDAC

"Resectability" in PDAC requires lack of vascular involvement, particularly of the SMA, celiac and hepatic artery as described above and patent SMV-PV system [15]. Locally advanced and unresectable, however, included clinical presentations with significant vascular compromise. With increasing clinical experience, it became evident that there was a third, intermediate category where resection is still feasible in some cases with vascular reconstruction. This has now become possible due to multi-detector CT imaging that offers higher resolution images of the tumor vessel interface, with accurate assessment of the degree of abutment and encasement of adjacent vessels. Thus, tumors that have a limited degree of arterial abutment are now considered borderline resectable and are considered for neoadjuvant treatment protocols for tumor "downstaging" prior to resection (Fig. 12.2) [16]. Several systems have been proposed for classification of borderline resectable PDAC; the most recent International Consensus Guidelines are presented below [17]. These guidelines recognized that anatomical considerations by themselves could not determine resectability and both tumor biology and underlying medical conditions have to be accounted for within the classification.

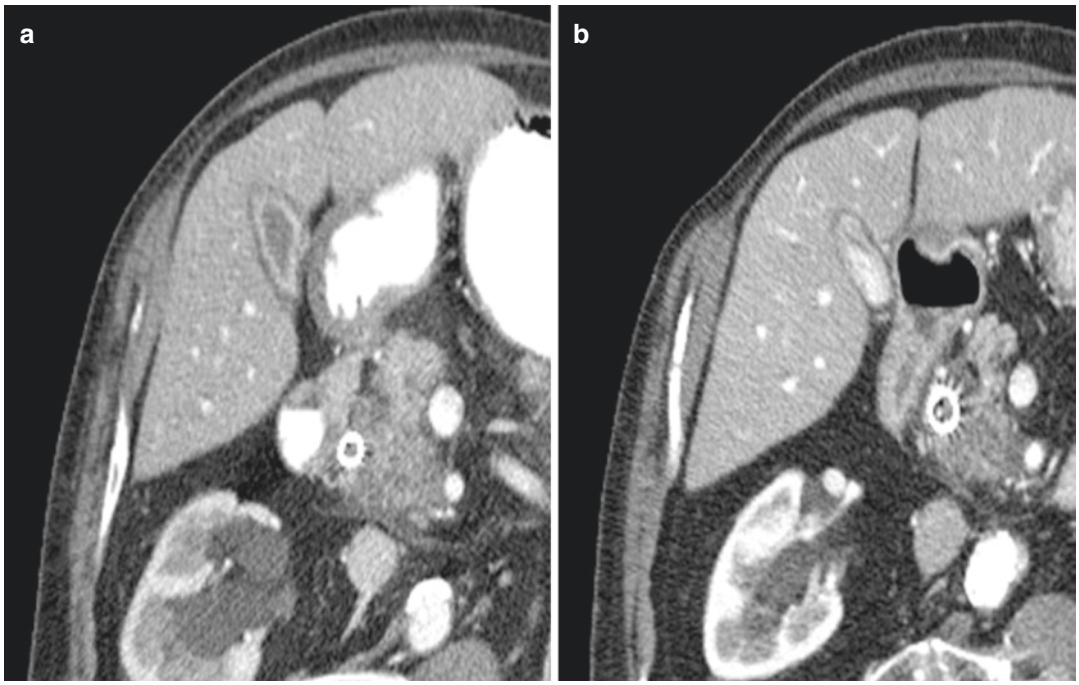

Fig. 12.2 Borderline resectable pancreatic cancer. (**a**) Before treatment. (**b**) After neoadjuvant therapy

The consensus guidelines defined patients with borderline resectable PDAC according to the three distinct dimensions: anatomical (A), biological (B), and conditional (C). Anatomic factors include tumor abutment with the superior mesenteric artery and/or celiac artery of less than 180°, tumor abutment with the SMV/SMV-PV but with proximal and distal ends amenable to reconstruction, this included bilateral narrowing or occlusion without extending beyond the inferior border of the duodenum. Biological factors include potentially resectable disease based on anatomic criteria but with clinical findings suspicious of distant metastases or regional lymph nodes metastases or serum carbohydrate antigen (CA) 19-9 level more than 500 units/ml. Conditional factors include the patients with potentially resectable disease based on anatomic and biologic criteria but with ECOG performance status of 2 or more. These patients are best treated with neoadjuvant therapy.

Neoadjuvant Therapy for PDAC

The rationale for neoadjuvant therapy for patients with resectable pancreatic cancer includes: (a) the potential for downstaging to maximize the chances of a margin-negative (R0) resection (b) treating micrometastatic disease early, (c) administering "adjuvant" therapy in a preoperative setting when it is better tolerated, and (d) using this approach to gauge the aggressiveness of the cancer and thereby select for surgery the patients who have the greatest likelihood of a favorable outcome. We have successfully completed five trials (Table 12.2) of neoadjuvant therapy for pancreatic cancer at the M.D. Anderson Cancer Center and our current treatment paradigm is based on the results of the same [18–21]. This is the largest reported single-center experience with neoadjuvant therapy for pancreatic cancer. Our studies have helped us stratify patients with surgically resectable cancer into two groups: (a) those who are likely to benefit from surgery (in our experience 75% of surgically resectable cases can undergo successful pancreaticoduodenectomy after neoadjuvant therapy) and (b) those for whom surgical resection is unlikely to be clinically beneficial (25% cannot undergo surgery after neoadjuvant therapy). In our recent study of neoadjuvant gemcitabine + radiation for patients with operable pancreatic cancer, the median survival duration was 34 months in patients who underwent surgical resection and 7 months in patients who did not [2]. The 5-year survival rates for those who did and did not undergo resection were 36% and 0%, respectively.

Table 12.2 Clinical trials of neoadjuvant therapy for pancreatic cancer at M.D. Anderson Cancer Center

	5-FU 50.4 Gy	5-FU 30 Gy	Paclitaxel 30 Gy	Gem-XRT	Gem-Cis XRT
No. of patients	28	35	37	86	90
Overall survival (mo)	NA	NA	12	23	17
No. who completed all treatment including PD (%)	17(60)	20(57)	20(54)	64 (74)	52 (66)
No. histologic response IIB-IV/total resected (%)	7 (41)	4 (20)	4/19 (21)	37(58)	31 (60)
No. SMA margin positive (%)	3 (18)	2 (10)	6/19 (32)	4(6)	1 (2)
No. death during treatment (%)	1 (4)	0	0	1 (1)	1 (1)
Median survival of patients who completed all treatment (mo)	NA	25	19	34	31
Median survival of patients who did not complete all treatment (mo)	NA	7	10	7.1	10.5

The use of neoadjuvant therapy in the case of borderline resectable PDAC is intuitive given the expectation that most but not all will undergo subsequent surgery. However, patients with borderline resectable disease are at a high risk for a margin positivity (R1) due to abutment with the vasculature, they require complex vascular reconstruction and have a high predilection for occult metastatic disease. As depicted in Table 12.2, an estimated 60–75% of patients receiving neoadjuvant therapy undergo subsequent resection. Prior neoadjuvant studies for PDAC are depicted in Table 12.3.

Majority of these studies were retrospective although some were prospective, single-arm trials. Until recently, there have been no randomized, prospective clinical trials of neoadjuvant therapy vs. upfront surgery.

The PREOPANC trial is the first randomized clinical trial of preoperative chemoradiotherapy vs. upfront surgical resection for resectable and borderline resectable PDAC [39]. This trial was conducted in 16 centers in Europe and 246 eligible patients were randomized to chemoradiotherapy, which consisted of three courses of gemcitabine, the second combined with 15 × 2.4 Gy radiotherapy, followed by surgery and four courses of adjuvant gemcitabine vs. immediate surgery and six courses of adjuvant gemcitabine. On intention to treat analysis, there was no median overall survival difference between the two arms [16.0 months with preoperative chemoradiotherapy and 14.3 months with immediate surgery (hazard ratio, 0.78; $p = 0.096$)]. A larger fraction of patients in the preoperative group received an R0 resection in the immediate surgery cohort ($P < 0.001$). Preoperative chemoradiotherapy was associated with significantly better disease-free survival and locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion.

As expected, not all patients receiving neoadjuvant therapy received surgical resection. Of the 119 patients who received neoadjuvant therapy, 72 (60%) were operated. This subgroup of patients with tumor resection followed by adjuvant treatment experienced a significantly improved median overall survival of 35.2 months in the preoperative chemoradiotherapy group and 19.8 months in the immediate surgery group (HR, 0.58; $p = 0.029$). The proportion of patients who suffered serious adverse events was higher in the neoadjuvant group 52% versus 41% ($P = 0.096$). Similar findings were reported by the ESCPAC-5 phase II trial where 90 patients with borderline resectable PDAC were randomized to immediate surgery, or neoadjuvant gemcitabine with capecitabine, FOLFIRINOX, or chemoradiation [40]. One year survival rate was 40% for immediate surgery and 77% for neoadjuvant therapy. Log-rank analysis showed an HR = 0.27, $p < 0.001$ in favor of neoadjuvant therapy.

These randomized clinical trials confirmed several points noted earlier in the prior non-randomized trials: (1) Neoadjuvant therapy offers survival advantage over upfront resection for PDAC patients with non-progressive disease after chemoradiotherapy, (2) neoadjuvant therapy is the preferred option for borderline resectable disease, and (3) chemoradiotherapy results in higher toxicity but this does not preclude surgery.

Role of Neoadjuvant Chemotherapy without Radiation

Neoadjuvant chemotherapy alone, without radiotherapy was examined in the prospective phase II SWOG 1505 clinical trial [41]. In this study, 147 patients with resectable PDAC were randomized to preoperative FOLFIRINOX or gemcitabine and nab-paclitaxel. Each treatment arm included the same regimen administered post-operatively and the primary study endpoint for 2-year overall survival. Resection was successfully performed in 70% of the patients who received neoadjuvant therapy. The two-year survival was similar (42% with FOLFIRINOX and 48% with gemcitabine and nab-paclitaxel, $p = 0.12$). There were no significant median overall survival differences between the two arms. At the current time, there are insufficient data to recommend chemotherapy vs. chemoradiotherapy as the preferred neoadjuvant modality prior to resection.

Table 12.3 Prior studies of resectable pancreatic cancer

Study	N	Type of neoadjuvant therapy	Resection rate	Median survival (months)
Ammori et al. (2003) [22]	67	Chemoradiation	9 (13%) R0: 6 (9%)	17.6 (surgery); 11.9 (no surgery)
Katz et al. (2008) [16]	160	Chemoradiation	66 (41%) R0: 62 (39%)	40.0 (surgery); 13.0 (no surgery)
Marti et al. (2008) [23]	26	Chemotherapy Chemoradiation	4 (15%)R0: 3 (11%)	13.0 (all patients); 12.0–62.0 for resected group
Massucco et al. (2006) [24]	28	Chemoradiation	8 (29%)R0: 7 (25%)	>21.0 (surgery); 10.0 (no surgery)
Landry et al. (2010) [25]	21	Chemotherapy Chemoradiation	5 (24%)R0: 3 (14%)	26.3 (surgery)
Brunner et al. (2008) [26]	12	Nelfinavir chemoradiation	6 (50%)R0: 6 (50%)	NA
Leone et al. (2012) [27]	39	Chemotherapy chemoradiation	11 (28%) R0: 9 (23%)	31.5 (surgery); 12.3 (no surgery)
Chun et al. (2010) [28]	74	Chemoradiation	74 (all patients) R0: 44 (59%)	23 (surgery); 15 (no surgery)
Stokes et al. (2011) [29]	41	Chemoradiation	16 (46%) R0: 12 (29%)	23 (surgery); 12 (no surgery)
Lee et al. (2012) [30]	18	Chemotherapy	15 (83%) R0: 13 (72%)	23.1 (surgery); 13.2 (no surgery)
Kang et al. (2012) [31]	67	Chemoradiation	32 (48%) R0: 28 (41%)	26.3 (surgery)
Takahashi et al. (2013) [32]	80	Chemotherapy Chemoradiation	43 (54%) R0: 43 (54%)	25 (surgery)
Chuong et al. (2013) [33]	57	Chemotherapy Chemoradiation	32 (56%) R0: 31 (54%)	19.3 (surgery)
Kim et al. (2013) [34]	39	Chemotherapy Chemoradiation	24 (62%) R0: 21 (54%)	25 (surgery)
Rose et al. (2014) [35]	64	Chemotherapy	31 (48) R0: 27 (42%)	23.6 (all patients); 15.4 (no surgery)
Golcher et al. (2015) [36]	66 (33 upfront, 33 neoadjuvant)	Chemotherapy Chemoradiation	R0: 17 (52%) R0: 16 (48%)	17.4 (neoadjuvant) 14.4 (upfront surgery)
Jang et al. (2018) [37]	35 (17 upfront, 18 neoadjuvant)	Chemotherapy Chemoradiation	R0: 14 (82%) R0: 6 (33%)	21 (neoadjuvant) 12 (upfront surgery)
Motoi et a. (2019) [38]	362 (180 upfront, 182 neoadjuvant)	Chemotherapy	NA	36.7 (neoadjuvant) 26.6 (upfront surgery)

Our treatment paradigm for resectable and borderline resectable disease, outside of a clinical trial includes a sequential approach of systemic chemotherapy, followed by chemoradiation and subsequent surgical resection. For patients who are not enrolled in a clinical trial, we offer induction chemotherapy with FOLFIRINOX or gemcitabine with nab-paclitaxel for 8 weeks followed by restaging CT scans. A multi-disciplinary decision follows regarding subsequent plan for systemic chemotherapy or consolidative chemoradiation. For patients experiencing a definite radiological response and robust CA 19-9 decrement, further chemotherapy is offered. Others without a radiologic response or with stable disease are offered chemoradiation. Patients experiencing systemic disease progression with distant metastases are no longer considered as surgical candidates and are offered second-line chemotherapy or clinical trials.

Radiation therapy along with concurrent 5-fluorouracil or capecitabine is typically administered in a dose of 50.4 Gy to the pancreatic head, body, or tail (depending on the tumor location) along with the vasculature: celiac artery, SMA, and SMV. Thus, the field targets area of local spread; in addition, only suspicious nodes are targeted and not the entire nodal basin which also spares toxicity. Restaging CT scans are typically obtained 6–8 weeks after completion of chemoradiation and before planned surgical resection.

Locally Advanced PDAC

These cancers would typically be considered as unresectable and are treated with systemic chemotherapy, sometimes followed by consolidative chemoradiation. Recently, locally advanced PDAC has been further subclassified into types A and B [42, 43]. Type A includes higher degree of SMA, hepatic arterial, or celiac abutment that is still amenable to vascular reconstruction, whereas type B is unresectable. This segregation has resulted from the fact that some patients with lower vascular compromise experience radiological improvement after multiagent chemotherapy and radiation. The type of surgery required includes complex vascular reconstruction and accompanied with morbidity and mortality and should be restricted to high-volume centers.

What Is the Role of Radiotherapy in the Neoadjuvant Setting for PDAC?

Iacobuzio-Donohue and colleagues demonstrated in rapid autopsy series that 30% of patients with PDAC die of local invasion and not distant failure [44]. It is important to note that most local recurrences develop within millimeters of the SMA and celiac artery because these vessels are immediately adjacent to a surgical margin and PDAC frequently extends along the perivascular nerves. Local control is therefore an important goal of therapy and is facilitated by radiotherapy. There has been one randomized, controlled trial to our knowledge investigating the role of radiotherapy vs. chemotherapy alone for PDAC.

The locally advanced PDAC (LAP07) phase 3 randomized trial enrolled 449 patients with locally advanced, unresectable disease who received gemcitabine ± erlotinib alone or followed by consolidative chemoradiation with 50.4 Gy [45]. The primary outcome was overall survival and there was no significant survival difference between the chemotherapy vs. chemoradiation arms. However, chemoradiotherapy was associated with decreased local progression (32% vs 46%, $P = 0.03$) and no increase in grade 3 to 4 toxicity, except for nausea. Although LAP07 was a study for unresectable locally advanced PDAC, the study results suggest that an improvement in local control from radiotherapy may result in incremental clinical benefit in earlier stage PDAC. Conventional external beam radiotherapy was used in this trial. However, there may be clinical advantages with the use of Intensity Modulated Radiation Therapy (IMRT) or Stereotactic Body Radiotherapy (SBRT), which can provide high doses over short periods of time. Phase II trials of SBRT suggest this approach is feasible and results in clinical benefit. Herman et al. treated 49 patients with locally

advanced PDAC with gemcitabine followed by SBRT (33.0 gray [Gy] in 5 fractions) [46]. After SBRT, patients received maintenance therapy with gemcitabine till progression. The median overall survival was 13.9 months and 80% were free of local disease progression. These encouraging data led to the Alliance A021501 trial of neoadjuvant SBRT followed by surgical resection for borderline resectable PDAC [47]. This study was unfortunately discontinued as on interim analysis, futility boundary for R0 resection was reached. SBRT may be potentially inferior to chemoradiotherapy as concurrent chemotherapy may offer a systemic antitumor effect. Neoadjuvant SBRT cannot be recommended at this time for resectable or borderline resectable PDAC outside the context of a clinical trial. However, concurrent chemoradiotherapy in a dose of 50.4 Gy is commonly used in our practice at MD Anderson Cancer Center along with capecitabine in the neoadjuvant setting for resectable and borderline resectable PDAC.

Histopathologic Assessment Following Neoadjuvant Therapy

Histopathologic assessment of the PDAC specimen after neoadjuvant therapy is complicated. The current College of American Pathology (CAP) grading for tumor response assessment is uniform across several cancers including esophagus, stomach, pancreas, and rectum. The assessment compares residual tumor with background fibrosis as follows: Grade 0, no viable residual tumor (pathologic complete response); Grade 1, marked response (minimal residual cancer with single cells or small groups of cancer cells); Grade 2, partial response (residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells); and Grade 3, poor or no response (extensive residual cancer with no evident tumor regression). This grading scheme for tumor response is the same as those used for carcinomas of esophagus, stomach and rectum in the current CAP protocols. However, there has been very limited prognostic validation of this grading and our retrospective data indicate no survival differences between grades 3 and 4. Therefore, we have proposed an alternative three-tier system as below: Histologic tumor response grade (HTRG) 0, no viable residual tumor (pathologic complete response); HTRG 1, marked response (less than 5% viable tumor cells, minimal residual cancer with single cells or small groups of cancer cells); HTRG 2, moderate to poor response (≥5% residual tumor cells). This system has been validated in a cohort of 223 PDAC resection specimens after prior neoadjuvant therapy [48, 49].

Tumor Surveillance in PDAC Using Circulating DNA (ctDNA)

CA19-9 is the most commonly used marker in pancreatic cancer with a sensitivity and specificity of 79–81% and 82–90%, respectively [50, 51]. However, it is not useful as a screening marker with a low positive predictive value (0.5–0.9%) and does not accurately predict prognosis [52, 53]. It is commonly elevated in other diseases such as biliary obstruction, cholangitis, and pancreatitis [54, 55], complicating clinical assessment of pancreatic cancer.

Tumor-specific DNA mutations can be detected in the cell-free component of peripheral blood in patients with advanced cancer [56]. This circulating tumor DNA (ctDNA) allows for non-invasive molecular characterization of tumors that provides indication to targeted therapies [57–59]. In addition to this therapeutic role, ctDNA has been supported as a biomarker and an independent prognostic marker in pancreatic adenocarcinoma. In a study of 104 patients with advanced pancreatic cancer, 50% of patients had detectable ctDNA levels, and 45% and 42.3% of patients revealed *TP53* and *KRAS* mutation. This study showed worse overall survival (8.4 vs. 16 months, $p < 0.0001$) and progression-free survival (3.2 vs. 7.9 months, $p < 0.0001$) in patients with ctDNA positive patients, compared with negative patients [52].

Another study validated a role of ctDNA as a prognostic marker in 112 patients with localized pancreatic cancer. Positive ctDNA detection in

the pre- and post-operative settings was associated with worse recurrence-free survival and overall survival. All the patients (13/13, 100%) with detectable ctDNA post-operatively had recurrence, and seven patients had recurrence while receiving gemcitabine-based adjuvant chemotherapy [60]. A meta-analysis of ctDNA in patients with resectable pancreatic adenocarcinoma confirmed that patients with detectable ctDNA had a higher risk for disease recurrence than those without detectable ctDNA (pre-surgery, HR 1.96, 95% CI 0.65–5.87; post-surgery HR 2.20, 95% CI 0.99–4.87).

Obtaining a sufficient biopsy tissue for molecular or pathology tests is often times not feasible in localized pancreatic cancer. For example, fine needle aspiration via endoscopic ultrasound or resection of pancreatic tumors with less viable cells status post-neoadjuvant chemotherapy sometimes provides insufficient tissues for molecular tests [61]. In this clinical scenario, ctDNA can be useful and lead to identification of actionable mutations, offering more therapeutic options such as targeted therapy or clinical trials. These mutations include cMET (2.5%), FGFR2 (1.2%), NTRK fusion (6%), mTOR (2%), or HER2 expression and amplification (2–6%) [62].

Neoadjuvant Therapy Followed by Metastasectomy for PDAC

Metastasectomy of an oligometastatic disease with liver or lung lesions has resulted in survival benefit in other cancer types. More than 50% of patients with colorectal cancer present with a metastatic disease at baseline, and the most common metastatic sites are the liver and lungs [63]. Resection of metastatic liver lesions offers five-year survival rate ranging from 24% to 58% [64, 65], while systemic chemotherapy alone has 10–11% [66]. Pulmonary metastasectomy is also considered for surgically fit patients with resectable lung metastases, and it confirmed survival benefit [67, 68].

The tumor biology of pancreatic adenocarcinoma is generally more aggressive than that of colorectal cancer for which liver and lung metastasectomy has offered survival benefit. In pancreatic adenocarcinoma, up to 12% of patients with no radiologic evidence of metastases in the pre-operative setting are later found to have liver or peritoneal metastases in the exploratory laparoscopy [69]. Survival benefit from metastasectomy is conflicting, and there have been no randomized controlled trials to clearly define clinical outcomes after metastasectomy [70]. The NCCN guideline does not recommend surgical resection in cases of distant metastases [71]. Surgery of the primary pancreatic tumor is challenging with a mortality rate ranging from 7.3% to 22.9% (5% in high-volume centers) [72, 73]. Therefore, synchronous (or even metachronous) resection of the primary pancreatic tumor and metastatic lesions can lead to a higher mortality rate. The liver is the most commonly affected metastatic site from pancreatic adenocarcinoma with the peritoneum and lungs following [57, 74], and many studies of hepatic metastasectomy have been published.

In a retrospective analysis of 6 European pancreas centers, 69 patients underwent synchronous resection of liver metastatic lesions and the primary pancreatic tumor, and clinical outcomes were compared with the other 69 patients who only underwent surgical exploration without tumor resection. Overall survival appeared to be prolonged in the group of resected patients (14 vs. 8 months, $p < 0.001$). Patients with a primary tumor in the head of the pancreas had survival benefit, but those with the tumor in the body or tail of the pancreas did not (14 vs. 15 months, $p = 0.31$). Although this study showed a clear survival benefit in patients who had synchronous resection of hepatic lesions and the primary tumor in the head of the pancreas, a strong conclusion cannot be drawn due to the limitations of retrospective study and a potential for selection bias [75].

Crippa et al. also investigated clinical outcomes in patients who received neoadjuvant chemotherapy followed by surgical resection of liver metastatic lesions. This study included 127 patients who received systemic chemotherapy including gemcitabine. Chemotherapy response rate was 44% (7% complete response and 37% partial response). After 12 months from the initial

diagnosis, surgical resection was performed for 11 patients. In this subgroup, median survival was longer (46 vs. 11 months, $p < 0.0001$) for patients undergoing resection. Of note, patients who received multiple chemotherapeutics (HR, 0.512) and surgical resection (HR, 0.360) had longer overall survival, while those with more than 5 metastatic lesions (HR, 3.515) and CA19-9 reduction less than 50% (HR, 2.708) had shorter overall survival. This study demonstrates a subset of patients with good response from chemotherapy may potentially benefit from surgical resection of the metastatic and primary pancreatic tumors [76].

Patients with isolated pulmonary recurrence are known to have better overall survival [77]. A study of 40 patients with isolated pulmonary recurrence showed median survival of 22.5 months (95% CI 19.1–31.8) after diagnosis of pulmonary metastasis. Patients with less than 10 lung metastases (31.3 vs. 18.7 months, $p = 0.003$) and a unilateral localization of lung involvement (31.3 vs. 21.8 months, $p = 0.03$) had longer survival [78]. In a retrospective study of 31 patients with isolated lung metastasis, nine patients underwent surgical resection after pulmonary recurrence. The median time from the resection of the primary pancreatic tumor to pulmonary metastasis was 34 months. The median overall survival was longer in patients who had pulmonary metastasectomy than those who did not (51 vs. 23 months, $p = 0.04$). Median relapse-free survival was 29 vs. 14 months ($p < 0.001$). There was a trend toward greater 2-year survival after relapse in the patient group with pulmonary metastasectomy, compared with those who did not undergo surgery (40 vs. 27%, $p = 0.2$) [79].

Above studies demonstrate that metastasectomy can be performed in PDAC in patients with favorable biology and response to systemic chemotherapy [70]. Patients with isolated, metachronous pulmonary metastasis after prior pancreatectomy have experienced clinical benefit including improved survival [79]. However, there have been no randomized clinical trials or prospective studies to better assess survival outcomes from metastasectomy in patients with stage IV pancreatic adenocarcinoma. At this point, the NCCN does not recommend surgical resection in patients with metastatic pancreatic adenocarcinoma. In our practice, we will consider resection of isolated, metachronous pulmonary metastases in patients who have undergone prior pancreatic surgery although this cannot be regarded as standard of care.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30.
2. Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, Kelsen DP, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. Br J Cancer. 2017;116(6):697–702.
3. Tamm EP, Silverman PM, Charnsangavej C, Evans DB. Diagnosis, staging, and surveillance of pancreatic cancer. AJR Am J Roentgenol. 2003;180(5):1311–23.
4. Canto MI, Kerdsirichairat T, Yeo CJ, Hruban RH, Shin EJ, Almario JA, et al. Surgical outcomes after pancreatic resection of screening-detected lesions in individuals at high risk for developing pancreatic cancer. J Gastrointest Surg. 2020;24(5):1101–10.
5. Seaton M, Hanna A, Boutros C, Hanna N. Adjuvant therapy for pancreatic body or tail adenocarcinoma: a study of the National Cancer Database. Ther Adv Med Oncol. 2019;11:1758835919842438.
6. Tempero MA, Reni M, Riess H, Pelzer U, O'Reilly EM, Winter JM, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol. 2019;37(15_suppl):4000.
7. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
8. Parmar A, Chaves-Porras J, Saluja R, Perry K, Rahmadian AP, Santos SD, et al. Adjuvant treatment for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2020;145:102817.
9. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer. 1987;59(12):2006–10.
10. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
11. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes

among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
12. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009;100(2):246–50.
13. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA. 2012;308(2):147–56.
14. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
15. Tran Cao HS, Balachandran A, Wang H, Nogueras-Gonzalez GM, Bailey CE, Lee JE, et al. Radiographic tumor-vein interface as a predictor of intraoperative, pathologic, and oncologic outcomes in resectable and borderline resectable pancreatic cancer. J Gastrointest Surg. 2014;18(2):269–78. Discussion 78
16. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206(5):833–46. Discussion 46–8
17. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernandez-Del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18(1):2–11.
18. Raut CP, Evans DB, Crane CH, Pisters PW, Wolff RA. Neoadjuvant therapy for resectable pancreatic cancer. Surg Oncol Clin N Am. 2004;13(4):639–61, ix
19. Evans DB, Wolff RA, Crane CH. Neoadjuvant strategies for pancreatic cancer. Oncology (Williston Park). 2001;15(6):727–37. Discussion 41–4, 47
20. Evans DB. The complexity of neoadjuvant therapy for operable pancreatic cancer: lessons learned from SWOG S1505. Ann Surg. 2020;272(3):487.
21. Katz MH, Wang H, Balachandran A, Bhosale P, Crane CH, Wang X, et al. Effect of neoadjuvant chemoradiation and surgical technique on recurrence of localized pancreatic cancer. J Gastrointest Surg. 2012;16(1):68–78. Discussion -9.
22. Ammori JB, Colletti LM, Zalupski MM, Eckhauser FE, Greenson JK, Dimick J, et al. Surgical resection following radiation therapy with concurrent gemcitabine in patients with previously unresectable adenocarcinoma of the pancreas. J Gastrointest Surg. 2003;7(6):766–72.
23. Marti JL, Hochster HS, Hiotis SP, Donahue B, Ryan T, Newman E. Phase I/II trial of induction chemotherapy followed by concurrent chemoradiotherapy and surgery for locoregionally advanced pancreatic cancer. Ann Surg Oncol. 2008;15(12):3521–31.
24. Massucco P, Capussotti L, Magnino A, Sperti E, Gatti M, Muratore A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol. 2006;13(9):1201–8.
25. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol. 2010;101(7):587–92.
26. Brunner TB, Geiger M, Grabenbauer GG, Lang-Welzenbach M, Mantoni TS, Cavallaro A, et al. Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2008;26(16):2699–706.
27. Leone F, Gatti M, Massucco P, Colombi F, Sperti E, Campanella D, et al. Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: a single institutional experience. Cancer. 2013;119(2):277–84.
28. Chun YS, Milestone BN, Watson JC, Cohen SJ, Burtness B, Engstrom PF, et al. Defining venous involvement in borderline resectable pancreatic cancer. Ann Surg Oncol. 2010;17(11):2832–8.
29. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, et al. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. Ann Surg Oncol. 2011;18(3):619–27.
30. Lee JL, Kim SC, Kim JH, Lee SS, Kim TW, Park DH, et al. Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma. Surgery. 2012;152(5):851–62.
31. Kang CM, Chung YE, Park JY, Sung JS, Hwang HK, Choi HJ, et al. Potential contribution of preoperative neoadjuvant concurrent chemoradiation therapy on margin-negative resection in borderline resectable pancreatic cancer. J Gastrointest Surg. 2012;16(3):509–17.
32. Takahashi S, Kinoshita T, Konishi M, Gotohda N, Kato Y, Kinoshita T, et al. Borderline resectable pancreatic cancer: rationale for multidisciplinary treatment. J Hepatobiliary Pancreat Sci. 2011;18(4):567–74.
33. Chuong MD, Hayman TJ, Patel MR, Russell MS, Malafa MP, Hodul PJ, et al. Comparison of 1-, 2-, and 3-dimensional tumor response assessment after neoadjuvant GTX-RT in borderline-Resectable pancreatic cancer. Gastrointest Cancer Res. 2011;4(4):128–34.
34. Kim EJ, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, Griffith KA, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and

oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer. 2013;119(15):2692–700.
35. Rose JB, Rocha FG, Alseidi A, Biehl T, Moonka R, Ryan JA, Lin B, Picozzi V, Helton S. Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. Ann Surg Oncol. 2014;21(5):1530–7.
36. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015;191(1):7–16.
37. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline Resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268(2):215–22.
38. Motoi F, Kosuge T, Ueno H, Yamaue H, Satoi S, Sho M, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). Jpn J Clin Oncol. 2019;49(2):190–4.
39. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for Resectable and borderline Resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020;38(16):1763–73.
40. Ghaneh P, Palmer DH, Cicconi S, Halloran C, Psarelli EE, Rawcliffe CL, et al. ESPAC-5F: four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. J Clin Oncol. 2020;38(15_suppl):4505.
41. Sohal D, McDonough SL, Ahmad SA, Gandhi N, Beg MS, Wang-Gillam A, et al. SWOG S1505: a randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinom. J Clin Oncol. 2017;35(4_suppl):TPS508-TPS.
42. Kim RY, Evans DB, Christians KK. Locally advanced pancreatic cancer: staging, operability, and the importance of multimodality therapy. Hepatobiliary Surg Nutr. 2020;9(4):497–500.
43. Evans DB. Commentary: surgery for locally advanced pancreatic cancer after neoadjuvant therapy. Surgery. 2021;169(5):1032–3.
44. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009;27(11):1806–13.
45. Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA. 2016;315(17):1844–53.
46. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multiinstitutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121(7):1128–37.
47. Katz MHG, Ou FS, Herman JM, Ahmad SA, Wolpin B, Marsh R, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. BMC Cancer. 2017;17(1):505.
48. Nagaria TS, Wang H, Chatterjee D, Wang H. Pathology of treated pancreatic ductal adenocarcinoma and its clinical implications. Arch Pathol Lab Med. 2020;144(7):838–45.
49. Lee SM, Katz MH, Liu L, Sundar M, Wang H, Varadhachary GR, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. Am J Surg Pathol. 2016;40(12):1653–60.
50. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105–19.
51. Scarà S, Bottoni P, Scatena R. CA 19-9: biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:247–60.
52. Uesato Y, Sasahira N, Ozaka M, Sasaki T, Takatsuki M, Zembutsu H. Evaluation of circulating tumor DNA as a biomarker in pancreatic cancer with liver metastasis. PLoS One. 2020;15(7):e0235623.
53. Zhang Y, Yang J, Li H, Wu Y, Zhang H, Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. Int J Clin Exp Med. 2015;8(7):11683–91.
54. Passerini R, Cassatella MC, Boveri S, Salvatici M, Radice D, Zorzino L, et al. The pitfalls of CA19-9: routine testing and comparison of two automated immunoassays in a reference oncology center. Am J Clin Pathol. 2012;138(2):281–7.
55. Tanaka N, Okada S, Ueno H, Okusaka T, Ikeda M. The usefulness of serial changes in serum CA19-9 levels in the diagnosis of pancreatic cancer. Pancreas. 2000;20(4):378–81.
56. Dasari A, Morris VK, Allegra CJ, Atreya C, Benson AB 3rd, Boland P, et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. Nat Rev Clin Oncol. 2020;17(12):757–70.

57. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med. 2008;132(6):931–9.
58. Misale S, Yaeger R, Hobor S, Scala E, Janakiraman M, Liska D, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature. 2012;486(7404):532–6.
59. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med. 2016;8(346):346ra92-ra92.
60. Lee B, Lipton L, Cohen J, Tie J, Javed AA, Li L, et al. Circulating tumor DNA as a potential marker of adjuvant chemotherapy benefit following surgery for localized pancreatic cancer. Ann Oncol. 2019;30(9):1472–8.
61. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018;24(19):2047–60.
62. Salem ME, Marshall J, Feldman R, Pishvaian MJ, El-Deiry WS, Hwang JJ, et al. Comparative molecular analyses of pancreatic cancer (PC): KRAS wild type vs. KRAS mutant tumors and primary tumors vs. distant metastases. J Clin Oncol. 2016;34(15_suppl):4121.
63. Gonzalez M, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. Fut oncol (Lond, Engl). 2015;11(2 Suppl):31–3.
64. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438–47. Discussion 47–50
65. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg. 1995;19(1):59–71.
66. Ferrarotto R, Pathak P, Maru D, Agarwal A, Overman M, Hoff PM, et al. Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. Clin Colorectal Cancer. 2011;10(3):178–82.
67. Jaklitsch MT, Mery CM, Lukanich JM, Richards WG, Bueno R, Swanson SJ, et al. Sequential thoracic metastasectomy prolongs survival by re-establishing local control within the chest. J Thorac Cardiovasc Surg. 2001;121(4):657–67.
68. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg. 2006;202(3):468–75.
69. Kneuertz PJ, Cunningham SC, Cameron JL, Torrez S, Tapazoglou N, Herman JM, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. J Gastrointest Surg. 2011;15(11):1917–27.
70. Voss N, Izbicki JR, Nentwich MF. Oligometastases in pancreatic cancer (synchronous resections of hepatic oligometastatic pancreatic cancer: disputing a principle in a time of safe pancreatic operations in a retrospective multicenter analysis). Ann Gastroenterol Surg. 2019;3(4):373–7.
71. Tempero MA, Malafa MP, Chiorean EG, Czito B, Scaife C, Narang AK, et al. Pancreatic adenocarcinoma, version 1.2019. J Nat Comprehen Cancer Netw. 2019;17(3):202–10.
72. Nimptsch U, Krautz C, Weber GF, Mansky T, Grützmann R. Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. Ann Surg. 2016;264(6):1082–90.
73. Strobel O, Berens V, Hinz U, Hartwig W, Hackert T, Bergmann F, et al. Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. Surgery. 2012;152(3 Suppl 1):S33–42.
74. Yachida S, Iacobuzio-Donahue CA. The pathology and genetics of metastatic pancreatic cancer. Arch Pathol Lab Med. 2009;133(3):413–22.
75. Tachezy M, Gebauer F, Janot M, Uhl W, Zerbi A, Montorsi M, et al. Synchronous resections of hepatic oligometastatic pancreatic cancer: disputing a principle in a time of safe pancreatic operations in a retrospective multicenter analysis. Surgery. 2016;160(1):136–44.
76. Crippa S, Bittoni A, Sebastiani E, Partelli S, Zanon S, Lanese A, et al. Is there a role for surgical resection in patients with pancreatic cancer with liver metastases responding to chemotherapy? Eur J Surg Oncol. 2016;42(10):1533–9.
77. Liu KH, Hung CY, Hsueh SW, Chang PH, Chen YY, Lu CH, et al. Lung metastases in patients with stage IV pancreatic cancer: prevalence, risk factors, and survival impact. J Clin Med. 2019;8(9):1402.
78. Kruger S, Haas M, Burger PJ, Ormanns S, Modest DP, Westphalen CB, et al. Isolated pulmonary metastases define a favorable subgroup in metastatic pancreatic cancer. Pancreatology. 2016;16(4):593–8.
79. Arnaoutakis GJ, Rangachari D, Laheru DA, Iacobuzio-Donahue CA, Hruban RH, Herman JM, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. J Gastrointest Surg. 2011;15(9):1611–7.