

## Review Article

# Redefining operability after neoadjuvant therapy in pancreatic ductal adenocarcinoma: a biology-driven surgical framework

Supreet Kumar\*

Department of Surgical Gastroenterology and GI Oncosurgery, Krishna Vikash Hospital, Sambalpur, Odisha, India

**Received:** 19 September 2026

**Accepted:** 21 October 2026

**\*Correspondence:**

Dr. Supreet Kumar,

E-mail: [supreet.mvj@gmail.com](mailto:supreet.mvj@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

Neoadjuvant therapy (NAT) has reshaped the management of pancreatic ductal adenocarcinoma (PDAC), improving systemic control and increasing margin-negative resection rates. However, it has also introduced complexity into surgical decision making. Post-treatment imaging, tumor markers, and pathologic findings frequently diverge, creating uncertainty regarding operability. Traditional anatomy-based frameworks are increasingly insufficient in the era of biologically driven therapy. The objective was to synthesize contemporary evidence and propose a practical, multidisciplinary framework for post-neoadjuvant surgical decision making in PDAC, particularly in the setting of discordant radiologic and biologic signals. A focused narrative review of PubMed-indexed literature (2015-2025) was conducted, emphasizing systematic reviews, prospective studies, and contemporary cohort analyses addressing response assessment, vascular resection, tumor regression grading, nodal downstaging, biomarker kinetics, and emerging technologies. Evidence was integrated into a structured tumor board-oriented decision framework. Post-NAT radiologic stability does not reliably indicate treatment failure, as therapy-induced fibrosis may mimic persistent vascular invasion. CA19-9 kinetics, staging laparoscopy, and patient physiologic reserve provide critical complementary information. Venous resection following NAT is oncologically justified in selected patients with favourable biology, whereas arterial resection requires stricter selection. Standardized pathology reporting, including tumor regression grading and nodal assessment, refines prognostication. Emerging tools such as circulating tumor DNA and radiomics show promise but require prospective validation. Post-neoadjuvant operability in PDAC demands integration of anatomy, biology, and patient resilience rather than reliance on a single modality. A structured, multidisciplinary framework enables biologically informed restraint or resection, ensuring that surgery is not merely technically feasible but oncologically justified.

**Keywords:** Pancreatic ductal adenocarcinoma, Neoadjuvant therapy, Surgical decision making, Tumor regression grading, Vascular resection, Circulating tumor DNA

## INTRODUCTION

The management of pancreatic ductal adenocarcinoma (PDAC) has undergone a decisive paradigm shift over the past decade, with neoadjuvant therapy (NAT) increasingly adopted for borderline resectable and selected locally advanced disease.<sup>1</sup> Contemporary international guidelines now endorse preoperative systemic therapy to address occult micrometastatic spread, improve margin-negative (R0) resection rates, and enable biologic selection of surgical candidates.<sup>2</sup>

Meta-analyses and prospective series have demonstrated higher R0 resection rates and encouraging survival outcomes in patients completing NAT compared with historical upfront surgery cohorts, reinforcing the systemic-first philosophy in PDAC.<sup>3</sup> Consequently, a growing proportion of patients are referred for surgical consideration only after several months of multi-agent chemotherapy with or without radiation.

This therapeutic evolution has created an interesting paradox. While NAT improves systemic disease control

and may downstage vascular involvement, it simultaneously renders surgical decision making more complex.<sup>4</sup> Treatment-induced fibrosis and desmoplastic remodelling frequently result in persistent radiologic vascular abutment despite substantial tumor necrosis. Conventional response criteria, particularly RECIST (Response evaluation criteria in solid tumors) based size assessment, inadequately capture treatment effect in PDAC, where tumor viability may decrease without significant dimensional change.<sup>5</sup> Radiologic stable disease may reflect favourable biology, whereas apparent regression may coexist with occult systemic progression.

In this setting, post-neoadjuvant evaluation must extend beyond anatomical resectability. Tumor marker kinetics, functional imaging, performance status, and intraoperative findings must be interpreted within a tumor biology-driven framework. The operative question is no longer merely whether resection is technically feasible, but whether surgery is oncologically justified.

This review examines the discordance between imaging, pathology, and tumor biology after NAT in PDAC and proposes a practical, surgeon-centered framework for post-neoadjuvant decision making.

## WHY DISCORDANCE HAPPENS

The discordance between post-neoadjuvant imaging, pathology, and clinical behaviour in pancreatic ductal adenocarcinoma (PDAC) arises from therapy-induced alterations in tumor architecture and stromal composition. Modern multi-agent regimens such as FOLFIRINOX frequently produce dense fibrosis and perivascular inflammatory remodelling, changes that may persist radiologically despite substantial tumor cell kill.<sup>6</sup> In several series evaluating patients treated with FOLFIRINOX, cross-sectional imaging continued to demonstrate vascular abutment or encasement even when final pathology revealed limited viable tumor at the

interface.<sup>6</sup> Thus, residual perivascular soft tissue density on computed tomography (CT) after NAT does not reliably equate to persistent arterial invasion.

Objective imaging accuracy after NAT remains imperfect. Diagnostic performance studies have shown limited sensitivity and specificity of CT in predicting margin-negative resection and true vascular involvement following neoadjuvant therapy.<sup>7</sup> Treatment-related fibrosis reduces contrast differentiation between viable tumor and scar, resulting in both overestimation of unresectability and underestimation of residual disease burden. This limitation is compounded by the reliance on RECIST criteria, which evaluate size change rather than tumor viability. In PDAC, where response may manifest as stromal remodelling without significant dimensional reduction, RECIST underestimates meaningful therapeutic effect.<sup>8</sup>

Pathologic response further illustrates the complexity of post-NAT assessment. Contemporary tumor regression grading systems, including the College of American Pathologists (CAP) criteria, demonstrate wide variability in histologic response patterns within the primary tumor and regional lymph nodes.<sup>9</sup> Complete or near-complete regression may be observed in the pancreatic parenchyma, while nodal metastases persist, or vice versa. Moreover, margin interpretation after NAT is influenced by fibrosis extending into peripancreatic tissues, complicating correlation between radiologic clearance and true R0 resection.

Together, these mechanisms explain why anatomical imaging alone cannot dictate post-neoadjuvant operability. The treated pancreas represents a biologically altered environment in which radiology, histopathology, and systemic behaviour frequently diverge.

The principal mechanisms contributing to post-neoadjuvant imaging-pathology discordance are summarized in Table 1.

**Table 1: Mechanisms of imaging-pathology discordance after neoadjuvant therapy in PDAC.**

| Mechanism                               | Radiologic appearance                       | Pathologic reality                                  | Clinical implication                            |
|-----------------------------------------|---------------------------------------------|-----------------------------------------------------|-------------------------------------------------|
| <b>Therapy-induced fibrosis</b>         | Persistent perivascular soft tissue density | Scar tissue with minimal viable tumor               | Stable vascular abutment ≠ unresectable disease |
| <b>Desmoplastic stromal remodelling</b> | No significant size reduction               | Major tumor cell kill without dimensional shrinkage | RECIST underestimates response                  |
| <b>Inflammatory change</b>              | Ill-defined tissue planes                   | Mixed viable tumor and fibrosis                     | Margin assessment must be cautious              |
| <b>Nodal heterogeneity</b>              | Stable nodal enlargement                    | Sterilized nodes or microscopic residual disease    | Radiology cannot define nodal biology           |
| <b>Micrometastatic disease</b>          | Negative imaging                            | Occult peritoneal/liver deposits                    | Staging laparoscopy retains value               |

**Table 2: Post-neoadjuvant operability algorithm: tumor board framework.**

| Domain                    | Favor proceed to surgery                                                | Favor deferral/abort                                 |
|---------------------------|-------------------------------------------------------------------------|------------------------------------------------------|
| <b>Imaging</b>            | Stable disease; no new metastases; reconstructible vascular involvement | New distant disease; progressive vascular encasement |
| <b>CA19-9 kinetics</b>    | >50% decline or normalization                                           | Rising trend or plateau despite therapy              |
| <b>Performance status</b> | ECOG 0–1; preserved muscle mass; acceptable frailty index               | Sarcopenia; deconditioning; ECOG $\geq 2$            |
| <b>Laparoscopy</b>        | Negative for metastasis                                                 | Positive peritoneal/hepatic disease                  |
| <b>Vascular resection</b> | Venous reconstruction feasible in high-volume centre                    | Arterial resection required with adverse biology     |
| <b>Biology</b>            | No progression during NAT                                               | Early progression or new symptoms                    |

**Table 3: Pathologic reporting after NAT: minimum essential elements.**

| Parameters                        | Why it matters                                 | Reporting standard                                           |
|-----------------------------------|------------------------------------------------|--------------------------------------------------------------|
| <b>CAP Tumor Regression Grade</b> | Correlates with survival                       | 4-tier CAP system                                            |
| <b>Margin status</b>              | Determines local control and adjuvant strategy | $\leq 1$ mm rule; specify margin involved                    |
| <b>Nodal status</b>               | Reflects systemic responsiveness               | Total nodes examined; nodes positive; evidence of regression |
| <b>Lymphovascular invasion</b>    | Marker of aggressive biology                   | Present/absent                                               |
| <b>Perineural invasion</b>        | Recurrence risk                                | Present/absent                                               |
| <b>Pathologic stage</b>           | Prognostic baseline                            | AJCC 8th edition                                             |

**Table 4: Failure scenarios and salvage strategies after NAT.**

| Scenario                                | Mechanism                          | Recommended Strategy                                  |
|-----------------------------------------|------------------------------------|-------------------------------------------------------|
| <b>Occult metastasis at exploration</b> | Microscopic systemic spread        | Abort resection; systemic therapy                     |
| <b>Persistent arterial encasement</b>   | Aggressive biology or non-response | Avoid arterial resection unless exceptional candidate |
| <b>Early postoperative recurrence</b>   | Pre-existing systemic disease      | Switch chemotherapy regimen; clinical trial           |
| <b>Frailty-related risk</b>             | Physiologic depletion              | Prehabilitation or defer surgery                      |

**Table 5: Emerging biomarkers for biology-driven operability.**

| Tool                          | Evidence level            | Current role                 | Limitation                   |
|-------------------------------|---------------------------|------------------------------|------------------------------|
| <b>ctDNA</b>                  | Retrospective cohort data | Prognostic adjunct           | Not yet decision-determinant |
| <b>Radiomics</b>              | Small validation studies  | Response prediction research | Poor external validation     |
| <b>PET metabolic response</b> | Moderate                  | Detect occult disease        | Limited standardization      |
| <b>Molecular profiling</b>    | Emerging                  | Trial stratification         | Not yet operability-defining |

## RESPONSE ASSESSMENT TOOLKIT

### *Cross-sectional imaging: what actually changes post-NAT and what does not*

Contrast-enhanced multidetector CT remains the primary modality for restaging after NAT in PDAC, yet its interpretive value changes fundamentally in the post-treatment setting.<sup>10</sup> Reduction in tumor size is neither necessary nor sufficient to define response. Following multi-agent chemotherapy, perivascular soft tissue thickening often persists despite substantial tumor cell

eradication, reflecting fibrosis and stromal remodelling rather than viable disease.<sup>11</sup> Consequently, degrees of arterial abutment frequently remain radiographically stable even in patients who ultimately achieve R0 resection.

Certain imaging features, however, retain prognostic relevance. Development of new metastatic lesions, progressive vascular contour irregularity, or increasing soft tissue density despite systemic therapy correlate with unfavourable biology.<sup>12</sup> Conversely, loss of tumor hypoenhancement, reduction in venous narrowing, and

stability without new disease may justify exploration even in the absence of dramatic shrinkage. Thus, post-NAT imaging is less a tool for declaring unresectability and more a filter to exclude systemic progression.

### **CA19-9 kinetics: thresholds and caveats**

Serum CA19-9 trends provide a dynamic biomarker of treatment response and systemic behaviour.<sup>13</sup> A significant decline during NAT—commonly defined as normalization or >50% reduction—has been associated with improved survival and higher likelihood of margin-negative resection.<sup>14</sup> Importantly, absolute post-treatment values may be less informative than trajectory.

However, interpretation demands caution. Obstructive jaundice can falsely elevate CA19-9 levels, necessitating reassessment after biliary decompression.<sup>15</sup> Furthermore, approximately 5–10% of patients are Lewis antigen-negative and unable to produce CA19-9, rendering the marker biologically silent in a subset of PDAC.<sup>16</sup> In these individuals, reliance on CA19-9 kinetics is misleading and alternative clinical indicators assume greater importance.

Thus, CA19-9 should not function as a solitary gatekeeper to surgery but rather as one component of a composite biologic assessment.

### **Staging laparoscopy: who benefits and when to repeat**

Occult metastatic disease remains a persistent concern even after modern NAT. Staging laparoscopy identifies radiographically occult peritoneal or liver metastases in a meaningful proportion of patients considered resectable by imaging.<sup>17</sup> The yield is highest in patients with borderline resectable or locally advanced tumors, elevated or rising CA19-9 after therapy, or equivocal imaging findings.

Repeat laparoscopy after completion of NAT may be considered in high-risk cases, particularly when initial staging was performed before systemic therapy. The rationale is biologically intuitive: NAT acts as a selection tool, but progression during therapy may manifest microscopically before radiologic detection. A negative laparoscopy does not guarantee absence of systemic disease, yet a positive finding spares patients a non-therapeutic laparotomy.

### **PET-CT, diffusion MRI, radiomics and AI: promising but not gospel**

Functional imaging modalities aim to bridge the gap between anatomy and biology. FDG PET-CT may detect occult metastases and metabolic response, with reduction in SUV associated with improved outcomes in selected series.<sup>10</sup> Diffusion-weighted MRI has demonstrated potential in differentiating fibrosis from viable tumor, though standardization remains limited.<sup>12</sup> Emerging

radiomic analyses and machine learning models attempt to extract predictive patterns from cross-sectional imaging, correlating textural features with pathologic response and survival.<sup>11</sup>

Yet enthusiasm must be tempered. Most studies remain retrospective, single-centre, and methodologically heterogeneous. External validation is inconsistent, and integration into routine clinical decision making is premature. These modalities should refine judgment, not replace it.

In sum, post-neoadjuvant assessment demands synthesis. No single modality, anatomic, serologic, laparoscopic, or metabolic, can independently determine operability. The surgeon must integrate imperfect signals into a coherent biologic narrative before committing the patient to resection.

## **DECISION NODES: A SURGEON'S FRAMEWORK**

Post-neoadjuvant decision making in PDAC cannot be reduced to imaging thresholds. It is a synthesis of anatomy, biology, and patient resilience. The framework must begin with reclassifying disease after completion of therapy.

### **Borderline resectable vs. locally advanced after NAT**

Traditional pre-treatment anatomical categories lose rigidity after NAT. Patients initially classified as borderline resectable (BRPC) or locally advanced (LAPC) may converge into a common decision space defined less by vessel interface and more by systemic behaviour.<sup>18</sup> Multiple contemporary series have demonstrated that patients with persistent vascular involvement after NAT can achieve R0 resection with acceptable morbidity, particularly when arterial encasement does not progress and venous reconstruction is technically feasible.<sup>19</sup>

Thus, post-NAT classification should prioritize absence of disease progression over complete radiologic clearance. Stable vascular abutment without new metastatic lesions often justifies exploration in high-volume centres experienced in vascular reconstruction.

A structured multidisciplinary decision matrix for post-neoadjuvant operability is presented in Table 2.

### **When to proceed despite stable imaging**

Radiologic stability is not synonymous with treatment failure in PDAC. In fact, stable disease after multi-agent NAT frequently reflects effective systemic control in a tumor known for limited dimensional shrinkage.<sup>20</sup> Several analyses have demonstrated that patients with radiographic stable disease may experience substantial pathologic response and favourable survival outcomes following resection.<sup>21</sup>

Proceeding to surgery despite stable imaging is justified when the following conditions are met: no new metastatic disease; declining or normalized CA19-9 levels; preserved performance status; and technically reconstructible vascular involvement. In this context, imaging stability represents biologic quiescence rather than resistance.

### ***When to stop despite partial response***

The inverse scenario is more dangerous. Apparent radiologic regression must not obscure systemic warning signs. Rising CA19-9 levels during or after NAT, emergence of new symptoms such as back pain or weight loss, or subtle radiologic signs of distant progression signal aggressive biology.<sup>22</sup> Data consistently demonstrate that early systemic progression during NAT portends poor survival even if the primary tumor appears downstaged.<sup>23</sup>

Surgery in this setting risks subjecting patients to high-morbidity operations without oncologic benefit. The decision to abort resection despite partial imaging response requires restraint but aligns with the principle that PDAC is primarily a systemic disease.

### ***Vascular resection decisions: technical feasibility versus biology***

Venous resection and reconstruction are increasingly accepted in experienced centres, with contemporary series reporting acceptable perioperative outcomes and survival comparable to standard resections when margin-negative resection is achieved.<sup>24</sup> Arterial resections, however, remain controversial and must be individualized.

After NAT, persistent venous narrowing should be interpreted in light of treatment effect. If biology appears favourable-evidenced by stable imaging and CA19-9 decline-venous resection may serve as a technical adjunct rather than a marker of aggressive disease. Conversely, technically feasible arterial resection in the presence of adverse biologic indicators rarely alters long-term survival.<sup>25</sup>

The decision is therefore not “can the vessel be reconstructed?” but “does the biology justify the reconstruction?”

### ***Performance status, frailty, and nutrition***

Oncologic algorithms are incomplete without consideration of patient reserve. Completion of prolonged NAT may result in sarcopenia, chemotherapy-induced neuropathy, or decline in functional capacity. Frailty indices and objective nutritional assessment correlate with postoperative morbidity and survival in PDAC.<sup>18</sup>

A technically resectable tumor in a physiologically depleted patient may yield inferior outcomes compared with continued systemic therapy or palliative strategies. Optimization, including nutritional rehabilitation and physical conditioning, should precede surgery whenever possible. The patient is not merely the host of the tumor; they are the determinant of whether resection is tolerable.

In aggregate, the post-neoadjuvant decision algorithm rests on four pillars: absence of progression, favourable biologic signals, technical feasibility in experienced hands, and adequate physiologic reserve. No single parameter is decisive. The surgeon must integrate discordant signals into a coherent narrative before committing to resection.

### ***PATHOLOGY: WHAT SHOULD BE REPORTED TO GUIDE FUTURE DECISIONS***

Post-neoadjuvant pathology in pancreatic ductal adenocarcinoma (PDAC) must extend beyond tumor size and margin status. In the modern NAT era, standardized reporting of treatment response is essential to interpret oncologic adequacy and to inform future systemic strategies.

Tumor regression grading (TRG) systems, particularly the College of American Pathologists (CAP) four-tier grading scheme, provide a structured assessment of residual viable tumor relative to therapy-induced fibrosis.<sup>26</sup> Studies have demonstrated that lower CAP scores (indicating major or complete response) correlate with improved disease-free and overall survival, reinforcing the prognostic value of histologic response beyond traditional T staging.<sup>27</sup> Importantly, pathologic complete response remains rare in PDAC, and partial regression should not be dismissed as biologically insignificant.

Margin assessment in the post-NAT specimen requires careful interpretation. Fibrosis extending into peripancreatic tissues may obscure the true tumor boundary, complicating the distinction between R0 and R1 resection.<sup>28</sup> Contemporary consensus recommends meticulous evaluation of the superior mesenteric artery (SMA) margin, portal vein groove, and posterior surface, with standardized definitions of margin positivity (typically  $\leq 1$  mm clearance). Reporting should specify which margin is involved rather than simply labelling the resection as R1.

Nodal evaluation is equally critical. NAT may sterilize the primary tumor while residual metastatic disease persists in regional lymph nodes, or conversely eradicate nodal disease despite viable primary tumor. The number of examined nodes, the presence of treated metastases, and evidence of nodal regression should be documented. Nodal sterilization has been associated with favourable survival and may serve as a surrogate marker of systemic responsiveness.

The minimum essential elements that should be included in standardized pathology reporting after neoadjuvant therapy are outlined in Table 3.

Standardized pathology reporting after NAT thus closes the loop between preoperative biology and postoperative strategy. It provides the objective substrate upon which adjuvant therapy decisions and prognostic counselling must rest.

## FAILURE MODES AND SALVAGE PATHWAYS

Despite careful selection, failure after NAT remains common in PDAC. Unexpected metastatic disease at exploration continues to occur even in patients deemed resectable on cross-sectional imaging and negative staging laparoscopy. Contemporary series report occult peritoneal or liver metastases in a meaningful minority of patients undergoing laparotomy after NAT, underscoring the systemic nature of PDAC.<sup>29</sup> Intraoperative detection of metastasis should prompt restraint; conversion to palliative bypass or aborting resection avoids the morbidity of futile pancreatectomy without oncologic gain.

Another failure mode is technically unresectable disease at exploration due to persistent arterial encasement or unexpected vascular involvement. In such scenarios, extended arterial resections have not consistently demonstrated survival advantage and may confer substantial morbidity when biology is unfavourable.<sup>30</sup> The threshold for abandoning resection must therefore remain low in the presence of poor intraoperative findings.

Postoperative failure, early recurrence within six months, represents a retrospective indicator of aggressive tumor biology. These cases highlight the limitations of current selection tools and reinforce the need for better systemic biomarkers.

Salvage strategies include continuation or modification of systemic therapy, enrollment in clinical trials, and symptom-directed palliation. Importantly, aborting resection should not be interpreted as therapeutic defeat, but as biologically informed decision making.

Common failure scenarios and corresponding salvage strategies are summarized in Table 4.

### Future directions

The next evolution in post-neoadjuvant decision making for PDAC lies in biologically driven operability. Circulating tumor DNA (ctDNA) has emerged as a promising marker of minimal residual disease, with detectable postoperative ctDNA correlating strongly with early recurrence and inferior survival in resected PDAC.<sup>31</sup> Early studies suggest that dynamic ctDNA clearance during neoadjuvant therapy may stratify

patients more accurately than imaging alone, potentially identifying those unlikely to benefit from surgery despite radiologic stability.

Radiomics and artificial intelligence (AI)-based imaging analysis similarly aim to extract predictive signatures from cross-sectional imaging beyond human interpretation. Preliminary models have demonstrated associations between radiomic features and pathologic response or survival outcomes following neoadjuvant therapy.<sup>32</sup> However, heterogeneity in acquisition protocols, limited external validation, and lack of prospective integration into clinical workflows temper enthusiasm.

Emerging biomarkers and investigational tools that may refine biologically driven operability assessment are summarized in Table 5.

Future frameworks will likely integrate ctDNA kinetics, standardized radiomic signatures, and molecular profiling to guide operability decisions. Until these tools are prospectively validated and reproducible across institutions, they should inform-not dictate-surgical judgment.

## CONCLUSION

Neoadjuvant therapy has redefined the surgical landscape of pancreatic ductal adenocarcinoma, shifting decision making from rigid anatomical criteria toward biologic interpretation. Yet this evolution has introduced complexity: imaging, pathology, and systemic behaviour frequently diverge after treatment. Radiologic stability may conceal meaningful response, while apparent regression may mask aggressive disease. Post-neoadjuvant operability cannot be determined by a single parameter. It requires integration of cross-sectional imaging, tumor marker kinetics, staging laparoscopy findings, vascular reconstructibility, and, critically-patient physiologic reserve. Pathologic response and nodal sterilization refine prognostic understanding but are available only after resection; thus, preoperative judgment remains imperfect. The modern surgeon must balance technical feasibility against tumor biology, recognizing that restraint can be as oncologically sound as resection. A structured, multidisciplinary framework is therefore essential to navigate discordant signals and to ensure that surgery is not merely possible, but justified.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

## REFERENCES

1. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. FOLFIRINOX or Gemcitabine as Adjuvant Therapy

- for Pancreatic Cancer. *N J Med.* 2018;379(25):2395-406.
2. Tempero MA, Malafa MP, Al-Hawary M. Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2021;19(4):439-57.
3. Suker M, Beumer BR, Sadot E. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol.* 2016;17(6):801-10.
4. Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol.* 2013;20(8):2787-95.
5. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg.* 2015;261(1):12-7.
6. Cassinotto C, Sa-Cunha A, Trillaud H. Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer. *Diagnost Interv Imag.* 2016;97(12):1225-32.
7. Jenvrin A, Sartoris R, Dokmak S. Comparison of radiological and pathological tools to assess response to neoadjuvant treatment in resected pancreatic ductal adenocarcinoma patients. *Ther Adv Med Oncol.* 2025;17:17588359251403909.
8. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *Pancreatol.* 2016;16(1):28-37.
9. College of American Pathologists. Protocol for the examination of specimens from patients with carcinoma of the pancreas (latest update). *CAP Cancer Protocols.* 2025.
10. Lee SM, Katz MH, Liu L, Sundar M, Wang H, Varadhachary GR, et al. Validation of a Proposed Tumor Regression Grading Scheme for Pancreatic Ductal Adenocarcinoma After Neoadjuvant Therapy as a Prognostic Indicator for Survival. *Am J Surg Pathol.* 2016;40(12):1653-60.
11. Hank T, Hinz U, Tarantino I, Kaiser J, Niesen W, Bergmann F, et al. Validation of at least 1 mm as cut-off for resection margins for pancreatic adenocarcinoma of the body and tail. *Br J Surg.* 2018;105(9):1171-81.
12. Okada K, Uemura K, Kondo N, Sumiyoshi T, Seo S, Otsuka H, et al. Neoadjuvant therapy contributes to nodal downstaging of pancreatic cancer. *Langen Arch Surg.* 2022;407(2):623-32.
13. Truty MJ, Kendrick ML, Nagorney DM, Smoot RL, Cleary SP, Graham RP, et al. Factors Predicting Response, Perioperative Outcomes, and Survival Following Total Neoadjuvant Therapy for Borderline/Locally Advanced Pancreatic Cancer. *Ann Surg.* 2021;273(2):341-9.
14. Cloyd JM, Ejaz A, Shen C, Dillhoff M, Williams TM, Noonan A, et al. Pathologic complete response following neoadjuvant therapy for pancreatic ductal adenocarcinoma: defining the incidence, predictors, and outcomes. *Int Hepato Pancreato Biliary Assoc.* 2020;22(11):1569-76.
15. Gudmundsdottir H, Yonkus JA, Alva-Ruiz R, Kendrick M, Smoot R, Warner S, et al. Yield of Staging Laparoscopy for Pancreatic Cancer in the Modern Era: Analysis of More than 1,000 Consecutive Patients. *J Am Coll Surg.* 2023;237(1):49-57.
16. De Rosa A, Cameron IC, Gomez D. Indications for staging laparoscopy in pancreatic cancer. *HPB (Oxford).* 2016;18(1):13-20.
17. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma. *J Gastrointest Oncol.* 2012;3(2):105-19.
18. Versteijne E, de Hingh IHJT, Homs MYV, Intven MPW, Klaase JM, van Santvoort HC, et al. Neoadjuvant Treatment for Resectable and Borderline Resectable Pancreatic Cancer: Chemotherapy or Chemoradiotherapy? *Front Oncol.* 2022;11:744161.
19. Xue K, Huang X, Zhao P, Zhang Y, Tian B. Perioperative and long-term survival outcomes of pancreatectomy with arterial resection in borderline resectable or locally advanced pancreatic cancer following neoadjuvant therapy: a systematic review and meta-analysis. *Int J Surg (London, England).* 2023;109(12):4309-21.
20. Abdelrahman AM, Goenka AH, Alva-Ruiz R. FDG-PET Predicts Neoadjuvant Therapy Response and Survival in Borderline Resectable/Locally Advanced Pancreatic Adenocarcinoma. *J Natl Compr Canc Netw.* 2022;20(9):1023-32.
21. Lee W, Oh M, Kim JS, Park Y, Kwon JW, Jun E, et al. Metabolic activity by FDG-PET/CT after neoadjuvant chemotherapy in borderline resectable and locally advanced pancreatic cancer and association with survival. *Br J Surg.* 2021;109(1):61-70.
22. Hammad AY, Hodges JC, AlMasri S, Paniccia A, Lee KK, Bahary N, et al. Evaluation of Adjuvant Chemotherapy Survival Outcomes Among Patients With Surgically Resected Pancreatic Carcinoma With Node-Negative Disease After Neoadjuvant Therapy. *JAMA Surg.* 2023;158(1):55-62.
23. Marti-Bonmati L, Cerdá-Alberich L, Pérez-Girbés A. Pancreatic cancer, radiomics and artificial intelligence. *Br J Radiol.* 2022;95(1137):20220072.
24. Yeung KTD, Kumar S, Cunningham D, Jiao LR, Bhogal RH. Surgical Outcomes Following Neoadjuvant Treatment for Locally Advanced and Borderline Resectable Pancreatic Ductal Adenocarcinoma. *Ann Surg.* 2024;5(3):e486.
25. Wittmann D, Hall WA, Christians KK, et al. Impact of Neoadjuvant Chemoradiation on Pathologic

- Response in Patients With Localized Pancreatic Cancer. *Front Oncol.* 2020;10:460.
26. Choi GW, Seo Y, Lee I. Evaluating Tumor Regression and Survival Outcomes in Pancreatic Ductal Adenocarcinoma After Neoadjuvant Treatment according to CAP Grading System: Clinical Usefulness and Limitations. *Ann Surg Oncol.* 2025;32:9956-65.
  27. Leonhardt CS, Niesen W, Kalkum E. Prognostic relevance of the revised R status definition in pancreatic cancer: meta-analysis. *BJS Open.* 2022;6(2):10.
  28. Jin WH, Mellon EA, Frakes JM, Murimwa GZ, Hodul PJ, Pimiento JM, et al. Impact of sarcopenia in borderline resectable and locally advanced pancreatic cancer patients receiving stereotactic body radiation therapy. *Journal of gastrointestinal oncology*, 2018;9(1):24-34.
  29. van Dongen JC, Versteijne E, Bonsing BA, Mieog JSD, de Hingh IHJT, Festen S, et al. The yield of staging laparoscopy for resectable and borderline resectable pancreatic cancer in the PREOPANC randomized controlled trial. *Eur J Surg Oncol.* 2023;49(4):811-7.
  30. Tinguely P, Hidalgo Salinas C, Staubli SM, Raptis DA, Fusai GK. . Analysis of Short-Term Outcomes in Pancreatic Surgery with Vascular Resection from a Prospective Multicenter Global Study. *Ann Surg Oncol.* 2025;32(12):8870-80.
  31. Leonhardt CS, Niesen W, Kalkum E, Klotz R, Hank T, Büchler W, et al. Prognostic relevance of the revised R status definition in pancreatic cancer: meta-analysis. *BJS Open.* 2022;6(2):10.
  32. Walma M, Maggino L, Smits FJ, Borggreve AS, Daamen LA, Groot VP, et al. The Difficulty of Detecting Occult Metastases in Patients with Potentially Resectable Pancreatic Cancer: Development and External Validation of a Preoperative Prediction Model. *J Clin Med.* 2024;13(6):1679.

**Cite this article as:** Kumar S. Redefining operability after neoadjuvant therapy in pancreatic ductal adenocarcinoma: a biology-driven surgical framework. *Int Surg J* 2026;13:2386-93.