Внутрипротоковые муцинозные опухоли поджелудочной железы
Intraductal mucinous tumors of the pancreas

ISSN 1995-5464 (Print); ISSN 2408-9524 (Online)
https://doi.org/10.16931/1995-5464.2025-3-63-69

Обзор классификаций внутрипротоковых папиллярных муцинозных неоплазий, показаний к хирургическому вмешательству и его результатов

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Внутрипротоковые папиллярные муцинозные неоплазии представляют собой кистозные новообразования поджелудочной железы с риском малигнизации. Обзор затрагивает современные рекомендации по лечению пациентов с этим заболеванием, показания к хирургическому вмешательству, результаты оперативного лечения и стратегии наблюдения за пациентами. В нем также освещены последние достижения в мини-инвазивной хирургии и новые биомаркеры, направленные на совершенствование распределения рисков по уровням и сокращение числа неоправданных оперативных вмешательств.

Ключевые слова: *внутрипротоковые папиллярные муцинозные неоплазии; хирургия; показания к хирургическому вмешательству в поджелудочную железу; результаты операций на поджелудочной железе*

Ссылка для цитирования: Đorđević V., Markovic M., Protić M., Knežević Đ., Basarić D., Antovic S., Grubor N., Radenković D. Обзор классификаций внутрипротоковых папиллярных муцинозных неоплазий, показаний к хирургическому вмешательству и его результатов. *Анналы хирургической гепатологии*. 2025; 30 (3): 63–69. https://doi.org/10.16931/1995-5464.2025-3-63-69

Авторы заявляют об отсутствии конфликта интересов.

A Review of Introductal Papillary Mucinous Neoplasia Classification, Surgical Indications, and Outcomes

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Intraductal papillary mucinous neoplasms (IPMNs) are pancreatic cystic lesions with malignant potential. This review outlines current guidelines, surgical indications, outcomes, and surveillance strategies. It also highlights recent advances in minimally invasive surgery and emerging biomarkers aimed at improving risk stratification and reducing unnecessary resections.

Keywords: *intraductal papillary mucinous neoplasms (IPMN); surgery; indications to pancreatic surgery; outcomes after pancreatic surgery*

For citation: Đorđević V., Markovic M., Protić M., Knežević Đ., Basarić D., Antovic S., Grubor N., Radenković D. A Review of Introductal Papillary Mucinous Neoplasia Classification, Surgical Indications, and Outcomes. *Annaly khirurgicheskoy gepatologii = Annals of HPB surgery*. 2025; 30 (3): 63–69. https://doi.org/10.16931/1995-5464.2025-3-63-69 (In Russian)

The authors declare no conflict of interest.

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are cystic precursor lesions of the pancreas characterized by intraductal papillary growth and thick mucin production. They were first described in 1982 as a distinct entity separate from other cystic tumors like mucinous cystic neoplasms (MCNs) and have since become a major focus in pancreatic oncology [1]. IPMNs account for about 25–50% of all pancreatic cystic neoplasms and are increasingly identified due to the widespread use of high-resolution abdominal imaging [2–3]. Many are discovered incidentally in asymptomatic patients, although larger IPMNs can cause symptoms such as pancreatitis, abdominal pain, or weight loss. IPMNs are also noted to be multifocal in up to 20–40% of cases, and patients with IPMN may have an increased incidence of other malignancies (e.g. colorectal cancer) compared to the general population [2]. These factors complicate clinical management, as clinicians must balance the risk of cancer arising from an IPMN against the risks of pancreatic surgery and the patient's overall health status.

Histologically, IPMNs exhibit a spectrum from low-grade dysplasia to high-grade dysplasia (carcinoma in situ) and can be associated with an invasive carcinoma. The World Health Organization classification now categorizes IPMNs by grade (low vs. high dysplasia) and recognizes several epithelial subtypes (gastric, intestinal, pancreatobiliary, oncocytic), which have differing biological behavior. Common genetic alterations in IPMNs include KRAS and GNAS mutations, among others, which are present even in low-grade lesions and play a role in the pathogenesis [4].

This review discusses the current approaches to IPMN classification, the indications for surgical intervention, and outcomes after resection, with an emphasis on recent advancements in guidelines, minimally invasive surgery, biomarkers, and surveillance strategies. We aim to provide clinicians with an up-to-date overview to inform decision-making in the management of IPMN patients.

Guidelines for IPMN Management

Several consensus guidelines have been developed to stratify IPMNs and guide the decision between surgical resection and non-operative surveillance. The most widely used are the International Consensus Guidelines (often called the Fukuoka guidelines) and the European evidence-based guidelines, with additional guidance from American societies (AGA and ACG).

Fukuoka Consensus Guidelines (2017): The Fukuoka guidelines (an update of the original Sendai criteria) outline specific high-risk stigmata (HRS) and worrisome features (WF) on imaging that correlate with malignancy in IPMN [3]. High-risk stigmata include the presence of obstructive jaundice (in a patient with a cystic lesion in the pancreatic head), an enhancing solid nodule (mural nodule) ⩾5 mm within the cyst, suspicion of malignancy and a main pancreatic duct (MPD) diameter ⩾10 mm [3]. If any high-risk stigma is present, immediate surgical resection is recommended in a surgically fit patient [3]. Worrisome features are more subtle findings that raise concern but are not absolute indications; these include cyst size ⩾3 cm, a non-enhancing mural nodule <5 mm or thickened cyst wall, MPD dilation of 5–9 mm, abrupt change in duct caliber with distal pancreatic atrophy, and lymphadenopathy [3]. When one or more worrisome features are present (but no high-risk stigma), the guidelines recommend additional evaluation, typically with endoscopic ultrasound (EUS) and fine-needle aspiration, rather than immediate surgery. Patients without any worrisome or high-risk features can be followed with periodic imaging. This two-tiered system achieves high sensitivity for detecting high-grade or invasive IPMN, but it has the drawback of low specificity – many patients ultimately undergo resection for lesions that prove to be low-risk on final pathology [5]. In one surgical series, only 43% of resected IPMNs that had met worrisome criteria were found to have advanced neoplasia, while up to 25% of resected benign lesions had exhibited worrisome features that prompted surgery [5]. This illustrates the limitation of current imaging-based criteria and the potential for overtreatment of indolent cysts.

European Evidence-Based Guidelines (2018): The European Study Group published guidelines that broadly align with the Fukuoka criteria but with some differences in thresholds and recommendations [2]. These guidelines stratify findings into "absolute" and "relative" indications for surgery. Absolute indications (which parallel high-risk stigmata) include the presence of obstructive jaundice, an enhancing solid component (nodule), and MPD ⩾10 mm, for which surgery is advised [2]. Relative indications are similar to worrisome features (cyst ⩾40 mm in size, MPD 5–9 mm, rapid cyst growth >5 mm/year, new-onset diabetes, etc.), and in such cases, either surgery or continued surveillance may be appropriate depending on patient factors [2]. A key contribution of the European guidelines was an evidence-based weighting of risk factors drawn from published studies, as well as recommendations on surveillance intervals. In general, the European approach is slightly more conservative about recommending immediate surgery for branch-duct lesions without very clear high-risk signs, especially in older patients or those with significant comorbidity. A comparative study of the Fukuoka and European guidelines in a cohort of patients found that both criteria had comparable accuracy in predicting advanced neoplasia, although they would select somewhat different subsets of patients for surgery [6].

AGA and ACG Guidelines: In 2015, the American Gastroenterological Association (AGA) issued

guidelines that took a more stringent approach – recommending surgical evaluation only for IPMNs with at least two high-risk features (mural nodule, dilated duct, or cyst ⩾3 cm) and even suggesting that patients with low-risk cysts that remain stable over 5 years of surveillance could consider discontinuing follow-up [7, 8]. This minimalist strategy aimed to avoid unnecessary surgeries, but it was criticized for potentially missing some malignancies. The American College of Gastroenterology (ACG) 2018 guideline represents a middle ground, largely endorsing the Fukuoka criteria with some modifications [9]. The ACG recommends resection for any IPMN with high-risk features (enhancing nodule or main duct ⩾10 mm), and consideration of resection for cysts >3 cm or with positive cytology, etc., while also suggesting that ongoing surveillance can be individualized based on patient age and comorbidities [9]. Notably, the ACG guideline allows that in older patients (e.g. >75 years) with small, asymptomatic branch-duct IPMNs, surveillance could be de-escalated or even stopped after a period of stability, since the risk of dying from unrelated causes might exceed the risk of the IPMN [9].

Overall, current guidelines agree that all main-duct IPMNs and mixed-type IPMNs should be resected in suitable surgical candidates due to their high rate of malignancy (estimated 60–70% have high-grade dysplasia or invasive cancer at surgery) [3, 6]. In contrast, the management of branch-duct IPMNs is risk-tailored. Small branch-duct lesions (<1,5–2 cm) without worrisome features can be observed with serial imaging, as their risk of progression is low (on the order of 2–5% per year or ~8% over 10 years) [9, 10]. Long-term studies from high-volume centers show that many branch-duct IPMNs remain indolent; for example [10] reported that the cumulative incidence of pancreatic malignancy was only ~15% at 5 years in patients with initially low-risk BD-IPMN under surveillance. These data justify the guidelines aggressive stance on surgical resection for any IPMN with high-risk features.

Surgical Approaches for IPMN

When an IPMN meets surgical criteria or is highly suspected of containing malignancy, the recommended treatment is surgical resection of the affected portion of the pancreas. The intent is curative: to remove the neoplastic epithelium before or at the stage of invasive cancer. The specific surgical approach depends on the location and extent of the IPMN, as well as patient factors. The fundamental principles of IPMN surgery are to achieve complete resection of all high-risk lesions with clear margins and to perform an oncologically correct operation (including lymph node dissection) if invasive cancer is present or suspected.

Indications for Surgery: Absolute indications for resection include any IPMN with high-risk stigmata as defined above (enhancing mural nodule, MPD ≥10 mm, obstructive jaundice, suspicions of malignancy) [3]. In addition, virtually all Main-Duct IPMNs warrant surgery if the patient is fit, given the high likelihood of malignancy: studies show that 57–92% of main-duct IPMNs harbor high-grade dysplasia or invasive carcinoma at the time of resection [2, 3]. Even diffuse main-duct dilatation ("pancreaticosis") without a distinct mass is considered risky, as occult carcinoma may be present. Branch-Duct IPMNs are selected for surgery if they exhibit several worrisome or just one high-risk features on imaging or cytology.

An area of nuance is the management of multifocal IPMNs. It is not uncommon for an MRI to show multiple cystic lesions throughout the pancreas in a patient with IPMN. Typically, only the dominant or highest-risk lesion is resected (often the one in the head or with worrisome features), and the remaining smaller IPMNs are kept under surveillance. Performing a total pancreatectomy to remove every IPMN is generally not recommended unless necessary (for diffuse main-duct involvement or multifocal high-grade dysplasia) because total pancreatectomy carries high morbidity and results in brittle insulin-dependent diabetes. Indeed, the decision to undertake a subtotal vs. total pancreatectomy must balance oncologic completeness with quality of life. Studies suggest that limited resection is adequate for multifocal branch-duct IPMNs as long as the resection margin is free of significant dysplasia – the residual small IPMNs in the remnant pancreas often remain indolent or can be managed with follow-up, intervening with another surgery later only if they show progression [11]. Thus, a parenchyma-sparing approach is favored to the extent that oncologic safety permits.

Type of Resection: IPMNs occur anywhere along the pancreas, so the surgical procedure is dictated by tumor location. For an IPMN in the pancreatic head or uncinate process (especially main-duct or mixed types), a pancreaticoduodenectomy (Whipple procedure) is indicated. For an IPMN in the body or tail of the pancreas, a distal pancreatectomy (with splenectomy in most cases) is performed. Some branch-duct IPMNs in the neck and body of the pancreas may be amenable to a central pancreatectomy, while those in the head for enucleation if they are small and benign-appearing. These limited resections aim to preserve pancreatic tissue and avoid the morbidity of formal resections.

Minimally Invasive Surgery: Advances in surgical technique allow many pancreatic resections for IPMN to be done via minimally invasive approaches. Laparoscopic and robotic pancreatectomy techniques have matured over the last decade, leading to reduced postoperative pain, shorter hospital stays, and faster recovery for patients compared to open surgery, without compromising oncologic outcomes.

For example, laparoscopic distal pancreatectomy for cystic neoplasms has become routine at many centers. Likewise, robotic-assisted pancreaticoduodenectomy is increasingly feasible in high-volume hospitals. A recent analysis of pancreatectomies performed for IPMN in the United States showed a clear trend: use of minimally invasive pancreatectomy increased significantly over time [12]. In that NSQIP database study of 3,912 IPMN resections, the proportion of cases done robotically rose from about 9% to 16%, while open surgeries correspondingly declined [12]. The conversion rate from minimally invasive to open was low, and there was also a noted decrease in postoperative pancreatic fistula rates over the years (possibly reflecting improved surgical technique) [12].

Intraoperative Decision-Making: A critical intraoperative consideration during IPMN resection is the status of the pancreatic resection margin. Because IPMNs, especially main-duct types, can have skip lesions or multifocal involvement, surgeons routinely send a frozen section of the pancreatic cut margin for immediate pathological evaluation. The presence of high-grade dysplasia or invasive carcinoma at a margin typically prompts further resection of the pancreas to achieve a clear margin [3]. For instance, if a patient is undergoing a distal pancreatectomy for a main-duct IPMN and the proximal margin shows IPMN with high-grade dysplasia, the surgeon may choose to extend the resection more proximally (and in some cases convert to a total pancreatectomy) to remove all at-risk epithelium. In contrast, if the margin shows only low-grade IPMN epithelium, many surgeons would not take additional pancreas, because low-grade dysplasia at the margin does not appear to impact recurrence or survival. Leonhardt et al. [13] reported that patients with low-grade IPMN remaining at the margin had no worse overall survival than those with completely negative margins. In their series of IPMN-associated carcinoma resections, low-grade dysplasia at the transection margin did not portend higher recurrence of cancer, whereas margins positive for high-grade or invasive disease did affect outcomes [13]. The conclusion was that additional resection is not beneficial for low-grade dysplasia at the margin and should be avoided to spare pancreatic parenchyma [13].

Oncologic Considerations: Whenever an IPMN is resected, especially if there is an associated invasive carcinoma, a standard oncologic operation with en bloc removal of regional lymph nodes is indicated. In pancreaticoduodenectomy for IPMN, for example, this means a formal lymphadenectomy of the peripancreatic, pyloric, hepatic artery, and SMA regions (similar to PDAC surgery). For distal pancreatectomy, the splenic artery and hilar nodes are removed. The reason is that one cannot reliably distinguish invasive cancer pre- or intra-operatively in all cases. If a cancer is present and nodes were not removed, the staging would be incomplete and the patient may even need a re-operation to clear lymph nodes. Therefore, the default is to perform node dissection as part of the initial IPMN resection [2]. This does not add significant risk but provides valuable prognostic information and potential therapeutic benefit if cancer is present. The importance of nodal status is underscored by long-term outcomes: patients with node-negative invasive IPMN have markedly better survival than those with node-positive disease [13, 14].

In summary, the surgical approach to IPMN is guided by oncologic prudence tempered with consideration for quality of life. Surgeons aim to remove all potentially malignant epithelium while preserving as much healthy pancreas as possible. Techniques such as frozen-section margin analysis help tailor the resection extent. Minimally invasive surgery is increasingly utilized to reduce perioperative morbidity. When appropriately applied, surgical resection of high-risk IPMNs is highly effective – it can prevent the development of pancreatic cancer and is potentially curative if an existing carcinoma is confined to the resected specimen.

Postoperative Surveillance

Follow-Up Protocols: Patients with IPMN require long-term surveillance, whether they undergo surgical resection or not. Surveillance strategies differ for those managed non-operatively vs. those who have had an IPMN removed. Both groups need ongoing monitoring due to the multifocal and recurrent nature of this disease. For patients under observation (unresected IPMN), current guidelines recommend periodic imaging and clinical evaluation. Typically, magnetic resonance imaging (MRI) or contrast-enhanced CT scans are obtained every 6–12 months, with the frequency determined by the risk profile of the IPMN. For example, a small (<1.5 cm) branch-duct IPMN with no worrisome features should be followed with yearly MRI, whereas a larger (2–3 cm) cyst or one with any change deserve to be imaged every 6 months [3, 8]. New-onset symptoms (like pancreatitis or abdominal pain) or changes in tumor markers during surveillance should prompt earlier investigation. The surveillance is usually continued indefinitely for patients who remain candidates for intervention, as IPMNs do not “expire” – even after a decade of stability, there is a small annual risk of progression. However, as noted, the Kyoto 2024 guidelines acknowledge that in elderly patients with long-term stability, cessation of surveillance may be reasonable [15]. Recent data quantifying this risk-benefit helped formulate such recommendations: a systematic review found that “low-risk” IPMNs (no high-risk features) have about an 8% chance of progressing to invasive cancer at 10 years, indicating that 92% will not progress in that timeframe [11]. For an elderly patient, the chance of dying of something else in 10 years may far exceed 8%, supporting

an individualized approach to stopping surveillance in select cases [11].

For patients who have undergone IPMN resection, postoperative surveillance of the remnant pancreas is standard. Even after complete resection of an IPMN, patients remain at risk for two categories of recurrence: (1) development of a new IPMN or pancreatic neoplasm in the remaining pancreas, and (2) recurrence of the original tumor (locally or distantly) if it was invasive. Thus, guidelines advise lifelong follow-up after IPMN surgery, though the intervals may be adjusted over time. A typical regimen after resection of a non-invasive IPMN is MRI or CT at 6 and 12 months post-op, then annually thereafter if no abnormalities are seen [3]. Some experts obtain imaging every 6 months for the first 2 years to catch early any rapidly growing new lesion. If the resected IPMN had high-grade dysplasia but no invasion, the risk of true recurrence (metastatic disease) is essentially zero, but the risk of a new, distinct IPMN in the remnant pancreas is significant – reported in the range of 5–10% at 5 years [16].

For patients whose resected IPMN had an associated invasive carcinoma, surveillance is even more critical. Invasive IPMN (IPMN-Ca) can recur in two ways: locoregionally (in the remnant pancreas or resection bed) or as distant metastases (liver, lung, peritoneum, etc.). Postoperative follow-up mirrors that for pancreatic cancer, with cross-sectional imaging (CT or MRI) every 3–6 months for the first two years and then every 6–12 months thereafter if no recurrence, along with periodic measurement of the tumor marker CA 19-9 [8]. It is considered a worrisome feature if CA 19-9 is >37 U/mL in the context of IPMN and may indicate occult invasion [3]. In the postoperative setting, a rising CA 19-9 can be an early harbinger of recurrence. However, CA 19-9 must be interpreted with caution, as false positives occur (e.g. cholangitis can raise it) and not all IPMN recurrences will produce it. Still, it has prognostic significance: one study noted that a CA 19-9 elevation ≥37 U/L in IPMN patients was associated with the presence of invasive cancer [5] and the Kyoto guidelines include CA 19-9 as a factor to consider during follow-up [15].

Recurrence and Outcomes: The prognosis after IPMN resection depends fundamentally on the pathology of the resected lesion – whether it was benign (low or intermediate dysplasia), high-grade dysplasia, or invasive cancer. Patients with non-invasive IPMN (low or high-grade dysplasia only) have an excellent prognosis after complete resection. Their survival is close to that of the general population matched for age, since they have been cured of a precancerous condition [11]. Their main risk is the development of a new IPMN or pancreatic cancer over the long term, as discussed. The recurrence rate in the remnant pancreas after resection of a non-invasive IPMN is in the range of 5–15% within 5 years, as noted. Most of these post-op "recurrences" are actually new IPMNs rather than true relapse of the removed lesion [16]. They are usually managed with further surveillance; if a new lesion meets criteria, a completion pancreatectomy might be considered.

For patients with invasive carcinoma arising from IPMN, outcomes are more variable. Invasive IPMNs tend to be less aggressive than conventional pancreatic cancers of similar stage – they often have a more indolent histology (e.g. colloid carcinoma in intestinal-type IPMN) and may present earlier (smaller tumor size) because the precursor cyst drew attention. A recent population-based analysis from Germany demonstrated that patients with invasive IPMN had significantly better survival than those with ordinary pancreatic ductal adenocarcinoma (PDAC). The median overall survival for invasive IPMN was 29 months vs. only 19 months for PDAC, and the 2-year disease-free survival was roughly double in the IPMN group [17, 18]. Additionally, patterns of recurrence differed: invasive IPMN had lower rates of distant metastases (especially less liver metastasis) and more instances of isolated lung metastasis compared to typical PDAC. These findings suggest a distinct, and somewhat more favorable, biology for IPMN-derived cancers. Likewise, an earlier analysis found that 5-year survival for resected invasive IPMN was around 50–60%, notably higher than the ~20% 5-year survival for sporadic pancreatic cancer [2, 11]. The most optimistic data come from single-institution series that caught many IPMN cancers at an early stage: Addeo et al. [14]. reported a five-year survival of 72% and ten-year survival of 62% among 78 patients with invasive IPMN who underwent resection. Such remarkable outcomes are linked to the fact that many of those invasive cancers were small (T1) and node-negative – indeed, on multivariate analysis, the factors associated with worse survival were the classic ones: jaundice (often signifying advanced local disease), lymph node positivity, advanced T-stage, and R1 resection. In their cohort , patients with early-stage IPMN-associated carcinoma (e.g. T1N0 and R0 resections) demonstrated favorable outcomes, with long-term survival observed in a substantial proportion of cases. Thus, if an IPMN-associated carcinoma is detected early (before it spreads to nodes or beyond the pancreas), surgical resection can be curative in a substantial proportion of patients.

Despite these encouraging results, invasive IPMN can and does recur. Recurrence rates for resected IPMN with invasive cancer are reported between ~30% and 65%, depending on pathological features [16, 17]. High-risk features such as lymph node metastases, poor differentiation, and positive margins drive most recurrences. Leonhardt et al. (2023), found that invasive IPMN with nodal involvement had a high incidence of distant relapse within 2 years, whereas node-negative patients rarely recurred [13].

Most recurrences are distant (liver, peritoneum, lung) rather than local. When recurrence occurs, the prognosis is poor, as is typical for metastatic pancreatic cancer. Hence, there has been the adoption of adjuvant chemotherapy for invasive IPMN by analogy to pancreatic cancer treatment. Guidelines generally recommend that any patient with an IPMN-related invasive carcinoma be considered for adjuvant therapy (e.g. gemcitabine-based or 5-FU-based chemotherapy for 6 months), especially if they have high-risk features [9].

Long-term follow-up is advisable for all patients after IPMN resection, regardless of pathology, because of the risk of metachronous lesions. In patients with initially low-risk IPMN, new lesions can appear years later; conversely, those with invasive disease need monitoring for relapse beyond the typical 5-year mark since late recurrences, though uncommon, can occur. In the study by Addeo et al. [14], patients who remained disease-free 5 years after surgery had an excellent long-term prognosis, although a small number developed new primary pancreatic lesions thereafter. Hence, many experts continue annual pancreas imaging even past 5–10 years post-op, especially if any pancreas remains.

Conclusion

IPMNs of the pancreas represent a spectrum of neoplastic diseases that demands a nuanced management strategy balancing the risks of malignancy against the risks of intervention. Significant progress has been made in recent years in stratifying IPMN patients through international guidelines, improved imaging techniques, and an accumulating evidence base. Early surgical resection of high-risk IPMNs can prevent the development of pancreatic cancer and offers an excellent long-term outcome, with many patients effectively cured. Advances in minimally invasive pancreatic surgery allow these resections to be performed without compromising oncologic efficacy. At the same time, an increasing emphasis on individually tailored surveillance has emerged – low-risk IPMNs can often be observed safely under close monitoring, especially in older patients, thereby avoiding unnecessary surgery. Postoperatively, patients require lifelong surveillance of the remnant pancreas given the non-negligible risk of recurrence or new primary lesions. The inclusion of emerging molecular and circulating biomarkers holds promise to further refine decision-making by identifying aggressive IPMNs that merit early resection and sparing truly benign cysts from surgery. Ongoing research and recent data continue to inform best practices – ultimately aiming to maximize cure rates for pancreatic neoplasia while minimizing intervention-related harm. With vigilant surveillance and timely surgical management when indicated, clinicians can significantly mitigate the threat of pancreatic cancer in patients with IPMN and ensure optimal outcomes.

Authors contributions

Đorđević V.[#] – concept and general plan of the study, writing text, editing, approval of the final version of the article, responsibility for the integrity of all parts of the article.

Markovic M. – concept and general plan of the study, writing text, editing, approval of the final version of the article, responsibility for the integrity of all parts of the article.

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Статья поступила в редакцию журнала 16.04.2025. Принята к публикации 24 июня 2025.
Received 16 April 2025. Accepted for publication 24 June 2025.