

WJG 20th Anniversary Special Issues (8): Gastric cancer

New approaches to gastric cancer staging: Beyond endoscopic ultrasound, computed tomography and positron emission tomography

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Author contributions: Lee DH designed the review paper, revised the manuscript, and approved the final version; Yoon H collected the data and wrote the paper.

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Received: February 28, 2014 Revised: April 16, 2014

Accepted: May 25, 2014

Published online: October 14, 2014

Abstract

Currently, there is no single gold standard modality for staging of gastric cancer and several methods have been used complementarily in the each clinical situation. To make up for the shortcomings of conventional modalities such as endoscopic ultrasound, computed tomography and ¹⁸F-fluoro-2-deoxyglucose positron emission tomography, numerous attempts with new approaches have been made for gastric cancer staging. For T staging, magnifying endoscopy with narrow-band was evaluated to differentiate mucosal cancer from submucosal cancer. Single/double contrast-enhanced ultrasound and diffusion-weighted magnetic resonance imaging were also tried to improve diagnostic accuracy of gastric cancer. For intraoperative staging with sentinel node mapping, indocyanine green infrared and fluorescence imaging was introduced. In addition, to detect micrometastasis, real-time reverse transcription-polymerase chain reaction system with multiple markers

was studied. Staging laparoscopy using 5-aminolevulinic acid-mediated photodynamic diagnosis and percutaneous diagnostic peritoneal lavage were also evaluated. However, most studies reporting new staging methods is preliminary and further studies for validation in clinical practice are needed. In this mini-review, we discuss new progress in gastric cancer staging. Especially, we focus on new diagnostic approach to gastric cancer staging beyond the conventional modalities and briefly review the remarkable clinical results of the studies published over the past three years.

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Key words: Gastric cancer; Neoplasm staging; Diagnostic accuracy; New methods; New approaches

Core tip: Currently, there is no single gold standard modality for staging of gastric cancer. To make up for the shortcomings of conventional modalities or to replace these traditional methods, numerous attempts with new approaches such as magnifying endoscopy with narrow-band imaging, single/double contrast-enhanced ultrasound, and diffusion-weighted magnetic resonance imaging have been made for gastric cancer staging. In addition, for intraoperative staging, several newer methods associated with sentinel node mapping and diagnostic laparoscopy have been studied. However, most studies reporting new staging methods are preliminary and further studies for validation in clinical practice are needed.

Yoon H, Lee DH. New approaches to gastric cancer staging: Beyond endoscopic ultrasound, computed tomography and positron emission tomography. *World J Gastroenterol* 2014; 20(38): 13783-13790 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i38/13783.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i38.13783>

INTRODUCTION

Gastric cancer remains the second leading cause of cancer death worldwide^[1]. Accurate staging of gastric cancer is pre-requisite to determine the most appropriate therapy. However, each modality which is currently used has limitations and no single staging modality has been accepted as the standard. Therefore, National Comprehensive Cancer Network practice guidelines for gastric cancer do not recommend specific modalities and suggest using a variety of techniques complementarily as staging work-up^[2]. Currently, endoscopic ultrasound (EUS), computed tomography (CT), and ¹⁸F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) have been mainly used for staging modality of gastric cancer^[3]. For T staging of gastric cancer, EUS has been established as the diagnostic modality of choice with pooled accuracy of 75%^[4]. Due to the development of imaging techniques such as multi-detector row CT (MDCT)^[5] and virtual gastroscopy by multi-planar reconstruction of images^[6], CT may achieve similar diagnostic accuracy in T staging to EUS. However, the diagnostic accuracy for T staging of these two modalities is usually less than 80%-90%^[7]. For N staging, the diagnostic performance of EUS is less reliable than for T-staging; pooled accuracy was 64% with sensitivity/specificity of 74%/80%^[4]. For M staging, FDG-PET/CT has been gaining more attention due to the high sensitivity for distant metastasis. Recent study reported that FDG-PET/CT identifies radiographically occult metastasis in approximately 10% of patients with locally advanced gastric cancer^[8]. However, the sensitivity of PET for peritoneal carcinomatosis is only approximately 50%^[9]. Taken together, current staging modalities of gastric cancer have many limitations.

In this mini-review, we discuss the new progress in gastric cancer staging. Especially, we focus on new diagnostic approach to gastric cancer staging beyond the conventional modalities and briefly review the remarkable clinical results of the studies published over the past three years.

ESOPHAGOGASTRODUODENOSCOPY

Esophagogastroduodenoscopy (EGD) has been usually used for detection and diagnosis of gastric cancer rather than staging of gastric cancer. However, for the pure purpose of prediction of depth of invasion of early gastric cancer (EGC) (T1a vs T1b), EGD was found to provide reliable accuracy (overall accuracy: 78.0%-79.0%) and may be an alternative method of EUS^[10,11]. Recently, Kubota *et al*^[12] first reported the usefulness of computer-aided diagnosis of gastric cancer invasion on endoscopic images. The authors investigated the efficacy of T staging of gastric cancer on endoscopic images using computer-aided pattern recognition about 344 patients who under-

went gastrectomy or endoscopic resection. Although the overall diagnostic accuracy was 64.7% due to the relatively lower accuracy for advanced T staging, the diagnostic accuracy and positive predictive value in the T1 staging was nearly equal to that obtained by endoscopic diagnosis (77.2% and 80.1%, respectively). Even though this is a primitive study, this modality has unique and remarkable merit in that this might lead to standardization and globalization of medicine, since physicians are required to have no specialized techniques or special knowledge to make a diagnosis.

MAGNIFYING ENDOSCOPY WITH NARROW-BAND IMAGING

The development of magnifying endoscopy with narrow-band imaging (ME-NBI) has allowed simple and clear visualization of vascular architecture and surface structure of the superficial mucosa in the gastrointestinal tract^[13]. In the field of gastric cancer, many studies demonstrated the usefulness of ME-NBI in distinguishing EGC from noncancerous lesions, evaluation of histologic types of EGC, and determination of tumor margin in EGC^[14-16]. However, whether ME-NBI is useful in predicting depth of invasion in EGC is unclear. In Asian-Pacific consensus which was published in 2011, a panel of experts denied the statement that ME-NBI is useful in predicting depth of gastric cancer^[17]. The panel reasoned that unlike superficial esophageal squamous carcinoma, for EGC the invasive tissue is often not exposed at the surface and mucosal structure remains, even when cancer invades the submucosa; therefore it is difficult to estimate reliably the depth of invasion by surface appearance only. However, thereafter, several studies have reported positive results on this subject. Li *et al*^[18] classified ME-NBI findings of suspected gastric lesions into 3 types: clear regular (type A), obscure irregular (type B), and no (type C) surface patterns and microvascular architecture. When a lesion was classified into type B or C pattern, the sensitivity, specificity, positive predictive value, and negative predictive value predicting deep submucosal invasion more than sm1 in EGC was 72.7%, 80.5%, 50.0%, and 91.7%, respectively; the total accuracy was 78.9% (95%CI: 66.0%-87.8%). Kobara *et al*^[19] reported that ME-NBI findings of non-structure, scattery vessels and multi-caliber vessels can possibly serve as indicators of deep submucosal invasion in differentiated and depressed-type of EGC. Kikuchi *et al*^[20] showed that when the presence of dilated vessels was considered a diagnostic criterion for submucosal EGC, diagnostic accuracy, sensitivity, and specificity were 81.5%, 37.5%, and 88.3%, respectively. Yagi *et al*^[21] suggested that in multivariate logistic regression analysis ME-NBI findings of a blurry mucosal pattern (OR = 12.15, 95%CI: 3.45-42.76, *P* = 0.000) and an irregular mesh pattern (OR = 22.55, 95%CI: 4.22-120.45, *P* = 0.000) were independent predictors of submucosal invasion in differentiated EGC. However, several limitations in these studies were also pointed out^[22]. First, the

absolute number of reports is too small to reach any kind of significance or consensus. Second, mostly the depressed and differentiated types of EGC have been studied. Third, applied criteria of ME-NBI to evaluate the depth of invasion varied according to the studies and inter-observe agreement of ME-NBI findings for these criteria was not certainly validated. In addition, some studies focused on differentiation between T1a and T1b and others tried to distinguish sm1 EGC from sm2/3 EGC. Nevertheless, because it is very important to predict depth of invasion in EGC to decide whether it could be treated by ESD or not^[23,24], the usefulness of ME-NBI in T staging of EGC deserves further investigation.

CONTRAST-ENHANCED ULTRASOUND

Conventional abdominal ultrasound is an attractive diagnostic method because of its general availability, simplicity and non-invasiveness. However, the value of this modality in staging of gastric cancer remains unclear and there are limited numbers of published studies. This is mainly originated from the relatively low diagnostic accuracy of T staging compared with other modalities^[25]. Double contrast-enhanced ultrasound is a transabdominal ultrasound technique using both intravenous and intraluminal contrast to enhance sonographic visualization. Recently, Zheng *et al.*^[26] compared retrospectively the staging accuracy of double contrast-enhanced ultrasound with EUS in the 162 gastric cancer patients. Double contrast-enhanced ultrasound was comparable to EUS in tumor depth evaluation (overall accuracy for T staging: 77.2% *vs* 74.7%) and superior to EUS in N staging (overall accuracy: 78.4% *vs* 57.4%, $P = 0.001$).

Very few studies have addressed the role of contrast-enhanced ultrasound (CEUS) using intravenous injection of microbubble contrast media in detection of metastatic gastric cancer. Most studies regarding the usefulness of CEUS for detection of metastatic cancer have been for liver metastases, since CT has limitations to detect and characterize subcentimetric liver lesions. Although it was not gastric cancer-specific study, Piscaglia *et al.*^[27] reported that CEUS is more sensitive than conventional ultrasound in the detection of liver metastases and could be complementarily used with CT to achieve maximum sensitivity in M staging of gastrointestinal cancer. Recently, Laghi *et al.*^[28] reported that CEUS can be helpful in demonstrating or excluding metastases in cancer patients with subcentimetric, indeterminate focal liver lesions detected by MDCT. The authors applied CEUS to the patients in whom ultrasound failed to recognize any abnormality or cystic imaging for indeterminate focal liver lesions by MDCT. CEUS recognized additional liver metastases in 8 cases, but it failed to detect 3 metastatic and benign lesions. In addition, this study also was not gastric-cancer specific; gastric cancer was the primary cancer only in 11 among 132 subjects. However, because single or double contrast-enhanced ultrasounds are noninvasive modalities,

they deserve to be evaluated for the staging of gastric cancer.

CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND

Although contrast-enhanced EUS was introduced in the early 1990s, most reports have been regarding pancreatic lesions^[29,30]. By contrast, the role of contrast-enhanced EUS in gastric cancer staging is unclear. Already more than 10 years ago, Nomura *et al.*^[31] performed EUS and additional contrast-enhanced EUS for 30 gastric cancers and reported that diagnostic accuracy for T staging of gastric cancer improved from 76.7% for EUS to 90% for contrast-enhanced EUS. However, we could not find other articles on this subject, thereafter. Further studies are strongly required.

MAGNETIC RESONANCE IMAGING

Even though there have been only a few studies regarding the usefulness of magnetic resonance imaging (MRI) for gastric cancer staging, meta-analysis showed that MRI had higher accuracy for T staging (83%) and similar accuracy for N staging (53%) compared to other staging modalities such as CT and PET^[25].

Recently, diffusion-weighted (DW)-MRI which had been generally utilized in the early diagnosis of brain ischemia has been studied in the diagnosis of solid tumor. DW-MRI applies a pair of diffusion-weighted gradient pulses to generate signals that are sensitive to localized water diffusibility and thus permit the cellular density of the tissue to be indirectly measured^[32]. In cancerous tissues, the Brownian motion of water molecules is confined as a result of the reduced interspace caused by proliferated cells and interstitial substances^[33]. Therefore, cancerous tissues display higher signal intensity on DW-MRI than normal tissue. For diagnosis of gastric cancer, Shinya *et al.*^[34] first suggested the potential efficacy of DW-MRI in a pilot study on 15 patients. Thereafter, Zhang *et al.*^[35] showed the addition of DW-imaging to T1/T2-weighted MRI could more exactly differentiate Borrmann type IV advanced gastric cancer from poorly distended stomach wall. Recently, Liu *et al.*^[36] reported the usefulness of DW-MRI in T staging of gastric cancer on larger subjects. When two radiologists independently interpreted T2-weighted, contrast-enhanced and DW-MRI in 51 patients with gastric cancer, the addition of DW-MRI significantly increased overall accuracy of T staging (76.5% *vs* 88.2%, $P = 0.031$). The authors emphasized that DW-MRI could overcome the over-estimation problem of T staging in advanced gastric cancer. However, the staging accuracy of DW-MRI for EGC was relatively low in this study. In addition, the staging criteria using DW-MRI has not been unified. Therefore, to prove the diagnostic efficacy of DW-MRI on gastric cancer staging, validation studies on larger subjects are required.

SENTINEL NODE MAPPING

In countries like South Korea and Japan where the rate of EGC is relatively high, minimally invasive gastric surgeries have been performed increasingly. Laparoscopic function-preserving gastrectomy including partial gastrectomy, segmental gastrectomy, and proximal gastrectomy would be expected to increase patients' quality of life by reducing late complications of gastric surgery, such as dumping syndrome and body weight loss. However, because function-preserving gastrectomy are performed with limited stomach resection and lymph node dissection, the absence of skip metastasis in the 2nd or 3rd compartment of regional lymph nodes is prerequisite to apply these procedures widely. To solve this problem, sentinel node (SN) mapping which is a novel diagnostic tool for the identification of clinically undetectable lymph node metastasis and SN navigation surgery based on SN mapping have been studied in patients with EGC^[37]. Clinical application and validity of SN mapping in patients with EGC has been a controversial issue for years. However, a recent meta-analysis on 38 studies including 2128 patients demonstrated acceptable diagnostic accuracy of SN mapping for lymph node status^[38]. The authors of this meta-analysis reported that pooled SN identification rate, sensitivity, negative predictive value, and accuracy were 93.7%, 76.9%, 90.3%, and 92.0%, respectively.

Sentinel node mapping and SN navigation surgery are gaining more and more supporting evidence for possible therapeutic option for EGC, especially cT1N0M0. However, further studies are needed to confirm the best procedure and standard criteria. At present, dual-tracer method with a radioactive colloid and blue dye is considered the most reliable method for SN mapping. Sentinel node detection rate with this method was reported as high as 97.5%^[39]. By contrast, SN detection rate of other modalities like preoperative imaging of SNs using CT lymphography is still relatively lower than with conventional dual-tracer method^[40]. Several newer methods like indocyanine green (ICG) infrared imaging^[41] and ICG fluorescence imaging^[42] have been introduced to improve the accuracy of SN detection by endoscopic dye-tracer.

Although the clinical significance of micrometastasis including isolated tumor cells in SNs of patients with EGC remains unclear^[43], histopathology and molecular analysis methods to detect micrometastasis in these patients have been steadily studied. The two main methods for detection of lymph node micrometastasis are immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR). Recently, Shimizu *et al*^[44] reported a more rapid and sensitive real-time RT-PCR system with multiple markers (cytokeratin-19, cytokeratin-20, and carcinoembryonic antigen) to detect micrometastasis. The authors showed that 27% (28/103 patients) of EGC had negative histopathological but positive RT-PCR findings. However, the time (80 min) to gain results is still too long to use in the intraoperative diagnosis of SN and more studies are needed to improve this problem. Yano

et al^[45] recently compared the efficacy of ICG and infrared ray laparoscopy system with immunohistochemistry for anti-cytokeratin antibody in SN navigation surgery. In 130 patients with EGC, immunohistochemistry staining additionally detected 15 patients with micrometastasis compared with hematoxylin and eosin staining (31 patients *vs* 16 patients). However, all 27 lymph nodes in these patients with metastasis by immunohistochemistry staining but not by hematoxylin and eosin staining were micrometastasis or less and included in the SN. Therefore, the authors concluded that ICG-positive lymphatic basin dissection by SN navigation surgery with infrared ray observation seems to be an adequate method of lymph node dissection for gastric cancer.

DIAGNOSTIC LAPAROSCOPY

FDG-PET has been suggested appropriate staging modality for distant metastases. The sensitivity/specificity of FDG-PET for detection of metastatic lymph node and distant metastasis were reported as 21%-40%/89%-100% and 35%-74%/74%-99%, respectively^[46]. However, FDG-PET has limitations such as frequent false-negative cases in signet-ring cell carcinoma and the lack of a unified criteria in how to interpret for management decisions^[47]. Therefore, patients with incurable or unresectable gastric cancer are still subjected to non-therapeutic laparotomy. To solve this problem, diagnostic laparoscopy has been advocated by some to be essential in decision-making in advanced gastric cancer^[48]. However, large retrospective series have demonstrated the yield of diagnostic laparoscopy in staging locally advanced gastric cancer to range from 13% to 40%^[49].

For recent years, several new approaches regarding diagnostic laparoscopy have been published. Positive peritoneal cytology has been shown to be an independent predictor for disease recurrence after curative resection and poor overall survival^[50,51]. Positive peritoneal cytology confers the same prognosis as clinical stage IV disease in gastric cancer. Therefore, it has been included in the seventh edition of the American Joint Committee on Cancer staging manual as M1 disease^[52]. However, the sensitivity of conventional cytology examination is lower than 60% due to sampling error^[53,54]. To overcome this problem, several studies have evaluated the clinical significance of RT-PCR in peritoneal lavage fluid in gastric cancer^[55-57]. These studies have demonstrated the increased sensitivity of RT-PCR when compared to cytology for the detection of peritoneal cancer cells. However, these studies have been carried in Asia and in the setting of metastatic disease. Recently, Wong *et al*^[58] additionally demonstrated that RT-PCR for carcinoembryonic antigen increases the detection of subclinical peritoneal disease and is more sensitive than cytology in curatively resected patients at a single Western institution. They collected peritoneal lavage samples prospectively from 156 patients with biopsy-proven gastric cancer undergoing staging laparoscopy. These washings were analyzed by both Papanicolaou

staining and RT-PCR for the carcinoembryonic antigen. Among 118 patients in whom peritoneal disease was not visible at laparoscopy, the rate of PCR-positive was higher than that of cytology-positive (24% *vs* 7%).

Recently, two pilot studies regarding staging laparoscopy using 5-aminolevulinic acid (ALA)-mediated photodynamic diagnosis in advanced gastric cancers were reported in Japan^[59,60]. 5-ALA is an endogenous substance and a natural precursor of the heme pathway. Orally administered 5-ALA is metabolized and accumulated as protoporphyrin IX, which is a photosensitizer. 5-ALA is immediately metabolized to heme in normal cells. On the other hand, since the activity of porphobilinogen deaminase is high in abnormal cells and the activity of ferrochelatase is low, protoporphyrin IX accumulates in the mitochondria in cancer cells^[61]. Oral 5-ALA and intravesically applied 5-ALA derivative have been approved as an optical imaging agent for the enhancement of the intraoperative detection of malignant glioma and bladder cancer, respectively in Europe^[62]. However, only a few experimental cases for gastric cancer patients have been reported^[63]. Kishi *et al*^[59] performed staging laparoscopy using 5-ALA photodynamic diagnosis in 13 patients with serosa-invading advanced gastric cancer, and the detection sensitivity of 5-ALA photodynamic diagnosis was compared to the observations using conventional white light. The tumor detection rate using 5-ALA photodynamic diagnosis was significantly higher than the detection rate using white light (72% *vs* 39%, $P < 0.001$). Murayama *et al*^[60] also applied the same methods in 13 patients with advanced gastric cancer. The accuracy of the fluorescence imaging was greater than that of the white light imaging (100% *vs* 85.7%). In both studies, there were no acute or major complications. These two studies demonstrated that staging laparoscopy with 5-ALA photodynamic diagnosis is safe and improves the diagnostic accuracy for peritoneal metastases in patients with gastric cancer. However, further clinical trials in larger number of subjects are required to generalize the results of these studies.

Percutaneous diagnostic peritoneal lavage (DPL) was initially introduced as a procedure to determine the likelihood of peritoneal penetration and injury to the abdominal viscera in trauma patients. In large studies, DPL has been shown to be rapid, safe, and effective in this setting^[64]. Typically, 1 L of saline is held above the patient and passively infused into the peritoneal cavity through a percutaneous catheter using the Seldinger technique. Following infusion, the empty bag is left to gravity and the effluent is measured for red blood cells and bilirubin to determine the presence of solid organ injury. Patients with positive peritoneal cytology on DPL could be spared from a non-curative radical resection and have expedited access to systemic therapies. Based on this idea, Mezhir *et al*^[65] studied whether DPL can be used to assess peritoneal cytology in patients with gastric cancer for the first time. Patients with gastric cancer were prospectively enrolled to undergo DPL prior to diagnostic laparoscopy.

Saline was instilled through a percutaneous catheter and fluid was collected for cytology. Washings obtained during diagnostic laparoscopy were used as controls. The sensitivity and specificity of DPL was 92% (9/10 cases) and 100% (12/12 cases), respectively. However, there were six patients with negative DPL-cytology who had visible M1 disease diagnosed with diagnostic laparoscopy (DPL evaluation of M1 disease: sensitivity 54.5% and specificity 100%). In addition, DPL was not successful in all patients (technical failure rate: 18.5%). The authors concluded that DPL is a safe method of detecting positive cytology in patients with gastric cancer, however gross M1 disease may be missed without visual inspection. Because of above-mentioned limitations, a larger series of patients would be required to determine the optimal patient population for DPL and the specific role of DPL in the staging workup of patients with gastric cancer.

OTHER NEW APPROACHES

Cui *et al*^[66] reported the first study on identification of genes whose expression patterns can serve as markers for overall cancer stages. Microarray gene-expression data of 54 paired gastric cancer and adjacent noncancerous gastric tissues were analyzed to establish gene signatures for cancer stages. The authors identified two signatures for cancer staging, consisting of 10 genes and 9 genes, respectively. These two genetic signatures provided high classification accuracies at 90.0% and 84.0%, among early (stage I + II) and advanced gastric cancer stages (stage III + IV), respectively. The expression patterns of these signature genes were successfully validated by other public dataset. In addition, the authors identified genes which consistently show high positive or negative correlation with different pathological stages (LANCL3, MFAP2 and PPA1).

So far, scoring systems have been frequently used to predict the outcome of patients with gastric cancer^[67-69]. However, most of these prognostic scoring systems took into account the postoperative pathologic properties of the tumor, so they did not work during preoperative decision-making. To improve the estimation of tumor status and facilitate the stage-dependent treatment planning, Chen *et al*^[70] suggested simple risk score system for prediction of TNM stages in gastric cancer. They prospectively collected clinicopathologic data from 108 curatively resected patients with gastric cancer. The risk score was established on the basis of independent predictive factors for tumor stages and its performance was evaluated by receiver operating characteristic (ROC) analysis. As a result, they found 4 independent factors (serum albumin levels, tumor size, T and N categories determined by helical CT). When a score at 7 was defined as the optimal cut-off point, the sensitivity and specificity for differentiating advanced stage (stage III + IV) from early stage (stage I + II) was 79.6% and 85.2%, respectively. The overall accuracy was 82.4% and the discriminative

ability was also good (the area under the ROC curve, 0.861-0.965). Therefore, the authors suggested that since patients with the risk score ≥ 7 are strongly suspected of having advanced stage of gastric cancer, D2 lymphadenectomy combined with perioperative adjuvant therapy should be recommended for these patients to increase the likelihood of curative resection and reduce the risk of recurrence. However, this study has some limitations in that the authors used the fifth edition of the American Joint Committee on Cancer staging manual. In addition, to apply this risk score in daily clinical practice, validating on another patient series is required.

CONCLUSION

At the present time, there is no single gold standard modality for staging of gastric cancer and several methods have been used complementarily in the each clinical situation. To make up for the shortcomings of conventional modalities such as EUS, CT, and PET-CT or to replace these traditional methods, numerous attempts with new approaches have been made for gastric cancer staging. In addition, for intraoperative staging, several newer methods associated with SN mapping and diagnostic laparoscopy have been studied. However, most studies reporting new staging methods are preliminary and further studies for validation in clinical practice are needed.

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P- Reviewer: Elbahrawy A S- Editor: Ding Y L- Editor: A
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