TOPIC HIGHLIGHT

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Role of imaging in predicting response to neoadjuvant chemotherapy in gastric cancer

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Abstract

With the proven overall benefit of neoadjuvant chemotherapy in patients with locally advanced gastric cancer, there has come a need to discriminate responders from non-responders. In this article, the current role of anatomical and molecular imaging in the prediction of response to neoadjuvant therapy in gastric cancer is outlined and future prospects are discussed.

Core tip: Studies have shown that there is an association between tumor response at anatomical imaging evaluation and histopathological response and survival in patients with gastric cancer who are treated with neoadjuvant chemotherapy. However, as it takes time for gross tumor changes to become apparent, anatomical imaging may be of limited value in the early assessment of neoadjuvant chemotherapy efficacy. Studies performing early response assessment with use of ^{18}F-fluoro-2-deoxy-D-glucose positron-emission tomography demonstrate controversial results. The usefulness of other molecular imaging modalities, among which diffusion-weighted-magnetic resonance imaging, remains to be investigated.

INTRODUCTION

Gastric cancer is the fourth most common cancer[1]. In 2008, 988602 new cases were diagnosed and 737419 people died of the disease worldwide[1]. In Japan and South Korea, gastric cancer is usually detected at an early stage owing to mass screening programmes[2]. In Western countries, however, gastric cancer is mostly detected at a more advanced stage, which incurs a poorer prognosis. Clinical trials have shown that neoadjuvant chemotherapy improves overall and disease-free survival of patients with advanced gastric cancer[3]. Perioperative chemotherapy based on the medical research council adjuvant gastric infusional chemotherapy-trial approach is currently an acceptable standard of care[4]. This approach consists of continuous intravenous infusion of epirubicin, cisplatin, and 5-fluorouracil in three 21-d cycles preoperatively and three 21-d cycles postoperatively[5]. However, not all patients benefit. The results of a meta-analysis indicated that the numbers needed to treat (NNT) with neoadjuvant chemotherapy to prevent one death in three years was as high as 84, whereas for a 3-year disease-free survival, the NNT was 8[3]. Chemotherapy-

induced adverse effects, among which gastrointestinal problems and leukopenia, have been reported to occur in 8.8% and 18.1% of patients, respectively[3]. In patients who will not respond sufficiently, costly but ineffective neoadjuvant chemotherapy should not be continued or, preferably, even not be started. There is therefore a need for a method to discriminate patients who will benefit from those who will not. In this article, the current role of imaging in the early prediction of response to neo-adjuvant therapy in gastric cancer is outlined and future prospects are discussed.

SEARCH STRATEGY AND SELECTION CRITERIA

Original publications concerning the value of imaging in predicting histopathological response, survival, and/or improvement in quality of life to neoadjuvant therapy in patients with resectable gastric cancer were retrieved. Data for this review were identified by a computer-aided search in the PubMed/MEDLINE database. The terms (gastric cancer or stomach cancer) and (neoadjuvant or chemotherapy) and [magnetic resonance (MR), MR imaging (MRI), NMR, fluorodeoxyglucose, or 2-fluoro-2-deoxy-D-glucose (FDG), positron emission tomography or positron-emission tomography (PET), computed tomography (CT) or ultrasound or ultrasonography (US)] were used. Bibliographies of relevant articles were screened for other relevant articles. Abstracts and reports from meetings were excluded. Only papers published up to September 2013 were included. The literature search resulted in 9 original articles on anatomical imaging[6-14] and 5 original articles on molecular imaging[8,15-18] in the assessment of response to neoadjuvant chemotherapy in patients with gastric cancer.

ANATOMICAL IMAGING

At present, the majority of clinical trials evaluating cancer treatments for objective response in solid tumors are using the response evaluation criteria in solid tumors (RECIST)[19]. Using these criteria, an assessment is made whether cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments[19]. However, RECIST requires the presence of a measurable lesion, which is often not the case in gastric cancer[6]. The Japanese classification of gastric carcinoma (JCGC) evaluation criteria were developed to evaluate response even for tumors without measurable lesions[20]. Kurokawa et al[6] assessed the value of both the RECIST and JCGC criteria in patients who were enrolled in two phase II trials. In both trials, the safety and efficacy of S-1 plus cisplatin were evaluated. After completion of neoadjuvant chemotherapy, response evaluation using RECIST in the JCOG0405 trial was based only on CT findings, whereas tumor response evaluated with JCGC criteria was based on CT, barium X-ray, and endoscopic findings in the JCOG0210 trial. The hazard ratios (HRs) for death

of responders to non-responders using RECIST and JCGC criteria and were found to be nonsignificant (HR = 0.67, *P* = 0.35; and HR = 0.54, *P* = 0.06, respectively). In contrast, histological response was found to be a significant predictor of overall survival (HRs = 0.40, *P* = 0.005).

Liu et al[7] investigated 48 patients with gastric cancer who were treated with 3 cycles of oxaliplatin and 5-fluorouracil-based neoadjuvant chemotherapy. All patients underwent radical resection performed within 2 wk after ending chemotherapy. Pre- and post-chemotherapy short-axis diameter and volumetric mean tumor attenuation of target lymph nodes on contrast-enhanced CT images were measured. Tumor response was assessed by using both RECIST[19] and adapted Choi criteria[21]. According to the adapted Choi criteria[21], tumor response was defined as at least a 10% decrease in the sum of short diameters or at least a 15% decrease in mean volumetric attenuation of target lymph nodes. The investigators found that both the RECIST and adapted Choi criteria had a significant predictive value for progression-free survival (*P* = 0.037 and *P* < 0.001, respectively) and overall survival (*P* = 0.012 and *P* < 0.001, respectively). However, the investigators found that RECIST might underestimate tumor response; post-therapy decreased tumor attenuation correlated with improved clinical outcome. They concluded that the adapted Choi criteria could be valuable to predict survival of these patients[7].

Lee et al[8] used their own CT criteria to evaluate tumor response in 33 patients with advanced gastric cancer who were prospectively enrolled. All these patients underwent CT before and after four cycles (8 wk) of neoadjuvant chemotherapy, including oxaliplatin, 5-fluorouracil, and leucovorin. Patients underwent radical resection within 2 wk after the completion of neoadjuvant chemotherapy. The percentage diameter or volume reduction rate of the primary tumor and the largest lymph node at CT were compared to histopathological response. Histopathological tumor response was assessed using the histopathologic criteria by Mandard et al[22]. Patients with tumor regression grade 1-3 were defined as responders, whereas patients with tumor regression grade 4-5 were defined as non-responders. Lee et al[8] found that only the volume reduction rate of the primary gastric cancer at CT was found to be significantly correlated to histopathological tumor response. When the optimal cutoff level of the percentage volume reduction rate of the primary gastric tumor was determined to be 35.6%, a sensitivity of 100% and a specificity of 58.8% were achieved. When the optimal cutoff level of the percentage volume reduction rate was determined to be 64.5%, a sensitivity of 56.3% and a specificity of 88.2% were obtained[8].

Guo et al[9] assessed the value of endoscopic ultrasonography (EUS), in 48 patients with advanced gastric cancer who underwent neoadjuvant chemotherapy for three cycles. The chemotherapy regimen consisted of leucovorin, 5-fluorouracil and oxaliplatin simultaneously. Radical gastric resection was performed 3 to 4 wk after

the third cycle of chemotherapy. EUS was performed before neoadjuvant chemotherapy and before R0 resection. T and/or N downstaging at EUS was used as criterion for tumor response. Using a cut-off point of more than two-thirds affected regressive and necrotic tumor cells within the tumor bed at histopathological analysis, EUS yielded a sensitivity of 72.2% and specificity of 90.0%. In the study of Guo *et al*[9], no correlation to survival was performed.

Ang *et al*[10] assessed the value of contrast-enhanced ultrasonography (CE-US) in 43 patients with advanced gastric cancer. US contrast agents are gas-filled microbubbles which behave as pure intravascular tracers, enabling assessment of the dynamic features of tumor vascularity. In Ang *et al*[10] study, patients randomly received either 5-fluorouracil plus oxaliplatin, or S-1 plus oxaliplatin as neoadjuvant chemotherapy regimen. Surgery was performed 3 to 5 wk after completion of neoadjuvant chemotherapy. All patients underwent CE-US before and after two courses of pre-operative neoadjuvant chemotherapy. The investigators stated that they assessed tumor response at CE-US according to the static change of ultrasonic echo, and the dynamic assessment of tumor vascularity and lymph nodes. Histopathological response was evaluated according to the criteria of Mandard's tumor regression grade[22] and served as standard of reference. Patients with tumor regression grade 1-2 were defined as responders, whereas patients with tumor regression grade 3-5 were defined as non-responders. Ang *et al*[10] found a moderate sensitivity of 62.9% and specificity of 56.3%. Furthermore, they found that the overall accuracy of CE-US was not significantly better than that of CT using RECIST criteria ($P = 0.663$)[10].

Other included studies used a combination of anatomical imaging modalities to assess tumor response[11-14]. Park *et al*[11] prospectively investigated 40 patients with locally advanced gastric cancer who underwent neoadjuvant chemotherapy, consisting of 3 cycles of intravenous docetaxel and cisplatin on days 1 and 8 of a 3-wk cycle. Surgery was performed within 6 wk after the start of the third cycle. TNM-staging[23] using EUS and CT was performed before and after neoadjuvant chemotherapy. The investigators found that the 3-year overall survival rate for patients downstaged with EUS for T and/or N-stage was greater than that for nondownstaged patients (69% *vs* 41%; $P = 0.05$). The 2-year recurrence-free survival rate was also better for the EUS-downstaged patients (77% *vs* 47%; $P = 0.04$). However, the differences in overall survival and recurrence-free survival between the patients downstaged with CT and those not downstaged were not found to be statistically significant. Park *et al*[11] did not give an explanation for the different prognostic values of EUS and CT.

D'Ugo *et al*[12] investigated 30 patients with resectable locally advanced gastric cancer who were treated with neoadjuvant polychemotherapy consisting of either a combination of etoposide, epirubicin, plus cisplatin, or of epirubicin, cisplatin, plus 5-fluorouracil. All patients underwent restaging with use of chest X-ray, CT, abdom-

inal ultrasonography after completion of preoperative chemotherapy. The investigators found that T-downstaging was significantly associated with survival.

In two studies a combination of endoscopic and CT findings was used to evaluate response[13,14]. Lorenzen *et al*[13] retrospectively evaluated a cohort of 410 patients with locally advanced gastric cancer who were treated with neoadjuvant chemotherapy. Neoadjuvant chemotherapy consisted of at least 6 wk of oxaliplatin or cisplatin, plus 5-fluorouracil. Patients aged 60 years or younger and those with a good health status were additionally treated with paclitaxel. A minority of patients (15%) received chemotherapy with doxorubicin, etoposide, and cisplatin. EUS and CT were performed before treatment and in the last 3 d of every cycle of chemotherapy. Assessment of response to neoadjuvant therapy was based on reduction of primary tumor size, as measured by upper endoscopy and CT scan. Clinical response was predefined as a reduction in bidimensional tumor diameter of > 50% compared to the pretherapeutic findings. The researchers found an association between clinical response and overall survival: patients who had a response had an estimated 2- and 5-year survival rate of 86.4% and 72.5%, respectively, whereas patients who did not clinically respond to therapy had an estimated 2- and 5-year survival rate of 56.3% and 34.3%, respectively[13]. Heger *et al*[14] retrospectively investigated 47 patients, of which most received two cycles of platinum, 5-fluorouracil, and leucovorin-based chemotherapy with or without the addition of paclitaxel lasting 36 d each with a 2-wk interval between the two cycles. All patients received baseline endoscopy and CT scans, and after 50% (6 wk) of their chemotherapy. Clinical response was defined as a reduction of > 75% of the tumor mass at endoscopy and > 50% in tumor wall diameter at CT. Patients with less than 10% residual tumor were classified as histopathological responders[24]. Endoscopic and CT response were found to be significantly associated with histopathological response and overall survival[14].

MOLECULAR IMAGING

Metabolic PET imaging using the glucose analog [18]FDG is widely used in clinical oncology. The prospective study by Ott *et al*[15], published in 2003, was one of the first to show its potential value in early response monitoring to neoadjuvant chemotherapy in gastric cancer. The investigators performed FDG PET at baseline and 14 d after initiation of polychemotherapy consisting of cisplatin, leucovorin, and 5-fluorouracil, in 44 patients with locally advanced gastric cancer. A reduction of tumor FDG standardized uptake value (SUV) by more than 35% between the two scans was used as a predefined criterion for response. Response at PET was correlated to histopathologic response after completion of therapy (defined as < 10% viable tumor cells in the resected specimen[24]) and patient survival. In 20% of patients, the primary tumor was visualized with insufficient contrast for quantitative analysis. In the remaining patients, the authors found that

response at PET predicted histopathologic response in 77% of responders and 86% of nonresponders. Median overall survival for patients with response at PET had not been reached (2-year survival rate, 90%), whereas for patients without a response at PET, median survival was only 18.9 mo (2-year survival rate, 25%; $P = 0.002$). Aforementioned study by Ott *et al*[15] was expanded with another 27 patients (total: 71 patients) with longer follow-up[16]. Again, responders at PET showed a high histopathologic response rate (69%) and a favorable prognosis (median survival not reached), whereas metabolic nonresponders showed a histopathologic response in only 17% and had a poor prognosis (median survival of 24.1 mo). However, later studies by researchers from other institutions[8,17] could not confirm Ott *et al*[15,16] findings: Lee *et al*[8] investigated the value of FDG PET in 33 patients with advanced gastric cancer. FDG PET was performed before and after four cycles (8 wk) of neoadjuvant chemotherapy, including oxaliplatin, 5-fluorouracil, and leucovorin. Using FDG PET, the reduction rate of the maximum SUV of the primary gastric tumor was assessed. Histopathological tumor response was defined as dominant fibrotic changes with a few tumor cells or groups or more regression. The percentage change in maximum SUV did not significantly correlate to the histopathologic grade of tumor regression[8]. Vallböhmer *et al*[17] investigated 42 patients with advanced gastric cancer who received two cycles of neoadjuvant chemotherapy consisting of a combination of cisplatin, leucovorin, and 5-fluorouracil. They found no significant correlation between pretreatment maximum tumor SUV, maximum SUV 2 wk after completion of neoadjuvant chemotherapy, and change in maximum SUV between the two scans, and histopathological tumor response (defined as less than 10% vital residual tumor cells). Moreover, they did not find any significant correlation either between the aforementioned FDG PET parameters and overall survival. Thus, the results concerning the use of FDG PET in predicting response to neoadjuvant chemotherapy in gastric cancer seem controversial. Moreover, not all tumors show FDG uptake, which may limit its utility in many patients. Especially diffusely growing and mucus containing tumors may exhibit low FDG uptake[25]. PET imaging with the proliferation marker 18F-fluorothymidine (FLT) may be an attractive alternative. In the study by Herrmann *et al*[26], all primary tumors showed focal FLT uptake, whereas as much as 31% did not show FDG uptake. Another study by Ott *et al*[18] tested the predictive value of FLT and compared it to that of FDG. They prospectively included 45 patients who underwent PET imaging before and 2 wk after initiation of preoperative chemotherapy, consisting of a combination cisplatin, leucovorin, and 5-fluorouracil. Tumor FLT and FDG uptake were assessed at both time points. Imaging findings were compared to histopathological response (patients with less than 10% residual tumor cells were classified as responders[24]) and survival. FLT uptake value 2 wk after start of chemotherapy was the only imaging parameter with significant prognostic impact on overall survival. FDG uptake was found to be a surro-gate parameter for neither histopathological response nor overall survival prognosis[18].

DISCUSSION

In this review, results of anatomical and molecular imaging modalities to predict tumor response to neoadjuvant chemotherapy in gastric cancer are outlined. Most of the included studies using anatomical imaging performed CT and/or EUS. Overall, these studies demonstrated that there is an association between anatomical tumor response and histopathological response and/or survival. Two studies evaluated the established RECIST criteria: one study found no association to survival[6], whereas the study did find a significant association[7]. Two studies demonstrated the usefulness of a combination of CT and endoscopic response evaluation[13,14]. One of the included studies performed CE-US to evaluate tumor response[10], but the sensitivity and specificity values they found seem too low to be used for response assessment in clinical practice. A clear disadvantage of anatomical imaging is that it takes time before gross tumor changes become apparent. Accordingly, the studies included in the review usually performed anatomical imaging late in the course of neoadjuvant treatment. Metabolic changes precede anatomical changes. Therefore, molecular imaging may predict tumor response to neoadjuvant chemotherapy much earlier in the course of treatment. Almost all of the included studies used FDG PET imaging. These studies[8,15-18] yielded controversial results. These interstudy differences may be explained by different methods to evaluate tumor FDG uptake and by differences in patient populations and tumor heterogeneity. Instead of measuring FDG PET SUVmax, future studies may aim at assessing the value of (partial volume corrected) total lesion glycolysis (also known as metabolic tumor volume) as a new quantitative FDG PET/CT approach to provide both better pretreatment risk stratification and early therapy response assessment in gastric cancer[27]. Only one of the studies assessed the value of FLT PET and found that FLT uptake value 2 wk after start of chemotherapy was an independent significant predictor of overall survival. Whether FLT PET is clinically useful to determine response to neoadjuvant chemotherapy in gastric cancer still remains to be further investigated.

The included studies used different study endpoints. Almost half of the included studies correlated imaging response to disease-free survival and/or overall survival, which are accepted study endpoints[28,29]. Other studies (also) used histopathological tumor regression as surrogate marker for survival, which has the advantage that no patient follow-up is needed. Histopathologic tumor regression to cytotoxic therapy is considered to be a prognostic marker for long-term survival in gastric carcinoma, as has been shown by several studies[24,30]. However, the included studies in this review used different criteria and cut-off points to define histopathologic tumor regression. In addition, the results of a recent study indicated that a multifactorial histopathological score, including the

UICC/AJCC ypT-category, ypN-category, and the degree of histopathological tumor regression, results in the most accurate prediction of survival for patients with gastric carcinoma after neoadjuvant chemotherapy followed by surgery[31]. Future studies using histopathological analysis as study endpoint may adhere to this multifactorial scoring system[31].

No studies using MRI to evaluate tumor response to neoadjuvant chemotherapy in gastric cancer were identified. Diffusion-weighted (DW)-MRI, in particular, is a promising MRI method[32]. DW-MRI is based on the principle that treatment with chemotherapy causes necrosis or cellular lysis which will lead to increases in tissue water diffusivity, thus lowering signal intensity on high-b value images with corresponding increases in apparent diffusion coefficient values. Since cell death in response to treatment precedes changes in lesion size, changes in DW-MRI may be an effective early marker of response to therapies that induce apoptosis[32]. DW-MRI for monitoring neoadjuvant therapy has already been applied in a wide variety of cancer types and organ sites, including the liver, breast, bone, soft tissue tumors, cervical tumors, head and neck tumors, as well as rectal cancer[32]. DW-MRI of gastric cancer is feasible[33], but technically challenging due movement related to respiration, peristalsis and cardiac motion, and the presence of local field inhomogeneities. Other molecular imaging techniques are currently still under investigation. For instance, it has been shown that 89Zr-trastuzumab PET can be used to delineate human epidermal growth factor receptor 2 (HER2)-positive gastric cancer and to monitor the pharmacodynamic effects of the epidermal growth factor receptor/HER2 tyrosine kinase inhibitor afatinib in mice[34]. Future studies using molecular imaging techniques should investigate the optimal timing of imaging; if imaging is performed too early, no significant effect of neoadjuvant treatment may be demonstrated. On the other hand, imaging should also not be performed too late, in order to allow for a timely modification of therapy.

Several studies have investigated the value of clinicopathologic features to predict outcome in gastric cancer patients who are preoperatively treated with chemotherapy[13,35,36]. One of the largest of these studies, by Lorenzen *et al*[13], retrospectively evaluated a cohort of 410 patients. Multivariate analysis showed that age, gender, body mass index, hemoglobin level, clinical staging and tumor location did not predict histopathological tumor response (defined as < 10% residual tumor cells[24]) and overall survival. Yet, tumor location in the middle third of the stomach, well-differentiated tumors, and intestinal tumor type according to the Lauren classification were significantly and independently associated with both histopathologic response and better survival. These findings need confirmation by future independent studies.

The molecular genetic basis of carcinogenesis, cancer progression and drug resistance is complex. Like antibiotic-resistant bacteria, tumors often show resistance to anticancer drugs, leading to inefficient chemotherapy. Several studies have shown promising results of predictive value of tumor biomarkers which can be obtained by biopsy. A possible advantage of this approach is that no "test period" of neoadjuvant chemotherapy may be needed before an assessment can be made whether the patient will benefit or not. For instance, it has been shown that expressions of certain chemotherapy-related genes are related to worse survival in gastric cancer patients who are treated with neoadjuvant chemotherapy[37,38]. However, there is still a lack of an established (set of) biomarker(s) for chemotherapeutic response prediction of gastric cancer. Many other biomarkers are still under investigation[39,40], but it is beyond the scope of this review to discuss these in full detail. For more information, the reader may refer to the excellent review article by Fareed *et al*[41].

In conclusion, studies have shown that there is an association between tumor response at anatomical imaging evaluation and histopathological response and survival in patients with gastric cancer who are treated with neoadjuvant chemotherapy. However, as it takes time for gross tumor changes to become apparent, anatomical imaging may be of limited value in the early assessment of neoadjuvant chemotherapy efficacy. Studies performing early response assessment with use of FDG PET demonstrate controversial results. The usefulness of other molecular imaging modalities, among which DW-MRI, remains to be investigated.

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