Neoadjuvant Treatment for Borderline Resectable Pancreatic Ductal Adenocarcinoma

Benedikt Kaufmann^a Daniel Hartmann^a Jan G. D'Haese^b Pavel Stupakov^a
Dejan Radenkovic^c Beat Gloor^d Helmut Friess^a

^aDepartment of Surgery, TUM School of Medicine, Klinikum Rechts der Isar, Technical University Munich, Munich, Germany; ^bDepartment of General, Visceral, Vascular, and Transplantation Surgery, Ludwig-Maximilians-University, Munich, Germany; ^cClinic of Digestive Surgery, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ^dDepartment of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, Bern, Switzerland

Keywords

Pancreatic ductal adenocarcinoma · Borderline resectable pancreatic cancer · Neoadjuvant treatment

Abstract

One of the main reasons for the dismal prognosis of pancreatic ductal adenocarcinoma (PDAC) is its late diagnosis. At the time of presentation, only approximately 15–20% of all patients with PDAC are considered resectable and around 30% are considered borderline resectable. A surgical approach, which is the only curative option, is limited in borderline resectable patients by local involvement of surrounding structures. In borderline resectable pancreatic cancer (BRPC), neoadjuvant treatment regimens have been introduced with the rationale to downstage and downsize the tumor in order to enable resection and eliminate microscopic distant metastases. However, there are no official guidelines for the preoperative treatment of BRPC. In the majority of cases, patients are administered Gemcitabine-based or FOLFIRINOX-based chemotherapy regimens with or without radiation. Radiologic restaging after neoadjuvant therapy has to be judged with caution

when it comes to predict tumor response and resectability, since inflammation induced by neoadjuvant therapy may mimic solid tumor. Patients who do not show any disease progression during neoadjuvant therapy should be offered surgical exploration, since a high percentage is likely to undergo resection with negative margins (R0) and, thus, achieve improved overall survival although imaging judged it unlikely. Despite the promising new approaches of neoadjuvant treatment regimens during the last 2 decades, surgery remains the first choice if the tumor appears to be primary resectable at the time of diagnosis. At present, there are no international guidelines regarding the preoperative treatment of BRPC. Therefore, in order to standardize and adjust neoadjuvant treatment in the future, new guidelines have to be determined on the basis of upcoming prospective randomized studies.

© 2018 S. Karger AG, Basel

B.K. and D.H. contributed equally to this work. Contribution from the EDS Visceral Medicine Course 2018, Moscow, Russia, February 27 until March 1, 2018. This Postgraduate Course was supported in part by United European Gastroenterology.

Background

With 53,670 new cases and estimated 43,090 deaths in 2017, pancreatic cancer is currently the fourth leading cause of cancer-related death and it is expected to be the second leading cause of cancer-related death in the United States until 2030 [1, 2]. In addition, pancreatic cancer showed an increasing mortality within the last decades rising from 8.1% in 1981 to 9.7% in 2009 as opposed to a strong decrease of overall cancer mortality by 15% since the mid-1990s [3]. The most common subtype of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC) responsible for over 90% of all pancreatic tumors [4].

Until today, surgery is the only curative treatment for PDAC. However, at the time of diagnosis the majority of patients present with metastatic disease excluding them from curative intended resection. Only 15–20% of the patients show a potentially curative resectable disease at the time of initial diagnosis. Despite surgery and additional adjuvant chemotherapy, 5-year-survival rates are not higher than 30% (European Study Group For Pancreatic Cancer Trial 4, ESPAC4) [5]. Approximately 30% of patients are identified as borderline resectable pancreatic cancer (BRPC) or locally advanced unresectable pancreatic cancer (LAPC). PDAC is defined as BRPC or LAPC if surrounding vascular structures or adjacent organs are involved, preventing primary resection [6–8]. Currently, there are several definitions for BRPC from different societies and institutions: (i) the National Comprehensive Cancer Network, (ii) the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT), and (iii) the MD Anderson Cancer Center. The current National Comprehensive Cancer Network definition is very similar to what has been defined by the AHPBA/SSO/SSAT consensus statement [9]. The definitions are listed in Table 1. Although the classification systems show minor differences, the term BRPC is mainly used to describe pancreatic cancer involvement of the mesentericoportal or arterial axis, which has been an exclusion criterion for surgery some years ago [6, 10]. In the last decade, the development and improvement of modern surgical techniques as well as new neoadjuvant treatments resulted in a higher number of resectable tumors that have been initially considered inoperable based on radiological criteria or findings during laparotomy. The main challenge for neoadjuvant treatment in patients with BRPC is downstaging and downsizing of the tumor in order to make it resectable and to achieve an R0 resection with tumor free resection margins >1 mm. Many patients

affected by BRPC are at high risk for an R1 resection (tumor-free resection margin <0–1 mm) and distant metastases. Therefore, several centers recommend neoadjuvant treatment, including chemotherapy with or without radiation, as a general treatment strategy for BRPC [11]. In this review, we focus on the development of neoadjuvant treatment strategies and current recommendations for BRPC.

Pancreatic Cancer, a Systemic Disease

Nowadays, PDAC is increasingly recognized in clinically apparent stages as a systemic disease with limited response to systemic treatment. Even tumors that have been diagnosed as localized and resectable are potentially considered to be treated in a way that systemic diseases are treated and not by surgery alone. This new understanding of PDAC is based on a significant rate of tumor recurrence even after R0 resection and a progression of disease toward distant metastases that have not been identified by imaging prior to surgery. Therefore, patients undergoing curative surgery should be managed in a multimodal setting including resection and adjuvant chemotherapy. In recent years, several studies suggested a benefit for patients who have been treated with perioperative/neoadjuvant systemic therapy [10–15]. Whether this benefit is related to the efficacy of the neoadjuvant treatment or to the selection of patients with better tumor biology is still controversial and not clear.

Neoadjuvant Treatment

Perioperative therapy is associated with a survival advantage even in early-stage PDAC and has been shown to improve resectability [16]. Neoadjuvant treatment for BRPC encompasses different approaches. Even though there is evidence supporting multimodal therapy for BRPC in order to improve outcomes, no standard treatment regimen has been established yet [15]. At present, the most favorable approach includes preoperative chemotherapy with or without radiation therapy. Different chemotherapy regimens are used in clinical practice, mainly Gemcitabine- or FOLFIRINOX-based (5-Fluorouracil, Leucovorin, Irinotecan and Oxaliplatin) regimens. Current studies demonstrate a notable benefit for new preoperative chemotherapy regimens for BRPC consisting of Gemcitabine plus nab-paclitaxel or FOLFIRINOX resulting in R0 resection rates of up to 92%, decreased

Table 1. Definitions for BRPC

Guideline by	Venous involvement		Arterial involvement	
NCCN (1.2016)	SMV-PV	<ul style="list-style-type: none"> – Solid tumor contact >180° (encasement) – Solid tumor contact <180° (abutment) plus contour irregularity – Free segment for safe clamping and reconstruction 	CHA	Solid tumor contact not extending to the celiac axis
	IVC	Solid tumor contact	SMA	Solid tumor contact <180°
			Variant arterial anatomy	Involved in tumor
MD Anderson [48]	SMV-PV	<ul style="list-style-type: none"> – Short segment occlusion with free segment for safe clamping and reconstruction – Contact of 180° or more 	HA	Short segment contact
			SMA or celiac trunk	Contact but less than 180°

lymph node positivity and perineural invasion, as well as improved overall survival (OS) [17–23]. In addition, a number of Gemcitabine-based treatment regimens, such as Gemcitabine plus S-1 or Gemcitabine plus docetaxel, seem to be the most and promising future neoadjuvant chemotherapy regimens for BRPC [18, 20, 24, 25]. Besides chemotherapy alone, neoadjuvant chemoradiation is another option for BRPC. In 2006, one of the first studies was released using neoadjuvant chemoradiation for BRPC. In this study, Gemcitabine combined with radiation for BRPC enabled successful resection in 39% of patients. The operative risk was independent of neoadjuvant therapy, and OS after R0 resection was similar to patients with primary resection for localized PDAC [26]. Since then, numerous studies have shown positive outcomes following neoadjuvant chemoradiation: Mainly Gemcitabine and FOLFIRINOX-based drug regimens combined with preoperative chemoradiation decreased recurrence rate and increased OS [17, 19, 20, 22, 27–30]. Another study evaluating Gemcitabine-based chemoradiation showed that a high percentage (26%) of patients with LAPC could undergo secondary resection with tumor-negative resection margins in 39% of cases. Long-term outcome after complete tumor resection was also quite promising with an OS of 22.1 months [31]. Recently published studies report of improved R0 resection rates of up to 92% after neoadjuvant therapy based on Gemcitabine or FOLFIRINOX [17, 28]. Although the number of patients was small, in 2018, one of the first multicenter randomized controlled trials of patients with BRPC demonstrated a significant increase of R0 resection (82.4 vs. 33.3%) and a 2-year survival rate (41 vs. 26%) after Gemcitabine-based neoadjuvant chemoradiation compared

to upfront surgery [28]. At the 2018 American Society of Clinical Oncology (ASCO) meeting, the preliminary results of the latest and largest phase III multicenter randomized trial comparing neoadjuvant chemoradiation with upfront surgery were presented. The authors showed a significant advantage for preoperative therapy with improved OS, DFS, and R0 resection rates [32].

The use of induction chemotherapy followed by neoadjuvant chemotherapy or chemoradiation can be considered an additional neoadjuvant approach. This therapeutic strategy is based on the hypothesis of occult microscopic metastases not detectable by imaging at the initial stage. A series of small studies released during the last decade indicate a favorable resection rate and median survival for preoperative induction chemotherapy [33–35].

A recently published study from Japan demonstrated that prolonged neoadjuvant therapy (initial chemoradiation followed by additional 6 months of chemotherapy) for LAPC is useful to selected candidates who benefit from surgical treatment and most importantly increases OS after tumor resection compared to patients without resection (3.63 vs. 1.01 years) [36].

Stereotactic body radiation therapy after induction chemotherapy seems to be a new technical approach that allows for high R0 resection rates, high rates of pathological response, and promising OS rates [37, 38]. In addition, further studies investigated the role of immunotherapy and targeted therapy agents, such as Cetuximab, Bevacizumab, and Trastuzumab. Up to date, the addition of these agents to established chemotherapy regimens did not show any benefit for patients with BRPC [10].

Despite numerous studies analyzing neoadjuvant therapy in BRPC, there are no general international guidelines for a standardized neoadjuvant treatment protocol for BRPC. Encouraged by promising results, different ongoing prospective studies are currently investigating the efficacy of preoperative chemotherapy in order to provide more evidence on such treatment strategies: (i) The NEOPAC (NCT01314027) study analyses adjuvant Gemcitabine versus Neoadjuvant Gemcitabine/Oxaliplatin + adjuvant Gemcitabine or preoperative FOLFIRINOX + adjuvant Gemcitabine for BRPC. (ii) The NEONAX (NCT01521702) trial will evaluate neoadjuvant Gemcitabine/nab-Paclitaxel + adjuvant Gemcitabine/nab-Paclitaxel versus adjuvant Gemcitabine/nab-Paclitaxel for primarily resectable PC. (iii) The NEOPA (NCT02047513) study will assess the effect of neoadjuvant Gemcitabine-based chemoradiation therapy + adjuvant Gemcitabine versus adjuvant Gemcitabine alone following resection [39].

Downsizing BRPC to a Resectable Stage

Neoadjuvant chemotherapy for BRPC plays a key role making a margin negative resection more likely. The main idea of neoadjuvant treatment for BRPC is downstaging and downsizing of the tumor, especially in the vicinity of arterial and perivascular infiltration. BRPC shows important differences compared to primary resectable PDAC. The risk for positive margins after resection is much higher and the operation technique is more challenging due to the involvement of venous or arterial structures requiring vascular resection and reconstruction. In addition, patients with BRPC are at risk for systemic disease progression resulting in distant metastases. Neoadjuvant chemotherapy or chemoradiation is considered to be particularly important for patients with arterial tumor attachment (so-called abutment) in the hope of sufficient response at the tumor periphery, thus increasing the likelihood of a negative margin of resection [10, 11, 14, 15]. To optimize the outcome of patients with BRPC, a neoadjuvant treatment is recommended for patients affected with this disease. Data suggest that up to 50% of patients initially staged BRPC/LAPC may become resectable after neoadjuvant therapy [13, 40, 41]. However, most studies are small, non-randomized and the study population and definitions of BRPC/LAPC were very heterogeneous. A neoadjuvant approach may also help to identify patients with unfavorable tumor biology. Despite neoadjuvant therapy, up

to 20–30% of patients develop tumor progression and distant metastases during induction therapy of 2–3 months [13]. These patients may then be excluded from surgery and thus avoid postoperative morbidity of unnecessary resection [13]. However, it remains unclear whether these patients that progress under neoadjuvant chemotherapy would have had a benefit from an earlier attempt and potentially successful radical surgical resection. It is thought that these patients are selected prior to surgery and that the morbidity of an initial surgery can be avoided, but we do not know if we selected the right patient cohort.

Identifying the Appropriate Patient for Surgery

The identification of patients who will respond to neoadjuvant treatment is an additional challenge. Inflammatory changes and fibrotic scar in the periphery of the tumor in consequence of initial chemotherapy or chemoradiation may mimic a solid tumor mass. Therefore, re-staging of BRPC using cross-sectional imaging after neoadjuvant therapy oftentimes does not reveal any disease response. CT imaging has indicated that up to 70% of patients had stable disease and only 12–20% had partial response after initial preoperative therapy while 19% showed progressive disease. However, negative resection margins (R0) were achieved in 80% of patients who did not have metastatic disease after neoadjuvant therapy. In addition, the median OS of patients who have been resected and had radiologically stable disease was comparable to the OS of patients who responded to preoperative therapy. Evaluation of the pathological response revealed partial or complete response to initial treatment (<50% remaining viable tumor cells) in 56% of patients. Therefore, determining BRPC as stable disease after induction therapy should not be an exclusion criterion for pancreatic resection. Instead, all patients with BRPC in sufficient physical condition that do not show any progression or distant metastases after neoadjuvant treatment should undergo surgical exploration to evaluate resectability, since imaging alone does not seem to be adequate enough to determine disease response to initial therapy [10, 17, 34, 42].

Surgical Approach

Although new drug regimens and radiation techniques are evolving, surgical resection remains the mainstay of treatment for PDAC. Due to the enormous progress in

imaging as well as the development of modern surgical techniques and neoadjuvant treatments, resection of BRPC has become more frequent, more radical and challenging. This results in the fact that nowadays more patients with BRPC receive a potentially curative therapy that was not conceivable a few years ago. Especially, patients with infiltration of the portal and superior mesenteric vein, or arterial vessels, such as the hepatic or superior mesenteric artery, may be selectively evaluated for surgery. However, vascular resection should be evaluated carefully for each individual patient and performed in high-volume centers with experienced surgical and multidisciplinary teams [43]. Particularly, arterial resection remains challenging and should not be done on a routine basis because of significantly increased morbidity and mortality [6, 20, 44–47]. Further studies also have to investigate the ideal time point for resection after neoadjuvant therapy. Currently, in most studies, pancreatic surgery was performed approximately 1–2 months after chemoradiation was finished.

Summary

Preoperative treatment of BRPC is evolving and becoming an essential component of the therapeutic strategy. There is increasingly strong evidence for the incorporation of neoadjuvant therapy followed by pancreatic

tomy and adjuvant treatment into the guidelines for the treatment of BRPC. The main goal of neoadjuvant therapy is downstaging and downsizing of the tumor in order to become resectable with wide tumor-free resection margins (>1 mm) and to eliminate distant micrometastases. The most common preoperative therapy comprises chemotherapy with or without radiation. The main chemotherapeutic regimens are Gemcitabine- or FOLFIRINOX-based. After preoperative treatment, every patient without any disease progression should undergo surgical exploration taking into consideration that postneoadjuvant imaging using CT has an accuracy level below 50%. Stable disease according to re-staging imaging is no exclusion criterion for resection, as inflammation induced by chemotherapy and/or radiation is capable of tumor-mimicking. Neoadjuvant therapy seems to increase the number of patients with BRPC who can undergo resection. In addition, resection shows a high rate of negative margins and improved OS. To evaluate the role of neoadjuvant therapy in the context of BRPC and to improve the treatment strategy, prospective randomized controlled studies are warranted. Moreover, a consensus for international guidelines is needed.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- 1 Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM: Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreatic cancers in the United States. *Cancer Res* 2014;74:2913–2921.
- 2 Siegel RL, Miller KD, Jemal A: Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
- 3 Europe WHOROf: The European Health Report 2012: Charting the way to well-being; in WHO G (ed), 2012.
- 4 Sharma C, Eltawil KM, Renfrew PD, Walsh MJ, Molinari M: Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990–2010. *World J Gastroenterol* 2011;17:867–897.
- 5 Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluy O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherrieff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Buchler MW; European Study Group for Pancreatic Cancer: 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;389:1011–1024.
- 6 Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Buchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhuth A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR; International Study Group of Pancreatic Surgery: Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014;155:977–988.
- 7 Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zulke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H: Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473–1481.
- 8 Surveillance NCI: Epidemiology and End Results Program SEER Stat Fact Sheets: Pancreas Cancer.
- 9 Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC: Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727–1733.
- 10 Toesca DAS, Koong AJ, Poultsides GA, Visser BC, Haraldsdottir S, Koong AC, Chang DT: Management of borderline resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2018;100:1155–1174.
- 11 Evans DB, George B, Tsai S: Non-metastatic pancreatic cancer: resectable, borderline resectable, and locally advanced-definitions of increasing importance for the optimal delivery of multimodality therapy. *Ann Surg Oncol* 2015;22:3409–3413.

- 12 Dhir M, Malhotra GK, Sohal DPS, Hein NA, Smith LM, O'Reilly EM, Bahary N, Are C: Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. *World J Surg Oncol* 2017;15:183.
- 13 Fathi A, Christians KK, George B, Ritch PS, Erickson BA, Tolat P, Johnston FM, Evans DB, Tsai S: Neoadjuvant therapy for localized pancreatic cancer: guiding principles. *J Gastrointest Oncol* 2015;6:418–429.
- 14 Nitsche U, Kong B, Balmert A, Friess H, Kleeff J: Should every patient with pancreatic cancer receive perioperative/neoadjuvant therapy? *Indian J Med Paediatr Oncol* 2016;37:211–213.
- 15 Nurmi A, Mustonen H, Parviainen H, Peltola K, Haglund C, Seppanen H: Neoadjuvant therapy offers longer survival than upfront surgery for poorly differentiated and higher stage pancreatic cancer. *Acta Oncol* 2018;57:799–806.
- 16 Lutfi W, Talamonti MS, Kantor O, Wang CH, Liederbach E, Stocker SJ, Brentrem DJ, Roggin KK, Winchester DJ, Marsh R, Prinz RA, Baker MS: Perioperative chemotherapy is associated with a survival advantage in early stage adenocarcinoma of the pancreatic head. *Surgery* 2016;160:714–724.
- 17 Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, Sabbatino F, Santos DD, Allen JN, Blaszkowsky LS, Clark JW, Faris JE, Goyal L, Kwak EL, Murphy JE, Ting DT, Wo JY, Zhu AX, Warshaw AL, Lillemoe KD, Fernandez-del Castillo C: Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015;261:12–17.
- 18 Ielpo B, Duran H, Diaz E, Fabra I, Caruso R, Ferri V, Malave L, Hidalgo M, Alvarez R, Plaza C, Quijano Y, Vicente E: Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. *Eur J Surg Oncol* 2016;42:1394–1400.
- 19 Kim SS, Nakakura EK, Wang ZJ, Kim GE, Corvera CU, Harris HW, Kirkwood KS, Hirose R, Tempero MA, Ko AH: Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy? *J Surg Oncol* 2016;114:587–596.
- 20 Loehrer AP, Ferrone CR: Treatment of locally advanced pancreatic ductal adenocarcinoma. *Dig Surg* 2016;33:343–350.
- 21 Okada KI, Hirono S, Kawai M, Miyazawa M, Shimizu A, Kitahata Y, Ueno M, Hayami S, Yamaue H: Phase I study of nab-paclitaxel plus gemcitabine as neoadjuvant therapy for borderline resectable pancreatic cancer. *Anticancer Res* 2017;37:853–858.
- 22 Paniccia A, Edil BH, Schulick RD, Byers JT, Meguid C, Gajdos C, McCarter MD: Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma: a retrospective cohort study. *Medicine (Baltimore)* 2014;93:e198.
- 23 Schorn S, Demir IE, Reyes CM, Saricaoglu C, Samm N, Schirren R, Tiefrunk E, Hartmann D, Friess H, Ceyhan GO: The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma – a systematic review and meta-analysis. *Cancer Treat Rev* 2017;55:96–106.
- 24 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;21:1530–1537.
- 25 Sahara K, Kuehrer I, Schindl M, Koelblinger C, Goetzinger P, Gnant M: NeoGemTax: gemcitabine and docetaxel as neoadjuvant treatment for locally advanced nonmetastatic pancreatic cancer. *World J Surg* 2011;35:1580–1589.
- 26 Motoi F, Ishida K, Fujishima F, Ottomo S, Oikawa M, Okada T, Shimamura H, Takemura S, Ono F, Akada M, Nakagawa K, Katayose Y, Egawa S, Unno M: Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multi-institutional phase 2 trial. *Ann Surg Oncol* 2013;20:3794–3801.
- 27 Cho IR, Chung MJ, Bang S, Park SW, Chung JB, Song SY, Seong J, Hwang HK, Kang CM, Lee WJ, Park JY: Gemcitabine based neoadjuvant chemoradiotherapy therapy in patients with borderline resectable pancreatic cancer. *Pancreatol* 2013;13:539–543.
- 28 Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, Oh DY, Chie EK, Lee JM, Heo JS, Park JO, Lim DH, Kim SH, Park SJ, Lee WJ, Koh YH, Park JS, Yoon DS, Lee IJ, Choi SH: 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;268:215–222.
- 29 Kim EJ, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, Griffith KA, Francis IR, Greenson JK, Simeone DM, Lawrence TS, Laheru D, Wolfgang CL, Williams T, Bloomston M, Moore MJ, Wei A, Zalupski MM: A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer* 2013;119:2692–2700.
- 30 Schorn S, Demir IE, Samm N, Scheufele F, Calavrezos L, Sargut M, Schirren RM, Friess H, Ceyhan GO: Meta-analysis of the impact of neoadjuvant therapy on patterns of recurrence in pancreatic ductal adenocarcinoma. *BJS Open* 2018;2:52–61.
- 31 Habermehl D, Kessel K, Welzel T, Hof H, Abdollahi A, Bergmann F, Rieken S, Weitz J, Werner J, Schirmacher P, Buchler MW, Debus J, Combs SE: Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer. *Radiat Oncol* 2012;7:28.
- 32 van Tienhoven G, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA: Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): a randomized, controlled, multicenter phase III trial. *J Clin Oncol* 2018;36:LBA4002.
- 33 Christians KK, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, Kelly T, Erickson B, Wang H, Evans DB, George B: Neoadjuvant FOLFIRINOX for borderline resectable pancreatic cancer: a new treatment paradigm? *Oncologist* 2014;19:266–274.
- 34 Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF: Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–846; discussion 846–838.
- 35 Katz MH, Shi Q, Ahmad SA, Herman JM, Marsh Rde W, Collisson E, Schwartz L, Frankel W, Martin R, Conway W, Truty M, Kindler H, Lowy AM, Bekaii-Saab T, Philip P, Talamonti M, Cardin D, LoConte N, Shen P, Hoffman JP, Venook AP: Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. *JAMA Surg* 2016;151:e161137.
- 36 Eguchi H, Yamada D, Iwagami Y, Gotoh K, Kawamoto K, Wada H, Asaoka T, Noda T, Takeda Y, Tanemura M, Sakai D, Satoh T, Kudo T, Isohashi F, Mori M, Doki Y: Prolonged neoadjuvant therapy for locally advanced pancreatic cancer. *Dig Surg* 2018;35:70–76.
- 37 Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, Hodul PJ, Malafa MP, Meredith KL, Hoffe SE, Shridhar R: Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys* 2013;86:516–522.
- 38 Rashid OM, Pimentel JM, Gamenthaler AW, Nguyen P, Ha TT, Hutchinson T, Springett G, Hoffe S, Shridhar R, Hodul PJ, Johnson BL, Illig K, Armstrong PA, Centeno BA, Fulp WJ, Chen DT, Malafa MP: Outcomes of a clinical pathway for borderline resectable pancreatic cancer. *Ann Surg Oncol* 2016;23:1371–1379.
- 39 Rahman SH, Urquhart R, Molinari M: Neoadjuvant therapy for resectable pancreatic cancer. *World J Gastrointest Oncol* 2017;9:457–465.
- 40 Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J: Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
- 41 Nitsche U, Wenzel P, Siveke JT, Braren R, Holzapfel K, Schlitter AM, Stoss C, Kong B, Esposito I, Erkan M, Michalski CW, Friess H, Kleeff J: Resectability after first-line FOLFIRINOX in initially unresectable locally advanced pancreatic cancer: a single-center experience. *Ann Surg Oncol* 2015;22(suppl 3):S1212–S1220.

- 42 Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, Wang H, Abbruzzese J, Pisters PW, Vauthey JN, Charnsangavej C, Tamm E, Crane CH, Balachandran A: Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012;118:5749–5756.
- 43 Demir IE, Jager C, Schlitter AM, Konukiewicz B, Stecher L, Schorn S, Tieftrunk E, Scheufele F, Calavrezos L, Schirren R, Esposito I, Weichert W, Friess H, Ceyhan GO: R0 versus R1 resection matters after pancreaticoduodenectomy, and less after distal or total pancreatectomy for pancreatic cancer. *Ann Surg* 2017, Epub ahead of print.
- 44 Bachellier P, Rosso E, Lucescu I, Oussoultzoglou E, Tracey J, Pessaux P, Ferreira N, Jaeck D: Is the need for an arterial resection a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma? A case-matched controlled study. *J Surg Oncol* 2011;103:75–84.
- 45 Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Buchler MW, Weitz J: Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–893.
- 46 Zhou Y, Zhang Z, Liu Y, Li B, Xu D: Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis. *World J Surg* 2012;36:884–891.
- 47 Jegatheeswaran S, Baltatzis M, Jamdar S, Siriwardena AK: Superior mesenteric artery (SMA) resection during pancreatectomy for malignant disease of the pancreas: a systematic review. *HPB (Oxford)* 2017;19:483–490.
- 48 Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, Kindler HL, Alberts SR, Philip P, Lowy AM, Pisters PW, Posner MC, Berlin JD, Ahmad SA: Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 2013;20:2787–2795.