

Early Metabolic Response Evaluation by Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography Allows *In vivo* Testing of Chemosensitivity in Gastric Cancer: Long-term Results of a Prospective Study

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Abstract Purpose: We prospectively evaluated the predictive value of positron emission tomography using fluorine-18 fluorodeoxyglucose (FDG-PET) for *in vivo* testing of chemosensitivity in locally advanced gastric cancer using an a priori definition of metabolic response (a decrease of >35% of the standard uptake value). The goal of the study was the definition of biologically different groups of patients prior to or early during induction therapy, with special emphasis on FDG non – avid tumors. **Experimental Design:** Based on our data, which was published in 2003, at least 36 patients with metabolic response or FDG non – avid tumors had to be recruited for an analysis of the group of FDG non – avid tumors with sufficient statistical power. Seventy-one patients (32 metabolic nonresponders, 17 metabolic responders, and 22 patients with FDG non – avid tumors) underwent FDG-PET at baseline. In FDG-avid tumors, FDG-PET was repeated 14 days after the initiation of chemotherapy. **Results:** Metabolic responders (17 of 49) showed a high histopathologic response rate (69%) and a favorable prognosis (median survival not reached), whereas metabolic nonresponders (32 of 49) had a poor prognosis (median survival, 24.1 months) and showed a histopathologic response in 17%. The histopathologic response rate (24%) for FDG-PET non – avid patients showed no significant difference compared with FDG-avid nonresponders ($P = 0.72$). Survival of FDG non – avid patients was 36.7 months (not significantly different from FDG-avid nonresponders, 24.1 months, $P = 0.46$). **Conclusion:** In locally advanced gastric cancer, three different metabolic groups exist. Response and survival was predicted by PET in FDG-avid tumors. Metabolic response assessment was not possible in FDG non – avid tumors; however, due to unfavorable outcome, therapy modification might also be considered in FDG non – avid tumors.

Recently, a randomized phase III study in patients with operable gastric or lower esophageal adenocarcinoma was published by Cunningham et al., demonstrating improved overall and progression-free survival following perioperative chemotherapy compared with surgery alone (1).

However, only 30% to 40% of patients showed a measurable clinical or histopathologic response after neoadjuvant treatment (2–6). Therefore, it would be important to identify patients who do not respond to chemotherapy early in the course of treatment, or even prior to treatment, in order to avoid ineffective therapy with its associated side effects and costs.

Current imaging modalities or molecular markers cannot reliably predict therapy response prior to or early in the course of the treatment—the time when this information is most important (7, 8). In contrast, positron emission tomography (PET) imaging after 2 weeks of chemotherapy is significantly correlated with histopathologic regression and prognosis in patients with adenocarcinoma of the esophagogastric junction (AEG) I and II (5, 6). Interestingly, approximately one third of patients with gastric cancer, even with locally advanced tumors, initially have insufficient fluorine-18 fluorodeoxyglucose (FDG) uptake for quantification (3, 9).

We have recently shown that a decrease in tumor FDG uptake by >35% of the baseline value allowed for accurate prediction of response in patients with gastric cancer 14 days after

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initiation of a cisplatin-based polychemotherapy with an overall accuracy of 83% for 35 patients if image contrast was sufficient for quantitative analysis (3). This study used a cutoff defining the metabolic response derived from patients suffering from locally advanced AEG (6). In approximately a quarter of the patients, tumor metabolic activity was too low for quantitative analysis. Median follow-up was only 18.7 months; long-term survival and recurrence were not assessed in the previous study.

In this study, we prospectively investigated a larger population of patients—including 44 patients published in 2003—with locally advanced gastric cancer with a long-term follow-up (3). We continued to evaluate the a priori-defined threshold for metabolic response using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) as an *in vivo* predictor of tumor response and prognosis. Special emphasis was placed on patients with FDG-PET non-avid tumors in terms of histopathologic characterization, response, and prognosis. The major aim of our study was the *in vivo* identification of subgroups of patients with locally advanced gastric cancer with different tumor biology prior to or early in the course of therapy. We hypothesized that there are three groups of patients that differ in tumor biology and can be differentiated by FDG-PET: (a) metabolic responders, (b) metabolic nonresponders (a and b representing FDG-avid tumors), and (c) FDG non-avid tumors.

Materials and Methods

Study design. The primary end point of the study was the outcome of patients with FDG-avid responding and FDG non-avid tumors. Our hypothesis was that FDG-avid responding patients have a better prognosis than FDG non-avid tumors. Furthermore, we intended to analyze the course and the histopathologic features of FDG non-avid tumors after cisplatin-based induction therapy. Our previous study (3) has suggested the following: (a) that a metabolic response is achieved in ~25% of the treated patients and that 25% showed a low FDG uptake insufficient for metabolic evaluation; (b) that the 2-year survival rate was 90% for FDG-avid metabolic responders and 53% for FDG-PET non-avid tumors (44 patients: 13 metabolic responders, 22 metabolic nonresponders, 9 FDG non-avid tumors; corresponding median survival not reached, 18.9, 35.2 months). We continued to include patients to fulfil the following criteria focusing on the comparison of patients with FDG-PET non-avid tumors versus metabolic responders. Including the patients from the previous study, a total accrual time of 72 months and a mean follow-up time of 24 months, 36 patients with metabolic response or FDG non-avid tumors had to be included in the study to detect a difference in overall survival with a power of 80% at a 5% significance level using a log-rank test (10). The secondary end point was to compare the outcome of patients with FDG non-avid tumors and FDG-avid nonresponding tumors.

Patient population. From June 3, 1996 to July 7, 2002, 71 patients [49% (71 of 146) of all neoadjuvantly treated patients with gastric cancer during this period: no difference with respect to survival ($P = 0.74$) and response (clinical, $P = 1.0$; histopathologic, $P = 0.24$) was found for the FDG-PET study subgroup] were included in this study. Eligibility requirements included the presence of biopsy-proven advanced gastric cancer with or without metastases in local lymph nodes (tumor stage cT_{3-4} , cN_{0-3} , and cM_0 in the tumor-node-metastasis classification). Details of the applied staging techniques have been published previously (11, 12). Eligible patients had to be fit for cisplatin-containing chemotherapy and consecutive surgical resection. Staging procedures except laparoscopy were repeated preoperatively for all patients and reduction of tumor size was evaluated as previously

described (6). The study protocol was approved by the Institutional Review Board at the Technische Universität München. Written informed consent was obtained from all patients.

Preoperative chemotherapy consisted of two cycles of combination chemotherapy, each of 36 days duration (cisplatin, 50 mg/m²/bovine serum albumin on days 1, 15, and 29; leucovorin, 500 mg/m²/bovine serum albumin, and 5-fluorouracil 2 g/m²/m² body surface area on days 1, 8, 15, 22, 29, and 36; refs. 3–5). Surgical resection of the tumor was scheduled 3 to 4 weeks after completion of chemotherapy.

Imaging studies. Baseline PET scan was done as part of the staging procedure on an ECAT EXACT full-ring PET scanner (CTI/Siemens). Patients fasted 6 h before the PET scan and blood glucose levels were measured before each PET examination. All measured values were <150 mg/dL and showed no significant changes during chemotherapy. Static emission images of the tumor region at a duration of 20 min were acquired 40 min after i.v. injection of 300 to 400 MBq of FDG. Data reconstruction and semiquantitative evaluation of the two PET studies was carried out as previously described (3, 6). For assessment of reproducibility of the quantitative evaluation of FDG-PET studies, all PET scans were analyzed by two independent experienced observers (W. Weber and H. Wieder).

Clinical response evaluation. Before surgery, a response evaluation was done by the interdisciplinary tumor board of the Technische Universität München, without knowledge of the results of the FDG-PET studies. Tumors were classified as responding or nonresponding using predefined criteria (3, 5, 6). The same criteria for response were used in our previous studies and have been shown to be of prognostic relevance (3–6).

Histopathologic response evaluation. Histopathologic analysis of the resected specimens was done by a single pathologist (K. Becker) who was unaware of the results of PET imaging. Tumor regression was assessed semiquantitatively according to a recently published scoring system (13). For the purposes of this study, all patients with <10% residual tumor cells (regression score, grade 1) were classified as responding. All other patients were classified as nonresponding.

Surgery. In patients with proximal gastric cancer, a transhiatal extended gastrectomy and an extended D2-lymphadenectomy (resection of the lymph node groups 1 and 2 according to the Japanese Research Society for Gastric Cancer), including a left retroperitoneal lymphadenectomy were done; for patients with tumor localization in the middle or distal third, a total gastrectomy with D2-lymphadenectomy was done (14, 15).

Patient follow-up. After surgical resection, patients were observed at 3-month intervals by computed tomography of the chest and abdomen and endoscopy in the first year, at 6 month intervals in the second and third year, and afterwards, at 12-month intervals. Overall survival was calculated from the first day of chemotherapy. In patients with curative (R₀) resection, survival was calculated from resection to death. No patient was lost to follow-up.

Statistical analysis. All quantitative data are expressed as mean \pm 1 SD. Differences in proportions of patients were analyzed by Fischer's exact test or χ^2 test, where appropriate. Interindividual and intraindividual comparisons of quantitative data were made by using a Mann-Whitney-U test and a Wilcoxon signed rank test, respectively. Survival rates were estimated according to Kaplan-Meier. Statistical comparisons between different groups of patients were done with a log-rank test and the proportional hazard model. Cohen's κ was used to assess the agreement between two measurements. All tests were two-sided and were done at the 5% level of significance by using SPSS 14 software (SPSS Inc.).

Results

Seventy-one patients were included in this study. Thirty-one are alive, 28 without recurrence. The median follow-up for the surviving patients was 56.0 months (35.1–104.2 months).

Table 1. Preoperative patient characteristics

	All patients	Evaluable patients*	Histopathologic responders	Histopathologic nonresponders	P value (responders vs. nonresponders)
N	71	49	16	33	—
Age	56 ± 10	56 ± 9	56 ± 13	56 ± 8	1.00
Male/female	50/21	37/12	11/5	26/7	0.49
Lauren classification					
Intestinal/nonintestinal	33/38	26/23	11/5	15/18	0.14
Localization					
Proximal/middle and distal	50/21	38/11	13/3	25/8	1.00
Tumor FDG uptake					
Baseline (SUV)	7.6	12.3 ± 6.9	13.1 ± 6.5	11.9 ± 7.2	0.34
Day 14 (SUV)	—	8.1 ± 4.2	6.1 ± 3.2	9.1 ± 4.4	0.03
Change (%)		-30 ± 24	-48 ± 22	-21 ± 20	<0.0007

*Patients with sufficient FDG uptake.

The primary tumor was localized in the proximal third in 50 patients (70%), 16 (23%) tumors were localized in the middle third, and 5 (7%) tumors were localized in the distal third of the stomach. According to the Lauren classification, 33 (46%) tumors were of the intestinal subtype and the remaining 38 (54%) tumors were of the nonintestinal subtype (Table 1). The majority of tumors (54; 76%) showed aggressive histology (grade 3 or 4). Sixty-six of the included patients were resected, five patients were not resected due to metastatic disease. The tumor resection was histopathologically complete (R₀) in 53 patients, and R₁ in 13 patients. The tumor stage was ypT₀ in 4, ypT₁ in 8, ypT₂ in 33, ypT₃ in 14, and ypT₄ in 7 patients. Twenty-seven patients showed no lymph node (ypN₀) metastases, whereas lymph node metastases were present in 39 patients (23 ypN₁, 12 ypN₂, and 4 ypN₃).

In the 49 patients assessable for early metabolic response, mean FDG uptake was 12.3 ± 6.9 standard uptake value (SUV; median, 11.5). In the second PET scan, mean SUV uptake decreased by 25 ± 24% to 8.1 ± 4.2 SUV (median, 7.0; P < 0.001; Table 1).

FDG-PET non-avid patients

Twenty-two of the included patients showed insufficient image contrast in the initial PET scan for early metabolic response evaluation (Fig. 1). FDG non-avid tumors often contained significantly more signet ring cells (12 of 22 versus 11 of 49; P = 0.013). Additionally, the proportion of FDG non-avid tumors compared with FDG-avid tumors was significantly higher (P = 0.029) in the middle and distal third of the stomach. Only 52% of the tumors not localized in the proximal third had sufficient FDG uptake for quantification (Table 2).

Response evaluation

Clinical response. The clinical response rate after completion of preoperative chemotherapy was 26% (18 of 71) in the whole group of patients and 27% (13 of 49) in patients with assessable PET scans. Clinical responders had a markedly higher SUV decrease during therapy (-50 ± 22%; median, -55%) than nonresponders (-23 ± 21%, median, -24%; P = 0.001). There was no difference in baseline (13.4 ± 7.1

versus 11.1 ± 6.9; P = 0.204) and in day 14 FDG uptake (6.3 ± 3.3 versus 8.7 ± 4.5; P = 0.094) between responders and nonresponders. In the subgroup of patients with FDG non-avid tumors, 23% (5 of 22) of the patients showed a clinical response. Metabolic responders (9 of 17; 53%) showed a

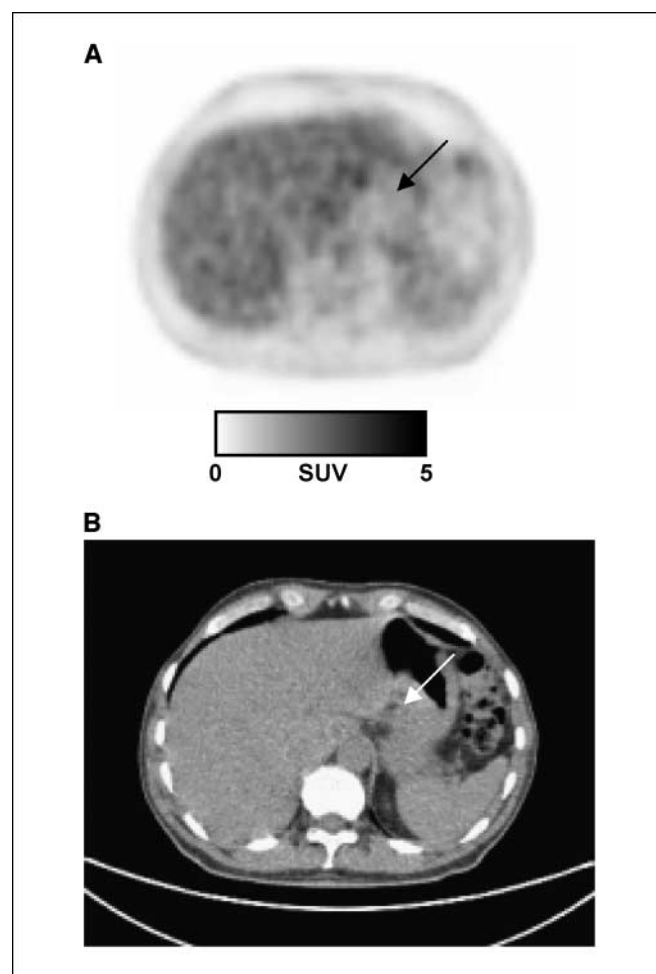


Fig. 1. Transaxial PET image of a PET-negative patient at baseline (A). There is no FDG accumulation in the tumor that is marked in the computed tomography scan (B).

Table 2. Tumor characteristics and metabolic response predicting histopathologic response

	Evaluable*	Sensitivity	Specificity	Accuracy	PPV †	NPV‡
Total	49/71 (69%)	11/16 (69%)	27/33 (82%)	38/49 (78%)	11/17 (65%)	27/32 (84%)
Localization						
Proximal third	38/50 (76%)	9/13 (69%)	20/25 (80%)	29/38 (76%)	9/14 (64%)	20/24 (83%)
Middle and distal third	11/21 (52%)	2/3 (67%)	7/8 (88%)	9/11 (82%)	2/3 (67%)	7/8 (88%)
Lauren classification						
Intestinal	26/33 (79%)	9/11 (82%)	13/15 (87%)	22/26 (85%)	9/11 (82%)	13/15 (87%)
Nonintestinal	23/38 (61%)	2/5 (40%)	14/18 (78%)	16/23 (70%)	2/6 (33%)	14/17 (82%)

*Patients with sufficient FDG uptake.
† PPV, positive predictive value.
‡ NPV, negative predictive value.

clinical response significantly more often compared with metabolic nonresponders (4 of 32; 13%) or patients with FDG non-avid tumors (5 of 22; 23%; $P = 0.008$).

Histopathologic response. A histopathologic response was found in 21 of 71 (30%) patients, and 4 of 71 (6%) patients showed complete regression of the primary tumor. The histopathologic response rate was 16 of 49 (33%) in patients with assessable PET scans. Histopathologic responders had a markedly higher SUV decrease during therapy ($-48 \pm 22\%$; median, -52%) compared with nonresponders ($-21 \pm 20\%$; median, -20% ; $P < 0.0001$) and a significantly lower FDG uptake at day 14 (6.1 ± 3.2 versus 9.1 ± 4.4 ; $P = 0.03$; Table 1). There was no difference in baseline FDG uptake between responders and nonresponders (13.1 ± 6.5 versus 11.9 ± 7.2 ; $P = 0.34$).

Metabolic response

Patients with FDG-avid tumors. In the group of patients with sufficient image contrast ($n = 49$), 17 patients (35%) were classified as metabolic responders, whereas 32 patients (65%) were classified as metabolic nonresponders. Of the 16 metabolic responders undergoing surgery, 11 patients (69%) achieved a histopathologic response. In contrast, only 5 of the 29 (17%) metabolic nonresponders undergoing surgery showed a histopathologic response ($P < 0.001$).

A metabolic response correctly predicted histopathologic regression in 11 of 16 responding and 27 of 33 nonresponding tumors. This resulted in a sensitivity and specificity of 69% [95% confidence interval (CI), 46-91%] and 82% (95% CI, 69-95%), respectively. Positive and negative predictive value for response were 65% (95% CI, 42-87%) and 84% (95% CI, 72-97%), respectively. The overall accuracy was 78% (95% CI, 66-89%). Sensitivity and positive predictive value for predicting histopathologic regression was low for the nonintestinal subtype (Table 2).

Patients with FDG non-avid tumors. Twenty-two of 71 (31%) patients had a low FDG uptake and therefore were not suitable for early metabolic response evaluation. Five of the 22 FDG non-avid patients (23%) showed a clinical response. Compared with the group of metabolic nonresponders (4 of 32 with clinical response; 13%) there were no statistical differences ($P = 0.46$). Similarly, 5 of the 21 (24%) resected and FDG non-avid tumors showed a histopathologic response. The histopathologic response rate for this group of patients was not statistically different compared with metabolic nonresponders ($P = 0.72$). In contrast, the clinical (5 of 22 patients, 23%) and histopathologic (5 of 21 resected patients, 24%) response rates

of FDG non-avid tumors were statistically different from the clinical (9 of 17 patients, 53%) and histopathologic (11 of 16 resected patients, 69%) response rates of metabolic responders ($P = 0.05$ and $P = 0.006$), respectively.

Prognosis

Median overall survival was 35.2 months. No statistically significant difference in survival could be shown between patients with FDG-avid and FDG non-avid tumors (median survival: FDG-avid, 33.4 months; FDG non-avid, 36.7; $P = 0.88$). Compared with the median survival of metabolic responders (median survival not reached), median survival was 24.1 months ($P = 0.037$) for metabolic nonresponders and 36.7 months ($P = 0.11$) for patients with FDG non-avid tumors. Therefore, the primary end point was not reached for the whole group of patients. The median survival of FDG non-avid patients was revealed to be slightly but not significantly better ($P = 0.46$) than the survival of PET nonresponders

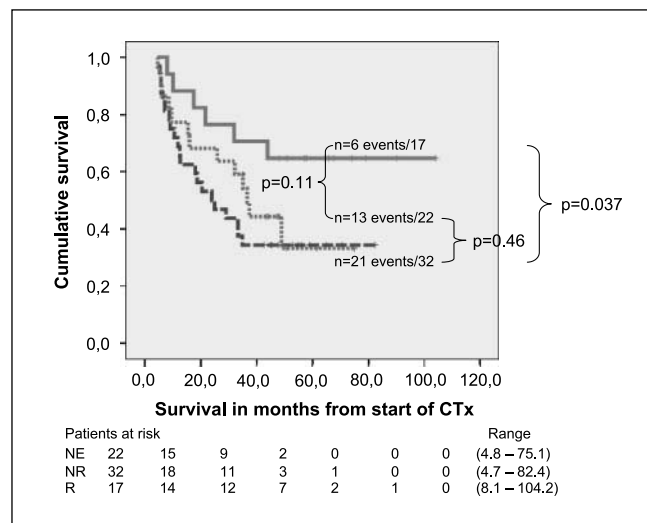


Fig. 2. Overall survival of all patients classified as metabolic responders (solid line), nonresponders (dashed line), and FDG non-avid patients (dotted line; $n = 71$). Median survival of metabolic responders ($n = 17$) was not reached during the follow-up period, whereas median survival was 24.1 m for metabolic nonresponders ($n = 32$) and 36.7 m for FDG non-avid patients ($n = 22$). The number of events during the period and the number of patients at risk after each 20-month interval are indicated (R, responder; NR, nonresponder; NE, not evaluable).

(Fig. 2). In a proportional hazard model, the risk of death for patients with a metabolic response was 39% for the patients without a metabolic response ($P = 0.045$) and 46% for the patients with FDG non-avid tumors ($P = 0.12$).

In patients with complete (R_0) tumor resection ($n = 53$), the median overall survival was also significantly better for metabolic responders than for nonresponders (median survival not reached and 35.0 months, respectively, $P = 0.026$). The median survival of metabolic responders was significantly better compared with FDG non-avid patients (45 months; $P = 0.043$; Fig. 3) as well. For the 53 completely resected patients, median disease-free survival was not reached. Twenty-eight patients showed no evidence of disease. For disease-free survival, there was a trend towards better survival for metabolic responders compared with metabolic nonresponders. Median disease-free survival of metabolic nonresponders was 27.8 months, whereas median disease-free survival was not reached for metabolic responders ($P = 0.058$). PET negative patients had a disease-free survival of 25.2 months ($P = 0.135$).

The univariate analysis for all patients revealed clinical response ($P < 0.001$), histopathologic response ($P < 0.0001$), and metabolic response ($P = 0.045$) as significant prognostic factors (Table 3A). A multivariate analysis including metabolic response, grading, Lauren classification [the agreement between pretherapeutic Lauren classification and postoperative Lauren classification was substantial ($\kappa = 0.67$; $P < 0.001$)] and location of the primary tumor, all of which were available prior to or early in the course of treatment, revealed metabolic response as the only significant presurgical predictor for survival ($P = 0.045$; relative risk, 0.39; 95% CI, 0.16-0.98; Table 3B). In a multivariate analysis comprising pretherapeutic and posttherapeutic variables (clinical response, histopathologic response, metabolic response, grading, ypT, ypN category, resection rate, baseline FDG uptake, and FDG uptake at day 14) only R_0 resection ($P < 0.001$; relative risk, 0.20; 95% CI, 0.08-0.53) and histopathologic response ($P = 0.012$; relative risk, 0.15; 95% CI, 0.03-0.65) were significantly correlated with survival (Table 3A). In the group of patients with complete (R_0) tumor resection, univariate and multivariate analyses showed essentially the same results as in all patients. In the multivariate analysis including pretherapeutic and posttherapeutic variables, a tumor category less than ypT₃ was established as an independent prognostic factor instead of R_0 resection (Table 3C and D).

Discussion

In patients with gastric cancer, this prospective study shows that quantification of tumor FDG uptake allows the prediction of histopathologic response as well as patient outcome prior to or early in the course of neo-adjuvant treatment. FDG-PET was particularly useful for identifying nonresponding patients, with a specificity of 82% and a negative predictive value of 84%. An important finding of our study was the unfavorable outcome of patients with FDG non-avid tumors, and a median survival of 36.7 months, which is not significantly different from that of FDG-avid nonresponders (24.1 months). In a subgroup of patients undergoing complete resection of the primary tumor, a significant difference in overall survival could also be shown between FDG non-avid patients and FDG-avid responders. However, in the whole patient collective, median survival did

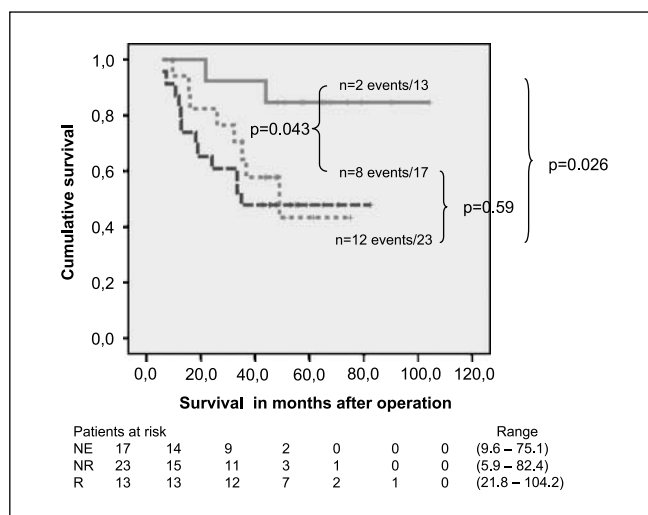


Fig. 3. Overall survival of all patients with complete tumor resection classified as metabolic responders (solid line), nonresponders (dashed line), and FDG non-avid patients (dotted line) on day 14 of the first chemotherapy cycle ($n = 53$). Median survival of metabolic responders ($n = 13$) was not reached during the follow-up period, whereas median survival was 35 m for metabolic nonresponders ($n = 23$) and 45 m for FDG non-avid patients ($n = 17$). The number of events during the period and the number of patients at risk after each 20-month interval are indicated (R, responder; NR, nonresponder; NE, not evaluable).

not differ significantly between either group. Our results indicate that, in addition to metabolic responders and nonresponders, FDG-PET identifies a third group of patients with a different tumor biology associated with poor outcome.

Reliable prediction of response to neo-adjuvant treatment is a highly desired goal, potentially resulting in superior patient outcome. Several tumor-related or constitutional molecular markers have been investigated in view of predicting tumor response and prognosis following neoadjuvant chemotherapy (16–22). However, all these studies were not designed prospectively, and to date, none of the examined variables could gain clinical relevance in gastric cancer. Especially in the group of FDG non-avid patients, who have essentially similar overall survival compared with the group of FDG-avid patients, the development of molecular markers predicting response would be of utmost interest.

The findings of this prospective study confirm previous studies on the predictive value of early changes in glucose metabolism after induction chemotherapy for response and prognosis in AEG I and II (3, 5, 6). Different from AEG I and II tumors, approximately one-third of gastric cancers cannot be visualized with sufficient contrast for quantification. In this study, 15 of the 22 (68%) tumors which were not assessable were of the nonintestinal subtype (eight contained signet cells). These findings are in agreement with reports in the literature that mention a reduced sensitivity of FDG-PET for the detection of nonintestinal gastric cancer (9, 23, 24). The proportion of FDG non-avid tumors, compared with PET-positive tumors, was significantly higher in the distal two-thirds of the stomach ($P = 0.029$) and the tumors with insufficient image contrast contained significantly more signet cells ($P = 0.013$). The tumors of the nonintestinal subtype were significantly more often localized in the distal two-thirds of the stomach ($P = 0.006$). It has been postulated that the low or absent FDG uptake in the nonintestinal subtype is a result of the high

content of mucin, leading to a reduced FDG concentration in the tumor. Another reason could be the lack of expression of the glucose transporter Glut-1 on the cell membrane of most nonintestinal gastric cancer tumors (25). Although in FDG non-avid patients, the metabolic response could not be assessed, the survival of these patients was only slightly better compared with metabolic nonresponders and the likelihood of a histopathologic or clinical response was low. Obviously, the initially low FDG uptake probably unmasks a group of biologically unfavorable tumors in which cisplatin/fluorouracil-based chemotherapy is not highly efficient. Only 23% and 24% of patients undergoing 3 months of neoadjuvant treatment show clinical or histopathologic responses to this regimen. These data are not statistically different from the response rates of the FDG-avid patients (27% and 33%), but are statistically different from those of FDG-avid responding patients (53% and 69%). An increase in the histopathologic response rate of 9% (comparing the FDG non-avid group and the FDG-avid group) and 45% (comparing the FDG non-avid group and the FDG-avid responding subgroup) would potentially justify the consideration of a modification of therapy in FDG non-avid patients. Given the data reported by Cunningham and Macdonald et al. (1, 26) showing a significant survival benefit

for perioperative chemotherapy or adjuvant RCTx compared with primary resection, in this group, a pretherapeutic PET-guided adjustment of the treatment regimen with a modified chemotherapy regimen or the additional administration of biological chemoresponse modifiers or postoperative therapy could be considered.

The metabolic response, as assessed by FDG-PET, was an independent prognostic factor in a multivariate model including presurgical variables as covariates for overall survival in the group of resected as well as completely resected patients. In a multivariate model, which also included postsurgical variables, response in FDG-PET was not an independent prognostic factor. However, the response of the tumors by FDG-PET could be assessed as early as 2 weeks after the first chemotherapy cycle, whereas ypT, R₀ category, and histopathologic response could only be determined after resection. Therefore, the present study provides evidence that FDG-PET is the only factor prior to or early in the course of therapy that allows the identification of patients with different chemosensitivities to the applied regimen. Consequently, patients without a metabolic response after 2 weeks of preoperative chemotherapy could receive an alternative therapy regimen early after the onset of preoperative chemotherapy. This would

Table 3. Cox regression analyses

	Univariate analysis		Multivariate analysis	
	Hazard ratio	P	Hazard ratio	P
(A) Cox regression analysis of prognostic factors in all patients (n = 71), overall survival				
Clinical response	0.19 (0.07-0.52)	0.001	—	—
Histopathologic response	0.15 (0.05-0.41)	<0.0001	0.15 (0.03-0.65)	0.012
Metabolic response	0.39 (0.16-0.98)	0.045	—	0.81
ypT category less than ypT ₃	0.24 (0.12-0.47)	<0.0001	—	0.10
ypN ₀ category	0.25 (0.15-0.67)	0.003	—	0.31
Grading less than G ₃	0.43 (0.18-1.02)	0.056	—	—
R ₀ category	0.13 (0.07-0.25)	<0.0001	0.20 (0.08-0.53)	0.001
Baseline FDG uptake*	—	0.51	—	—
FDG uptake at day 14*	—	0.29	—	—
(B) Cox regression analysis of presurgical prognostic factors in all patients (n = 71), overall survival				
Metabolic response	0.39 (0.16-0.98)	0.045	0.39 (0.16-0.98)	0.045
Grading less than G ₃	0.43 (0.18-1.02)	0.056	—	—
Lauren classification	—	0.13	—	—
Localization	—	0.72	—	—
(C) Cox regression analysis of prognostic factors in patients with complete resection (n = 53), survival				
Clinical response	0.29 (0.10-0.86)	0.025	—	—
Histopathologic response	0.22 (0.08-0.67)	0.007	0.20 (0.04-0.92)	0.04
Metabolic response	0.22 (0.05-0.96)	0.044	—	0.54
ypT category less than ypT ₃	0.21 (0.09-0.50)	<0.0001	0.18 (0.05-0.57)	0.004
ypN ₀ category	0.31 (0.12-0.80)	0.015	—	0.49
Grading less than G ₃	0.61 (0.22-1.65)	0.33	—	—
Baseline FDG uptake †	—	0.25	—	—
FDG uptake at day 14 †	—	0.60	—	—
(D) Cox regression analysis of presurgical prognostic factors in patients with complete resection (n = 53), survival				
Metabolic response	0.22 (0.05-0.96)	0.044	0.22 (0.05-0.96)	0.044
Grading less than G ₃	0.61 (0.22-1.65)	0.33	—	—
Lauren classification	0.58 (0.25-1.36)	0.21	—	—
Localization	1.79 (0.61-5.29)	0.29	—	—

NOTE: Values in parentheses indicate the 95% CI of the hazard ratio.

*FDG uptake less than the median (7.6 and 7.0 SUV, respectively).

†FDG uptake less than the median (7.2 and 5.5 SUV, respectively).

potentially imply individual changes in therapeutic management in 32 of 49 patients (65%) early in the course of treatment. In the MUNICON study, chemotherapy was stopped after 2 weeks in metabolic nonresponding patients with AEG I and II. Median recurrence-free and overall survival were, respectively, 14.1 and 25.8 months in these patients compared with 10 and 18 months in a previous study with similar tumor stages and similar chemotherapy continued in metabolically nonresponsive patients for 3 months (5, 27, 28). Such changes would not be possible on the basis of postoperative prognostic factors which could only lead to an adjustment of the postoperative adjuvant treatment. In metabolic nonresponding patients, two cycles of chemotherapy with a duration of >3 months did not seem to be appropriate, as this resulted in neither a high histopathologic response rate nor in a satisfying prognosis. Early resection, in combination with postoperative treatment in metabolic nonresponders, may be discussed (26). Taken together, in the whole cohort of patients, a PET-guided adjustment of the treatment strategy pretherapeutically or early in the course of therapy might be useful in 32 FDG-avid nonresponders and could also be potentially considered in the 22 FDG-PET non-avid patients with response rates of 23% to 24%, and

therefore, might lead to a change of the therapeutic management in up to 76% of patients.

In conclusion, tumor response and survival in locally advanced gastric cancer was predicted with sufficient accuracy by an a priori-defined metabolic response cutoff value of 35%. In contrast to AEG I and II, FDG-PET identified three metabolic groups with different biological behaviors and chemosensitivities. To improve the response rates and the prognosis of PET nonresponding patients, alternative treatment concepts such as immediate resection after 2 weeks of chemotherapy or adjustment of chemotherapy with or without adjuvant treatment or potentially more intense perioperative chemotherapeutic regimens—possibly including biologically targeted drugs—in initially FDG non-avid tumors should be considered. In patients with FDG non-avid tumors, there is no possibility to identify those patients with PET who may benefit from a cisplatin-based regimen. However, response and survival in FDG non-avid patients were not significantly different compared with metabolic nonresponders. Therefore, FDG “nonavidity” enables to define a subgroup of patients with gastric cancer with poor response rate and unfavorable prognosis in completely resected patients also implying clinical consequences.

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