The Concept of Biological Resectability in Pancreatic Ductal Adenocarcinoma — An Updated Narrative Review

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Resectability in pancreatic ductal adenocarcinoma (PDAC) has traditionally been defined according to tumor–vessel relationship on cross-sectional imaging. However, anatomical criteria alone fail to identify occult systemic disease and do not reliably predict early postoperative recurrence or the likelihood of meaningful oncological benefit from surgery. This structured narrative review evaluated contemporary evidence regarding biological resectability and the emerging role of biomarkers in perioperative decision-making. A literature search was conducted using PubMed/MEDLINE, Embase, and Web of Science, focusing on studies published between January 2017 and March 2026, with inclusion of seminal earlier publications where relevant. Priority was given to consensus statements, clinical practice guidelines, meta-analyses, randomized controlled trials, prospective cohort studies, and large multicentre series. Evidence was qualitatively synthesized and biomarkers were classified according to their level of clinical maturity. Emerging data suggest that many anatomically resectable PDACs exhibit biologically aggressive disease associated with occult metastases, early recurrence, and limited benefit from upfront surgery. Among available biomarkers, carbohydrate antigen 19-9 remains the most clinically established and should be interpreted in the context of biliary status, treatment response, and multidisciplinary assessment. Circulating tumor DNA shows promise for molecular staging and recurrence risk stratification, although prospective interventional validation remains limited. Transcriptomic subtypes, positron emission tomography (PET)-derived biomarkers, radiomics, and hybrid multimodal models provide additional biological insights but remain largely investigational. Biological resectability is increasingly recognized as an important complement to anatomical staging, helping to refine patient selection and treatment sequencing. Nevertheless, prospective validation, assay standardization, and biomarker-guided clinical trials are required before widespread implementation in routine multidisciplinary practice.

Keywords: pancreatic ductal adenocarcinoma; biological resectability; carbohydrate antigen 19-9; circulating tumor DNA; neoadjuvant therapy

Introduction

For almost two decades, the definition of resectability in pancreatic ductal adenocarcinoma (PDAC) has been almost exclusively anatomical, and the suitability of a patient for surgical resection has been determined largely by the relationship of the primary tumor to the major peripancreatic vessels on high-quality cross-sectional imaging [1,2,3,4]. The classification of disease into resectable, borderline resectable and locally advanced has been widely accepted, because the anatomy-based paradigm is important for operative planning, assessment of technical resectability and estimation of the risks of vascular resection [2,3,4]. However, it relies on the implicit assumption that the local extent of the tumor is the principal determinant of whether surgical resection will offer an oncological benefit, although a growing body of evidence suggests that this assumption is too simplistic and that other biological and systemic factors must also be considered [5,6].

The constraints of an anatomy-based approach to staging are becoming increasingly clear. A significant proportion of patients who undergo apparently curative pancreatectomy develop tumor recurrence within the first postoperative year. Furthermore, the patterns of failure encountered are more indicative of distant metastatic dissemination rather than of isolated locoregional recurrence [7,8]. Meta-analyses and contemporary cohort studies have uniformly identified the liver and peritoneum as common sites of first recurrence and shown that early relapse constitutes a major clinical challenge which is strongly correlated with poor

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survival following recurrence [6,9,10]. Collectively, these observations suggest that many tumors which appear localized on imaging are biologically aggressive with systemic potential at the outset. Therefore, technical resectability should no longer be considered synonymous with oncological fitness for surgery [6,7,8,9,10].

This increasing recognition of the disconnection between technical resectability and clinical outcome has fostered significant interest in the concept of biological resectability [4,11,12,13]. Broadly, this describes an approach that incorporates biomarkers, context, and response to therapy to select those patients most likely to experience long-term benefit from surgical resection, while also sparing patients from technically possible but biologically futile surgery [4,11,12].

In this review, biological resectability is defined as the likelihood that surgical resection will provide meaningful oncological benefit based on the biological behavior of the tumor, rather than on technical operability alone. Biological resectability is therefore not synonymous with anatomical resectability and should not be viewed as an independent staging category that replaces established anatomical classifications. Instead, it functions as a complementary clinical framework that refines patient selection and treatment sequencing by identifying features associated with occult systemic disease, early recurrence, resistance to therapy, molecular residual disease, and ultimately the risk of oncologically futile surgery. Within this framework, biomarkers such as carbohydrate antigen 19-9 (CA19-9) and circulating tumor DNA (ctDNA) are evaluated according to their ability to identify biologically favorable or unfavorable disease and thereby improve the alignment between technical operability and expected oncological outcomes.

Despite growing interest in biological resectability, important uncertainties remain regarding the relative clinical maturity, evidentiary support, and practical applicability of emerging biomarkers. Existing literature has largely focused on individual biomarkers or specific aspects of biological staging, whereas a comprehensive synthesis integrating biomarker performance, evidence quality, and clinical decision-making remains lacking. The objective of this review is therefore to critically evaluate the evolution of resectability in PDAC from an anatomy-based to a biology-based concept, compare available biomarkers according to their level of clinical maturity and evidentiary support, examine their potential role in perioperative decision-making, and propose a practical framework for incorporating biological information into multidisciplinary treatment planning. In addition, we highlight the methodological, technical, and clinical challenges that must be addressed before biological resectability can be routinely implemented in clinical practice.

Methods

A structured narrative review of the literature was performed using PubMed/MEDLINE, Embase, and Web of Science, with a primary focus on literature published between January 2017 and March 2026. Earlier seminal papers were included where pertinent to provide historical context regarding the development of resectability criteria, perioperative treatment strategies, and biomarker development in PDAC. The search strategy incorporated combinations of keywords and Medical Subject Headings (MeSH) related to anatomical resectability, borderline resectable pancreatic cancer, biological resectability, CA19-9, ctDNA, molecular residual disease, transcriptomic subtypes, positron emission tomography (PET)-based biomarkers, radiomics, occult metastases, neoadjuvant therapy, postoperative recurrence, and perioperative decision-making in PDAC. Eligible publications included consensus statements, clinical practice guidelines, meta-analyses, randomized controlled trials, prospective cohort studies, and large multicentre retrospective studies. Case reports, small single-centre studies with limited clinical applicability, conference abstracts, and non-English publications were generally excluded unless considered particularly influential or historically important.

Titles and abstracts were screened for relevance to the role of biomarkers in surgical decision-making, patient selection, treatment stratification, and recurrence prediction in PDAC. Full-text review was subsequently undertaken for studies considered most informative and clinically relevant. Given the narrative nature of the review, no formal risk-of-bias assessment or quantitative synthesis was performed.

Biomarkers were categorized according to their level of clinical maturity based on a qualitative assessment of the available evidence. Biomarkers were considered clinically validated when supported by consistent evidence across multiple clinical studies and incorporated into contemporary clinical practice or guideline recommendations. Biomarkers were considered promising when substantial clinical evidence suggested potential utility but further prospective or external validation was required. Biomarkers were considered investigational when evidence remained preliminary, exploratory, or primarily limited to translational and early-phase clinical studies. Classification was based on the strength, consistency, reproducibility, and clinical applicability of the available literature, together with the potential impact on multidisciplinary management of PDAC.

Figures were generated using Gemini Advanced (Google LLC, Mountain View, CA, USA) and subsequently edited using Adobe Photoshop version 26.5 (Adobe Inc., San Jose, CA, USA). Artificial intelligence was used solely for visual figure generation and formatting. All scientific content, interpretation, and final figure design were reviewed, modified where necessary, and approved by the authors.

Why Anatomy Alone Is Insufficient

The traditional paradigm for assessing resectability in PDAC has been almost exclusively anatomically based. Since the advent of multidetector computed tomography (MDCT) in the staging process, the anatomic relationship between the primary tumor and the major peripancreatic vessels has been the primary criterion for classifying disease as resectable, borderline resectable or locally advanced [1,2,3]. This was an important advancement in terms of standardizing technical assessment, facilitating communication between institutions, operative planning (especially in terms of vascular resection and reconstruction), clinical trial design, and multidisciplinary care coordination [1,2,3]. However, this approach was based on the overly simplistic and incorrect assumption that the local extent of the tumor alone is sufficient to fully reflect the overall biological behavior of the disease [3,11].

The primary weakness of an anatomy-only approach to staging is the inability to detect micrometastatic disease. Recurrence after technically curative surgery for PDAC is more likely systemic than local, suggesting that tumors which appear localized on imaging have already developed metastatic potential at the time of diagnosis [11,14]. This is supported by patterns of recurrence after resection. A meta-analysis of 89 studies including 17,313 patients found a weighted median rate of the liver as the first site of recurrence of 26.5% compared with 20.8% for locoregional recurrence, while peritoneal dissemination contributed a further 13.5% of initial failures [6]. Survival following liver or peritoneal relapse was poor, highlighting that the most important limitation of anatomy-based staging is not only underestimating local tumor extent but also failing to identify disease that has already escaped radiographic detection [6,11,14].

A clear limitation of the anatomy-based system is illustrated by studies of occult metastases. In a 2024 cohort study of 279 patients with resectable or borderline resectable PDAC who underwent curative-intent resection or staging laparoscopy, occult metastases were defined as distant metastases found intraoperatively or disease recurrence occurring within 6 months of pancreatectomy. Overall prognosis was similar in patients in whom metastases were identified at surgery and patients who developed recurrence within 6 months, suggesting that both groups reflect the same biological state: systemically advanced disease that was present before resection but undetected by standard preoperative imaging. In that study, a preoperative tumor diameter of 22 mm or more and a CA19-9 concentration of 118.8 U/mL or more were independent predictors of the presence of occult metastases, and both were strongly associated with poor overall survival after pancreatectomy [15]. Collectively, the above data show that the main limitation of anatomy-based staging is not suboptimal local risk stratification but failure to identify biologically advanced disease presenting as a technically operable cancer [15,16,17].

A second important limitation is that anatomical staging only explains a portion of the marked heterogeneity in outcomes that exists among patients with localized disease [4,18,19]. This issue was examined by the Trans-Atlantic Pancreatic Surgery (TAPS) consortium in a cohort of 1835 patients with localized PDAC who underwent initial (m)FOLFIRINOX at five high-volume centers. In this analysis, anatomical stage remained a significant prognostic factor, but a CA19-9 concentration of greater than 500 U/mL and an impaired performance status were also identified as independent predictors of overall survival. When anatomical, biological and conditional variables were combined into an integrated model, median overall survival decreased in a stepwise fashion from 49.7 months in patients with the most favorable composite score to 14.9 months in those with the least favorable score [19]. These observations raise an important implication: two patients with similar vascular anatomy may be placed into different prognostic categories once tumor biology and host factors are considered. Anatomy remains important for operative planning, but it is not sufficient to estimate the probability that surgery will provide durable oncological benefit, because anatomical staging only provides a portion of the necessary information to determine patient outcomes [1,18,19].

This distinction is critical, as pancreatectomy is not a harmless diagnostic test but a major therapeutic intervention with substantial associated risk. In a 2020 prospective international snapshot study of 4223 pancreatic resections in 67 countries, postoperative complications of any severity occurred in 68.7% of patients, and major complications occurred in 18% to 27% of patients, according to treatment setting, and overall 90-day mortality was 5.4% [20]. Even in the most specialized of health care systems, where postoperative mortality can be minimized to approximately 0% to 3%, morbidity is still substantial, with an incidence of 30% to 50% [21,22]. It is also worth noting that these burdens extend beyond the immediate perioperative period. In a 2024 study published in Journal of the American Medical Association (JAMA) Surgery, the investigators evaluated 1426 patients with anatomically resectable PDAC and defined futile upfront pancreatectomy as death or disease recurrence within six months of surgery, and by this definition, futility occurred in 18.9% of cases [23]. Principal preoperative predictors of futile resection were American Society of Anesthesiology (ASA) class, CA19-9 concentration, and radiologically assessed tumor size. Collectively, these findings suggest that even among patients with anatomically resectable disease, a meaningful subset is unlikely to derive a survival benefit from immediate surgery [23].

Together, these issues account for the growing emphasis on biological resectability. Anatomical assessment is required for the purpose of ascertaining whether a surgical procedure can be performed safely and with a reasonable expectation of complete resection [11,13,19]. However, anatomical assessment alone does not consistently identify patients

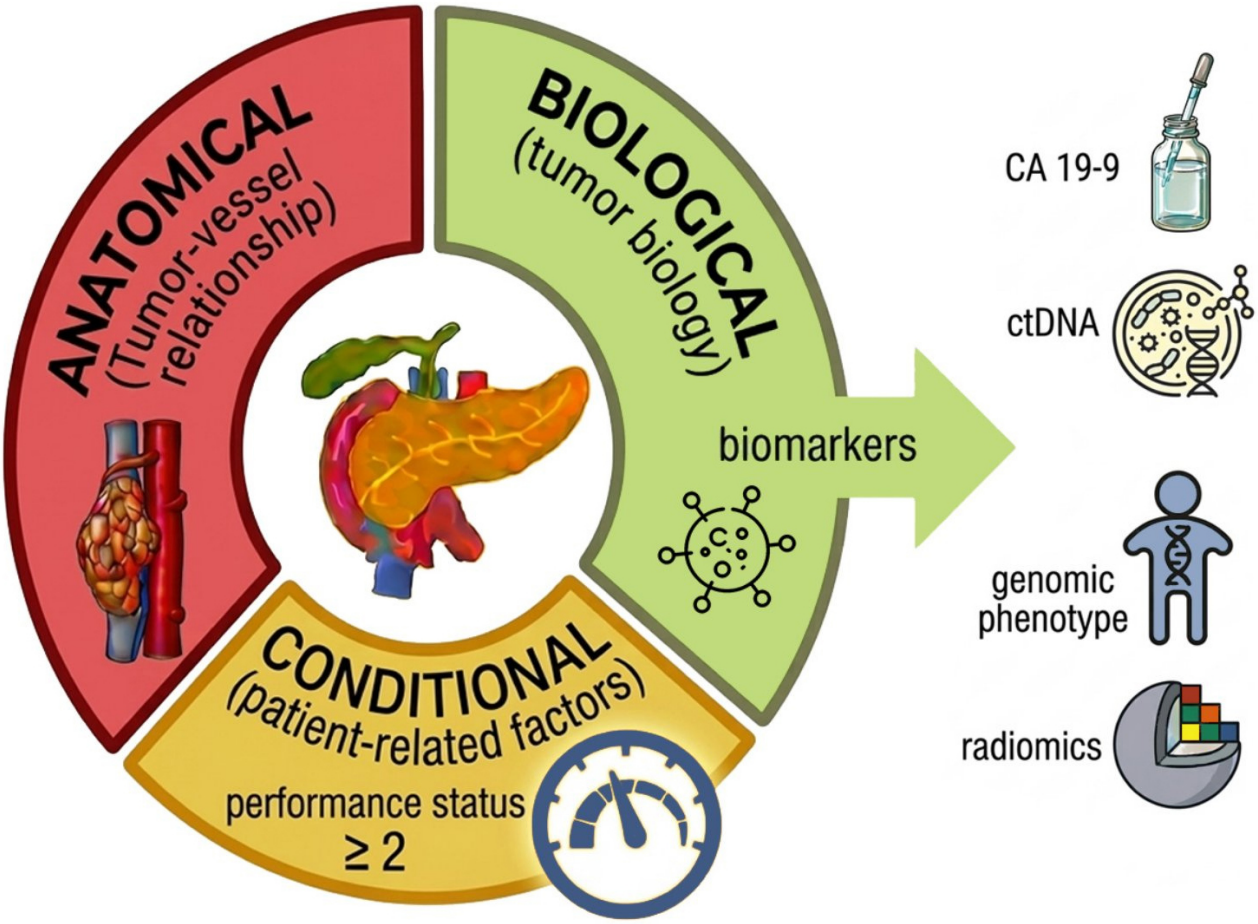

Fig. 1. Three-domain approach for assessing resectability of pancreatic ductal adenocarcinoma. Figure created by the authors using Google Gemini (version: Gemini 3.1 Pro, Google) and subsequently edited using Adobe Photoshop version 26.5 (Adobe Inc., San Jose, CA, USA; https://www.adobe.com). CA19-9, carbohydrate antigen 19-9; ctDNA, circulating tumor DNA.

with occult systemic disease, those at risk of early recurrence following an apparently curative procedure, or those destined to undergo a technically successful yet oncologically futile laparotomy [13,19,23]. This provides a compelling rationale for the inclusion of biomarkers in preoperative decision-making. The major challenge, discussed in the next section, is that the array of candidate biomarkers differs significantly with respect to biological plausibility, strength of evidence, and readiness for incorporation into contemporary multidisciplinary care [11,13,24,25].

From Anatomical to Biological Resectability: Evolution of the Concept

The 2017 International Association of Pancreatology (IAP) consensus statement represented a paradigm shift in the conceptualization of resectability in PDAC. Given the decades of confusion over the definition of borderline resectable disease, the IAP proposed a three-dimensional approach that incorporates anatomical, biological and conditional domains [4,11]. The biological domain of this approach includes tumors that are technically resectable but with suspicious features for distant metastasis, biopsy- or PET-confirmed regional lymph node metastasis and serum CA19-9 levels >500 U/mL, while the conditional domain includes compromised physiological reserve as demonstrated by an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater [4]. Importantly, this approach officially acknowledges that resectability is not determined solely by vascular anatomy, but also by risk of metastasis and overall fitness of the patient, and thus it redefines borderline resectability as a multidimensional entity that better approximates clinical reality (Fig. 1) [4,11,18].

All subsequent recommendations have expanded upon this broader conceptual framework. A commentary on the 2023 European Society for Medical Oncology (ESMO) pancreatic cancer guidelines pointed out that ESMO has adopted the IAP definition of borderline resectability and explicitly includes biological parameters (CA19-9 concentration and performance status) and therefore broadens the population that is considered a candidate for neoadjuvant therapy [11,26,27]. The same commentary also pointed out a critical limitation: the randomized trials that support the use of neoadjuvant therapy for borderline resectable PDAC have

been based largely on anatomical criteria rather than biological risk factor-enriched staging schemas [26,28,29]. In this light, the ESMO guidelines can be viewed as an important intermediate step, acknowledging that anatomical assessment is not sufficient, but not providing a fully validated, biologically informed staging schema to inform surgical decision-making, because the guidelines have been based largely on anatomical criteria [11,26,27,28,29].

The 2024 REDISCOVER recommendations built upon this evolving paradigm shift by listing 34 recommendations for the perioperative management of borderline resectable and locally advanced PDAC, and the authors explicitly highlighted the tumor biology as the major determinant of resectability [13,30], which is a significant shift in surgical philosophy where surgery is viewed as a step in an oncological selection process rather than the final step after local anatomical staging alone [13,31]. In addition, the REDISCOVER authors also identified areas of uncertainty, including management of persistently elevated CA19-9 after neoadjuvant therapy, the optimal timing and duration of preoperative therapy, and the role of resection in more advanced stages of the disease [13].

Together, the shift from traditional anatomy-based staging to the models proposed by IAP 2017, ESMO 2023 and REDISCOVER 2024 represents an important conceptual step forward. Resectability is increasingly viewed as extending beyond the tumor-vessel interface to metastatic potential, response to systemic therapy and patient fitness [4,13,26,27]. However, this conceptual step forward has run ahead of the evidence base. While there is broad agreement that tumor biology is clinically relevant, there is no consensus on how to incorporate biological variables into perioperative decision-making in a standardized fashion [11,13,32]. This gap emphasizes the need for a rigorous assessment of candidate biomarkers and a clear differentiation between those which are mature enough to inform contemporary clinical practice and those which should remain in the investigative phase for the purposes of surgical selection [11,13,32].

Biomarkers of Biological Resectability

For the concept of biological resectability to transcend a purely theoretical critique of anatomy-based staging, it must be underpinned by biomarkers that are capable of reliably detecting occult metastatic disease, predicting early systemic recurrence and identifying operations that are biologically futile in patients who appear to have localized tumors [4,11,32]. The biomarkers that are currently under evaluation differ widely in terms of their clinical maturity, with some having already been incorporated into consensus definitions and used as a matter of routine in multidisciplinary decision making, while others, although promising, are not yet adequately validated for widespread clinical application [4,11,24,26,32]. Considered along a spectrum of clinical readiness, CA19-9 has been widely validated and represents the gold standard. ctDNA is the most important emerging biomarker, while transcriptomic subtypes, PET-derived metrics and radiomic or hybrid prediction models should, for now, be regarded as investigational (Table 1, Ref. [4,13,19,24,26,27,33,34,35,36,37,38,39,40,41,42]) [11,43,44].

CA19-9: The Current Clinical Benchmark

Among the proposed biological markers, CA19-9 is the most firmly established in clinical practice. Its widespread availability, its integration in consensus definitions, and its relationship to survival in localized PDAC constitute the reasons for its status as a reference biomarker [4,32]. The 2017 IAP consensus accepted as biologically borderline, potentially resectable tumors with CA19-9 >500 U/mL, thereby formally acknowledging that an elevated tumor marker is a resectability criterion that is complementary to vascular anatomy [4]. The subsequent guidance, including the 2023 ESMO framework, maintains the same position and further recommends the use of CA19-9 to guide perioperative decisions [26,27].

The clinical relevance of CA19-9 is largely due to its persistent correlation with unfavorable tumor biology [19,33]. In a 2024 Dutch nationwide cohort of patients undergoing upfront resection for anatomically resectable PDAC, overall survival was significantly worse in patients with preoperative CA19-9 concentrations of 500 U/mL or higher, while performance status did not remain an independent prognostic factor; sensitivity analyses also showed that even lower cut-off values may identify biologically high-risk subgroups [33]. Similar results were reported by the TAPS consortium in patients with localized PDAC treated with initial (m)FOLFIRINOX [19]. Therefore, these data support the use of CA19-9 as the default biological marker in contemporary staging and treatment selection algorithms for PDAC [4,19,33].

More recent evidence is especially relevant in view of potential therapeutic implications [26,45]. In a 2025 retrospective cohort of patients with anatomically resectable PDAC and preoperative CA19-9 levels >500 U/mL, intensive neoadjuvant chemotherapy was associated with a significantly longer median overall survival (OS) compared with upfront surgery, a benefit that persisted even in patients with CA19-9 levels >2000 U/mL [45]. Although these data are retrospective and therefore not definitive for standard practice, they suggest that substantial CA19-9 elevation may identify a subgroup of anatomically resectable yet biologically high-risk disease, in whom more intensive systemic evaluation and consideration of preoperative therapy are appropriate [4,26,45].

Limitations of CA19-9

Despite obvious clinical utility, CA19-9 remains an indirect and context-dependent surrogate marker of metastatic potential, rather than a direct marker of metastatic potenti-

Table 1. Biomarkers informing biological resectability in PDAC.

Biomarker/domain	What it captures	Representative evidence	Strengths	Limitations	Current role	Key sources
CA19-9 (baseline)	Surrogate of burden/aggressive biology; flags occult spread.	IAP includes >500 U/mL as a biologic criterion. High preoperative values, especially ≥500 U/mL, predict worse survival and improve ABC/TAPS prognostication.	Widely available, inexpensive, and already used in MDT practice.	Affected by cholestasis/inflammation; false-negatives in Lewis non-expressors; cutoffs vary.	Routine adjunct to anatomic staging after biliary decompression and clinical contextualization.	Isaji et al., 2018 [4]; Schouten et al., 2024 [33]; Dekker et al., 2024 [19]
CA19-9 kinetics	Treatment response and adequacy of systemic control during NAT.	Normalization or a major fall (commonly ≥50%) is favourable; normalization may be more prognostic than percentage decline alone.	Dynamic, intuitive, and easy to track during NAT.	No standard timing or thresholds; evidence is mostly retrospective.	Adjunct for post-NAT restaging and surgical re-evaluation, not a stand-alone rule.	Boggi et al., 2024 [13]; Tsai et al., 2020 [35]; Liu et al., 2020 [36]
CA19-9 non-expression / genotype adjustment	Avoids false reassurance in non-secretors and refines interpretation between patients.	About 4.5% of NCDB patients were non-expressors, with more metastatic disease and worse OS. FUT2/FUT3 adjustment modestly improves prognostic discrimination.	Highlights an important blind spot in standard CA19-9 use.	Not routine; adds complexity; prospective treatment utility is unproven.	Contextual refinement in specialist or research settings.	Sugawara et al., 2024 [34]; Ando et al., 2024 [42]
ctDNA (preoperative)	Molecular evidence of occult systemic disease before resection.	Meta-analysis links positivity to worse DFS and OS; prospective cohorts link it to occult metastases and poor postoperative outcomes.	Tumour-derived signal with strong relevance for molecular staging.	Assays vary; sensitivity is limited in localized low-shedding disease; no interventional validation.	Promising adjunct in research programs and selected expert centres; not yet a routine stand-alone determinant.	Borges et al., 2026 [24]; Murakami et al., 2025 [37]
ctDNA (postoperative / MRD)	Molecular residual disease and relapse risk after surgery.	Postoperative ctDNA positivity predicts recurrence and worse survival, with stronger adverse associations than preoperative positivity.	Strong biologic rationale for MRD assessment.	Management implications are unclear; assay timing and platforms are not standardized.	Research tool and postoperative trial stratifier.	Borges et al., 2026 [24]; Hata et al., 2023 [38]
Peritoneal + plasma KRAS ctDNA	Occult peritoneal dissemination missed by imaging or plasma-only testing.	A prospective Mayo cohort linked plasma and/or peritoneal mutant KRAS ctDNA to metastases and worse survival; dual-compartment positivity identified the highest-risk subgroup.	May improve sensitivity beyond plasma alone.	Sampling strategy is not standardized; external validation is limited; peritoneal sampling reduces scalability.	High-priority investigational approach in selected centres.	Leiting et al., 2025 [39]
Transcriptomic subtype	Intrinsic tumour phenotype and metastatic propensity beyond anatomy.	Basal-like/squamous signatures predict worse outcomes regardless of chemotherapy regimen.	Biologically compelling; may explain why technically resectable tumours fail systemically.	Needs adequate tissue; assays are complex; sampling bias and no strategy-changing prospective trials.	Investigational; possible future tool for biology-driven perioperative stratification.	Singh et al., 2024 [43]; Robertson et al., 2024 [40]
PET, radiomics, and hybrid models	Noninvasive imaging surrogates of aggressive biology and early recurrence risk.	Routine PET-CT is not recommended for general staging. One retrospective study found CA19-9 plus dual-time-point FDG-PET highly specific for early recurrence.	Noninvasive, scalable, and potentially useful in composite models.	False positives/negatives, marked heterogeneity, and limited external validation.	Investigational and hypothesis-generating rather than determinative for routine care.	Conroy et al., 2023 [27]; Springfeld et al., 2024 [26]; Kobayashi et al., 2024 [41]

Abbreviations: ABC, anatomic-biologic-conditional; ctDNA, circulating tumor DNA; FDG-PET, fluorodeoxyglucose positron emission tomography; IAP, International Association of Pancreatology; MDT, multidisciplinary team; MRD, molecular residual disease; NAT, neoadjuvant therapy; NCDB, National Cancer Database; OS, overall survival; CT, computed tomography; PDAC, pancreatic ductal adenocarcinoma; CA19-9, carbohydrate antigen 19-9; TAPS, Trans-Atlantic Pancreatic Surgery; DFS, disease-free survival.

al [27,32,46]. Interpretation is confounded by obstructive jaundice and inflammatory biliary disease, while false-negative values are observed in those patients who are non-secretors of the Lewis antigen [46,47,48,49]. Foundational studies have shown that non-expression of the Lewis antigen occurs in approximately 5% to 10% of patients and that cholestasis can independently elevate serum CA19-9 levels, regardless of tumor burden [47,48,49]. These limitations are clinically relevant, as they influence the degree to which an elevated CA19-9 level may be considered a true marker of aggressive tumor biology [32,47].

Further evidence for this concern has come from a number of recent studies. Analysis of the 2024 National Cancer Database of 88,749 patients demonstrated that 4.5% of these patients were CA19-9 non-expressors [34], and this subgroup was demonstrated to have a higher rate of distant metastatic disease at presentation and shorter median overall survival for resected non-metastatic patients compared to those with normal range CA19-9 values [34]. Therefore, non-elevated CA19-9 does not constitute, per se, a reliable indicator of biologically favorable disease, and can occasionally mask an underlying aggressive tumor phenotype [34]. For this reason, CA19-9 should not be considered a single criterion for determining surgical candidacy [32,50].

CA19-9 should not be used as a criterion for surgery because another limitation is that the prognostic implications of a given CA19-9 concentration may vary between individuals. A 2024 Johns Hopkins study demonstrated that a FUT2/FUT3-based tumor marker genotyping assay modestly enhanced the prognostic performance of CA19-9 following pancreatic cancer resection, and suggested that genotype-adjusted normalization may better identify patients with a major pathological response and those at increased risk of early recurrence [42]. Although not yet appropriate for routine clinical use, this approach supports the need for a more personalized, genotype-informed, and context-dependent interpretation of CA19-9 values in clinical practice, because it may lead to more accurate predictions, and consequently, better treatment outcomes [32,42].

Importantly, the evidentiary basis supporting CA19-9 is not uniform. The strongest support derives from its incorporation into international consensus frameworks and its reproducible association with outcomes across large multicentre and nationwide cohorts. However, much of the available evidence remains observational and is therefore susceptible to residual confounding, selection bias, and treatment allocation bias. Furthermore, the CA19-9 thresholds proposed for defining biologically high-risk disease vary substantially across studies, reflecting differences in patient populations, biliary drainage practices, treatment strategies, and endpoint definitions. Although the consistency of the observed associations supports the biological relevance of CA19-9, the evidence supporting its use to direct specific treatment pathways remains less robust than the evidence supporting its prognostic value.

Dynamic CA19-9 Response

Another major conceptual breakthrough has been the appreciation that tumor biology is a dynamic, rather than static, phenomenon. Baseline CA19-9 levels primarily represent pre-treatment disease burden and intrinsic biological aggressiveness, whereas serial CA19-9 changes during systemic therapy more directly represent treatment-modified tumor biology. Both a reduction of CA19-9 levels of at least 50% and normalization of CA19-9 after neoadjuvant therapy have been associated with improved long-term survival after resection, according to the REDISCOVER recommendations [13,35,36]. Conversely, rising CA19-9 levels after induction therapy are predictive of a poor prognosis and necessitate careful multidisciplinary re-evaluation of the therapeutic strategy [13,35,36].

It is also becoming clear that not all dynamic CA19-9 changes are created equal [35,36]. In the 2020 study by Tsai et al. [35], normalization of post-neoadjuvant CA19-9 seemed to be a more potent long-term prognostic indicator than the degree of decline itself. Similarly, Liu et al. [36] found that either normalization or a decline of more than 50% appeared to identify patients who would not benefit from additional adjuvant therapy, while patients with smaller declines seemed more likely to benefit from further postoperative treatment. Together, these data suggest that post-treatment CA19-9 kinetics could further refine both surgical selection and perioperative treatment approaches; however, while standardized cut-off values and robust prospective validation are lacking, dynamic changes in CA19-9 should be considered within the context of a comprehensive, multidisciplinary evaluation rather than in isolation [32,35,36].

From a practical perspective, CA19-9 should not be interpreted as a standalone biological staging tool. Rather, it should be viewed as a clinically useful adjunct to anatomical staging and multidisciplinary assessment. Interpretation requires consideration of the clinical context, particularly biliary obstruction, inflammatory biliary disease, Lewis antigen status when known, and the temporal relationship to systemic therapy. When obstructive jaundice is present, CA19-9 values should ideally be reassessed following adequate biliary drainage before being incorporated into biological risk assessment. Similarly, in patients with unexpectedly low or undetectable CA19-9 levels despite clinically aggressive disease, the possibility of Lewis antigen non-expression should be considered. In such circumstances, reliance on CA19-9 alone may underestimate biological risk and alternative biomarkers, imaging findings, and clinical features become particularly important.

Furthermore, discordance between baseline CA19-9 levels and treatment-related kinetics should be interpreted cautiously. Dynamic changes during therapy may provide information regarding treatment responsiveness that complements, rather than replaces, baseline biological risk assessment. Therefore, both baseline values and longitu-

dinal trends should be incorporated into multidisciplinary decision-making.

ctDNA and Molecular Staging

Although CA19-9 is still the mainstay biomarker of current clinical practice, ctDNA represents the most promising next-generation marker, primarily because it circumvents one of the main pitfalls of anatomy-based staging; the inability to reliably detect occult systemic dissemination [24,37,51]. In contrast to CA19-9, ctDNA is a molecular signal emitted by the tumor cells themselves, not an indirect surrogate of tumor burden [24,52], and its potential clinical utility lies across three key settings: preoperatively as a marker of occult metastatic potential, postoperatively as a marker of molecular residual disease, and during perioperative therapy as a guide for biologically informed treatment intensification or de-escalation [37,38,51,52].

The evidence base for surgical ctDNA has evolved far beyond theoretical interest. In a 2026 systematic review and meta-analysis of 18 studies (965 patients), preoperative ctDNA positivity was associated with significantly worse disease-free survival (hazard ratio (HR) 2.08) and overall survival (HR 2.31), and postoperative positivity conferred even greater risk with more pronounced adverse associations with disease-free survival (HR 3.29) and overall survival (HR 3.42) [24]. The prognostic value of ctDNA was maintained in both upfront resection and neoadjuvant therapy. While the aggregated data do not demonstrate that ctDNA-guided therapeutic strategies result in improved clinical outcomes, they convincingly demonstrate that ctDNA consistently identifies a high-risk biological signal associated with adverse oncological outcomes. However, current evidence remains predominantly prognostic in nature, and there is presently no prospective evidence demonstrating that altering treatment strategies on the basis of ctDNA status alone improves clinical outcomes. Consequently, ctDNA should currently be viewed as a tool for biological risk stratification rather than a standalone determinant of surgical decision-making [24,53].

Several prospective cohort studies have replicated these findings. A 2025 prospective cohort study of patients with resectable and borderline resectable PDAC found that preoperative ctDNA was an independent predictor of occult metastatic disease and was a reliable discriminator of the highest-risk patients who would have poor postoperative outcomes. ctDNA-positive patients had a median recurrence-free survival of 10.2 months (vs. ~26 months for ctDNA-negative patients) and a median overall survival of 22.9 months (vs. ~41 months for patients without detectable ctDNA) [37]. Another prospective cohort study from the Mayo Clinic in 2025 expanded upon these findings by examining mutant KRAS ctDNA in plasma and peritoneal fluid, and positive peritoneal fluid was associated with positive staging laparoscopy, subsequent metastatic progression, and worse overall survival [39]. Importantly, positivity in both plasma and peritoneal compartments identified the highest-risk group, with a median overall survival of 10.4 months compared to 28.4 months in patients who were negative in both compartments [39]. Together, these studies are especially important because they suggest that ctDNA can be used not only as a general prognostic marker, but as a means of molecular staging to risk stratify patients beyond what is possible with conventional clinical and radiographic evaluation [37,39].

The main limitations of ctDNA remain practical, rather than theoretical at this time [53,54]. Assay heterogeneity is still significant, including ongoing uncertainty about the relative merits of tumor-informed versus tumor-agnostic approaches [54,55]. An additional source of heterogeneity arises from differences between tumor-informed and tumor-agnostic ctDNA assays. Tumor-informed approaches utilize patient-specific mutations identified from tumor tissue and generally provide greater analytical sensitivity for detecting minimal residual disease and low-volume tumor burden. In contrast, tumor-agnostic platforms rely on predefined mutation panels and offer broader clinical applicability and faster implementation but may be less sensitive, particularly in patients with low ctDNA shedding. This distinction has important clinical implications because biomarker classification and risk stratification may vary according to the assay employed. Consequently, differences in assay design likely contribute to the variability observed across studies and currently limit direct comparison of ctDNA performance between cohorts. From a practical perspective, tumor-informed assays may be particularly attractive for postoperative molecular residual disease assessment, whereas tumor-agnostic assays may be more feasible in the preoperative setting when tumor tissue is unavailable or limited. However, prospective studies directly comparing these strategies in the context of biological resectability remain lacking.

The current ctDNA literature is strengthened by the presence of prospective cohort studies and recent pooled analyses demonstrating consistent associations with recurrence and survival. Nevertheless, important methodological limitations remain. Studies differ substantially in assay design, including tumor-informed versus tumor-agnostic approaches, targeted mutations, detection thresholds, sampling timing, and biological compartments analyzed. Furthermore, most studies evaluate prognostic associations rather than biomarker-guided interventions, meaning that ctDNA positivity identifies high-risk disease but has not yet been conclusively shown to improve outcomes when used to direct treatment decisions. Consequently, the evidence supporting ctDNA as a prognostic biomarker is stronger than the evidence supporting its routine use as a determinant of perioperative management. Current data in pancreatic cancer favor tumor-informed assays on the basis of higher detection rates, but limited sensitivity in early-stage disease and other technical variability continue to hinder

assay harmonization and broad standardization [53,54,56]. Taken together, these results suggest that ctDNA should be considered a promising emerging biomarker for molecular staging and risk stratification. Nevertheless, before ctDNA can be incorporated as a determinant of treatment sequencing or operability, prospective studies demonstrating clinical benefit from ctDNA-guided interventions will be required [53,54].

Transcriptomic Subtype and Genomic Phenotype

Transcriptomic subtyping is biologically rational because it seeks to define the intrinsic phenotype of the tumor itself, rather than just its downstream clinical phenotypic expression [57,58]. The distinction between classical and squamous or basal-like subtypes offers an explanation for why some technically resectable tumors behave in a more aggressive systemic way [57,58]. Recent data, including a 2024 study among others, suggest that a strong basal or squamous transcriptomic signature independently predicts inferior outcomes, regardless of chemotherapy regimen used, suggesting that subtype is a fundamental prognostic attribute, rather than simply a surrogate for treatment choice [43]. The routine clinical application of transcriptomic subtyping is limited by a number of factors, including the need for adequate tissue, the complexity of the assay, concerns about representativeness of sampling and lack of prospective trials in which surgical decision-making is explicitly driven by molecular subtype. In addition, much of the supporting evidence originates from translational and retrospective analyses rather than prospective biomarker-stratified clinical trials. Although the association between basal-like or squamous phenotypes and adverse outcomes has been reproduced across several cohorts, uncertainty remains regarding assay standardization, intra-tumoral heterogeneity, and the optimal integration of subtype information into clinical decision-making. As a result, the prognostic significance of transcriptomic subtypes currently exceeds their demonstrated clinical utility for guiding treatment selection. Therefore, transcriptomic subtype should, at present, be viewed as a promising future component of biological staging, rather than a definitive criterion for determining resectability [40,59].

PET, Radiomics, and Hybrid Imaging-Biomarker Models

PET-based and radiomic forms of staging represent something of a compromise between purely anatomical and purely biological strategies. The major advantage of these techniques lies in their non-invasive and reproducible assessment of metabolic and phenotypic aspects of tumor biology that cannot be visualized using standard vascular imaging [60,61]. The clinical utility of these techniques at present is markedly limited, however, by profound methodological heterogeneity and only partial validation [62,63]. PET/computed tomography (CT), in particular, is further compromised by diagnostic overlap with inflammatory conditions and by clinically significant rates of both false-positive and false-negative results [27,60]. Compared with CA19-9 and ctDNA, the evidence supporting PET-derived and radiomic biomarkers remains less mature. Most available studies are retrospective, single-centre investigations with limited external validation and considerable methodological heterogeneity. Variability in image acquisition protocols, segmentation methods, feature extraction pipelines, and endpoint definitions has hindered reproducibility and prevented broad clinical implementation. Consequently, while these technologies provide valuable biological insights, their evidentiary foundation is currently weaker than that of more established serum or liquid biopsy biomarkers.

Ultimately, the use of hybrid approaches may prove more informative than the single use of any imaging parameter. A 2024 retrospective analysis demonstrated that elevated CA19-9 combined with unfavorable change in dual-time-point fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) SUVmax was able to identify a high-risk subgroup of patients at increased risk of early postoperative recurrence, with a specificity of 94.5% for relapse within one year and independent prognostic value for inferior relapse-free survival [41]. Consequently, these data suggest that future definitions of biological resectability are likely to be based on composite models that incorporate serum biomarkers, liquid biopsy, molecular phenotype, and imaging-derived markers of biologically aggressive disease [11]. Importantly, the current evidence supporting these models is primarily prognostic. Although they may improve identification of patients at increased risk of recurrence or adverse outcomes, there is currently no prospective evidence demonstrating that management changes based on these models improve survival or reduce futile surgery. Therefore, their role remains hypothesis-generating rather than practice-defining [27,62].

Integrating Biological Resectability Into Perioperative Decision-Making

A critical distinction must be made between prognostic biomarkers and predictive tools capable of guiding treatment decisions. Many biomarkers discussed in this review, including ctDNA, transcriptomic signatures, and hybrid imaging-biomarker models, have demonstrated consistent associations with recurrence and survival outcomes. However, such associations do not necessarily establish that modifying treatment strategies according to biomarker status improves patient outcomes. Consequently, the current evidence base supports the use of these biomarkers primarily for biological risk assessment and multidisciplinary decision support, whereas prospective validation of biomarker-guided treatment algorithms remains an important unmet need.

The strength of evidence supporting individual biomarkers varies substantially and should be considered when incorporating biological information into clinical decision-making. CA19-9 currently has the most mature evidence base, supported by international consensus recommendations and multiple large observational studies. ctDNA has demonstrated strong and consistent prognostic performance across prospective cohorts and pooled analyses, but lacks prospective interventional validation. Transcriptomic, radiomic, and hybrid biomarker approaches remain largely investigational because their supporting evidence is derived predominantly from translational and retrospective studies. Therefore, the degree to which individual biomarkers should influence treatment sequencing should reflect the maturity and quality of the underlying evidence.

The clinical utility of biological resectability does not reside in the replacement of anatomical staging, but in the improvement of perioperative decision-making in cases where anatomical information alone is insufficient to estimate the potential oncological benefit. However, the current evidence base is not yet sufficient to support a universally accepted, biology-driven algorithm for the treatment of localized PDAC, although the available evidence supports the selective use of biological markers as an adjunct to staging, to guide the use of neoadjuvant therapy, and to reinforce multidisciplinary determinations of the suitability of surgery (Table 2, Ref. [4,15,19,23,24,33,37,39,41,43,45]) [11,13,35,56]. In this sense, biological resectability should be viewed as a prognostic and treatment-guiding framework rather than a formal resectability category. Its role is to complement anatomical staging by identifying patients in whom the anticipated oncological benefit of immediate surgery may be limited because of biologically aggressive disease. Consequently, biological resectability is best understood as a modifier of clinical decision-making and treatment sequencing, rather than as a replacement for established anatomical classifications. Biological resectability is increasingly being incorporated into contemporary clinical reasoning and multidisciplinary decision-making, although its operational implementation has not yet been prospectively validated [4,11,13,19,33]. A natural next step is therefore the creation of an integrated model that preserves existing anatomical categories and systematically refines them with relevant biological variables, with the explicit goal of distinguishing between technical operability and the likelihood of achieving a significant oncological benefit [4,11,13,19,33].

In practical terms, this framework can be represented as a four-step model that continues to use traditional anatomical classification while incorporating a biological risk stratification to aid clinical decision-making. Step 1 is based on the conventional anatomical classification of resectable, borderline resectable and locally advanced disease, with vascular involvement as the main criterion [4,11,19]. Step 2 evaluates tumor biology using biomarkers associated with occult systemic spread and early postoperative recurrence, while Step 3 stratifies patients into favorable, indeterminate, or adverse biological categories based on these findings [4,11,15,19,33,37]. Favorable biology is defined by the absence of extrapancreatic findings suspicious for metastatic disease, CA19-9 findings that are not indicative of biologically aggressive disease following appropriate consideration of biliary drainage status and other potential confounders, and, when available, the absence of detectable ctDNA. Conversely, adverse biology is characterized by high-risk biological features, including persistently elevated or unfavorable dynamic CA19-9 profiles despite adequate biliary decompression, detectable ctDNA, or other evidence suggestive of occult systemic dissemination [4,15,33,35,37,64,65,66]. In Step 4, this combined anatomical and biological classification may then direct the choice of treatment strategy, including upfront surgery, induction therapy and restaging or deferral of resection in favor of systemic disease control (Fig. 2) [11,13,15,19,35,66].

The proposed framework is intended as a conceptual aid to multidisciplinary decision-making rather than a prescriptive treatment algorithm. In clinical practice, biological signals are frequently discordant. For example, a patient may demonstrate markedly elevated CA19-9 levels despite negative ctDNA testing, favorable CA19-9 kinetics despite persistent radiological concern for occult metastases, or inconclusive biological assessment because advanced biomarkers are unavailable. In such circumstances, no single biomarker should be considered determinative. Rather, discordant findings should prompt individualized multidisciplinary review, consideration of additional staging investigations such as staging laparoscopy or repeat imaging, and reassessment following systemic therapy when appropriate. The overall biological profile, rather than any isolated biomarker result, should guide treatment planning.

For patients with unequivocally resectable PDAC and no obvious high-risk biological features, upfront surgery remains the most appropriate standard of care, as is reflected in the 2023 ESMO guidelines and supported by 2024 individual patient-level meta-analytic data demonstrating no overall survival benefit from neoadjuvant therapy in unselected patients with resectable disease [27,67,68,69]. Biological features do not negate anatomical resectability, although they may modulate the degree of confidence in proceeding directly to surgery. Patients with indeterminate or adverse biological features should not automatically be excluded from immediate resection on the basis of biomarker findings alone. Rather, such findings should prompt intensified multidisciplinary evaluation, consideration of additional staging investigations, and individualized discussion regarding the potential role of neoadjuvant therapy. While biological markers may identify patients at increased oncological risk, evidence demonstrating improved outcomes through biomarker-guided treatment allocation remains limited for most biomarkers beyond CA19-

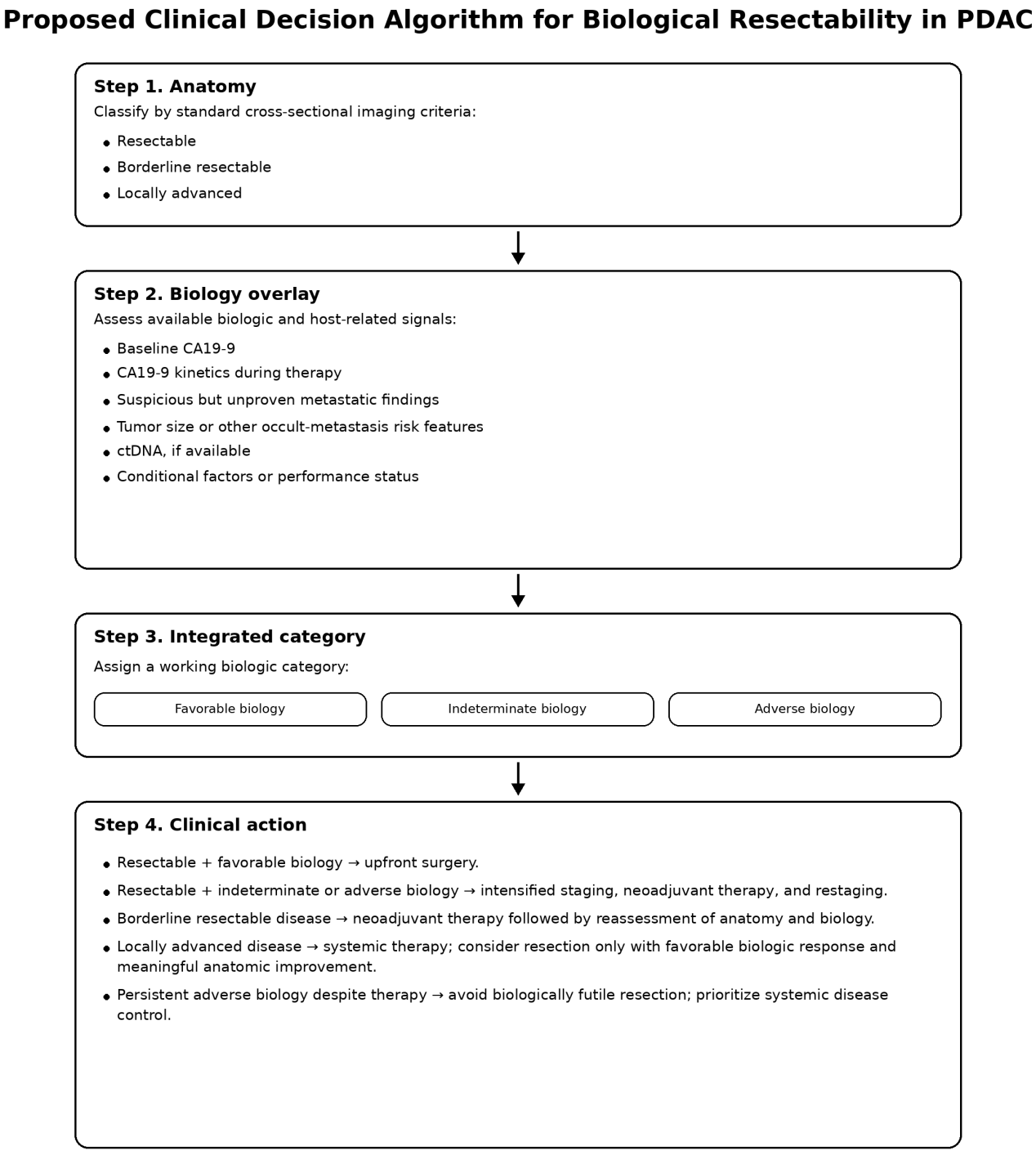

Fig. 2. A proposed four-step model integrating anatomical and biological criteria in pancreatic ductal adenocarcinoma resectability. Figure created by the authors using Google Gemini (version: Gemini 3.1 Pro, Google) and subsequently edited using Adobe Photoshop version 26.5 (Adobe Inc., San Jose, CA, USA; https://www.adobe.com).

9 [15,33,70,71,72,73,74]. Importantly, the indeterminate biology category also encompasses patients with discordant biological signals. Examples include markedly elevated CA19-9 levels in the absence of detectable ctDNA, favorable biomarker kinetics despite persistent radiological suspicion of metastatic disease, or conflicting results among multiple biomarker platforms. In such situations, the available evidence does not support prioritizing a single biomarker over all others. Instead, these patients should undergo further multidisciplinary evaluation and, when app-

Table 2. Key studies supporting biological resectability and multi-dimensional approach in localized PDAC.

Study	Design	Population	Biologic focus	Principal finding	Highest level of evidence	Clinical maturity	Clinical implication
Isaji et al., 2018 [4]	International consensus statement	N/A	ABC framework	Introduced biologic and conditional dimensions; CA19-9 >500 U/mL defined biologic risk.	Consensus framework	Clinically validated concept	Foundational shift beyond anatomy.
Dekker et al., 2024 [19]	Multicenter cohort	Localized PDAC, n = 1835	Anatomy, CA19-9, performance status	Each factor independently predicted OS; the integrated ABC score stratified survival.	Large multicenter cohort	Clinically useful but evolving	Supports integrated staging.
Schouten et al., 2024 [33]	Nationwide cohort	Upfront-resected anatomically resectable PDAC, n = 688	CA19-9	OS worsened at CA19-9 ≥500 U/mL; lower thresholds were informative in sensitivity analyses.	Nationwide cohort	Clinically validated	Supports biologic upstaging in resectable disease.
Murakami et al., 2024 [15]	Cohort	Potentially resectable PDAC, n = 279	Occult metastasis predictors	CA19-9 ≥118.8 U/mL and tumor size ≥22 mm predicted occult metastases and worse OS.	Observational cohort	Clinically useful but evolving	Shows anatomy alone understages biology.
Crippa et al., 2024 [23]	Model development/validation	Anatomically resectable PDAC, n = 1426	Futile upfront surgery	Futile pancreatectomy occurred in 18.9%; preoperative predictors were ASA class, CA19-9, and tumor size.	Multicenter validation cohort	Clinically useful but evolving	Operationalizes futile surgery as an endpoint.
Omiya et al., 2025 [45]	Retrospective cohort	Resectable PDAC with CA19-9 >500 U/mL, n = 184	Intensive NAT vs upfront surgery	Median OS of 52.7 vs 22.7 months favored intensive NAT.	Retrospective comparative study	Hypothesis-generating	Suggests preoperative enrichment in biologically high-risk resectable disease.
Borges et al., 2026 [24]	Systematic review/meta-analysis	18 studies; 965 patients	Pre- and postoperative ctDNA	ctDNA positivity before and after surgery was associated with worse DFS and OS.	Meta-analysis	Promising	Supports ctDNA as an emerging molecular staging and MRD biomarker.
Murakami et al., 2025 [37]	Prospective cohort	Resectable/BR PDAC, n = 135	Preoperative ctDNA	ctDNA positivity predicted occult metastases and worse RFS and OS.	Prospective cohort	Promising	Supports ctDNA for preoperative risk enrichment.
Leiting et al., 2025 [39]	Prospective cohort	Localized PDAC, n = 785 overall (n = 377 paired plasma/peritoneal)	Plasma and peritoneal mKRAS ctDNA	Combined positivity marked the highest metastatic risk and worst survival.	Prospective cohort	Promising	Suggests value of compartment-specific molecular staging.
Singh et al., 2024 [43]	Translational/clinical cohort	PDAC with subtype profiling; biomarker cohort n = 7250, outcomes cohort n = 5335	Basal/squamous subtype	Basal/squamous subtype independently predicted worse outcomes across upfront regimens.	Translational + observational evidence	Investigational	Biologically informative, but not yet practice-directive.
Kobayashi et al., 2024 [41]	Retrospective cohort	Resected PDAC with PET plus CA19-9, n = 86	CA19-9 plus dual-time-point FDG-PET	The combined adverse profile had 94.5% specificity for early recurrence.	Retrospective exploratory study	Investigational	Supports hybrid models as investigational surrogates.

Abbreviations: BR, borderline resectable; RFS, recurrence-free survival; N/A, not applicable; ASA, American Society of Anesthesiology.

ropriate, additional staging or interval reassessment before definitive treatment decisions are made. Although current randomized evidence does not support routine use of neoadjuvant therapy for all patients with resectable PDAC, retrospective biomarker-enriched analyses suggest that carefully selected biologically high-risk subgroups may derive meaningful benefit from such an approach [33,67,68,69,70,71,72].

For patients with anatomically borderline resectable PDAC, neoadjuvant therapy is the standard of care. A 2025 meta-analysis of randomised trials showing a significant overall survival benefit in this setting has provided strong evidence for the standardisation of this approach, an opinion also reflected in the 2023 ESMO guidelines [26,27,75,76]. Inside this anatomically defined category, biological factors do not redefine borderline resectability but rather refine the prognostication and guide treatment decisions among the treatment options available [4,11,13,77]. In practice, patients with favorable biological features may proceed from induction therapy to surgical resection while patients with persistent adverse biological features should undergo a reassessment of the expected benefit from surgery [11,13,51,66,77]. After neoadjuvant treatment, the main question is thus not only if the tumor is technically operable but also if adequate systemic disease control has been achieved [11,13,51,77]. In this setting, favorable CA19-9 kinetics are associated with improved outcomes and preoperative ctDNA evaluation may provide additional molecular staging information, even if, for the time being, it is considered complementary rather than conclusive [13,15,35,37,53,64,66,77].

In the locally advanced PDAC population, surgical resection should be considered in highly selected circumstances, specifically, when there is a clear demonstration of both clinically significant anatomical downstaging and a favorable biological response to therapy [11,13,27,78,79]. In all anatomical settings, however, the persistence of adverse biological features despite therapy should strongly contraindicate surgical resection as this pattern is highly predictive of an oncologically futile operation [11,13,19,78,79,80]. Stated differently, local technical operability should not be equated with the appropriateness of surgical resection [11,13,79]. When the biological profile remains unfavorable, the treatment approach should be shifted away from immediate pancreatectomy and towards additional systemic therapy, further staging evaluations, or a basic reappraisal of whether surgical resection is oncologically justified at all [11,13,19,27,78,79,80]. Consequently, in this setting, technical feasibility alone should never trump a biological risk profile that suggests little or no meaningful benefit from surgical resection [11,13,19,78,79].

The main limitation of the proposed framework is arguably that of the field as a whole: the underlying evidence base is patchy [4,11,19,33]. Although CA19-9 is sufficiently well established to be of value for current clinical triage, most other biomarkers are either too non-standardized or are investigational in nature [4,11,19,33,53,64,81]. Moreover, the four-step model should not be considered a fully validated classification system in the same sense as TNM staging, because its purpose is instead to offer a logical and pragmatic taxonomy for describing biologically favorable, biologically borderline and biologically unfavorable disease in a manner that usefully complements, but does not supersede, pure anatomical assessment [4,11,19,33].

Controversies and Unresolved Questions

The first main area of uncertainty is definitional, i.e., what in practical terms constitutes biologically high-risk disease. The 2017 IAP consensus suggested that a CA19-9 level >500 U/mL was a defining biological criterion; however, more recent studies have also shown that lower cut-offs define subgroups with poor outcome [4,18,33]. For patients with anatomically resectable PDAC treated by up-front surgery, survival was worse not only in patients with CA19-9 levels ≥500 U/mL but also when a threshold of 200 U/mL was applied in sensitivity analyses. Moreover, for a separate cohort studied specifically for occult metastases, a preoperative CA19-9 level of 118.8 U/mL, when combined with a tumor size of ≥22 mm, predicted occult dissemination [15,33]. In addition, the results from REDISCOVER and other perioperative trials suggest that dynamic changes in CA19-9 levels (normalization or a significant decrease following induction therapy) are more informative than any single baseline value [13,35,36]. Consequently, the field still does not have a universally accepted answer to the question of whether biological resectability should be defined by a fixed cut-off, by treatment-related kinetics, or by a combined composite of both. The validation studies consistently validate the prognostic value of the biological criteria, but have not yet determined how these criteria should be used in clinical practice across the spectrum of clinical scenarios [13,18].

The second area of controversy concerns the standardisation of ctDNA measurement and the optimal sampling strategy. There is an emerging recognition that both preoperative and postoperative ctDNA positivity are associated with a poor prognosis, and pooled analyses demonstrate its prognostic significance in both up-front surgical patients and those receiving neoadjuvant therapy [24,53]. Nevertheless, there are several unresolved practical issues, including whether ctDNA should be measured in plasma only or also in peritoneal fluid, whether assays should be tumor-informed or tumor-agnostic, which sampling time points are of greatest clinical utility, and how best to assess patients with localized low-shedding tumors [39,53,54,55]. A 2025 Mayo cohort suggested that assessment of mutant KRAS in peritoneal fluid may reveal occult dissemination not evident by plasma testing alone, whereas a 2026 meta-analysis and the aforementioned postoperative studies suggested that, although biologically informative, ctDNA re-

mains too insensitive to supplant conventional staging and surveillance as a solitary modality [24,53,82]. Thus, the central question has transitioned from whether ctDNA is biologically informative to whether it can be standardized and validated to the point at which it can be reliably used to inform clinical decision making [53,55].

A third remaining question is the endpoint against which biologic resectability should be validated. While overall survival is the pre-eminent ultimate outcome, it is probably too distant in time to be the only metric for validation of a preoperative staging system [11,18]. Because of this, several recent studies have sought to focus on more proximal outcomes, including occult metastases, early recurrence, and futile surgery. In a 2024 occult metastasis study, intraoperative metastases and recurrence within 6 months were regarded as two different clinical manifestations of the same adverse tumor biology. In a 2024 JAMA Surgery futility model, futile pancreatectomy was defined as death or recurrence within 6 months, and was identified in nearly one fifth of anatomically resectable cases [15,23]. Collectively, these results imply that the most clinically relevant endpoint may not be survival alone, but rather the ability to avoid technically successful but oncologically futile resections [11,15,18,23].

Another area of controversy concerns therapeutic strategy, i.e., for whom to change the treatment sequence, and how. Current randomized trials and meta-analyses indicate that neoadjuvant therapy should be applied in borderline resectable PDAC but not in unselected patients with resectable disease [67,75]. One question that remains to be resolved is whether biologically high-risk but anatomically resectable tumors represent another entity in whom more intensive preoperative therapy should become the standard of care, and if so, which regimen, treatment duration, and stopping criteria to use [13,67,83,84]. REDISCOVER itself pointed out several outstanding issues, including the clinical significance and management of persistently elevated CA19-9 levels following induction therapy, the optimum duration of preoperative treatment, and the role of resection in more advanced disease [13]. These issues also include the limits of surgery per se, i.e., whether poor biological features should still prompt surgery in highly selected cases of locally advanced or oligometastatic disease, or, conversely, whether they should lead to avoidance of surgery in patients with technically resectable tumors but systemically dominant disease [13,85,86,87].

Another important unresolved issue is the distinction between prognostic utility and clinical actionability. Although several biomarkers consistently identify patients at increased risk of occult metastatic disease, early recurrence, or poor survival, there remains limited prospective evidence demonstrating that treatment modifications based on these biomarkers improve outcomes. Future studies should therefore focus not only on validating prognostic performance but also on determining whether biomarker-guided therapeutic strategies lead to superior patient-centered outcomes compared with current standards of care.

Future Research

The most pressing research question is that of prospective validation of an integrated staging system encompassing anatomic and biologic parameters. There is no longer a need for further proof of the clinical importance of tumor biology, but rather a need for standardised, reproducible definitions that can be applied uniformly across centers. This includes determining whether biological risk is best reflected by baseline CA19-9 concentrations, treatment-related kinetic profiles, composite risk models, or a combination of these parameters, and formal testing of pragmatic categories (e.g., biologically favorable, borderline, unfavorable disease) against clinically relevant outcomes. The second key priority is the standardisation of ctDNA assessment and its systematic integration into interventional studies, which includes resolution of issues related to assay design, optimal sampling time points and the relative merits of plasma and peritoneal testing for informing prognosis and therapy. Third, study endpoints should be refined to evaluate biological resectability not only based on overall survival but also in terms of occult metastases, early recurrence and non-beneficial (futile) pancreatectomy. Fourth, perioperative trials should stratify or selectively enroll patients according to biological risk, particularly in the subgroup of patients who are anatomically resectable but have high-risk biological features. Finally, multimodal and implementation-oriented research is needed as composite models incorporating serum biomarkers, liquid biopsy metrics, imaging data, molecular phenotypes and host-related factors are likely to be more informative than any single marker used alone.

Conclusions

The concept of biological resectability in PDAC has developed into an evidence-based framework to justify why anatomical staging alone is insufficient to accurately select the subset of patients most likely to benefit from surgery. The challenge now is to integrate biological metrics into perioperative decision-making to a degree that is commensurate with the current level of evidence. Of the biomarkers, CA19-9 remains the most established and clinically informative biomarker currently available for routine practice. However, its value lies primarily in its integration with anatomical staging, treatment response assessment, and multidisciplinary evaluation rather than in its use as an isolated determinant of biological resectability.

Overall, biological resectability should be used to complement, rather than supersede, traditional anatomical staging. At present, it is best regarded as a prognostic and treatment-guiding framework that helps distinguish technical operability from the likelihood of meaningful oncological benefit. Its principal value lies in refining patient

selection, informing treatment sequencing, and reducing the risk of oncologically futile surgery. Nevertheless, biological resectability remains an evolving concept, and current biomarkers should primarily be viewed as tools that support risk stratification and multidisciplinary decision-making rather than definitive determinants of operability. Prospective validation of biomarker-guided treatment algorithms remains necessary before these approaches can be routinely incorporated into clinical practice.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: CL and IK. Data curation: CL, DK, GP, AB, and EK. Formal analysis: CL, DK, and GP. Investigation: CL, DK, AB, and EK. Methodology: CL and GP. Project administration: CL and IK. Resources: CL, GP, and AB. Software: CL and DK. Supervision: IK. Validation: DK and IK. Visualization: CL and DK. Writing - original draft: CL, AB, and GP. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

Artificial intelligence Google Gemini (version: Gemini 3.1 Pro, Google) was used solely for visual figure generation and formatting. All scientific content, interpretation, and final figure design were reviewed, modified where necessary, and approved by the authors.

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