Pancreatic Cancer: “Whether to Cross the Border”?

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Received: 7 October 2020 / Accepted: 29 April 2021 / Published online: 8 May 2021
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Keywords Borderline resectable pancreatic cancer · Neoadjuvant therapy · Pancreatic adenocarcinoma · Pancreatic cancer · Pancreatic ductal adenocarcinoma

Pancreatic cancer (PC), also called pancreatic ductal adenocarcinoma (PDAC), is classified as resectable pancreatic cancer (RPC), locally advanced pancreatic cancer (LAPC), and metastatic pancreatic cancer (MPC). Only 15–20% of PDAC are resectable; they are locally advanced in 25–30% and metastatic in as many as 50–60% [1]. Resection with a negative margin (R0) is the key factor for long-term survival of this aggressive malignancy. RPC should be operated upfront; LAPC should receive neoadjuvant therapy (NAT) and MPC should be managed with non-surgical palliation [2]. Survival, however, remains poor; 2- and 5-year overall survivals (OS) for patients with resected PC are 40–50% and 15–20%, respectively. Rates of local and systemic recurrence after resection also remain high—35–60% and 80–90%, respectively.

The term borderline resectable pancreatic cancer (BRPC) or borderline resectable pancreatic ductal adenocarcinoma (BR PDAC) was first adopted by the National Comprehensive Cancer Network (NCCN) in 2006 [3].

In the absence of distant metastases and distant lymph nodes, resectability of PDAC largely depends on the relationship of the tumor to large vessels, e.g., celiac axis (CA), common hepatic artery (CHA), proper hepatic artery (PHA) and superior mesenteric artery (SMA), and superior mesenteric vein (SMV) and portal vein (PV). Resectability should be assessed using pancreatic protocol computed tomography (CT) of abdomen and pelvis performed within 4 weeks of

the planned operation. Resectability is decided based on the extent of the involvement, viz., tumor contact, contour, occlusion, length of segment, thrombosis, and availability of suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and reconstruction. The definition of contact (also called interface or invasion) between the tumor and the vessels is described as abutment $<180^\circ$ (also called impingement), encasement $\geq 180^\circ$, or complete occlusion.

Katz et al. (2008), from the MD Anderson Cancer Center, Houston, TX, USA, proposed additional biological (presence of possible metastatic disease) and conditional (performance status and/or severe medical co-morbidities) criteria for resectability [4]. During the 20th meeting of the International Association of Pancreatology (IAP) held at Sendai, Japan in 2016, an international consensus on BRPC provided a broader definition of BRPC. In addition to anatomy (A), it included biological (B) and the conditional (C) factors also and suggested to use the “ABC” method [5]. The NCCN guidelines [3] had earlier proposed that BRPC should also include “no contact with the most proximal draining jejunal branch into the superior mesenteric vein (SMV).” But the first jejunal vein (J1V) and the second jejunal vein (J2V) usually form a common trunk; separate drainage of J1V and J2V into the SMV is uncommon [3]. Moreover, it is difficult to identify on imaging which tributary of the SMV, whether J1V or J2V, is invaded by the tumor. Because of these difficulties, this aspect, i.e., involvement of jejunal vein, was not included in the IAP consensus statement [5].

Management of BRPC, whether upfront surgery or NAT followed by surgery, is debatable. Patients with BRPC are at a higher risk to end up with positive margin (R1) resection if upfront surgery is performed. Many studies have showed that NAT improves the chances of R0 resection from 71 to 93% [6], 25 to 39% [6], 40 to 100% [7], 33 to 82% [8], 17 to 72% [9], and 70 to 86% [10]. Median OS (mOS) also improved from 20.1 to 28.4 [7], 12 to 21 [8], 25 to 52 [9], and 13.1 to

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29.1 [10] months. There is a lot of controversy whether neoadjuvant chemotherapy (NACT) or neoadjuvant chemoradiotherapy (NACRT) is the better form of NAT. Four head-to-head studies have compared the OS between NACT and NACRT; there was no significant difference between NACT and NACRT [11–14].

Several systematic reviews and meta-analyses have confirmed that the cohort which had undergone NAT had higher R0 resection rates and improved OS. In a meta-analysis of prospective studies, Zhan et al. showed that NAT was beneficial for patients with BRPC and LAPC but NACRT did not achieve a better OS than NACT alone (median OS: 16.7 months vs 16.8 months) [15]. In a meta-analysis of 38 studies (total 3484 patients), 12 including upfront surgery (1746 patients) and 26 including NAT (administered to 1723, i.e., 99% of 1738 patients, mostly NACRT), weighted mOS of 1746 patients undergoing upfront surgery was 14.8 (range 11.6–25.3) months, (17.7 (12–25.3) months for 819 patients with RPC vs. 12.8 (11.6–16.3) months for 927 patients with BRPC), while the weighted mOS after NAT was 18.2 (10–50.2) months 857 in RPC and 19.2 (11–32) months in 881 patients with BRPC [16]. Interestingly, Schorn et al. in the meta-analysis of observational studies for BRPC and LAPC found that NAT reduced the risk of local recurrence (RR 0.42, 95% CI 0.32–0.55) but not the risk of distant metastasis (RR 1.02, 95% CI 0.91–1.14) [17]. Hu et al. performed a network meta-analysis comparing NACRT, NACT, and upfront surgery in patients with RPC, BRPC, and LAPC. According to the established network, based on the consistency model, NACRT increased the R0 resection rate over upfront surgery (HR 0.15, 95% CI 0.02–0.56), whereas NACT did not increase the R0 resection rate over upfront surgery. Contrary to the results from the traditional pairwise meta-analysis, NACT showed advantage for OS over NACRT (HR 0.72, 95% CI 0.58–0.88) or upfront surgery (HR 0.85, 95% CI 0.72–0.99) in the network meta-analysis. For R0 resection rate, NACRT had the highest probability of ranking one compared with NACT or upfront surgery. For OS, NACT had the highest probability of ranking one compared with NACRT or upfront surgery [18]. A recent systematic review and meta-analysis of 17 trials including 2286 participants by Pan et al. showed improved OS with resection after NACRT ($P = 0.001$) in comparison to surgery first (i.e., upfront surgery) in patients with BRPC. There was no difference in overall resection rate ($P = 0.159$), but the R0 resection rate, recurrence rate, and disease-free survival were in favor of NACRT. Similarly, the overall resection rate was lower (OR 0.50; 95% CI 0.25–0.99; $P = 0.048$) but R0 resection rate and the OS was higher in patients who underwent resection after NACRT ($P = 0.001$) as compared to surgery-first in RPC. The authors concluded that NACRT can provide survival benefits in BRPC and a subgroup of RPC compared with surgery first [19].

The International Study Group for Pancreatic Surgery (ISGPS) recommends straightforward (upfront) operative exploration and resection in the presence of reconstructable

mesentericoportal (venous) axis involvement in BRPC and operative exploration for potential resection in BRPC patients with suspected but not proven distant metastasis in the absence of disease progression after NAT [20]. The expert consensus statement of the Americas Hepato-Pancreato-Biliary Association (AHPBA) (2009), on the other hand, states that NAT provides a rational alternative to upfront surgery approach and could be considered in all patients, i.e., not only with BRPC but even RPC [21]. All patients with BRPC should be discussed in a tumor board and managed by a multidisciplinary team consisting of gastroenterologists, oncologists, radiologists, and surgeons/surgical oncologists. NACRT might be the treatment of choice for non-metastatic PDAC, especially LAPC, and, may be, BRPC also.

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