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TOPIC HIGHLIGHT

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Modern imaging techniques for preoperative detection of distant metastases in gastric cancer

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Abstract

A substantial portion of patients with newly diagnosed gastric cancer has distant metastases (M1 disease). These patients have a very poor prognosis and it is generally accepted that they should be treated with noncurative intent. Because it dramatically changes prognosis and treatment plans, it is very important to diagnose distant metastases. In this article, the definition, pathways, incidence and sites of distant metastases in gastric cancer are described. Subsequently, the current performance of imaging in detecting distant metastases in newly diagnosed gastric cancer is outlined and future prospects are discussed.

Key words: Gastric cancer; Ultrasonography; Distant metastases; Metastatic disease; Imaging; Computed tomography; Positron emission tomography; Magnetic resonance imaging; Scintigraphy

Core tip: Computed tomography is currently the primary imaging modality for M staging. Evaluation of ascites by endoscopic ultrasonography is useful because it has a high probability for the presence of peritoneal metastases. Staging laparoscopy is still necessary in patients with locally advanced disease with no definite evidence of peritoneal metastases at imaging. The roles of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography and magnetic resonance imaging need to be further explored. New imaging techniques and strategies are needed to improve M staging.

INTRODUCTION

Gastric cancer is the fifth most common malignancy in the world[1]. In 2012, 952000 new cases were diagnosed and 723000 people died of the disease worldwide[1]. The management of gastric cancer is complex and requires a multidisciplinary approach[2]. Selected patients with early gastric cancer can be treated with endoscopic resection[2,3]. In patients with more locally advanced disease but without distant metastases, perioperative chemotherapy, (sub)total gastrectomy and regional lymph node dissection is the current acceptable standard of care[2-4]. However, a substantial portion of patients with newly diagnosed gastric cancer has distant metastases (M1 disease), which incurs a very poor prognosis, with a median overall survival of only 6.2 mo[5]. Although some selected patients with solitary liver metastases may be treated by surgical resection[6,7], it is generally accepted that patients with M1 disease are incurable and that they should be treated with noncurative intent[2,3]. Because it dramatically changes prognosis and treatment plans, it is very important to diagnose distant metastases. In this article, the definition, incidence and sites of distant metastases in gastric cancer are described. Subsequently, the current performance of imaging in detecting distant metastases in newly diagnosed gastric cancer is outlined and future prospects are discussed.

DEFINITION, PATHWAYS, INCIDENCE AND SITES OF DISTANT METASTASES

According to both the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual[8] and the 3rd edition of the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (JGCA)[9], M1 disease is defined as the presence of positive peritoneal cytology or metastasis to sites other than regional lymph nodes. The para-aortic lymph node region is defined as the terminal nodes of the stomach; these nodes and beyond are classified as M1 nodes[8,9].

Gastric cancer can spread to the peritoneum *via* the exfoliation of free cancer cells from tumor which has invaded the gastric serosa[10]. Distant lymph nodes are affected by spread through the lymphatic pathways. Liver metastases occur by hematogenous spread, with the portal vein being the major conduit. Metastases to the ovaries in women, also known as Krukenberg tumors, presumably occur by lymphatic spread[11]. The lungs and bones may be affected by both hematogenic and lymphatic spread[12-14].

The higher the T and N stages at the time of diagnosis, the higher the incidence of synchronous distant metastases. In a Korean study in 2283 consecutive patients with newly diagnosed gastric adenocarcinoma, 16% had distant metastases and more than two organs were involved in 19% at the time of gastric cancer diagnosis[15]. In a study from the United Kingdom by Sarela *et al*[16], 32% of 211 consecutive patients with newly diagnosed gastric adenocarcinoma had distant metastases. In a large Canadian study involving 2424 consecutive patients diagnosed with gastric adenocarcinoma, even as much as 59% had synchronous distant metastases, which were present at more than one site in 42%[5]. The significant lower incidence of distant metastases in the first-mentioned Korean study[15] is probably because gastric cancer is generally detected at earlier stages by mass screening in this country[17].

Peritoneal seeding is most common site of distant metastasis (61%-80%[5,15,16]), followed by distant lymph nodes (44%-50%[5,15]) and the liver (26%-38%[5,15,16]). Other, less common sites of distant metastases are the lung (10%), bone (6%), ovary (2%), abdominal wall (2%), brain (< 0.4%), and prostate (< 0.4%)[5]. In Sarela *et al*[16]'s study, M1 disease was limited to the peritoneum in 58%, whereas 20% had exclusively nonperitoneal distant metastasis mainly involving the liver (82%), lung (9%) and bone (9%).

LITERATURE SEARCH

Articles concerning the performance of imaging in detecting distant metastases in newly diagnosed gastric cancer were retrieved. Data for this review were identified by a computer-aided search in the PubMed/MEDLINE database. The title and/or abstract terms (gastric cancer OR stomach cancer) AND [(ultrasound OR ultrasonography OR US) OR (computed tomography OR CT) OR (bone scan OR scintigraphy OR SPECT OR single-photon emission computerized tomography OR MDP OR MIBI OR sestamibi OR Tc99m OR 99mTc) OR (fluorodeoxyglucose OR 2-fluoro-2-deoxy-D-glucose OR FDG OR positron emission tomography OR positron-emission tomography OR PET) OR (magnetic resonance OR MR imaging OR MRI OR NMR)] AND (metastasis OR metastases OR metastatic OR TNM) were used. Bibliographies of relevant articles were screened for other relevant articles. Only articles published up to February 2015 were included. The final selection was based on relevance, as judged by the authors.

IMAGING MODALITIES TO DETECT DISTANT METASTASES

Endoscopic ultrasonography

In endoscopic ultrasonography (EUS), the ultrasound transducer which is integrated at the distal end of the endoscope provides excellent high-resolution images, although depth of penetration is relatively limited. EUS is primarily used for T staging of gastric cancer[18].

Feng *et al*[19] investigated the M staging accuracy

of EUS and in 610 patients with gastric cancer who underwent surgical resection. Patients who had received endoscopic mucosal resection or endoscopic submucosal dissection and patients with widespread metastatic disease who had not yet undergone surgical resection were excluded. A standard probe with variable frequencies of 5, 7.5, 15 and 20 MHz and a miniprobe with 12 or 20 MHz frequencies was used. The researchers did not report the criteria they used to define M1 disease at EUS. Using histological analysis as standard of reference, indicating that 66 patients (11%) had distant metastases, sensitivity and specificity of EUS were 10.6% and 99.6%, respectively[19]. Chu *et al*[20] studied whether ascites, as detected by EUS using a 12 MHz transducer, predicted the presence of peritoneal metastases in 402 patients with histopathologically confirmed gastric cancer[20]. Histopathological examination after staging laparoscopy showed that peritoneal metastases were present in 66 patients (16%). EUS-detected ascites had a sensitivity and specificity of 35% and 96% for diagnosing peritoneal metastases. Lee *et al*[21] performed a similar study in 301 consecutive patients, using a 7.5 and 12 MHz transducer. They found that EUS-detected ascites had a sensitivity of 73% and a specificity of 84%[21]. The lower sensitivity of Chu *et al*[20]'s study can be explained because they excluded patients with systemic metastases or evidence of ascites on physical examination or CT[20]. In Lee *et al*[21]'s study, sensitivity of EUS in predicting peritoneal metastases was higher than that of transabdominal ultrasography and older generation helical CT combined (73% *vs* 18%), but specificity was lower (84% *vs* 99%)[21].

Standard ultrasonography

Standard external ultrasonography is relatively cheap compared to other imaging modalities. However it has also disadvantages, among which the limited field of view, dependency of image quality on the presence of interfering fat, bowel gas, or bone, and operator dependency.

Stell *et al*[22] investigated the accuracy of transabdominal ultrasonography in detecting peritoneal and hepatic metastases in 103 patients with gastric cancer. A 3.5 MHz curved array transducer was used, but the researchers did not report the criteria they used to define metastases. Histological analysis served as standard of reference, indicating that peritoneal and hepatic metastases were present in 13% and 26% of patients, respectively[22]. Sensitivity and specificity of transabdominal ultrasonography in detecting peritoneal metastases were 23% and 100%, respectively[22]. Sensitivity and specificity in detecting liver metastases were 37% and 95%, respectively[22]. In a later study by Kayaalp *et al*[23], transabdominal ultrasonography was performed in 118 patients with gastric cancer. Presence of peritoneal metastasis was

defined as omental thickening at ultrasonography[23], but the ultrasonographic criteria for liver metastases were not reported. Surgical findings were used as reference standard[23]. Performance of transabdominal ultrasonography did not differ much from Stell *et al*[22]'s study, with sensitivities and specificities in detecting peritoneal and liver metastases of 9% and 98%, and 50% and 98%, respectively[23].

Bhatia *et al*[24] assessed the usefulness of ultrasonography in the detection of cervical lymph node metastases in 233 patients with histologically proven gastric cancer. A 12.5 MHz or 13.5 MHz linear array transducer was used to evaluate cervical lymph nodes with B-mode and power Doppler. Lymph nodes were regarded as metastatic based on size, presence of necrosis, cortical irregularity, shape, echogenicity and peripheral vascularity. Abnormal cervical lymph nodes were detected in 14 patients, of which 7 had true metastatic lymph nodes as confirmed by fine needle aspiration cytology and clinical follow-up[24]. Tumor stage was altered in only 2 of 233 patients (0.9%)[24].

Multidetector-row CT

With current CT scanners, thin-section isotropic images can be obtained in a very short time with large coverage. The use of intravenous nonionic contrast material is needed to detect metastases to the peritoneum and liver.

In the above mentioned EUS study by Feng *et al*[19], all 610 included patients also underwent CT, on either a 16-slice or 64-slice scanner. A multiphasic protocol, including unenhanced scanning and scanning in the arterial and portal-venous phases after intravenous administration of nonionic contrast material, was applied. The scan area included the diaphragmatic domes to the inferior pole of the kidney. The CT criteria to define M1 disease were not reported. The sensitivity of CT in detecting distant metastases was higher than EUS (59.1% *vs* 10.6%, $P < 0.001$), whereas specificity was not different (99.8% *vs* 99.6%, $P = 0.999$)[19].

Pan *et al*[25] performed multiphasic CT on a 16-slice scanner in 350 patients with gastric cancer. Scan coverage of the unenhanced scan and the arterial and delayed phases included the whole stomach, whereas scan coverage of the parenchymal phase included the entire abdomen[25]. The authors did not specifically report which criteria they used to define distant metastases at CT. Thirty-five patients (10%) had distant metastases, as proven by surgical and pathological findings[25]. CT achieved an overall sensitivity and specificity of 14% and 93%, respectively[25]. The reported sensitivities and specificities for each location were as follows: peritoneum 90% and 97%, liver 80% and 99%, distant lymph nodes 91% and 97%, pelvis 100% and 99%, respectively[25].

Kim *et al*[26] studied the accuracy of CT in detecting peritoneal metastases in 498 patients with ≥ T2 stage

gastric cancer using 16-slice of 64-slice scanners. Monophasic scanning after intravenous administration of nonionic contrast material was performed from the diaphragm to symphysis pubis[26]. Fifty-three patients (10.6%) had peritoneal metastases confirmed at surgery and pathology[26]. A diagnosis of peritoneal metastases at CT was based on the presence of findings such as omental cake, ascites, peritoneal thickening with abnormal contrast enhancement, soft tissue plaques or nodules on the peritoneal surface, and soft-tissue stranding in the intraabdominal fat[26]. The interpreters of the CT studies did not use specific guidelines for the integration of the findings. When equivocal and definitely positive CT findings where considered as a positive CT reading, sensitivity and specificity were 50.9% and 96.2%[26]. When only definitely positive CT findings where considered as a positive CT reading, sensitivity and specificity were 28.3% and 98.9%[26].

Pongpornsup *et al*[27] studied the preoperative 64-slice CT scans of 50 gastric cancer patients for the presence of signs suggestive of peritoneal metastases, including ascites, increased peritoneal fat density, peritoneal thickening/enhancement, and peritoneal nodules. The researchers combined several CT criteria, but did not find a combination which achieved superior accuracy over the other[27].

Marrelli *et al*[28] investigated the accuracy of 64-slice CT in the detection of para-aortic lymph node metastases, which are currently classified as M1 nodes[8,9]. In 13 of 92 included patients (14%), histological examination confirmed the presence of para-aortic lymph node metastases[28]. Using a short axis diameter of 8 mm or more as cut-off for metastatic para-aortic lymph nodes, preoperative CT achieved a sensitivity and specificity of 85% and 95%, respectively[28].

Positron emission tomography

Current clinical positron emission tomography (PET) systems are integrated with a CT scanner (PET/CT), which is used for attenuation correction and more precise localization of tracer uptake. ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), the most commonly used PET tracer in clinical oncology, is a glucose analog which is taken up by metabolically active tumor. ^{18}F-FDG PET should be interpreted with caution in patients with mucinous and signet ring cell adeno-carcinoma, since these tumor types show lower ^{18}F-FDG uptake than tubular adenocarcinoma[29,30]. The high content of metabolically inert mucus and/or the lack of expression of the glucose transporter Glut-1 on the cell membrane may be the reasons for reduced ^{18}F-FDG uptake[30,31], which can decrease the sensitivity of ^{18}F-FDG PET in detecting distant metastases.

In a South Korean study in 156 patients with gastric cancer, the accuracy of preoperative ^{18}F-FDG PET/CT and CT in detecting peritoneal metastases was investigated. A focal maximum standardized uptake value of > 2.5 was used as criterion at ^{18}F-FDG PET/CT, but the researchers did not report the criteria they used to define peritoneal metastases at CT. Using pathological findings as reference standard, the researchers found a sensitivity of ^{18}F-FDG PET/CT in detecting peritoneal metastases of 22.2%, which was even lower than the 44.4% sensitivity of CT[32]. Sensitivity of ^{18}F-FDG PET in detecting distant metastases to other sites was only 14.3%[32]. Unfortunately, the researchers did not report the specificity values of both imaging modalities in detecting distant metastases.

Ma *et al*[33] retrospectively investigated the per-formance of ^{18}F-FDG PET/CT and planar bone scinti-graphy in detecting bone metastases in 170 patients who underwent both imaging modalities within 3 mo of each other. Imaging and follow-up were used to confirm the presence of bone metastases. Sensitivity and specificity of ^{18}F-FDG PET/CT *vs*. bone scintigraphy were 93.5% *vs* 93.5%, and 25.0% *vs* 37.5%, respectively. Eighty-eight percent of patients with bone metastasis showed positive findings on two modalities, whereas 15% of solitary bone metastases were positive on ^{18}F-FDG PET/CT only. The authors concluded that ^{18}F-FDG PET/CT was superior to bone scintigraphy for the detection of synchronous bone metastasis. It should be noted that Ma *et al*[33] only included patients who had positive findings at either ^{18}F-FDG PET/CT or bone scintigraphy, both imaging modalities also formed part of the reference standard, and none of their patients had histological confirmation.

Smyth *et al*[34] investigated the potential added benefit of ^{18}F-FDG PET/CT to standard staging, which included CT, EUS, and laparoscopy. In their study, the sensitivity of ^{18}F-FDG PET/CT for the detection of M1 disease was 35% (95%CI: 19%-55%) and specificity was 99% (95%CI: 93%-100%)[34]. Notably, they also showed that sensitivity was lower in all patients compared to patients with FDG-avid primary tumors only (35% *vs* 50%), whereas specificity remained unchanged (99% *vs* 98%)[34]. Sites of occult metastatic disease detected at ^{18}F-FDG PET/CT included bone, liver, and distant lymph nodes. In the 113 included patients with locally advanced gastric cancer, 31 (27%) had occult distant metastases detected by ^{18}F-FDG PET ($n = 11$, 10%) and/or laparoscopy ($n = 21$, 19%), with only a single overlap[34]. Thus, if ^{18}F-FDG PET/CT would have been omitted, 10% of patients would have undergone unnecessary surgery. Economic modelling suggested that the addition of ^{18}F-FDG PET/CT to the standard staging evaluation would result in an estimated cost saving of approximately US $13000 per patient[34].

^{18}F-fluoro-3'-deoxy-3'-fluorothymidine (^{18}F-FLT), a thymidine analog, is another PET tracer. It is retained in proliferating cells and can thus be used to visualize cellular proliferation. Zhou *et al*[35] investigated

39 consecutive patients with gastric cancer who underwent pretreatment with both ^{18}F-FLT PET/CT and ^{18}F-FDG PET/CT. All patients had already been diagnosed with multiple metastases at CT[35]. Sensitivities in detecting peritoneal and ovarian metastases were not significantly different between the two modalities: 89.5% *vs* 94.7%, and 90.9% *vs* 90.9% for ^{18}F-FLT PET/CT *vs* ^{18}F-FDG PET/CT, respectively[35]. However, sensitivities of ^{18}F-FLT PET/CT for detecting liver metastases and bone metastases were significantly lower than ^{18}F-FDG PET/CT: 30% *vs* 100%, and 20% *vs* 100%, respectively[35]. This significant difference was explained due to the high physiological uptake of ^{18}F-FLT in the liver and bone marrow[35].

Bone scintigraphy

Bone scintigraphy evaluates the distribution of active bone formation in the body, using Tc99m MDP as tracer. Planar scintigraphy uses one single gamma camera, whereas single photon emission CT uses more rotating cameras to detect tracer uptake, providing cross-sectional images.

For the results of the study by Ma *et al*[33] on bone scintigraphy, we refer to the paragraph on PET above. Choi *et al*[36] also performed a retrospective study on the use of planar bone scintigraphy, in 234 patients of whom most had stage III or stage IV disease. They found bone abnormalities in 45.3% of their patients[36]. The researchers reported that the most frequent osseous metastatic sites, in decreasing order, were the spine (66%), ribs (59%), pelvis (43%), femur (30%), skull (22%), and shoulder girdle (17%)[36]. Only 11% of patients had a single lesion, which was most frequently found in the spine, rib, pelvis, and femur[36]. Unfortunately, the authors did neither clearly mention which reference test they used to confirm or exclude the presence of bone metastases, nor did they report the accuracy of bone scintigraphy. To our knowledge, there are no other formal studies on bone scintigraphy in gastric cancer reporting accuracy values.

MRI

MRI has superior soft-tissue contrast compared to other imaging modalities. Technical advances in fast MRI, among which the introduction of parallel imaging, have greatly enhanced the clinical applications of body MRI.

There are only few studies investigating the role of MRI in M staging of gastric cancer. In one of the first MR studies in 15 patients[37], MRI was performed at a 1.0-T scanner, using 2D axial T1-weighted and axial and coronal T2-weighted turbo spin echo (TSE) sequences with and without fat suppression, and a 3D coronal heavily T2-weighted TSE sequence with fat saturation[37]. The researchers reported a diagnostic accuracy of 85.7% in detecting M1 disease[37]. However, they neither specifically mentioned which body area was covered by their scanning protocol, nor did they report the prevalence and locations of the distant metastases they detected[37].

Shinya *et al*[38] investigated the usefulness of diffusion-weighted imaging (DWI) at 1.5-T in the staging of gastric cancer in 15 patients. Axial T1-weighted images were used to aid in localizing areas of restricted diffusion[38]. Although not supported by any statistical analysis, the researchers stated that DWI could detect peritoneal seeding and liver metastasis more clearly than CT[38].

A South Korean study[39] made a direct comparison between dedicated MRI at 3-T and CT. In their study[39], axial half-Fourier acquisition single-shot TSE T2-weighted images with and without fat suppression, true fast imaging with steady-state precession, T2-weighted 3D gradient-recalled-echo (GRE) in- and out-of-phase images, T1-weighted fat suppressed 3D GRE images, DW images, and dynamic images after the intravenous administration of a gadolinium-based contrast agent were obtained[39]. Scan coverage included the area from the hepatic dome to below the symphysis pubis[39]. CT was performed using 8-, 16-, and 64-channel scanners[39]. In the three patients with histologically confirmed peritoneal metastases, both MRI and CT correctly diagnosed them in one patient, but failed to diagnose them in the other two[39]. The remaining 46 patients were correctly diagnosed as having M0 disease by both MRI and CT[39]. To our knowledge, there are no other published studies on the diagnostic performance of MRI in detecting distant metastases in gastric cancer.

DISCUSSION

Recurrence after R0 resection of gastric cancer usually occurs within 2 years and is rapidly fatal[40]. Data from large retrospective studies in patients who had undergone R0 resection show that approximately 50% of recurrences occur only at distant sites, without signs of locoregional recurrence[40,41]. It is likely that in at least a part of these patients occult distant (micro)metastases were already present at the time of operation. This emphasizes that there is a need for more accurate preoperative M staging. In this article, imaging modalities in the preoperative detection of distant metastases in gastric cancer have been reviewed (Table 1). Overall sensitivity of EUS in detecting distant metastases is poor, but specificity is high. The very poor overall sensitivity of EUS can be explained by the limited detection distance of this modality, which is only around 5-7 cm[19]. When EUS is performed for T staging, it is useful to determine whether ascites is present, because it has a high probability for the presence of peritoneal metastases. The sensitivity of transabdominal ultrasonography in detecting peritoneal and hepatic metastases is poor, whereas specificity is high. The yield of cervical

Table 1 Summary of the current performance of modern imaging techniques in the preoperative detection of distant metastases in gastric cancer			
	(Dis)advantages	Sensitivity	Specificity
EUS	Limited detection distance	Overall poor	Overall high
Standard ultrasonography	Operator and patient dependent	Overall poor	Overall high
CT	Fast scanning, large coverage	Overall poor to moderate	Overall high
PET using the tracer ^{18}F-FDG	Integrated with CT, whole-body coverage	Overall poor	Reported to be very high; more studies needed
Bone scintigraphy	Only for detection of bone metastases	Unclear	Unclear
MRI	Versatile technique	Reported to be moderate;	Reported to be very high; more studies needed
	Superior soft-tissue contrast	more studies needed	

EUS: Endoscopic ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; ^{18}F-FDG: ^{18}F-fluoro-2-deoxy-D-glucose.

lymph node ultrasonography is very low and therefore it is not recommended to use it in routine staging. Reported sensitivity of CT ranges from poor to moderate, whereas specificity is high. CT outperforms ultrasonography in terms of overall accuracy and reliability and it is currently the primary imaging modality for M staging[2]. Sensitivity of ^{18}F-FDG PET/CT in detecting peritoneal and distant metastases in general is poor. One ^{18}F-FDG PET/CT study reported a high specificity in diagnosing M1 disease[34]. According to a 2014 consensus paper on the optimal management of gastric cancer by an international multidisciplinary expert panel, preoperative staging by ^{18}F-FDG PET is not routinely indicated[2]. However, the study by Smyth *et al*[34] showed that ^{18}F-FDG PET/CT revealed distant metastases in 10% of patients with locally advanced gastric cancer, which were not detected by EUS, CT and laparoscopic staging. This study also suggested that the use of preoperative ^{18}F-FDG PET/CT would lead to reduced morbidity from fewer futile surgeries and lower patient care costs[34]. Yet another ^{18}F-FDG PET/CT study showed that as many as 882 findings considered not to be related to gastric cancer were detected in 386 of 421 (91.7%) patients; 129 additional outpatient visits and 10 additional hospitalizations were needed to evaluate these incidental findings, whereas the treatment strategy for gastric cancer was changed in only one patient, leading to much extra costs[42]. Although the most common sites of distant metastases are the peritoneum and liver, exclusive bone metastases may occur in 9% of patients[16]. Therefore, it seems important to analyze patients with gastric cancer for the presence of bone metastases. To date, the accuracy of bone scintigraphy in the assessment of bone involvement in gastric cancer is not clear and at present it has no role in the initial evaluation of patients with gastric cancer. Notably, one study suggested that ^{18}F-FDG PET/CT may be superior to bone scintigraphy in the detection of bone metastases[33]. ^{18}F-FLT PET is not competent enough to evaluate liver and bone metastases. Initial studies have demonstrated the feasibility of MRI in diagnosing distant metastases. To date, there is no imaging modality which is sufficiently sensitive to rule out peritoneal metastases. Therefore, when findings of

any imaging modality are not definitely positive for the presence of peritoneal metastases, except for patients with early gastric cancer, diagnostic laparoscopy should be performed[2]. Indeed, a systematic review demonstrated that the use of diagnostic laparoscopy changed the management in 8.5% up to 59.6% of gastric cancer patients who were initially deemed resectable by preoperative imaging[43]. Important disadvantages of diagnostic laparoscopy are the costs, the need for anaesthesia and the small risk of operative complications.

Future prospective accuracy studies and formal cost-effective analyses are needed to determine whether or not ^{18}F-FDG PET/CT should become integrated in the standard staging algorithm for localized gastric cancer. The use of ^{18}F-FDG PET combined with a diagnostic contrast-enhanced CT in one single examination and/or the use of integrated ^{18}F-FDG PET/MRI may prove to be more efficient and sensitive than currently used stand-alone imaging modalities, which could lower the number of diagnostic laparoscopies. Future well-designed studies should investigate which imaging modality has the highest accuracy in detecting bone metastases in gastric cancer and whether its yield justifies routine clinical use. The value and clinical applicability of MRI, among which whole-body MRI including diffusion-weighted whole-body imaging with background-body-signal-suppression[44] needs to be further explored. Furthermore, the development of new molecularly targeted imaging techniques for clinical use may also help to improve the detection of distant metastases in gastric cancer. Several gene expression profiles related to metastatic potential of gastric cancer have already been identified, among which phosphoglycerate kinase 1[45], peroxisome proliferator-activated receptorδ[46], S100A4 and E-cadherin[47]; these may be used to identify patients at high risk for distant metastases, especially when initial preoperative staging is negative.

In conclusion, CT is currently the primary imaging modality for M staging. Evaluation of ascites by EUS is useful because it has a high probability for the presence of peritoneal metastases. Staging laparoscopy is still necessary in patients with locally advanced disease with no definite evidence of peritoneal metastases at imaging. The roles of ^{18}F-FDG

PET and MRI need to be further explored. New imaging techniques and strategies are needed to improve M staging.

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