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ORIGINAL RESEARCH

Predictive Value of Preoperative [^{18}F]FDG PET/CT-Derived Heterogeneity Index for Occult Lymph Node Metastasis in Clinical N0 Gastric Adenocarcinoma

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Objective: To investigate the predictive value of preoperative [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography/computed tomography (PET/CT)-derived heterogeneity index (HI) for occult lymph node metastasis (OLM) in clinical N0 gastric adenocarcinoma.

Methods: This retrospective study included 83 patients with clinical N0 gastric adenocarcinoma who underwent [^{18}F]FDG PET/CT scans before radical surgery between March 2018 and June 2024. Patients were classified as OLM-positive (n=40) or OLM-negative (n=43) based on postoperative pathology. Clinical characteristics, PET/CT metabolic parameters [maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), peak standardized uptake value (SUVpeak), tumor-to-liver ratio (TLR), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)], and heterogeneity indices (HI-1 and HI-2) were analyzed. Univariate and multivariate logistic regression models were applied to identify independent predictors of OLM. ROC curve analysis was performed to assess diagnostic performance. Statistical analysis was conducted using SPSS version 26.0, with $P<0.05$ considered statistically significant.

Results: Gender, tumor differentiation, and pathological T stage differed significantly between the two groups ($P<0.05$). HI-2 was significantly higher, while SUVmax, SUVmean, and HI-1 were significantly lower in the OLM-positive group ($P<0.05$). Multivariate analysis identified pathological T stage (T3-T4, OR=4.778, P=0.022) and HI-2 >4.959 (OR=6.887, P=0.002) as independent predictors of OLM. ROC analysis revealed that HI-2 had an AUC of 0.711 (95% CI: 0.596–0.824, P=0.001), with 52.5% sensitivity and 88.37% specificity at the optimal threshold.

Conclusion: HI-2 derived from preoperative [^{18}F]FDG PET/CT is a significant independent predictor of OLM in clinical N0 gastric adenocarcinoma patients, alongside pathological T stage.

Keywords: ^{18}F-FDG PET/CT, heterogeneity index, gastric adenocarcinoma, occult lymph node metastasis, predictive value

Introduction

Gastric adenocarcinoma is one of the most common and lethal malignancies worldwide. According to the most recent global cancer data published by GLOBOCAN 2022, gastric cancer ranks fifth in incidence and fourth in cancer-related mortality globally, with more than 770,000 deaths annually, and the highest burden occurring in East Asia.[1] Despite advances in early detection and treatment, the long-term prognosis of gastric cancer remains unsatisfactory, mainly due to tumor invasion, lymph node metastasis (LNM), and, notably, occult lymph node metastasis (OLM).[2–4] OLM refers to metastasis that is not identified by preoperative imaging but is confirmed through postoperative pathology. The inability

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to detect OLM before surgery often leads to under-staging, suboptimal treatment decisions, and increased risk of recurrence or metastasis.[5–7]

In recent years, $[^{18}F]$fluorodeoxyglucose ($[^{18}F]$FDG) positron emission tomography/computed tomography (PET/CT) has emerged as a valuable imaging modality in oncology, integrating metabolic and anatomical information for better tumor detection, staging, and response assessment.[8–10] In many solid tumors and hematological malignancies, including lymphoma, lung cancer, and colorectal cancer, $[^{18}F]$FDG PET/CT has demonstrated strong diagnostic and prognostic value.[11–13] In gastric adenocarcinoma, although FDG uptake is relatively heterogeneous, metabolic parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) have been linked to tumor aggressiveness, treatment response, and survival outcomes.[14,15]

Beyond conventional metabolic parameters, metabolic heterogeneity has gained attention as a reflection of the spatial variation in tumor cell activity. The heterogeneity index (HI), derived from FDG uptake variability within the tumor, provides additional biological information not captured by mean metabolic values alone.[16,17] Studies have shown that high metabolic heterogeneity is associated with poor differentiation, invasiveness, metastasis, and treatment resistance in several cancers.[18]

However, whether PET-derived HI can effectively predict OLM in gastric adenocarcinoma remains underexplored. To our knowledge, limited studies have directly addressed this specific topic. Therefore, this retrospective study aimed to evaluate the diagnostic value of $[^{18}F]$FDG PET/CT metabolic parameters and HI in predicting OLM in clinical N0 gastric adenocarcinoma. Our goal is to provide imaging-based evidence to support preoperative risk stratification, improve staging accuracy, and contribute to the broader understanding of tumor metabolic heterogeneity.

Materials and Methods

Study Subjects

A retrospective analysis was conducted on the clinical data of 83 patients with gastric adenocarcinoma who underwent preoperative $[^{18}F]$FDG PET/CT scans at our hospital from March 2018 to June 2024. The clinical data included the patient's age, sex, primary tumor location, degree of differentiation, Lauren classification, pathological T stage, carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), etc. Tumor staging was based on the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system for gastric cancer.[19] Inclusion criteria: (1) Histopathological examination confirmed gastric adenocarcinoma; (2) Age ≥18 years, no gender limitation; (3) Patients had not received any form of neoadjuvant systemic treatment (such as chemotherapy, radiotherapy, targeted therapy, or immunotherapy) prior to $[^{18}F]$FDG PET/CT and surgery; (4) Underwent gastric adenocarcinoma radical surgery within one month after the $[^{18}F]$FDG PET/CT scan; (5) Received standardized $[^{18}F]$FDG PET/CT scans with complete imaging data clearly showing the primary gastric tumor and related lesions; (6) Complete clinical data available for analysis; (7) Informed consent was obtained from the patient and their family, and the relevant informed consent forms were signed. Exclusion criteria: (1) Preoperative imaging found any suspicious metastatic lymph nodes in any region (lymph node short diameter ≥10 mm on CT or MRI images, or SUVmax ≥2.5 on $[^{18}F]$FDG PET/CT images); (2) Distant metastasis present; (3) Presence of other malignant tumors; (4) Severe infections or immune, hematological system diseases; (5) Poor image quality; (6) No histopathological examination results and/or incomplete clinical data. All patients underwent gastric adenocarcinoma radical surgery within one month after the $[^{18}F]$FDG PET/CT scan. Based on postoperative histopathological examination, the patients were divided into two groups: the control group (n=43, OLM negative) and the study group (n=40, OLM positive). This study was approved by the Medical Ethics Committee of the 960th Hospital of the PLA Joint Logistics Support Force. (Approval No. XH-24WA013), and the research was conducted in strict accordance with the ethical guidelines of the Declaration of Helsinki.

$[^{18}F]$FDG PET/CT Imaging

In this study, a Siemens Biograph Truepoint 64 PET/CT scanner was used for imaging acquisition. 18F-FDG was synthesized using the HM-20 medical cyclotron and automated synthesis module from the Sumitomo Group in Japan, ensuring that the radiochemical purity exceeded 98%. Prior to the $[^{18}F]$FDG PET/CT scan, participants were required to fast for at least 6 hours, and their fasting blood glucose level should not exceed 11.1 mmol/L. To ensure optimal image quality, patients were also instructed to remain still during the scan to avoid movement or excessive tension. Based on the patient's body weight, 18F-FDG was intravenously injected at a dose range of 3.70–5.55 MBq/kg. After the injection, patients rested quietly for about 60 minutes to ensure that 18F-FDG fully entered the tissues and reached an ideal metabolic level. The PET/CT scan covered the body from the head to the upper thigh. The CT scan of the head was set with a tube voltage of 120 kV, tube current of 380 mA, and slice thickness of 3 mm. For body CT scans, the tube voltage was maintained at 120 kV, while the tube current was automatically adjusted by the scanner based on the patient's body type and scanning area to achieve optimal image quality, with a scan time interval of 0.8 seconds per rotation. Afterward, a 3D PET scan was performed, with a scan time of 3 minutes per bed for the head and 2.5 minutes per bed for the body, collecting images from 4 to 6 beds. Upon completion of the scan, the PET and CT images were fused and reconstructed using Siemens Syngo True D software, generating high-contrast, high-resolution cross-sectional PET/CT fusion images.

[^{18}F]FDG PET/CT Image Analysis

All metabolic and heterogeneity parameters were extracted from the primary gastric tumor only, and no nodal or distant lesions were included in the analysis. The image analysis was independently performed by two nuclear medicine specialists with more than 5 years of clinical experience. If there was a discrepancy in image interpretation, the analysis was further discussed with a senior physician to reach a consensus. During image analysis, for the patient's primary tumor, Regions of interest (ROI) were manually delineated slice-by-slice by two nuclear medicine physicians based on a threshold of SUVmax ≥2.5, using visual correlation with anatomical CT images to accurately contour the primary tumor. This process required precise identification and delineation of the tumor's metabolic region to ensure the representativeness of the metabolic parameters. The following commonly used metabolic parameters were extracted from the ROI area: maximum standard uptake value (SUVmax), mean standard uptake value (SUVmean), and peak standard uptake value (SUVpeak). To further evaluate the metabolic activity of the tumor, the tumor/liver ratio (TLR) was calculated, which is the ratio between the SUVmax of the primary tumor and the SUVmean of the liver region. In addition to the above metabolic parameters, the tumor metabolic volume (MTV) and total lesion glycolysis (TLG) were also assessed. Tumor metabolic heterogeneity, an important biological feature, was evaluated using two different heterogeneity indices (HI), as follows: HI-1 (Coefficient of Variation): This is calculated by the ratio of the SUV standard deviation (SD) to the SUVmean of the tumor area. The coefficient of variation (CV = SD/SUVmean) serves as a measure of metabolic heterogeneity, reflecting the degree of metabolic activity dispersion within the tumor.[20] HI-2 (Linear Regression Slope Based on SUV Threshold): This heterogeneity index assesses the trend of change in tumor metabolic volume based on different SUV thresholds (40%, 60%, and 80% of SUVmax). A linear regression of MTV at different SUV thresholds is performed, and the absolute value of the slope is calculated, based on the modified methods from previous studies.[21,22]

Statistical Methods

Data were analyzed using IBM SPSS 27.0 software. Measurement data that followed a normal distribution were presented as ($\bar{x} \pm s$), and comparisons between groups were performed using the independent samples *t*-test (for equal variances). Categorical data were expressed as n (%) and compared between groups using the chi-square test. Logistic regression models were used for univariate and multivariate analyses of the risk factors for OLM. Factors with $P<0.05$ in the univariate analysis were included in the multivariate analysis to determine independent risk factors for OLM. Receiver operating characteristic (ROC) curves were drawn to evaluate the diagnostic efficacy of the statistically significant metabolic parameters identified by the multivariate logistic regression analysis. A P-value of <0.05 was considered statistically significant.

Results

General Demographic, Clinical, and Pathological Characteristics of All Patients

Among the 83 patients included in this study, 65 (78.31%) were male and 18 (21.69%) were female, with a mean age of 63.93 ± 9.45 years. Overall, 39 patients (46.99%) had tumors located at the GEJ and gastric fundus, 19 (22.89%) in the gastric body and greater curvature, and 25 (30.12%) in the gastric antrum and pyloric region. Significant differences were observed in gender, differentiation degree, and pathological T staging between the OLM-positive (study) and OLM-negative (control) groups ($P<0.05$). However, no significant differences were found for age, tumor location, Lauren classification, CA199 or CEA levels ($P>0.05$). A summary of the demographic and baseline characteristics of all patients, as well as comparisons between the study and control groups, is shown in Tables 1–3.

Comparison of [^{18}F]FDG PET/CT Metabolic Parameters

The HI-2 value of the study group was significantly higher than that of the control group. Conversely, SUVmax, SUVmean, and HI-1 were significantly lower in the study group ($P<0.05$). No significant differences were found in SUVpeak, TLR, MTV, or TLG ($P>0.05$).

Table 1 Comparison of Clinical Characteristics Between Groups and Overall Patient Characteristics ($\bar{x} \pm s$, n[%], n=83)

	Total population (n)	Control (n=43)	Study (n=40)	t/x^2	*P*
Gender	–	–	–	5.315	0.021
Male	65 (78.31)	38 (88.37)	27 (67.50)	–	–
Female	18 (21.69)	5 (11.63)	13 (32.50)	–	–
Age (years)	–	64.93±8.36	62.85±10.47	1.003	0.318
Tumor Primary Site	–	–	–	0.624	0.429
GEJ and gastric fundus	39 (46.99)	22 (51.16)	17 (42.50)	–	–
Gastric body and greater curvature	19 (22.89)	9 (20.93)	10 (25.00)	–	–
Gastric antrum and pyloric region	25 (30.12)	12 (27.91)	13 (32.50)	–	–
Degree of Differentiation	–	–	–	4.603	0.031
Moderately differentiated	26 (31.33)	18 (41.86)	8 (20.00)	–	–
Moderately-low differentiated	26 (31.33)	14 (32.56)	12 (30.00)	-	-
Poorly differentiated	31 (37.35)	11 (25.58)	20 (50.00)	-	-
Lauren Classification	-	-	-	2.678	0.101
Intestinal type	43 (51.81)	26 (60.46)	17 (42.50)	-	-
Diffuse type	21 (25.30)	10 (23.26)	11 (27.50)	-	-
Mixed type	19 (22.89)	7 (16.28)	12 (30.00)	-	-
Pathological T Staging	-	-	-	5.247	0.022
T1~T2	22 (26.51)	16 (37.21)	6 (15.00)	-	-
T3~T4	61 (73.49)	27 (62.79)	34 (85.00)	-	-
Elevated CA199 Levels	15 (18.07)	9 (20.93)	6 (15.00)	1.874	0.171
Elevated CEA Levels	8 (9.64)	4 (9.30)	4 (10.00)	0.070	0.791

Table 2 Comparison of [^{18}F]FDG PET/CT Metabolic Parameters ($\bar{x} \pm s$)

	Control (n=43)	Study (n=40)	*t*	*P*
SUVmax	6.98±3.51	5.57±2.26	2.157	0.033
SUVmean	3.67±0.89	3.32±0.41	2.272	0.025
SUVpeak	4.71±1.08	4.36±0.98	1.542	0.126
TLR	3.01±1.06	2.74±0.85	1.274	0.206
MTV (cm^3)	12.31±4.97	11.95±5.39	0.316	0.752
TLG (g)	43.05±11.68	39.86±9.47	1.360	0.177
HI-1	0.30±0.15	0.22±0.13	2.587	0.011
HI-2	2.63±1.77	4.99±2.61	4.851	<0.001
	4.92			

Table 3 Univariate and Multivariate Logistic Regression of Factors Related to OLM

Clinical Characteristics and Metabolic Parameters	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Degree of Differentiation	–	–	–	–
Moderate differentiation	1.000	–	1.000	–
Moderate-low differentiation	1.964 (0.623~6.195)	0.253	-	-
Low differentiation	4.032 (1.287~12.591)	0.015	3.468 (0.916~13.092)	0.065
Pathological T Stage	-	-	-	-
T1~T2	1.000	-	1.000	-
T3~T4	4.076 (1.299~12.695)	0.014	4.778 (1.235~18.453)	0.022
Metabolic Parameters	-	-	-	-
SUVmax	0.893 (0.791~1.005)	0.057	-	-
SUVmean	0.604 (0.362~1.009)	0.053	-	-
SUVpeak	0.875 (0.756~1.017)	0.074	-	-
TLR	0.811 (0.634~1.036)	0.092	-	-
MTV (cm³)	0.998 (0.975~1.023)	0.900	-	-
TLG (g)	0.996 (0.989~1.005)	0.427	-	-
HI-1	0.027 (0.003~0.995)	0.046	0.539 (0.006~39.531)	0.776
HI-2	-	-	-	-
>4.959	7.364 (2.391~22.773)	<0.001	6.887 (1.918~24.720)	0.002
≤4.959	1.000	-	1.000	-

Logistic Regression Analysis of Clinical and Imaging Factors

Univariate analysis revealed that poor differentiation, pathological stage T3–T4, low HI-1, and HI-2 > 4.959 were associated with OLM ($P<0.05$). Multivariate logistic regression analysis showed that pathological T3–T4 staging (OR=4.778, P=0.022) and HI-2 > 4.959 (OR=6.887, P=0.002) were independent risk factors for OLM.

Predictive Value of HI-2 for OLM

The ROC curve showed an AUC of 0.711 (95% CI: 0.596–0.824, P=0.001) for HI-2 in predicting OLM. At the optimal cutoff value of HI-2 > 4.959, the sensitivity was 52.50% and specificity was 88.37% (Figure 1).

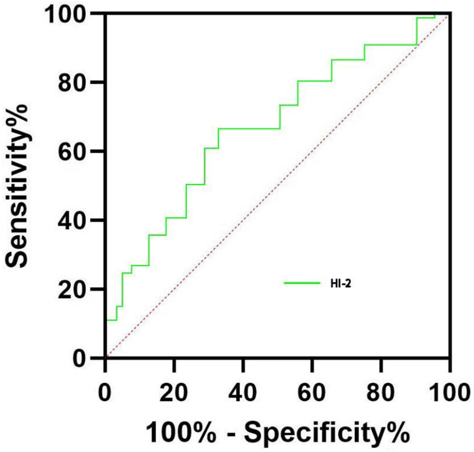

Figure 1 ROC curve of HI-2 in predicting OLM.

Discussion

In the treatment regimen for gastric adenocarcinoma, surgical resection remains the most commonly used and effective approach. However, despite the significant improvement in survival rates due to surgical treatment, many patients still face a high risk of recurrence after surgery.[23] OLM is considered one of the important factors leading to postoperative recurrence in gastric adenocarcinoma.[24] Therefore, accurately assessing the LNM status of gastric cancer patients preoperatively, especially OLM, becomes crucial for improving clinical outcomes and formulating individualized treatment plans. In recent years, [^{18}F]FDG PET/CT has made significant progress in evaluating the metabolic activity of cancers and LNM, particularly in the application of the HI parameter. The metabolic heterogeneity of HI can reveal metabolic differences in different regions of the tumor, thus providing a more detailed analysis of tumor characteristics for clinical use.[25] A study by Kim et al[26] demonstrated the important value of HI in predicting LNM in esophageal cancer, and this result provides theoretical support for understanding the application of HI in other gastrointestinal tumors. Zhang et al[27] showed that the HI of the primary site in gastric cancer is closely related to patient prognosis. In this study, univariate and multivariate logistic regression analyses indicated that HI-2 is an independent risk factor for OLM in gastric adenocarcinoma. HI-2 is calculated by analyzing the linear regression slope of MTV at different SUV threshold values, and it has high reproducibility and stability, which can be easily obtained on imaging workstations. This characteristic makes HI-2 highly operable and reproducible in clinical applications, and it can serve as an effective clinical tool for early prediction of LNM risk in gastric adenocarcinoma patients. Although [^{18}F]FDG PET/CT has been widely used in the diagnosis of gastric cancer LNM, existing literature[28,29] shows that its sensitivity in diagnosing gastric cancer LNM is relatively low, typically between 40% and 54.7%, while its specificity is higher, usually ranging from 73% to 92%. This discrepancy suggests that relying solely on [^{18}F]FDG PET/CT for diagnosing OLM may have certain limitations. In this study, the diagnostic sensitivity of HI-2 was 52.50%, and the specificity was 88.37%, showing relatively good overall diagnostic performance. The high specificity, in particular, gives it high clinical value in excluding LNM diagnoses, providing more reliable evidence for clinicians when evaluating patients' lymph node status preoperatively.

The results of this study show that the SUVmax, SUVmean, SUVpeak, and TLR of the primary tumor did not demonstrate significant clinical value in predicting OLM in gastric adenocarcinoma, which is consistent with the conclusions of Na et al.[30] However, other studies have proposed different views on the prognostic capabilities of these metabolic parameters. For example, Yamada et al, in a study analyzing 113 cases of advanced gastric cancer,[31] indicated that SUVmax of the primary tumor could be an effective predictor for LNM, suggesting that this metabolic parameter might have predictive value in some clinical scenarios. Additionally, Oh et al[32] pointed out that SUVpeak may be an independent risk factor for LNM in gastric cancer patients. The differences in these research results may arise from several influencing factors. First, the inherent heterogeneity of tumors may cause different metabolic parameters to behave differently across different patient populations. Factors such as tumor biological behavior, microenvironment, and differences among subtypes may all influence the tumor's metabolic uptake of 18F-FDG, thereby affecting the reliability of SUV values. Second, some volume effects may also influence the calculation of tumor metabolic parameters, especially in cases where the tumor is small or has unclear boundaries, which can lead to overestimation or under-estimation of SUV values. Additionally, differences in sample populations across studies are an important reason for the inconsistency of results. Clinical staging, tumor differentiation, and other related clinical factors can all affect the expression of metabolic parameters. Our study data further show that the SUVmax, SUVmean, and HI-1 of the primary tumors in the study group were significantly lower than those in the control group ($P < 0.05$). This suggests that poorly differentiated adenocarcinomas in gastric cancer patients may exhibit lower metabolic activity. The reason may be that the control group included more well-differentiated adenocarcinomas, resulting in relatively higher metabolic parameters (such as SUVmax and SUVmean), which reflects the metabolic differences between different tumor subtypes. This result is consistent with previous studies.[33,34]

MTV and TLG, as important metabolic parameters reflecting tumor load, have shown potential for predicting metastasis and assessing prognosis in many cancer types. However, they did not show significant value in predicting LNM in gastric adenocarcinoma in this study, which differs from the conclusions of some existing studies. Zhou et al[35] found that MTV and TLG were moderately positively correlated with the N stage of gastric cancer, suggesting that these two parameters may have predictive value in reflecting tumor load and predicting LNM. Moreover, Xue et al[36] further proposed that MTV and TLG, as independent prognostic factors, play an important role in early prediction of gastric cancer LNM. These studies indicate that metabolic parameters can provide valuable information for clinical staging and prognosis assessment of gastric cancer. However, Wang et al[37] found that MTV and TLG had no significant correlation with the N stage of gastric cancer, suggesting that in some patient populations, these metabolic parameters may not effectively predict the occurrence of lymph node metastasis. The discrepancies in these research conclusions may arise from the following differences: (1) Non-standardized methods for obtaining MTV: The calculation method for MTV is not yet unified, and different studies have used different SUV threshold values to determine tumor regions, leading to significant variations in data across studies. (2) Differences in sample populations: This study focused only on gastric cancer patients with cN0 stage, while previous studies may have covered a broader gastric cancer patient population, including patients with different clinical stages. This difference in sample selection may be an important reason for the inconsistency in study results. (3) Interference from gastric inflammation and Helicobacter pylori infection: Gastric inflammation and Helicobacter pylori infection are important factors affecting 18F-FDG uptake in gastric cancer patients. Inflammatory reactions and infections can lead to excessive physiological uptake of 18F-FDG in the gastric wall region, affecting the accuracy of metabolic parameters and thus influencing the measurement of tumor metabolic load.

In summary, this study demonstrates that the metabolic heterogeneity index HI-2 derived from [^{18}F]FDG PET/CT is an independent predictor of OLM in gastric adenocarcinoma patients and has notable diagnostic specificity. These findings are consistent with our results and underscore the potential of HI-2 as a novel imaging biomarker for preoperative risk stratification. While classic metabolic parameters such as SUVmax and SUVmean showed limited significance in this context, HI-2 may complement these indices, offering a more comprehensive evaluation tool. Considering the current limitations, future research with larger multicenter cohorts and standardized imaging protocols is warranted. Additionally, integrating more detailed clinical parameters such as tumor size, Borrmann classification, and broader tumor markers (eg, CA72-4, CA15-3, CA12-5) may further enhance our understanding of OLM-related risk factors. These efforts will contribute to optimizing surgical decision-making and improving patient prognosis through more precise and individualized treatment strategies.

Conclusion

This study reveals that the [^{18}F]FDG PET/CT-derived metabolic heterogeneity index HI-2 serves as an independent and effective predictor of occult lymph node metastasis in gastric adenocarcinoma. HI-2 demonstrated high specificity and moderate sensitivity, making it a valuable preoperative diagnostic indicator. When combined with clinical staging, HI-2 can help identify high-risk patients and guide the extent of lymph node dissection during surgery. Although traditional metabolic parameters were not independently predictive, their adjunctive use alongside HI-2 may still offer diagnostic support. Future prospective and standardized studies are needed to validate and expand upon these findings, ultimately promoting more accurate and personalized management of gastric cancer patients.

Disclosure

The authors report no conflicts of interest in this work.

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