Pancreatic ductal adenocarcinoma in 2017: Time to change the therapeutic algorithm?

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BACKGROUND

Historically, patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC) were offered surgical resection as the first modality of therapy. However, the vast majority of patients who undergo surgical resection will develop tumor-relapse. In >75% of them, distant metastases represent the first site of recurrence.[1] For this reason, systemic therapy is recommended for all the patients following a resection for pancreatic cancer. This high rate of distant relapse is likely related to the presence of occult metastatic disease in the setting of radiologically localized pancreatic cancer. In this light, different trials have evaluated the possible benefit of adjuvant chemotherapy. The CONKO-001 trial randomly assigned 368 patients to 6 months of adjuvant gemcitabine chemotherapy *versus* observation. In this study, gemcitabine doubled the 5-year survival from 10% to 21%, but median survival was improved only from 20 to 23 months.[2] The recently published ESPAC 4 trial randomly assigned 366 patients to receive gemcitabine and 364 to gemcitabine plus capecitabine. The median overall survival (OS) for patients in the gemcitabine plus capecitabine group was 28.0 months compared with 25.5 months in the gemcitabine group.[3] Other randomized trials evaluating the role of gemcitabine plus nab-paclitaxel or FOLFIRINOX in an adjuvant setting are still ongoing. Of note, pathological examination of the specimens shows that most patients undergoing upfront surgical resection have poor pathological prognostic factors including G3 tumors, presence of lymph nodes metastases, and presence of microscopically involved surgical margins.[2-5] For example, in the ESPAC 4 trial, median tumor size was 30 mm, 80% of patients had nodal metastases and 60% had an R1 resection.[3] These pathological features highlight the biological aggressiveness of pancreatic cancer, even in the setting of "early stage," resectable disease.

POSSIBLE LIMITATIONS OF THE SURGERY PLUS ADJUVANT THERAPY APPROACH IN RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA

The strategy based on upfront surgery plus adjuvant therapy may present different limitations. First, at present, despite the use of high-resolution imaging

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techniques including multidetector computed tomography, magnetic resonance imaging, and positron emission tomography, we are unable to identify the presence of occult micrometastases. The rate of patients who developed tumor recurrence and died within 1 year from surgery can be as high as 37%, and this is likely due to micrometastatic disease already present at the time of diagnosis.[6,7] Preoperative carbohydrate antigen (CA) 19.9 level has been associated with the burden of disease in pancreatic cancer and with the risk of early recurrence. High preoperative CA19.9, with a cutoff >200 U/mL, has been correlated with the presence of micrometastatic disease.[7-9] A recent study analyzing 10,806 patients with early stage PDAC from the National Cancer Database (NCDB) showed that those with CA19.9 >37 U/mL had significantly decreased survival at 1 and 3 years (56% *vs.* 68% and 15% *vs.* 25%, respectively) compared to patients with normal levels (<37 U/mL).[8] Second, pancreatic resections are associated with a significant risk of postoperative morbidity.[5] Postoperative morbidity associated with pancreatic resection may preclude the delivery of adjuvant therapy. In this setting, adjuvant trials had a major selection bias because they excluded patients who experienced significant surgical morbidity rendering them ineligible for trial enrollment after surgery. Moreover, postoperative complications and poor nutritional status after surgery may interfere with the completion of adjuvant therapy.[10,11] Only 62% of patients in the CONKO-001 trial received the planned full dose of adjuvant gemcitabine.[2] Even more impressive is the data of the patients who got adjuvant therapy. In fact, data from large national databases from the United States show a rate of only 51%–54% of adjuvant chemotherapy.[10,11]

THE ISSUE OF BORDERLINE RESECTABLE PANCREATIC CANCER

The definition of anatomic borderline resectable pancreatic cancer (BRPC) underlines the presence of a "technically resectable" pancreatic cancer that is in proximity or that directly involves of venous and/or arterial vessels. The 2016 NCCN guidelines consider anatomic BRPC as the following:[12]

- Solid tumor contact with superior mesenteric vein-portal vein (SMV-PV) >180°, contact of ≤180° with contour irregularity of the vein or thrombosis allowing for safe and complete resection and reconstruction;
- Solid tumor contact ≤180° with superior mesenteric artery; presence of variant arterial anatomy (*e.g.*, accessory right hepatic artery and replaced right hepatic artery) should be also considered;
- Solid tumor contact with common hepatic artery without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.

Anatomic BRPC often requires a vascular resection associated with pancreatectomy. A recent meta-analysis showed that, compared to patients undergoing standard pancreatectomy, those undergoing upfront surgery with SMV-PV resection had a significantly increased risk of postoperative mortality, R1/R2 resection, and of poorer 5-year OS rates (hazard ratio 3.18).[13] Even more impressive are the data reported for pancreatectomy with resection of superior mesenteric artery/common hepatic artery/celiac trunk. In a meta-analysis, arterial resections were associated with a significantly increased risk of perioperative mortality (odds ratio [OR]: 5.04) and of poor 3-year survival (OR: 0.39) compared with patients without arterial resection.[14] In keeping with these data, the infiltration of splenic artery has recently emerged as a new possible prognostic factor. Infiltration of splenic artery is not included in the formal definition of anatomic BRPC since this is a "technically" resectable disease. Partelli *et al.* showed a 5-year OS of 31.5% for 68 patients who underwent distal pancreatectomy for PDAC without an involvement of splenic artery compared to 0% in 19 patients with splenic artery infiltration.[15] It is likely that the morphological evidence of vascular infiltration represents the stigmata of a more advanced disease leading to a higher risk of incomplete resection and early recurrence.

CHANGING THE THERAPEUTIC ALGORITHM IN RESECTABLE/ BORDERLINE RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA: THE NEOADJUVANT TREATMENT STRATEGY

Based on these data, early delivery of chemotherapy in the neoadjuvant setting can be considered as an alternative and more appropriate strategy. In fact, neoadjuvant chemotherapy or chemoradiation may present several potential advantages. First, the treatment is delivered in a patient who did not undergo previous surgery (with its potential complications), and theoretically, the patient may better last the treatment.

Second, neoadjuvant therapy can help in selecting patients with unfavorable tumor biology who are at risk for developing the early metastatic disease. In these patients, a useless operation can be avoided and patients can undergo an alternative systemic therapy. Of note, the 2016 NCCN guidelines do not recommend upfront surgery for BRPC and suggest an initial approach involving neoadjuvant therapy for all these patients.[12]

Several retrospective or population-based studies have been published to analyze the role of neoadjuvant treatment in the setting of resectable/borderline resectable PDAC. Although there is a certain level of heterogeneity considering the regimen of chemotherapy/chemoradiation used, recent data support the advantages of neoadjuvant approach. These studies show a resectability rates of 60%–80% for patients with BRPC following neoadjuvant treatment, R0 resections rate of 80%–90% and median OS rate of up to 30 months in an intention-to-treat analysis for those resected, similar to survival rates of patients with early-stage PDAC undergoing resection.[16-20] Of note, neoadjuvant therapy was not associated with increasing postoperative morbidity and mortality rates.[19] Mokdad *et al.*[16] analyzed a large cohort of resected patients with stage I-II pancreatic cancer from the NCDB. They matched 2005 patients who underwent neoadjuvant therapy with 6,015 patients who underwent upfront resection. The patient who underwent neoadjuvant treatment had improved survival (26 months *vs.* 21 months) and showed that neoadjuvant chemotherapy was associated with improved OS, lower pathologic T and N stage (pT3/T4: 73% *vs.* 86%; pN1: 48% *vs.* 73%), and lower rates of positive resection margins (17% *vs.* 24%).[16] In keeping with the previous study, Lutfi *et al.*[18] evaluated 7,881 patients with stage I-II PDAC who underwent resection from the NCDB. Of these, 27.5% received no chemotherapy, 57.4% received adjuvant chemotherapy, 10.2% received neoadjuvant chemotherapy alone, and 4.9% received perioperative chemotherapy (neoadjuvant + adjuvant chemotherapy). Patients who received neoadjuvant chemotherapy alone or perioperative chemotherapy had greater rates of margin negative (80.2% *vs.* 73.0%, $P < 0.001$) and node negative (58.2% *vs.* 28.7%, $P < 0.001$) resections.[18] Importantly, in this study, patients receiving perioperative chemotherapy demonstrated a significant OS advantage compared with those receiving adjuvant chemotherapy. Another study identified 593 patients with stage III PC from the NCDB.[17] Of these, 377 (63.6%) underwent neoadjuvant treatment, and 273 (46%) had a subsequent resection, wherein 216 (36.4%) were in the surgery-first cohort. Intention-to-treat Kaplan–Meier analysis demonstrated superior survival for neoadjuvant compared to surgery-first strategy (median OS: 20.7 months *vs.* 13.7 months). These results underline that early stage PDAC can benefit from a neoadjuvant strategy.

CONCLUSION

Growing evidence supports the use of neoadjuvant treatment for localized resectable or borderline resectable PDAC. There is, of course, some additional work to do to establish the most appropriate chemotherapy regimens and to define a possible role of chemoradiation *versus* chemotherapy alone in the neoadjuvant setting.

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