The Value of PET Imaging in Patients with Localized Gastroesophageal Cancer

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ABSTRACT

Preoperative induction therapy in stages II and III adenocarcinoma of the esophagogastric junction (AEG) and gastric cancer is now an accepted treatment choice in the Western world. Patients who respond to induction therapy have significantly improved survival compared to nonresponding patients. Until recently, however, no prospectively tested markers for predicting response and/or prognosis in this setting were available. The MUNICON I study recently showed the utility of fluorodeoxyglucose-positron emission tomography (FDG-PET) in predicting response and prognosis in AEG and indicated the feasibility of a PET-guided treatment algorithm. These findings are an important step forward in tailoring multimodal treatment to tumor biology. In gastric cancer, the issue is more complicated, because approximately 30% of these cancers cannot be visualized with sufficient contrast for quantification. Insufficient FDG uptake is mostly associated with diffuse-type gastric cancer with signet cells and mucinous content. In FDG avid patients, FDG-PET can be used for response evaluation. The prognosis of non-avid patients is similar to metabolic nonresponders. The addition of new tracers (eg, fluorothymidine) might increase the accuracy of these tests in the future. In AEG types I and II, PET-guided induction therapy is feasible and will undergo further evaluation in a randomized multicenter trial. In gastric cancer, there should be consideration of such treatment concepts as immediate resection after 2 weeks of induction therapy with or without adjuvant treatment in metabolic nonresponders or modified chemotherapy regimens possibly including biologically targeted drugs in FDG non-avid tumors.

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After the publication of three randomized controlled trials showing benefit, neoadjuvant chemotherapy has become an accepted choice for the treatment of locally advanced adenocarcinomas of the esophagus and the esophagogastric junction (AEG) and gastric cancer.[1–3] The use of neoadjuvant chemotherapy without the addition of radiotherapy is not generally accepted for AEG type I. In many institutions, concurrent or sequential radiotherapy is delivered, but a recent meta-analysis provides justification for both the neoadjuvant chemotherapy and chemoradiotherapy approach in the treatment of resectable adenocarcinomas of the esophagus.[4] However, there is also some evidence that the addition of radiation therapy might increase the risk of postoperative morbidity and mortality compared to chemotherapy alone, which may be due to immunosuppression associated with radiation therapy.[5,6] Due to these facts, neoadjuvant chemotherapy has been the treatment of choice for locally advanced esophageal adenocarcinomas in the authors' and others' institutions.

The potential benefits of giving chemotherapy before surgery are downsizing and downstaging of the primary tumor and lymph node metastases, early treatment of micrometastases, increased rates of curative resections, and improved tumor-related symptoms. A newer potential advantage is the possibility of testing in vivo the chemosensitivity of the primary tumor, which may influence choice of chemotherapy in the adjuvant setting.

The feasibility of neoadjuvant treatment in locally advanced gastric cancer has been shown in numerous phase II studies with different regimens.[7–10] Compared to historical controls, prognosis of patients receiving neoadjuvant treatment seems to be improved and toxicity has been moderate in most studies.[8,11] Treatment acceptance and compliance have been high and treatment has been well tolerated, with nearly all patients being able to receive the complete neoadjuvant dose.

In adenocarcinomas of the distal esophagus, an abdominothoracic approach

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and reconstruction with a small gastric tube interposition in the posterior mediastinum with intrathoracic anastomosis (Ivor-Lewis operation) including a two-field lymphadenectomy has become the procedure of choice.[12] In Europe, an abdominal D2 lymphadenectomy is performed at most centers with extensive experience with gastric cancer and (in contrast to US centers) postoperative chemoradiotherapy is not a standard of care.[13–15]

IMPORTANCE OF PRETHERAPEUTIC STAGING IN GASTROESOPHAGEAL CANCER

Current treatment options for gastroesophageal cancer range from endoscopic mucosal resection to preoperative chemotherapy or chemoradiotherapy followed by esophagectomy or gastrectomy.[16–18] Most of these approaches are associated with substantial morbidity and mortality, as well as long-term compromise in quality of life. Accurate pretherapeutic staging by imaging techniques is therefore crucial to selecting the appropriate form of therapy.

Generally, the first step in this process is to distinguish between patients with locoregional disease and those with systemic disease. For patients presenting with distant metastases (M1), no curative treatment is available and palliative treatment is required. Palliative resections should be considered only on an individualized basis for relief of symptoms or after response to chemotherapy or chemoradiotherapy in metastatic disease. Flourodeoxyglucose-positron emission tomography (FDG-PET) reaches sufficient sensitivity (67%) and good specificity (97%) in the detection of metastatic disease and is superior in this regard to computed tomography (CT) and other available diagnostic tools.[16,19–28] A pretherapeutic change of planned treatment based on conventional staging modalities is generated by PET in about 20% of patients.[16,21,25,29–31]

In patients with locoregional disease, assessment of local tumor infiltration (T category) and regional lymph node involvement (N category) is necessary to decide whether a complete tumor resection (R0) is feasible.[32] Local tumor infiltration is also frequently used for therapy stratification. Whereas patients with T1b and T2 disease without lymph node metastases are treated by primary resection and lymph node dissection, patients with T3 and T4 tumors frequently are offered preoperative chemotherapy or chemoradiotherapy to improve the rate of curative resections and, potentially, overall survival.[33,34] Pretherapeutic assessment of T status by imaging techniques, therefore, has important consequences for the selection of therapy. Not FDG-PET, but endoscopic endoluminal ultrasound and CT scans are the required examinations for exact staging of pretherapeutic T status. For resectable tumors, the removal of the primary tumor together with a systematic lymphadenectomy is necessary for histopathologic lymph node staging and is the accepted standard therapy. FDG-PET offers a low sensitivity of 51% and a sufficient specificity of 84% for locoregional lymph node staging.[16,26–28,35,36]

Approximately one third of patients with gastric cancer, including locally advanced tumors, initially have insufficient FDG uptake for quantification.[37] Distal-third tumors with diffuse growth pattern are especially unlikely to be visualized by FDG-PET. Therefore, FDG-PET is not routinely used for pretherapeutic staging in gastric cancer outside of the clinical study setting.

RESPONSE EVALUATION

Since 1999, it generally has been accepted that patients who respond to induction chemotherapy have significantly improved survival compared to nonresponding patients.[38] However, no standardized measures for evaluating response have been established so far. Clinical response evaluation by morphologic imaging techniques has specific limitations in gastric cancer. According to strict World Health Organization criteria, gastroesophageal cancer is not bidimensionally measureable.[39] Criteria from the Response Evaluation Criteria in Solid Tumor (RECIST) Group, which use one-dimensional measurements, are, in principle, applicable to gastroesophageal cancer.[40] However, measurement of wall thickness is critically dependent on the distension of the stomach during the examination. Only a few phase II trials of induction therapy have used RECIST criteria so far.[41–45] Careful clinical response evaluation by a combination of endoluminal ultrasound, endoscopy, and CT scan used for restaging after one cycle or before surgery is predictive of histopathologic regression and prognosis in experienced centers.[7,38,46–49]

Histopathologic regression often is used for response evaluation. Yet, including only patients who undergo resection would cause a significant bias; thus, clinical response evaluation has to be included, and patients with progression during chemotherapy have to be classified as nonresponding patients. Although similar criteria for histopathologic regression have been used in several studies, these criteria are not standardized yet and may be investigator dependent.

A modification of the regression score used by Mandard and colleagues,[50] who first described histopathologic regression for esophageal cancer after chemoradiotherapy, was published by Becker et al for gastric cancer.[51] In this scoring system, patients with less than 10% residual tumor cells after neoadjuvant treatment are classified as histopathologic responders (score 1a = complete response and score 1b = less than 10% residual tumor cells). In other publications, only patients with complete tumor regression are classified as histopathologic responders.[52,53] In contrast, Shah et al defined even patients with less than 50% residual tumor cells as histopathologic responders.[54]

All types of response evaluation, whether clinical or histopathologic, are strongly correlated with prognosis in the literature. However, a homogenization of the scoring systems used for clinical and histopathologic response evaluation is desirable in order to permit easier comparison of results of studies of induction therapy.

Model of Metabolic Response Evaluation in AEG

Measurements of early changes in tumor glucose uptake after only 2 weeks of induction therapy via FDG-PET has yielded reproducible results indicating accuracy in prediction of clinical and histopathologic response to neoadjuvant treatment in adenocarcinomas of the distal esophagus types I and II.[47,48] In a study by our group, the cutoff value of a decrease of more than 35% of the initial standardized uptake

value (SUV) after 2 weeks of induction therapy predicted response and prognosis.[47] Our major interest was to identify nonresponding patients early in the course of therapy to avoid toxic, expensive, and ineffective treatment. The cutoff value was confirmed in an independent patient population.[48] Specifically, we have demonstrated that the 35% decrease in initial SUV after 2 weeks of chemotherapy is highly accurate in identifying nonresponding patients.

This finding was used to individualize treatment in the MUNICON trial (the Metabolic response evalUatioN for Individualisation of neoadjuvant Chemotherapy in oesOphageal and oesophagogastric adeNocarcinoma).[55,56] Metabolic responders after 2 weeks of induction chemotherapy continued to receive chemotherapy for a maximum of 12 weeks before undergoing surgery, whereas metabolic nonresponders discontinued chemotherapy after 2 weeks and were immediately transferred to surgery. Overall, 110 patients were evaluable for metabolic response in this trial, and 49% were classified as metabolic responders; 104 patients underwent resection.

Histopathologic regression with less than 10% residual tumor cells was achieved in 58% of the metabolic responders, but no histopathologic regression 1a or 1b was achieved in metabolic nonresponders. The median overall survival for metabolic responders was not reached, whereas the median survival for metabolic nonresponders was 25.8 months (P = .015). Event-free survival was 29.7 months for metabolic responders and 14.1 months for nonresponders (P = .002).[55,56] Interestingly, metabolic nonresponders, who underwent resection after only 2 weeks of induction therapy, had slightly better survival compared to historic controls consisting of metabolic nonresponders who completed two cycles of neoadjuvant treatment (Figure 1).[48,55]

In summary, the MUNICON study prospectively confirmed the usefulness of metabolic response evaluation in AEG I and II and showed for the first time that a PET-guided treatment algorithm is feasible in the multidisciplinary treatment setting and leads to favorable treatment results. Based on these results, tailoring of multimodal treatment in accordance with indi-

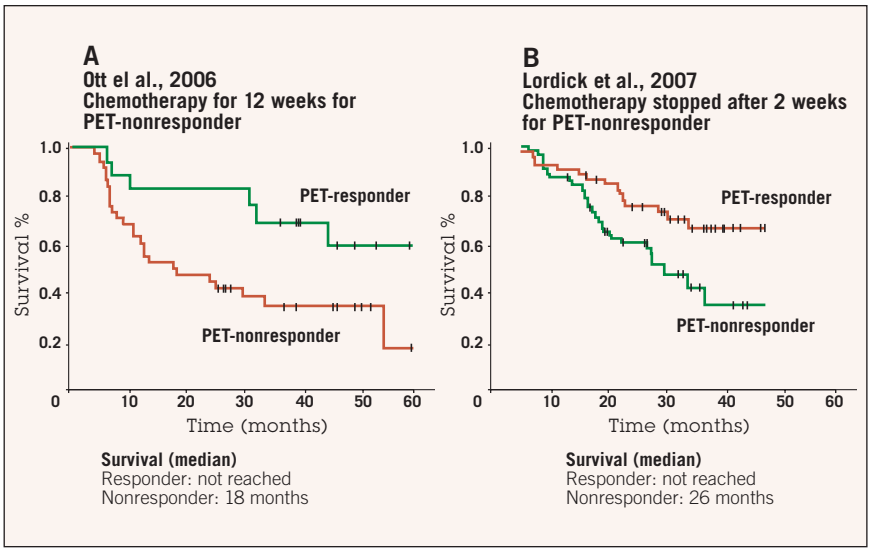

Figure 1. Comparison of overall survival of (A) patients with complete chemotherapy for 3 months[48] and (B) patients with metabolic response-based neoadjuvant treatment.[55] The median survival was 26 months in metabolic nonresponding patients with immediate resection after 2 weeks and 18 months in patients with complete chemotherapy in the historical control group. Stopping chemotherapy, thus, seems not to worsen prognosis of metabolic nonresponding patients.

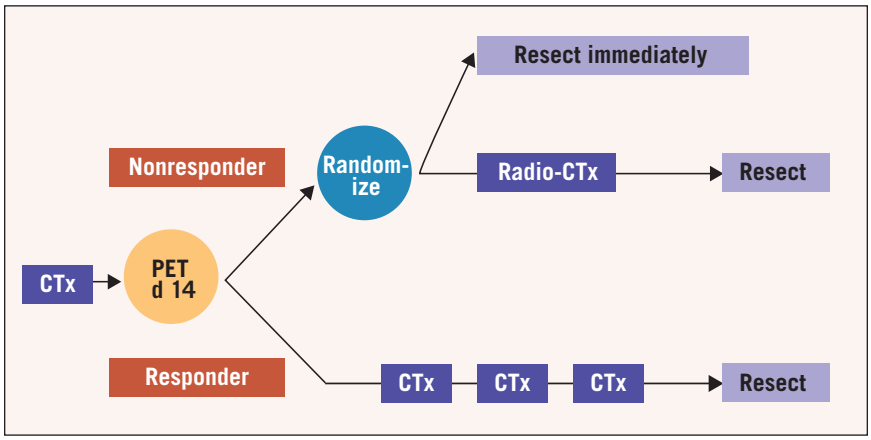

Figure 2. Design of the planned EUROCON study with randomization of nonresponding patients after 2 weeks of chemotherapy (CTx) to immediate resection or chemoradiation therapy (Radio-CTx) followed by surgery. Abbreviation: d = day.

Table 1. Proportion of FDG avid tumors in gastric cancer

Study	N	No. evaluable	%
Ott 2008[67]	71	49	69
Shah 2007[54]	41	31	76
Shah 2007[66]	82	52	63
Wang 2006[64]	29	25	86
Kim 2006[60]	73	70	96
Chen 2005[61]	68	64	94
Yun 2005[65]	81	71	88
Tain 2004[62]	30	25	83
Mochiki 2004[63]	85	64	75
Stahl 2003[37]	40	24	60
Ott 2003[46]	44	35	80

Table 2. Association between metabolic and clinical or histopathologic response

Study	Location	N	Clinical response (*P* value)	Histopathologic response (*P* value)
Weber 2001[47]	AEG I/II	40	—	.001
Ott 2003[46]	Gastric	44	.0002	.0002
Ott 2006[48]	AEG I/II	65	<.001	.001
Shah 2007[54]	Gastric	41	—	.007
Lordick 2007[55]	AEG I/II	110	—	.001
Ott 2008[67]	Gastric	71	.008	<.001

vidual tumor biology might be possible in future randomized trials; the EUROCON study is planned to randomize metabolic nonresponders after 2 weeks of chemotherapy to immediate resection or chemoradiation followed by surgery (Figure 2).

FDG-PET in Gastric Cancer

Current imaging modalities or molecular markers cannot reliably predict therapy response before or early in the course of treatment for gastric cancer.[57–59] As noted above, approximately one third of gastric cancer patients initially have insufficient FDG uptake for quantification (Table 1):[37,46,54,60–67] FDG non-avid tumors are associated with diffuse Lauren classification, small tumor size, good differentiation, mucinous content, and localization in the distal third.[37,59–63,66]

We have shown that a decrease in tumor FDG uptake by more than 35% of the baseline value permitted prediction of response in patients with gastric cancer 2 weeks after initiation of cisplatin-based chemotherapy with an overall accuracy of 83% for 35 patients for whom image contrast was sufficient for quantitative analysis. Metabolic response in FDG-avid gastric cancer including AEG II is associated with histopathologic or clinical response, as shown in Table 2.[46-48,54,55,67]

In our study, median survival for patients with a metabolic response was not reached (2-year survival rate 90%), whereas median survival was 18.9 months in nonresponders (2-year survival rate 25%, $P = .002$) (Figure 3).[46] In a retrospective study by Shah et al in 41 patients with gastric cancer staged cT2-4NanycM0, a decrease of more than 45% in initial SUV after 35 days was identified as the best criterion for predicting response and prognosis; this cutoff value was significantly correlated with histopathologic response (less than 50% residual tumor, $P = .007$) and disease-free survival ($P = .01$).[54] Further work must be done in defining cutoff values and standardizing test methodology before any of these findings can be translated to routine clinical practice.

Another open question is whether early metabolic response evaluation is possible in patients with adenocarcinomas of the esophagogastric junction and the stomach treated with preoperative chemoradiotherapy.[10,68] No data providing guidance in this setting are available so far. Finally, a large proportion of gastric carcinomas are FDG non-avid and thus not suitable for response monitoring using the PET tracer 18F-FDG.

With regard to the latter finding, however, it is of interest that the response rate and prognosis of patients with FDG non-avid tumors seem to be similar to metabolic nonresponders, suggesting that non-avidity may define a subgroup of biologically unfavorable tumors (Figure 4).[67] Our prospective in vivo testing of chemosensitivity by FDG-PET in 71 patients with locally advanced gastric cancer,[67] including those in our earlier study,[46] revealed three different metabolic response groups. Response and prognosis were predicted by FDG-PET in FDG-avid tumors. Metabolic responders showed a high histopathologic response rate (69%) and a favorable prognosis (median survival not reached), whereas metabolic nonresponders had a poorer prognosis (median survival 24.1 months) and a histopathologic response rate of only 17%. The histopathologic response rate of 24% in the third metabolic group, the non-avid tumors, was similar to FDG-avid nonresponders ($P = .72$). Survival of the

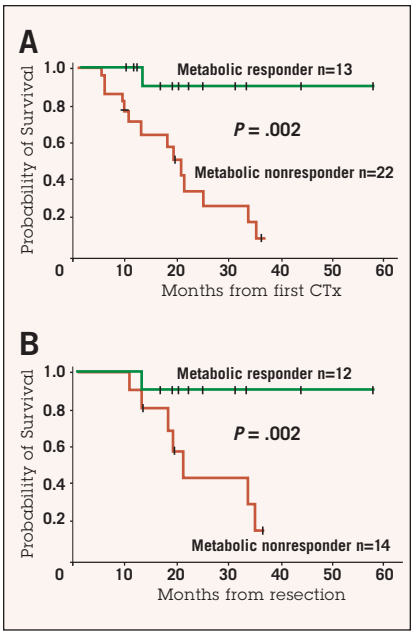

Figure 3: Overall survival of patients with locally advanced gastric cancer who had metabolic response or metabolic nonresponse calculated from the beginning of chemotherapy (A) and from time of complete resection (B). On both analyses, metabolic responders had significantly improved survival compared to metabolic nonresponders. Adapted with permission from Ott et al.[46]

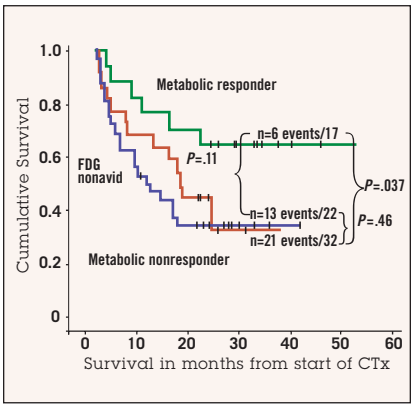

Figure 4: Overall survival of FDG-avid metabolic responding patients (green line), FDG-avid metabolic nonresponding patients (blue line), and FDG non-avid patients (red line). Prognosis of metabolic responding patients is significantly improved compared to metabolic nonresponding patients ($P = .037$). Prognosis of patients with non-avid tumors and FDG-avid nonresponding patients is not statistically different ($P = .46$). There is a trend for improved survival of metabolic responding patients compared to FDG non-avid patients ($P = .11$).
Adapted with permission from Ott et al.[67]

non-avid patients (median 36.7 months) was not different from FDG-avid nonresponders ($P = .46$) (Figure 4).

In a recent study in 45 patients, we compared fluorothymidine (FLT)-PET and FDG-PET for detection of locally advanced gastric cancer.[69] FLT-PET had a higher sensitivity than FDG-PET and might serve as a useful diagnostic adjunct reflecting the quantitative assessment of proliferation (Figure 5). In the future, the addition of FLT-PET to FDG-PET could improve early evaluation of response to neoadjuvant treatment of gastric cancer.

TREATMENT OF THE FUTURE: PET-GUIDED INDUCTION THERAPY

Recent randomized phase III studies have shown that induction therapy is effective in locally advanced gastroesophageal cancer.[1,2] It is generally accepted that responders have improved survival compared to nonresponding patients.[38] Thus far, however, no prospectively tested clinical, histopathologic, or molecular markers predicting response or prognosis prior to induction therapy are available for gastric cancer. Only metabolic response has predicted histologic response and survival with sufficient accuracy.[46,47,54-56]

There is ongoing discussion regarding whether responders or nonresponders after induction therapy in esophageal cancer are candidates for surgery. It is generally accepted that responding patients have a significantly improved prognosis compared to nonresponding patients after resection.[38,52,70] However, in considering treatment outcomes, it is important to differentiate among treatment regimens (eg, chemoradiotherapy or chemotherapy) and histopathology (eg, AEG I or squamous cell cancer).[71–73] Chemoradiotherapy is a local therapy targeting the primary tumor and the regional lymph nodes, with histopathologic response rates up to 50%.[74,75] In contrast, chemotherapy is a systemic treatment, affecting both the primary tumor and potential distant micrometastases in all compartments. The histopathologic response rate of about 20% for the primary tumor in responding patients with adenocarcinomas of the esophagus after systemic chemotherapy is far less than after chemoradiotherapy in squamous cell esophageal cancer.[7,46-48,76]

It is of interest that chemoradiotherapy in patients with squamous cell carcinoma of the esophagus results in the suppression of T lymphocyte function. The proliferative defects of T cells after chemoradiotherapy may be linked to an impaired immune surveillance of cancer and to a higher risk of surgical complications associated with esophagectomy.[5,6] In squamous cell cancer, nonresponding patients have increased postoperative mortality, morbidity, and complication rate in our department.[77] Based on such findings, we recommend resection for all responding patients after induction therapy (chemotherapy and chemoradiotherapy) who are fit for extended surgery.[78,79] For the nonresponding patients with squamous cell esophageal

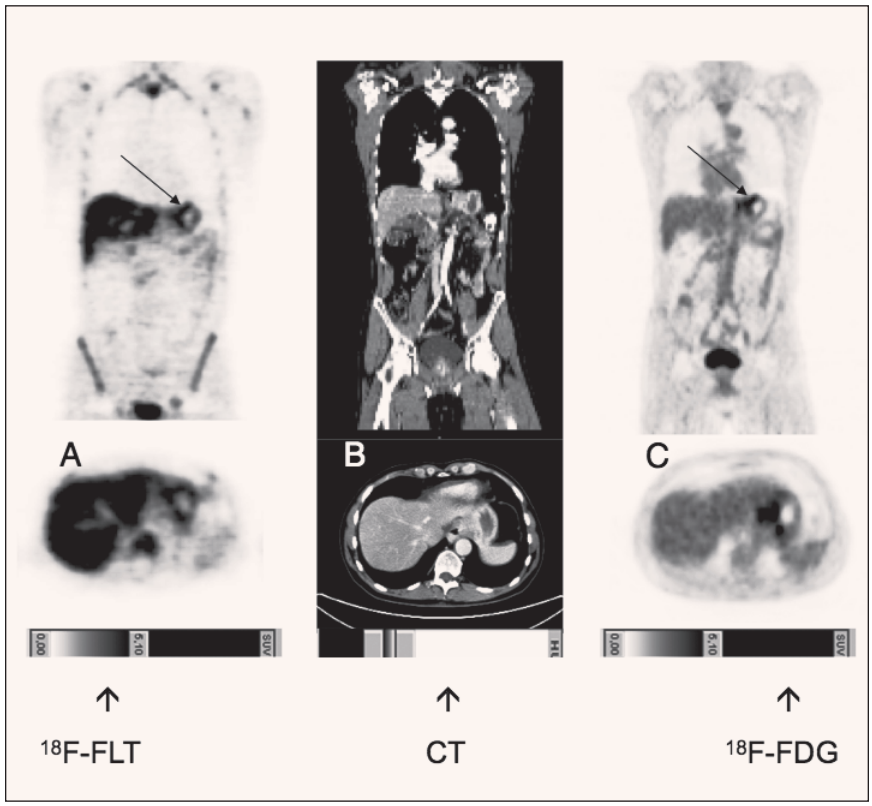

Figure 5. Visualization of locally advanced gastric cancer with FDG-PET and FLT-PET.

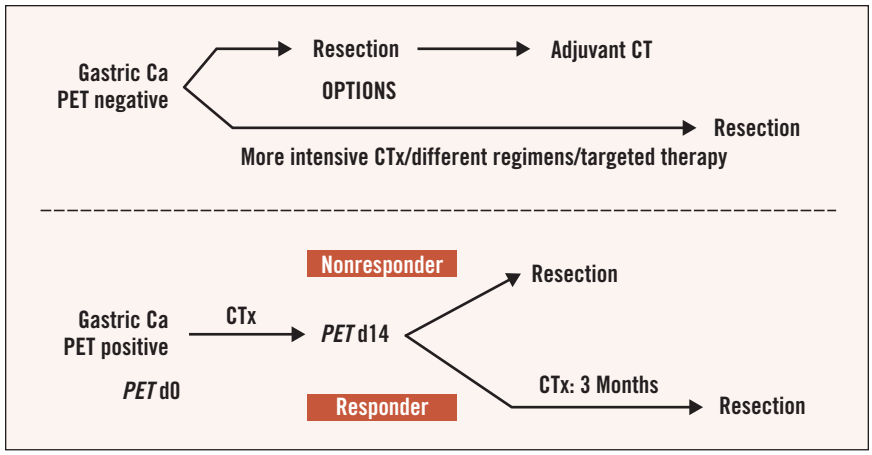

Figure 6: Theoretical model of an individualized FDG-PET–based treatment strategy in locally advanced gastric cancer (ca).
Abbreviations: CTx = chemotherapy; d = day.

cancer, definitive palliative treatment is indicated, with palliative surgery being reserved for individual cases due to the high postoperative complication rate and bad prognosis.[77]

Due to lower immunosuppression and lower complication rate in nonresponders with adenocarcinomas of the distal esophagus compared to squamous cell carcinomas, we suggest surgery even in nonresponding patients with the former.[56] The MUNICON study has shown no increased complication rate or postoperative morbidity or mortality in metabolic nonresponding patients.[55,56] Intensive efforts should be made to determine whether the integration of chemoradiotherapy for metabolic nonresponding adenocarcinomas early in the course of therapy can increase response rates and improve survival in nonresponding patients.

DISCUSSION

In summary, accurate methods to predict response and prognosis are essential to establishing individualized treatment approaches in esophageal cancer. FDG-PET after 2 weeks of induction therapy offers accurate prediction of both response and prognosis. The early response evaluation by FDG-PET offers for the first time the possibility of a modification of treatment early in the course of therapy in esophageal cancer. The results of the MUNICON trial now have to be confirmed in a prospective, randomized multicenter trial (Figure 2).

Given the large proportion of FDG-PET non-avid tumors, the situation is not so straightforward in gastric cancer. Response and survival for non-avid patients were not significantly better than metabolic nonresponders. Alternative treatment concepts that might be considered in these patients include immediate resection after 2 weeks of chemotherapy or adjustment of chemotherapy with or without adjuvant treatment for metabolic nonresponders, or modified or potentially more intensive perioperative chemotherapy regimens — possibly including biologically targeted drugs or intensity-modulated high precision radiotherapy — in initially FDG-PET non-avid tumors (Figure 6). Other techniques for early prediction of response/prognosis, including use of FLT-PET or histopathologic or molecular markers, are likely to be of importance in individualizing therapy in gastric cancer.[69]

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.