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TOPIC HIGHLIGHT

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Is endoscopic ultrasonography still the modality of choice in preoperative staging of gastric cancer?

Sung Wook Hwang, Dong Ho Lee

Sung Wook Hwang, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul 110-744, South Korea
Dong Ho Lee, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do 463-707, South Korea
Author contributions: Hwang SW and Lee DH equally wrote the paper.
Correspondence to: Dong Ho Lee, MD, Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi-do 463-707, South Korea. dhljohn@yahoo.co.kr
Telephone: + 82-31-7877008 Fax: +82-31-7874051
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Abstract

The treatment option for gastric cancer is usually based on preoperative staging by imaging modalities. Endoscopic ultrasonography (EUS) and computed tomography (CT) have been used as the diagnostic modality of choice in preoperative staging of gastric cancer. Magnetic resonance imaging (MRI) has been employed in several studies, and (^{18}F) 2-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) has emerged as a new promising imaging modality. The purpose of this article is to provide summarized information on preoperative staging using EUS, multi-detector row CT (MDCT), MRI and PET for gastric cancer. In T staging, both EUS and MDCT show high accuracy. MRI seemed to have better performance, but the number of MRI studies is limited. FDG-PET is not able to properly evaluate the depth of invasion. In N staging, the diagnostic accuracy of EUS, MDCT and MRI is not sufficient. In preoperative M staging, MDCT and FDG-PET showed similar diagnostic accuracies. FDG-PET/CT fusion could be expected to show better performance in the future. Physicians should keep in mind that each diagnostic modality has advantages and limitations and choose an appropriate diagnostic strategy tailored for each patient.

Key words: Gastric cancer; Endoscopic ultrasonography; Computed tomography; Magnetic resonance imaging; Positron emission tomography

Core tip: Endoscopic ultrasonography (EUS) and computed tomography (CT) have been used as the diagnostic modality of choice in preoperative staging of gastric cancer. Magnetic resonance imaging (MRI) and (^{18}F) 2-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) were also employed. The purpose of this article is to provide concisely summarized information in preoperative staging of EUS, multi-detector row CT (MDCT), MRI and PET for gastric cancer. In T staging, both EUS and MDCT show high accuracy. In N staging, the diagnostic accuracy of EUS, MDCT and MRI is not sufficient, but the specificity of FDG-PET was the highest among the modalities.

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INTRODUCTION

Gastric cancer is one of the most common cancers and is related with poor prognosis and high mortality[1,2]. The treatment option for gastric cancer is usually based on the preoperative staging by imaging modalities. With curative intent, radical surgery is still the mainstay of the

treatment[3-5]. However, new therapeutic options such as endoscopic mucosal resection (EMR) and neoadjuvant chemotherapy have been introduced[4,6-9], and precise preoperative staging for gastric cancer is becoming increasingly important. An unnecessary treatment could be avoided with accurate preoperative staging. The 5-year survival of patients with gastric cancer ranges from 5% to 95%, and the prognosis of gastric cancer has been established to depend on the depth of invasion (T stage), lymph node (LN) status (N stage) and distant metastasis (M stage)[1,10-12]. Therefore, the optimal assessment of the preoperative staging in gastric cancer is crucial for appropriate treatment planning.

Over the past decades, endoscopic ultrasonography (EUS) has been used as the diagnostic modality of choice in preoperative T and N staging of gastric cancer[13-15]. Especially, EUS is able to differentiate the layers of the gastric wall and has been considered as the modality with higher accuracy in assessing the depth of invasion of gastric cancer compared to other modalities[14,15]. However, there were several reports concerning understaging and overstaging of the depth of invasion and the nodal invasion, which may be influenced by inflammation around the tumor or lymph nodes[16]. With high frequency transducer, the visualization of more distant LN is difficult using EUS due to the limited depth of penetration, and metastatic diseases are also not properly assessed by EUS[14,17]. In contrast, computed tomography (CT) was routinely used to detect the presence of distant metastasis[18]. Moreover, recent advanced technologies such as multi-detector scanners (Multi-Detector row Computed Tomography, MDCT) have provided better performance in preoperative staging of gastric cancer, in which the results were comparable with those using EUS[14,15,19,20]. In addition, magnetic resonance imaging (MRI) has been employed for preoperative gastric cancer staging in several studies[14,15,19,21], and (^{18}F) 2-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) has emerged as a new promising imaging modality[22].

Recently, numerous original studies regarding the preoperative staging of gastric cancer have been reported, and several meta-analysis and systematic reviews of EUS, MDCT, MRI and FDG-PET have been published[14,15,17,19,22-25]. However, a simple review concisely considering all four modalities is limited in the literature. The purpose of this article is to provide summarized information on preoperative gastric cancer staging using EUS, MDCT, MRI and PET.

EUS IN PREOPERATIVE GASTRIC CANCER STAGING

EUS has been used since the early 1980s and has been considered as the imaging modality of choice in locoregional staging for gastric cancer[14,20,26]. Especially, EUS was reported to have very high accuracy of T staging in the 1990s, ranging from 75% to 92%[20,27]. However, EUS is operator-dependent, and several recent studies showed a lower accuracy of EUS compared to the previous reports[28,29], indicating the possibilities of publication bias. In a recent prospective study with 116 German patients, the overall accuracy for T staging was found to be 78%: 80% for T1, 63% for T2, 95% for T3, 83% for T4[27]. In a prospective study conducted in South Korea, the overall accuracy for T staging was 87.5%: 87.1% for T1, 50.0% for T2, 92.9% for T3, 100% for T4[30]. The sensitivity and specificity were 82.4% and 96%, respectively[30]. Ang *et al*[31] retrospectively reported the overall accuracy of 77.2% in Singapore: 82.9% for T1, 57.1% for T2, 81.8% for T3. Shimoyama *et al*[32] retrospectively reported that the overall accuracy of T staging was 71% in 45 Japanese patients with gastric cardia cancer.

For the appropriate evaluation of the usefulness of EUS in preoperative gastric cancer staging, meta-analysis and systematic reviews were needed, and several studies have been reported[14,15,17,23-25]. The key findings from the meta-analysis and systematic reviews are summarized in Tables 1 and 2. With 23 studies using EUS, Kwee *et al*[14] reported that the overall accuracy of T staging varied between 65% and 92.1%, and in assessing serosal invasion, the sensitivity and specificity were between 77.8% and 100% and between 67.9% and 100%, respectively. Puli *et al*[23] demonstrated pooled sensitivity and specificity of each T stage from 22 EUS studies, and interestingly, when the accuracy of EUS was calculated according to the three periods of time, the sensitivity of EUS for T1 staging was found to have been improved over the past two decades (56.3% in "1986 to 1994", 82.2% in "1995 to 1999", and 84.8% in "2000 to 2006")[23]. Mocellin *et al*[24] reported that, in the subgroup analysis, only the publication year was found to have a significant impact on EUS performance. The average sensitivity and specificity of studies conducted before the year 2000 were higher than those of studies conducted after the year 2000 (93% *vs* 80%, 94% *vs* 89%, respectively)[24]. Cardoso *et al*[25] did not show any association between EUS performance and EUS annual volume in the subgroup analysis.

Miniprobe EUS, which is performed by conventional endoscopy with small and high frequency probes (12-20 MHz) through biopsy channel, is widely used in preoperative staging[14]. The high frequency provides excellent resolution of the intestinal wall layers, but the depth of penetration is limited. In late 1990s, Okamura *et al*[33] reported that the diagnostic accuracy of T staging with miniprobes was 71.7%. Hünerbein *et al*[34] retrospectively reported that the overall accuracy of T staging with miniprobe EUS was 88% in a recent study. The accuracy of miniprobes may decrease with increasing tumor size due to the limited penetration[34], and therefore, the miniprobe EUS was frequently used for early gastric cancer in the clinical practice, especially for assessing the possibility of endoscopic resection[17]. In two Japanese prospective studies, the accuracies for detecting mucosal cancer with miniprobes were 69% and 71%[35,36]. In a systematic review including 18 studies concerning the differentiation of mucosal lesion, subgroup analysis

Table 1 Summarized results of endoscopic ultrasonography in preoperative T staging[1]

Ref.	Year	Number of studies (*n*)	Stage	Accuracy (pooled, %)	Sensitivity (pooled, %)	Specificity (pooled, %)
Kwee *et al*[14]	2007	23	overall T	265-92.1	-	-
Puli *et al*[23]	2008	22	T1	-	88.1	100.0
			T2	-	82.3	95.6
			T3	-	89.7	94.7
			T4	-	99.2	96.7
Mocellin *et al*[24]	2011	54	T1-2 *vs* T3-4	-	86.0	91.0
			T1	-	83.0	96.0
			T2	-	65.0	91.0
			T3	-	86.0	85.0
			T4	-	66.0	98.0
Cardoso *et al*[25]	2012	22	Overall T	75 ([2]56.9-87.7)	-	-
			T1	77 ([2]14-100)	-	-
			T2	65 ([2]24-90)	-	-
			T3	85 ([2]50-100)	-	-
			T4	79 ([2]22-100)	-	-

[1]Based on meta-analyses and systematic reviews; [2]Range value.

Table 2 Summarized results of endoscopic ultrasonography in preoperative N staging[1]

Ref.	Year	Number of studies (*n*)	Stage	Accuracy (pooled, %)	Sensitivity (pooled, %)	Specificity (pooled, %)
Puli *et al*[23]	2008	22	N1	-	58.2	87.2
			N2	-	64.9	92.4
Kwee *et al*[15]	2009	30	N	-	16.7-98.8[2]	48.4-100[2]
Mocellin *et al*[24]	2011	48	N	-	69.0	84.0
Cardoso *et al*[25]	2012	22	N	64 ([2]30-90)	74 ([2]16.6-96.8)	80 (57.1-100)[2]

[1]Based on meta-analyses and systematic reviews; [2]Range value.

showed that the type of EUS transducer (conventional *vs* miniprobe) did not cause between-study heterogeneity[17]. Similarly, in a Korean retrospective study, the overall accuracies of T staging according to the EUS transducer types were not significantly different (conventional 7.5 MHz, 71.1%; 12 MHz, 78.4%; 20 MHz, 60.9%; miniprobe 20 MHz, 68.8%)[37]. In most studies, miniprobes were usually used together with conventional EUS based on the physician's decision[17,37,38], and thus the role of miniprobe EUS in preoperative gastric cancer staging needs to be clarified in the future.

In assessing LN metastasis (N staging), Puli *et al*[23] reported lower diagnostic performance compared to T staging (Table 2). The pooled sensitivity and specificity for N1 were 58.2% and 87.2%, while the pooled sensitivity and specificity for N2 were 64.9% and 92.4%, respectively. The other three studies also demonstrated similar results: the pooled accuracy reported by Cardoso *et al*[25] was 64%. In EUS, the LN metastasis is usually diagnosed based on the morphological characteristics, echogenicity and size of LN[15]. In the previous study, over half of the metastatic lymph nodes were reported to be 5mm or less in diameter[39]. Thus, LN size, which is most commonly utilized in N staging of EUS among the criteria in practice, is not a reliable criterion of LN metastasis, and the low performance of EUS in N staging could be explained.

With the advanced technology of EUS devices, EUS-guided Fine Needle Aspiration (FNA) can take a sample of LN both safely and accurately[40,41]. In the literature, the sensitivity and specificity of EUS-FNA for detecting metastatic LNs ranged from 63% to 98% and from 87.5% to 100%, respectively[40]. The accuracy for evaluating peri-intestinal LN by EUS-FNA was reported from 86% and 95%[42], and the accuracy of N staging for esophageal cancer by EUS-FNA was 89%[43]. The data regarding the role of EUS-FNA for preoperative gastric cancer staging has been very limited in the literature, and recently, Hassan *et al*[41] reported their experience in 81 gastric cancer patients in whom EUS-FNA was performed. Among 99 lesions, 91 (62%) lesions were found to be malignant, and in 38 of 81 patients (42%), distant metastasis was confirmed by EUS-FNA. By using EUS-FNA in the evaluation of gastric cancer patients, the treatment plan was changed in 15% of the cases, and Hassan *et al*[41] concluded that EUS-FNA was a very important modality and should be integrated as a routine procedure in preoperative gastric cancer staging. Although more data is needed to definitely establish the role of EUS-FNA, this modality could be considered in the clinical setting to avoid unnecessary surgery.

In the past, the importance of EUS for preoperative gastric cancer staging was considered as controversial: some authors believed that preoperative EUS was not essential, especially for advanced gastric cancer, because the principle management of these patients was surgery

Table 3 Summarized results of multi-detector row computed tomography in preoperative TNM staging[1]

Ref.	Year	Number of studies (*n*)	Stage	Accuracy (pooled, %)	Sensitivity (pooled, %)	Specificity (pooled, %)
Kwee *et al*[14,15]	2007	6	Overall T	[2]77.1-88.9	-	-
	2009	10	N	-	[2]62.5-91.9	[2]50.0-87.9
Seevaratnam *et al*[19]	2012	32	Overall T	80.4	-	-
			T1	75.2	-	-
			T2	80.0	-	-
			T3	84.5	-	-
			T4	78.8	-	-
			N	67.1	75.8	78.8
			M	82.2	-	-

[1]Based on meta-analyses and systematic reviews; [2]Range value.

or palliative treatment. However, the advance of imaging modalities has provided more reliable preoperative diagnosis avoiding unnecessary surgery, and new therapeutic options such as neoadjuvant could be considered[4,6,7]. In Repiso *et al*[44] retrospective report including 46 gastric cancer patients, the EUS result led to a modification in the later therapeutic approach in 13 patients (28%): based on conventional diagnostic techniques, 33 patients were planned to undergo radical gastrectomy, but after EUS 2 and 3 patients had neoadjuvant and palliative treatment, respectively. Chu *et al*[45] prospectively reported that the ascites which had not been detected by CT was detected by EUS in 36 cases (9%) among 402 gastric cancer patients. Lee *et al*[46] also prospectively reported that EUS was more sensitive (87.1%) to detect ascites than combined conventional ultrasonography and CT (16.1%) and operative findings (40.9%). These results support the usefulness of preoperative EUS even in advanced gastric cancer.

MDCT IN PREOPERATIVE GASTRIC CANCER STAGING

In terms of locoregional staging, the diagnostic accuracy of conventional CT was not high, compared to that of EUS[19,20]. The overall accuracy of T staging ranged from 43% to 82%[14]. Instead, conventional CT was usually used to detect the presence of distant metastasis. With the introduction of multi-detector, faster imaging time, less respiratory artifact, thinner imaging thickness and multiplanar reconstruction (MPR) became feasible, and more detailed preoperative staging of gastric cancer could be performed by MDCT[47]. The recent studies using MDCT for preoperative staging of gastric cancer have shown improved accuracy, approaching that of EUS[14,15,19,20,48]. In a prospective study with 126 Korean patients, the overall accuracy for T staging was 77% with transverse CT imaging and 84% with volumetric CT imaging[49]. The overall accuracy for N staging was 62% with transverse imaging and 64% with volumetric imaging. Stabile Ianora *et al*[50] reported that the accuracy of T staging using MPR images was 85% in 65 Japanese patients. In an Italian study, the accuracies of T and N stage in MDCT were 88.9% and 70.4%, respectively. Bhandari *et al*[30] showed that, when directly comparing the diagnostic accuracies of EUS and MDCT, the accuracies of T staging in EUS and MDCT were 87.5% and 83.3%, and the accuracies of N staging were 79.1% and 75.0%, respectively. There was no significant difference between MDCT and EUS. Our group also retrospectively reported that the overall accuracies of T staging in EUS and MDCT were 61.7% and 63.8%, and the overall accuracies of N staging were 66% and 62.8%, respectively[20]. In addition, the performance of EUS and MDCT for large lesions and lesions located at cardia and angle had significantly lower accuracies[20]. For early gastric cancer with ulceration, EUS showed a significantly lower accuracy compared to lesions without ulceration (30.8% *vs* 93.3%), while the accuracy of MDCT did not differ between lesions with and without ulceration (61.5% *vs* 86.7%). These results suggest that the precise T and N staging conducted by MDCT may be useful in some gastric cancer patients with unclear EUS results, although more EUS and MDCT comparison studies are needed.

The key findings of meta-analyses regarding the diagnostic performance of MDCT for gastric cancer are summarized in Table 3. Kwee *et al*[14] reviewed the six MDCT studies, and the overall MDCT accuracy for T staging was from 77.1% to 88.9%. The sensitivity and specificity for serosal invasion varied between 82.8% and 100% and between 80% and 96.8%, respectively. With 32 studies, Seevaratnam *et al*[19] reported pooled accuracy of CT in preoperative TNM staging, and when the pooled accuracy of CT scanners with < 4 detectors was compared to that with ⩾ 4 detectors, CT scanners with ⩾ 4 detectors showed better results of T staging as shown in Table 3. The performance of T staging with CT scanners using MPR images was also significantly improved: overall T, 81.9%; T1, 76.4%; T2, 77.7%; T3, 85.3%; T4, 83.5%. However, the detector number and additional MPR images did not influence N or M staging results. Similar to EUS, because the nodal assessment is usually based on the size in MDCT, the limitation of diagnostic criterion of LN metastasis in EUS could also exist in MDCT[15,19].

Table 4 Performance of magnetic resonance imaging in preoperative T and N staging

Ref.	Year	Number of patients (*n*)	Stage	Accuracy (%)	Overstaging (%)	Understaging (%)
Sohn *et al*[53]	2000	30	Overall T	73.3	6.7	20
			N	55.2	10.3	34.5
Kang *et al*[51]	2000	46	Overall T	82.6	2.2	15.2
			N	52.2	17.4	30.4
Wang *et al*[54]	2000	33	Overall T	87.9	6	6
Kim *et al*[52]	2000	26 (AGC)	Overall T	80.7	19.2	0
			N	65.4	0	34.6
Zhong *et al*[55]	2005	16	Overall T	64.3	14.3	21.4
Arocena *et al*[21]	2006	17	Overall T	53	23.5	23.5
			N	50	25	25

MRI IN PREOPERATIVE GASTRIC CANCER STAGING

With MRI, only several prospective studies have been reported in the literatures[21,51-55]. The summarized result is shown in Table 4. The overall accuracy of MRI for T staging ranged from 53% to 87.9%, and the overall accuracy for N staging was from 50% to 65.4%. With three studies using MRI, Kwee *et al*[14] reported that the accuracy for overall T staging varied between 71.4% and 82.6%, and the sensitivity and specificity for detecting serosal invasion varied between 89.5% and 93.1% and between 94.1% and 100%, respectively. The sensitivity and specificity for N staging varied between 54.6% and 85.3% and between 50.0% and 100%[15]. Seevaratnam *et al*[19] demonstrated a similar result including the three MRI studies conducted in the year 2000[51,53,54]: for T staging, pooled overall accuracy, 82.9%; pooled T1 accuracy, 86.3%; pooled T2 accuracy, 76.7%; pooled T3 accuracy, 86.8%; pooled T4 accuracy, 80.2%. The pooled overall accuracy, sensitivity and specificity for N staging were 53.4%, 85.3% and 75.0%, respectively. From the studies, the accuracy of MRI for T staging seemed to be similar or slightly higher compared to EUS and MDCT, in contrast to the low accuracy for N staging[14,15,19]. However, this should be interpreted carefully as all the studies showing such excellent performance were reported in the same early period[51-54]. The fact that reports on MRI in preoperative staging have been rarely reported recently supports this phenomenon. The respiratory motion artifacts, long study time and high cost of MRI imaging are also problematic[14,19]. Thus, MRI is not routinely considered for preoperative staging of gastric cancer in clinical practice.

PET IN PREOPERATIVE GASTRIC CANCER STAGING

FDG-PET is a semi-quantitative method, and the Standardized Uptake Value (SUV) is used to assess the uptake of FDG in cancer[56]. The value is measured by FDG-uptake in a tumor volume normalized on the basis of a distribution volume and is dependent on several factors such as time after FDG injection, tumor size and blood glucose level[56]. Because of the inability to evaluate the depth of invasion, the primary tumor detection rate rather than T staging was usually reported in the previous reports[19,22]. Seevaratnam *et al*[19] revealed a pooled detection rate of 80.4% (from 58.1% to 95.9%), which was considered to be lower compared to those of other modalities. The detection rate in advanced gastric cancer (83%-100%) was higher than in early gastric cancer (26%-63%)[19]. Smyth *et al*[22] reported that the sensitivity and specificity for detection of gastric lesions in several series ranged from 21% to 100% and from 78% to 100%, respectively. As a screening test for gastric cancer, the effectiveness of PET in asymptomatic individuals was disappointing[57,58]. The reported sensitivity was only 10% and the positive predictive value was 8.3%, which meant that FDG-PET was poorly sensitive for detection of gastric cancer in the early stage[57]. Due to the low sensitivity, FDG-PET alone was considered not suitable for primary detection of gastric cancer[56]. Interestingly, the detection rate varies with histological subtype: 65.5%-83% for intestinal type, 41%-79% for non-intestinal type and 0%-78% for signet ring cell carcinoma[19]. This result may reflect that the glucose transporter 1 (GLUT-1) is preferentially expressed on the intestinal type of gastric cancer[59].

In assessing LN status, the results of FDG-PET studies are summarized in Table 5. The sensitivity of FDG-PET for N staging was generally low, ranging from approximately 23% to 60%[22,60-63]. A pooled sensitivity of 40.3% was reported by Seevaratnam *et al*[19]. Thus, despite the higher specificity than those of other modalities, the possibility of inaccuracies for detecting true metastatic nodes should always be considered. FDG-PET/CT fusion provides more accurate localization with increased FDG uptake, and it seemed to overcome some limitations of FDG-PET alone mentioned above. However, the FDG-PET/CT study conducted by Yang *et al*[64] did not demonstrate significantly improved sensitivity and specificity.

In terms of metastatic disease, Seevaratnam *et al*[19] showed that the overall accuracy did not differ between MDCT and PET (82.2% *vs* 88.2%). Furthermore, PET is not reliable for peritoneal metastasis, which is a common site of gastric cancer spread; the sensitivity was from 9% to 50%[22,61]. In contrast, the sensitivity of CT for peritoneal disease was reported to be approximately 80%[22].

Table 5 Performance of positron emission tomography in preoperative N staging

Ref.	Year	Number of patients (*n*)	Staging	Accuracy (%)	Sensitivity (%)	Specificity (%)
Mochiki *et al*[60]	2004	85	N	-	23.3	100
Tian *et al*[63]	2004	30	N	73.3	52.9	100
Chen *et al*[61]	2005	68	L-LN	63	56	92
			D-LN	95	88	96
Yun *et al*[69]	2005	81	N1	56	34	96
			N2	72	34	96
			N3	95	50	99
Kim *et al*[62]	2006	73	N	-	40	95.2
Mukai *et al*[70]	2006	62	N	67.7	34.5	97
Yang *et al*[64] (PET/CT)	2008	78	N	55.1	31	97.2

L-LN: Local lymph node; D-DN: Distant lymph node; PET: Positron emission tomography; CT: Computed tomography.

However, FDG-PET/CT fusion was reported to be able to detect occult metastatic lesions in approximately 10% of patients with locally advanced gastric cancer in a prospective study[65]. Among 113 patients, 11 patients were found to have metastatic disease by using FDG-PET/CT, which was not detected by CT. In a retrospective study with 396 gastric cancer patients, 9 cases (2.2%) were diagnosed as metastatic by FDG-PET/CT[66]. Therefore, the role of FDG-PET/CT for metastatic disease should be determined with more advanced technologies in the future.

CONCLUSION

In preoperative T staging, both EUS and MDCT show high accuracy for overall and each T stage. MRI seemed to have better performance, but the number of MRI studies is limited. FDG-PET is not able to properly evaluate the depth of invasion, and it showed low detection rate of gastric cancer. In preoperative N staging, the diagnostic accuracy of EUS, MDCT, and MRI is not sufficient to appropriately assess LN status. In preoperative M staging, MDCT and FDG-PET showed similar diagnostic accuracies. FDG-PET/CT fusion could be expected to show better performance in the future.

The National Comprehensive Cancer Network (NCCN) guideline for gastric cancer indicates that clinical staging has greatly improved with the availability of diagnostic modalities such as EUS, chest/abdomen/pelvis CT, PET/CT, MRI and laparoscopic staging[67]. This indicates that the treatment and prognosis of patients with gastric cancer could be largely influenced by the quality of preoperative imaging[67,68]. However, the guideline did not specify a modality of choice. Instead, a various combination of the diagnostic modalities is routinely used for preoperative staging in clinical practice because the modalities are complementary to each other[19]. Physicians should keep in mind that each diagnostic modality has advantages and limitations and choose an appropriate diagnostic strategy tailored for each patient.

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