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Invited Commentary

Purely resectable *versus* biological borderline resectable pancreatic cancer: closely related or worlds apart?

Laura Maggino*

Unit of General Surgery, Mater Salutis Hospital, Verona, Italy

*Correspondence to: Laura Maggino, Unit of General Surgery, Mater Salutis Hospital, Via Carlo Gianella 1, Legnago, Verona 37045, Italy (e-mail: laura.maggino@hotmail.it)

The definition of borderline resectable pancreatic ductal adenocarcinoma (PDAC), first introduced to characterize the imprecise anatomical continuum between resectable and unresectable disease, has progressively evolved to incorporate surrogate measures of tumour biology and the performance status of individual patients. Specifically, biological borderline resectability (BBR) identifies patients with features suggestive, but not diagnostic, of aggressive biology and distant metastases. This approach addresses the logical inconsistency whereby, although PDAC prognosis appears predominantly dictated by biological factors, the decisional algorithms in localized disease still rely on anatomical criteria. Despite its conceptual appeal, this entity has faced uneven acceptance, with considerable variability in definitions and management (*Table 1*).

In the current issue of *BJS Open*, Belfiori *et al.*[9] retrospectively analysed patients with PDAC with resectable tumour anatomy exhibiting BBR features, to investigate whether they represent a distinct clinical and prognostic entity relative to purely resectable (R) PDAC. BBR status was classified based on institutional criteria, including cancer antigen 19-9 (CA19-9) levels ≥ 200 units/ml, tumour-related symptoms lasting > 40 days, and/or lymph node metastases. Although there were no differences in pathological profiles between BBR and R patients in the overall cohort, among upfront-resected patients BBR-PDAC exhibited significantly worse pathological features. This discrepancy is likely due to the influence of neoadjuvant treatment (NAT), which was threefold more frequent in the BBR than R group (60.5 *versus* 20.7%; $P < 0.001$). In survival analyses, patients with BBR had worse median disease-specific survival (DSS) (40 *versus* 59 months; $P < 0.001$) and event-free survival (EFS) (19 *versus* 29 months; $P < 0.001$), with a higher early recurrence rate, than patients with R-PDAC. Notably, BBR status was an independent predictor of both DSS and EFS in multivariable analysis, both overall and in the subset of patients who underwent upfront resection[9].

These results support the notion that BBR status identifies a distinct population with particularly aggressive tumour biology. However, the extent to which this aggressiveness reflects a non-modifiable, inherent feature of BBR-PDAC, rather than an actionable factor, is unclear. Indeed, in the postneoadjuvant setting, patients with BBR still exhibited shorter DSS and EFS than those with R-PDAC[9]. Overall, whether NAT can alter the adverse prognosis of BBR-PDAC remains uncertain.

The findings reported by Belfiori *et al.*[9] must be interpreted within the context of several limitations. First, by design, the study focused on resected patients, thus excluding those who deteriorated or progressed during chemotherapy and failed to undergo resection. Therefore, conclusions on the broader BBR population cannot be drawn from these results. Importantly, the analysis was not designed to clarify the role of NAT in BBR-PDAC.

Second, institutional practices regarding treatment allocation, response evaluation, and postneoadjuvant surgical selection may have influenced the results.

Third, survival analyses should be interpreted cautiously because of the possibility of selection bias. For example, Belfiori *et al.*[9] acknowledge that, in their practice, patients with BBR are preferentially given NAT. This likely leads to an over-representation of 'marginal cases' among patients with BBR who undergo upfront resection, thus overemphasizing differences with the R-PDAC group. In turn, the BBR cohort is enriched in patients who successfully underwent the biological and conditional filter of NAT, potentially enhancing their outcomes compared with patients undergoing upfront resection. Furthermore, because survival outcomes were assessed from treatment initiation, immortal time bias may have led to spurious improvements of survival in patients who received NAT.

Finally, the definition of BBR is controversial. The recording of tumour-related symptoms is relatively subjective, and the 40-day cut-off is unvalidated. In addition, a threshold of 200 units/ml was used for CA19-9, whereas current literature suggests a cut-off of 500 units/ml (*Table 1*). Importantly, the individual components of BBR status were not recorded separately, so that their occurrence and prognostic significance (and even the legitimacy of their inclusion in the BBR definition) could not be ascertained.

Despite these limitations, this study adds to the growing body of literature suggesting that, despite identical anatomical appearances, BBR and R PDAC represent distinct prognostic entities and should be classified as separate diseases. Far beyond semantics, this has crucial implications for comparative research and trial design. Trials on NAT in anatomically resectable PDAC

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Table 1 Characteristics of the main studies providing a definition of BBR pancreatic cancer

Reference (year)	Study type and region of origin	Time frame	Definition of BBR	CA19-9 cut-off (units/ml)	Tumour anatomy of patients with BBR	No. of patients with BBR	Management of BBR
Katz *et al.*[1] (2008)	Single-centre retrospective (USA)	1999–2006	Patients with CT findings suspicious for, but not diagnostic of, metastatic disease and those with known N1 disease from either prereferral laparotomy or EUS fine-needle aspiration	Not provided	Resectable or borderline resectable	44	All received NAT, 50% subsequently had resection
Tzeng *et al.*[2] (2012)	Single-centre retrospective (USA)	2002–2007	Indeterminate liver lesions, CA19-9 > 1000 units/ml (with normal total bilirubin), or biopsy-proven involvement of regional lymph nodes	> 1000	Resectable	41	All received NAT, 46% subsequently had resection
Isaji *et al.*[3] (2018)	IAP international consensus definition	–	CA19-9 > 500 units/ml or regional lymph node metastasis (biopsy or PET–CT)	> 500	Resectable*	–	–
Uzunoglu *et al.*[4] (2019)	Multicentre retrospective (Europe)	2005–2016	Clinical findings suspicious for, but not diagnostic of, extrapancreatic disease (e.g. indeterminate liver lesions, suspect distant lymph nodes), CA19-9 > 1000 units/ml (with normal total bilirubin), or biopsy-proven involvement of regional lymph nodes	> 1000	Resectable or borderline resectable	93	All received upfront resection (patients treated with NAT excluded)
Kato *et al.*[5†] (2019)	Single-centre retrospective (Japan)	2001–2017	CA19-9 > 500 units/ml or regional lymph node metastasis (biopsy or PET–CT)	> 500	Resectable*	97	All received upfront resection (patients treated with NAT excluded)
Anger *et al.*[6†] (2021)	Bi-institutional retrospective (Europe)	2003–2017	CA19-9 > 500 units/ml	> 500	Resectable	62	All received upfront resection (patients treated with NAT excluded)
Lee *et al.*[7†] (2023)	Single-centre retrospective (Korea)	2004–2020	CA19-9 > 500 units/ml or regional lymph node metastasis (biopsy or PET–CT)	> 500	Resectable*	81	All received upfront resection (patients treated with NAT excluded)
Dekker *et al.*[8] (2024)	Multicentre retrospective (TAPS Consortium)	2012–2019	CA19-9 > 500 units/ml	> 500	Resectable, borderline resectable or locally advanced	559	All received induction mFOLFIRINOX; overall resection rate 38%[‡]
Belfiori *et al.*[9] (2025)	Single-centre retrospective (Italy)	2015–2022	CA19-9 ≥ 200 units/ml, symptoms likely related to the disease lasting > 40 days, and/or radiological signs or cytologically proven lymph node metastases	> 200	Resectable	223	Surgical series; 135 patients (60.5%) received NAT, 88 (39.5%) received upfront resection

*Patients who are both anatomically and biologically borderline resectable are classified as a distinct category (borderline resectable type AB). †Validation studies of the International Association of Pancreatology (IAP) consensus definition of BBR. ‡Resection rate in the subset of patients with CA 19-9 > 500 units/ml not available. CT, computed tomography; EUS, endoscopic ultrasound examination; CA 19-9, cancer antigen 19-9; NAT, neoadjuvant treatment; PET, positron emission tomography; TAPS, Trans-Atlantic Pancreatic Surgery; mFOLFIRINOX, modified FOLIFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin).

have yielded conflicting results, contributing to the variability in guideline recommendations and clinical practice. This inconsistency may stem, at least in part, from the lack of biologically based stratification: lumping together R-PDAC and BBR-PDAC could be misleading. In this light, the standardized identification of BBR-PDAC as a distinct entity is a crucial step towards a more precise approach to PDAC management.

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