^{18}F-FDG PET/CT Predicts Survival After Radioembolization of Hepatic Metastases from Breast Cancer

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^{90}Y radioembolization (selective internal radiation therapy [SIRT]) has emerged as a valuable therapeutic option in unresectable, chemotherapy-refractory hepatic metastases from breast cancer. The objective of the present study was to evaluate ^{18}F-FDG PET/CT for predicting survival in these patients. **Methods:** Fifty-eight consecutive patients with hepatic metastases from breast cancer were treated with SIRT. Before therapy, all patients underwent MRI of the liver. ^{18}F-FDG PET/CT was performed at baseline and 3 mo after SIRT to calculate percentage changes in maximum ^{18}F-FDG standardized uptake value (SUV_{max}) relative to baseline. A decrease of more than 30% in the follow-up scan, compared with the baseline examination, indicated therapy response. Treatment response at 3 mo was also assessed in 43 patients using contrast-enhanced MRI and CT on the basis of the Response Evaluation Criteria in Solid Tumors. All patients were followed to complete survival data. **Results:** Overall median survival after SIRT was 47 wk. Response as assessed with SUV_{max} correlated significantly with survival after radioembolization, with responders having significantly longer survival (65 wk) than nonresponders (43 wk; $P < 0.05$). In multivariate analysis the change in SUV_{max} was identified as the only independent predictor of survival (hazard ratio, 0.23; $P < 0.005$). Furthermore, a high pretherapeutic SUV_{max} (>20) was associated with a significantly shorter median survival than was an SUV_{max} of 20 or less (21 vs. 52 wk; $P < 0.005$). The presence of extrahepatic metastases (mean survival in both groups, 47 wk; $P = 0.92$), hormone receptor status (estrogen, $P = 0.53$; progesterone, $P = 0.79$; Her-2/*neu*, $P = 0.49$), and MRI/CT response ($P = 0.91$) did not predict survival. **Conclusion:** The change in SUV_{max} as assessed by ^{18}F-FDG PET/CT before and 3 mo after SIRT was identified as the only independent predictor of survival in patients with hepatic metastases of breast cancer.

Key Words: ^{18}F-FDG PET; breast cancer; hepatic metastases; radioembolization; ^{90}Y

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Breast cancer is the most common malignancy affecting women in developed countries. Despite advances in adjuvant treatment, about 20% of patients with initially local disease will still develop metastases (*1*), frequently involving the liver. In most patients, curative surgical resection of liver metastases is not an option because of the presence of extrahepatic disease or multisegmental involvement of the liver. Other local therapies, such as radiofrequency ablation, are feasible in only a limited number of patients exhibiting only a few, small hepatic metastases. Despite significant advances in chemotherapeutic options in metastatic breast cancer, the presence of liver metastases limits survival in up to 60% of patients. Median survival in women exhibiting liver metastases of breast cancer has been estimated at about 18 mo (*2*).

More recently, radioembolization using ^{90}Y-microspheres (selective internal radiation therapy [SIRT]) has emerged as a palliative treatment for hepatic metastases of various tumors (*3–6*). In hepatic metastases of breast cancer (*7–9*), reported response rates to SIRT have ranged from 39% to 61%, with subsequent mean survival of 2–14 mo (*9*). The high variability of these findings is explained in part by differences in histologic tumor grading and by the presence of hormone receptors or the Her-2/*neu* receptor status on the surface of breast cancer cells, which are well-known prognostic factors influencing survival of metastasized breast cancer patients (*10*). Other factors, such as a tumor burden of less than 25% and a good performance status of the patient, were also associated with longer survival after radioembolization, though these factors did not reach statistical significance (*7*). Furthermore, the findings of a recent preliminary study suggested that response to SIRT as assessed by CT or MRI reliably predicts survival (*9*).

Compared with morphologic imaging modalities such as CT and MRI, PET with the glucose analog ^{18}F-FDG returned superior results in monitoring therapy response and predicting survival in patients with various tumors (*11–15*). The first published results indicate a high prognostic power for ^{18}F-FDG PET in the prediction of survival after SIRT in patients with intrahepatic cholangiocellular carcinoma (*16*).

The aim of the present study was to evaluate the role of ^{18}F-FDG PET in predicting survival after SIRT in patients with hepatic metastases of breast cancer. We hypothesized that a significant decrease of glucose metabolism after SIRT is associated with longer survival and that metabolic imaging is superior to both morphologic imaging modalities and biologic parameters such as patients' hormone and Her-2/*neu* receptor status.

MATERIALS AND METHODS

Included in the present study were patients meeting the following criteria: over 18 y of age; confirmed hepatic metastases from breast cancer; unresectable, chemotherapy-refractory, progressive tumor; preserved liver function, as defined by a serum bilirubin level of 2.0 mg/dL or less; performance status of 60 or more on the Karnofsky index; life expectancy of more than 3 mo; and ability to undergo angiography. Patients with limited extrahepatic metastases were not excluded if the hepatic metastases were deemed to be the predominant and presumptively life-limiting disease. Exclusion criteria were as follows: liver failure (bilirubin level > 2.0 mg/dL or presence of ascites); evidence of any uncorrectable flow to the gastrointestinal tract observed on angiography or ^{99m}Tc-macroaggregated albumin scintigraphy; lung shunt greater than 20% as estimated with ^{99m}Tc-macroaggregated albumin scintigraphy (*17,18*); and complete portal venous occlusion. At study inclusion, patients' history, including date of initial diagnosis of breast cancer, previous chemotherapies, and local therapies such as radiofrequency ablation, chemoembolization, or surgery, were recorded. Patient characteristics are presented in Table 1.

Pretherapeutic Examinations

All patients underwent pretherapeutic imaging with whole-body ^{18}F-FDG PET/CT performed in 3-dimensional mode (3 min per bed position) using a Gemini (Philips) or a Biograph 64 TruePoint (Siemens Medical Solutions). The emission sequence was initiated 60 min after completion of intravenous injections of 20 mg of furosemide, 20 mg of butylscopolamine, and 300 MBq of ^{18}F-FDG. Emission data were reconstructed with attenuation correction based on a diagnostic CT scan (100–190 mAs, depending on the scanned organ region, 120 kV, 2 × 5 mm collimation, pitch of 1.5) of the head, thorax, abdomen, and pelvis after intravenous injection of 120 mL of iodine-containing contrast agent at 2.5 mL/s (Ultravist 300; Schering). This CT scan was delayed for 50 s after contrast injection to depict the portal venous phase of the liver. Based on the results of phantom studies conducted with the 2 PET scanners used in the present study, we calculated a standardized uptake value conversion factor that allows pooling of the baseline scan results. To further strengthen this conversion factor, we separately analyzed the patients scanned with the different PET/CT scanners.

After a short interval, patients underwent contrast-enhanced MRI of the liver. After relevant laboratory tests had been performed (liver function, coagulation profiles, metabolic panel, blood count) and the clinical history had been taken, all patients underwent angiography with visceral catheterization to evaluate vascular anatomy and identify aberrant vessels. As deemed necessary, prophylactic embolization of the gastroduodenal, right gastric, and other extrahepatic arteries was performed before SIRT (*19*). The shunt fraction of ^{90}Y-microspheres to the lungs was estimated on the basis of ^{99m}Tc-macroaggregated albumin scintigraphy after application of 100 MBq of ^{99m}Tc-macroaggregated albumin into the hepatic artery (*20,21*). In addition, baseline MRI and CT images were evaluated for the percentage tumor involvement of the liver, the presence of extrahepatic metastases, and portal venous occlusion.

^{90}Y Device and Therapeutic Procedure

SIR-spheres (SIRTEX Medical) are nonbiodegradable resin microspheres with ^{90}Y as an integral constituent. ^{90}Y is a β-emitting isotope with a 64.2-h half-life, a mean energy of 0.935 MeV, and an average tissue penetration of 2.5 mm (maximum, 11 mm). The mean diameter of the microspheres is 29–35 μm. All patients received treatment of the entire liver within a single session. The applied activity of SIR-spheres was calculated according to the percentage involvement of the liver (tumor volume/liver volume × 100) and the body surface area as follows:

$$\text{Activity in GBq} = (\text{body surface area} - 0.2) + (\text{liver involvement}\,(\%)/100)$$

or according to the percentage involvement of the liver (<25% involvement: 2.0 GBq; >25% involvement: 2.5 GBq).

Assessment of Response

The follow-up protocol included physical examination, laboratory tests (including liver function, carcinoembryonic antigen, and cancer antigen 15-3), MRI of the liver, and ^{18}F-FDG PET/CT 3 mo after radioembolization. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, on the CT scans (partial response, stable disease, or progressive disease) (*22*). Two nuclear medicine specialists interpreted side-by-side coregistered PET/CT images by consensus using a dedicated software package (Hermes Hybrid Viewer; Hermes Medical Solutions). Pre- and posttherapeutic PET/CT scans of each patient were always obtained with the same scanner. To assess metabolic response using the ^{18}F-FDG PET images, we measured the maximum standardized uptake value, corrected for body weight (SUV_{max}), of the hepatic metastases. For this response assessment, we summed the SUV_{max} measurements of up to 5 of the most notable hepatic metastases and calculated the percentage change on the follow-up scan relative to the baseline measurements. Any decrease exceeding 30% of the summed baseline SUV_{max} was taken to indicate a therapy response (responder), whereas any lesser decrease or any increase in SUV_{max} or appearance of new hepatic lesions was considered a lack of response (nonresponder) (*23*). For toxicity assessment, the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) was used (*24*).

Statistical Analysis

Statistical analyses were performed using the SPSS software package (version 15.0, SPSS, Inc.). The survival rates were estimated by Kaplan–Meier analyses, with the last date of contact as a censored observation and death from any cause as an interesting event. Variables were analyzed for an association with overall survival by the log-rank test. The multivariate Cox proportional hazards model was used to obtain hazard ratio estimates and 95% confidence intervals of several parameters, with response as the time-dependent variable and pretherapeutic SUV_{max} as the continuous variable. To compare the characteristics in responders versus nonresponders, the *t* test was used. A statistically significant difference was defined as $P < 0.05$. Quantitative data are presented as mean ± SD.

TABLE 1
Characteristics of Study Cohort at Baseline ($n = 58$)

Characteristic	Total	Responder	Nonresponder	*P*
Mean age ± SD (y)	58.0 ± 10.9	56.3 ± 12.8	58.1 ± 9.8	0.62
Mean TDR ± SD (wk)	438 ± 342	295 ± 237	360 ± 423	0.08
Estrogen receptor status positive (*n*)	45/51	17	17	0.69
Progesterone receptor status positive (*n*)	37/50	15	13	0.66
Her-2/*neu* status positive (*n*)	23/48	8	9	0.35
Hepatic tumor burden > 25% (*n*)	20	6	7	0.68
Extrahepatic metastases (*n*)	38/58	15	17	0.35
Radioembolization				
Mean radioactivity delivered ± SD (MBq)	1,774 ± 492	1,717 ± 532	1,809 ± 381	0.51
Toxicity grades 3 and 4				
Bilirubin (*n*)	3	1	1	0.89
Transaminases (*n*)	4	2	1	0.67
Mean number of prior chemotherapies ± SD	3.1 ± 1.8	3.1 ± 1.6	3.3 ± 1.9	0.80
Taxanes (%)	86	80	95	0.17
Anthracyclines (%)	96	90	100	0.16
Antihormonal therapies (%)	85	91	87	0.30
Prior local hepatic therapies (%)	17	16	25	0.48
PET parameters				
Mean SUV_{max} at baseline ± SD	11.5 ± 6.0	11.6 ± 4.5	10.7 ± 7.7	0.65
SUV_{max} at baseline > 20 (*n*)	6	0	4	0.04
Change in SUV_{max} (%)	11.6	−19.6	−3.3	<0.001

TDR = time interval between initial diagnosis and radioembolization.

RESULTS

Patients

Fifty-eight women (mean age, 58 ± 10.9 y) were included in the study between March 2003 and October 2010 and were treated with ^{90}Y-microspheres after providing informed consent. The mean interval between initial diagnosis and SIRT was 467 ± 365 wk. Estrogen, progesterone, and Her-2/*neu* receptor status was positive in 45 of 51, 37 of 50, and 23 of 48 patients, respectively. Mean hepatic tumor burden was 17.5%, and 20 patients presented with a hepatic tumor burden of more than 25% (*25*). Thirty-eight patients (66%) exhibited extrahepatic metastases (Table 1).

Toxicity

Patients were treated with a mean activity of 1.8 ± 0.5 GBq of ^{90}Y-microspheres. In 12 patients, the intended dose could not be completely administered because of intrahepatic arterial stasis. There were 11 grade 1, 7 grade 2, 2 grade 3, and 1 grade 4 toxicities based on bilirubin and 28 grade 1, 11 grade 2, 3 grade 3, and 1 grade 4 toxicities based on hepatic transaminase concentrations. Two deaths were observed within 3 mo after the procedure. The patients died 12 and 8 wk after radioembolization; death was most probably attributable to treatment-related hepatic toxicity. The first patient had been treated with 2 different chemotherapies (including taxanes and anthracyclines), antihormonal therapy, and radiofrequency ablation of hepatic metastases. The second patient had undergone 4 different chemotherapies (including taxanes, anthracyclines, capecitabine, vinorelbine), bevacizumab, and trastuzumab. Six patients experienced SIRT-induced gastric or duodenal ulcerations, in 2 of whom we observed extrahepatic deposition of SIR-Spheres on SPECT/CT. Five of the 6 ulceration cases occurred before our introduction of frequent intratherapeutic monitoring controls of hepatic arterial flow, with application of contrast agent during the angiography.

Response and Survival

Survival data were available for all 58 patients. Thirty-eight women died during follow-up. Twenty women are still alive after a mean follow-up of 27.5 wk (range, 13–60 wk). Response assessment with CT/MRI and ^{18}F-FDG PET was available in 43 of 58 patients.

With the exception of the frequency of patients presenting with an SUV_{max} greater than 20 for the metastases (which was present in nonresponders only; Table 1), there were no significant differences in patient characteristics between the responders and nonresponders.

Overall median survival after SIRT was 47 wk (Fig. 1); median survival after the initial diagnosis of breast cancer was 468 ± 341 wk. A pretherapeutic SUV_{max} greater than 20 for the most intense hepatic metastasis per patient was associated with significantly shorter survival than was an SUV_{max} of 20 or less (median survival: 52 wk vs. 21 wk; $P < 0.005$). The results were comparable for women examined with the Gemini (median survival for patients with $SUV_{max} > 20$: 21 wk vs. 52 wk) and those scanned with the Biograph (median survival for patients with $SUV_{max} > 20$: 21 wk vs. 47 wk). There were 22 responders (51%) and 21 nonresponders (49%), 7 of whom had progressive disease based on the change in SUV_{max} measurements. Response as assessed with SUV_{max} correlated significantly

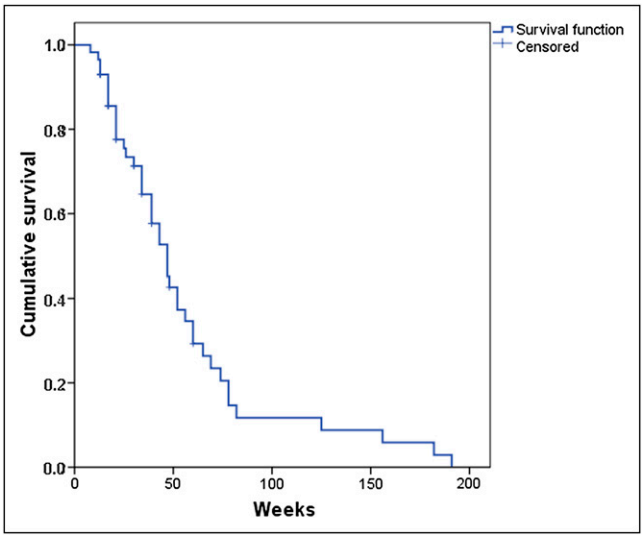

FIGURE 1. Kaplan–Meier survival curve of study cohort after SIRT.

with survival after SIRT (median survival: responders, 65 wk; nonresponders, 43 wk; $P < 0.05$; Fig. 2; Table 2).

Of the 43 patients for whom CT/MRI findings were available, 11 (25.6%) showed a partial response, 27 (62.8%) showed stable disease, and 5 (11.6%) showed progressive disease. Response as assessed with CT/MRI showed no significant correlation with survival according to the log-rank test ($P = 0.98$, Fig. 3). The presence of extrahepatic metastases was not associated with a shorter survival (median survival in both groups was 47 wk; $P = 0.92$; hazard ratio, 1.57 [95% CI, 0.46–5.32]; $P = 0.47$; Table 2). Neither hepatic tumor involvement as measured with CT/MRI (median survival: tumor involvement < 25%, 47 wk; >25%, 34 wk; $P = 0.65$) nor hormone receptor status exerted a significant influence on survival (Table 2).

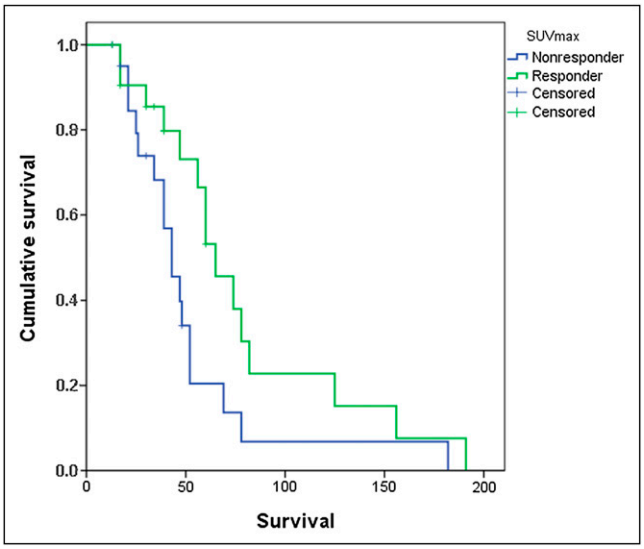

FIGURE 2. Kaplan–Meier survival curves as function of change in SUV_{max}. Responder (green line) showed significantly longer survival than nonresponder (blue line; $P < 0.05$).

TABLE 2
Kaplan–Meier Survival Analysis

Variable	Survival (wk)	*P*
Change in size		0.91
Partial response	60 [19–101]	
Stable disease	52 [42–62]	
Progressive disease	48 [46–50]	
SUV_{max} at baseline		0.002
>20	21 [15–27]	
≤20	52 [44–60]	
Change in SUV_{max}		<0.05
Responder	65 [49–81]	
Nonresponder	43 [32–54]	
Extrahepatic metastases		0.92
Present	47 [37–57]	
Not present	47 [31–63]	
Percentage tumor involvement liver		0.65
>25%	34 [20–48]	
≤25%	47 [38–56]	
Estrogen receptor status		0.53
Positive	47 [37–57]	
Negative	60 [51–69]	
Progesterone receptor status		0.79
Positive	47 [37–57]	
Negative	56 [36–76]	
Her-2/*neu* receptor status		0.49
Positive	47 [40–54]	
Negative	47 [29–65]	

Data in brackets are 95% confidence intervals.

Univariate analyses identified change in SUV_{max} as the only predictor for survival (hazard ratio, 0.48 [95% CI, 0.23–0.99]; $P < 0.05$, Fig. 4). Pretherapeutic SUV_{max}, however, showed a near-significant trend (hazard ratio, 1.06 [95% CI, 0.99–1.13]; $P = 0.08$). In the multivariate analysis, only response assessed on the basis of SUV_{max} was significantly associated with survival (hazard ratio, 0.26; $P < 0.005$; Table 3).

DISCUSSION

This study confirmed the effectiveness of SIRT in breast cancer patients with hepatic metastases. The response rates in our patient population were comparable to previously published studies, with a similar overall survival of 47 wk (*7–9*). To date, only a limited number of prognostic factors such as performance status (as measured with the Eastern Cooperative Oncology Group criteria) have been validated for identifying patients at risk for poor outcomes after radioembolization. Other risk factors, such as treatment response determined according to the RECIST criteria, the presence of extrahepatic metastases, or patients' hepatic tumor burden, remain controversial (*7,9*). Indeed, in our study, the presence of extrahepatic metastases did not emerge as a significant prognostic factor, probably because patients selected for SIRT usually present with a low extrahepatic tumor burden. Response as assessed with the RECIST criteria and the pretherapeutic tumor burden did

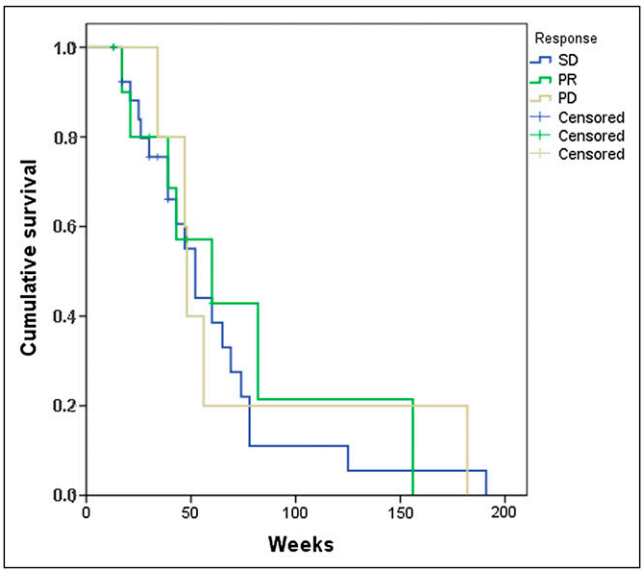

FIGURE 3. Kaplan–Meier survival curves as function of response as assessed with CT/MRI. Log-rank test revealed no significant difference ($P = 0.98$). SD = stable disease; PD = progressive disease.

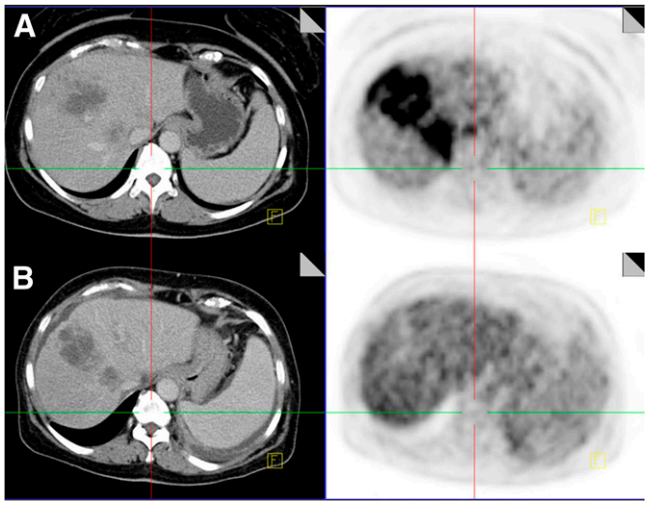

FIGURE 4. Axial slices of CT (left) and fused PET/CT (right) scans before therapy (A) and after therapy (B) demonstrating large liver metastases. SUV_{max} decreased markedly (−73%) after radioembolization, indicating therapy response, whereas tumor size as measured with CT did not change significantly.

not significantly predict survival in our study, though patients with progressive disease after SIRT and a high tumor burden tended to have a shorter survival. However, this finding simply underscores the controversies regarding the prognostic value of morphologic tumor response.

Although some authors have reported a higher response rate on ^{18}F-FDG PET than on CT and MRI in patients treated with SIRT (*26–30*), the prognostic value of metabolic treatment response assessment has only rarely been evaluated in cases of hepatic metastases. In a preliminary study focusing on cholangiocellular carcinoma (*16*), we found higher discrimination between SIRT responders and nonresponders for ^{18}F-FDG PET than for CT or MRI. To date, however, no study has compared the results of ^{18}F-FDG PET in hepatic metastases from breast cancer with endpoints such as survival.

The prognostic value of ^{18}F-FDG PET is well known and has been established in other systemic treatments of breast cancer patients (*31–33*). The results of the present study indicate that response to ^{18}F-FDG PET based on SUV_{max} significantly predicts survival in our patient population. Responders had a median survival of 65 wk, compared with only 43 wk in nonresponders. In our study, the response rate using ^{18}F-FDG PET was only 51%, whereas in another study, response rates of up to 90% were described. That study, however, was conducted on patient populations that had various tumor types, and no standardized response criteria were used (*25*). Furthermore, no correlation with survival was reported in that study. In the present study, the change of SUV_{max} was the only independent predictor of survival. The presence of hormone receptors or the Her-2/*neu* receptor, which are well-known prognostic factors in breast cancer patients (*10*), did not influence overall survival in our patient population. In the present study, ^{18}F-FDG PET using SUV_{max} was significantly associated with survival regardless of patients' receptor status. This finding may be explained by the fact that receptor-positive women had already been treated with, and were refractory to, antihormonal medication or trastuzumab.

For our assessment of response, we modified the PET Response Criteria in Solid Tumors, wherein only the change of SUV_{max} in the 2 hottest lesions per organ is considered.

TABLE 3
Analysis of Factors and Values as Predictors of Survival

Parameter	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Pretherapeutic SUV_{max}	1.06 [0.99–1.13]	0.08	1.06 [0.98–1.14]	0.14
Change in SUV_{max}	0.48 [0.23–0.99]	<0.05	0.23 [0.09–0.61]	0.003
Extrahepatic metastases	1.73 [0.75–4.00]	0.20	1.40 [0.41–4.80]	0.60
Estrogen receptor status	1.05 [0.39–2.83]	0.92	0.99 [0.32–3.08]	0.98
Her-2/*neu* receptor status	0.59 [0.26–1.38]	0.23	0.52 [0.20–1.36]	0.18

Data in brackets are 95% confidence intervals.

Instead, our definition of response was based on the summed percentage change in SUV_{max} in up to 5 of the most prominent hepatic lesions. This approach is based on the observation that the attainable radiation dose within different hepatic metastases of the same patient regularly shows huge variations, which apparently arise because of an inhomogeneous distribution of the SIR-Spheres. Consequently, measuring only the hottest lesion may not be the appropriate method to cover a heterogeneous treatment response. Indeed, 1 patient in the present study was classified as a responder by the criterion of a greater than 30% decrease in summed SUV_{max}, despite the occurrence of an SUV_{max} increase within a single hepatic metastasis. This patient had a comparatively short survival of 17 wk, such that having classified her as a nonresponder would not have changed the main conclusion of the study. However, the occurrence of one such anomaly underlines the need for further studies to identify the optimal method for metabolic response assessment. The SUV_{max} of primary breast cancer seems to correlate with tumor aggressiveness (*34*). This observation is in line with the finding in our study that patients with a high pretherapeutic SUV_{max} for their liver metastases had a significantly briefer survival by Kaplan–Meier analysis (only 21 wk), although in the multivariate analysis, this difference failed to reach statistical significance.

The potential of ^{18}F-FDG PET for predicting survival in patients with metastatic breast cancer undergoing treatments other than SIRT has been shown in several studies. In patients with bone metastases, ^{18}F-FDG PET was the sole independent predictor of overall survival (*35*). In addition, ^{18}F-FDG PET response was also able to predict overall survival in patients with metastasized breast cancer who started a new line of therapy (*36*). Therefore, the results of our study of patients undergoing local treatment are in line with published reports of experience with systemic therapies. Early identification of patients likely to experience poor outcome after SIRT permits the timely transition to alternative treatments. Alternative chemotherapeutic agents such as gemcitabine and carboplatin have a response rate of 31% and overall survival of 13.2 mo in extensively pretreated patients with metastatic breast cancer (*37*). Use of other cytotoxic agents, such as vinorelbine and capecitabine, has also been recommended in a recent consensus report (*38*). Furthermore, several novel drugs, including the poly(adenosine diphosphate ribose) polymerase inhibitors iniparib and olaparib, or ixabepilone in combination with capecitabine, have shown a high therapeutic potential in initial studies, which included patients with taxane- and anthracycline-resistant metastatic breast cancer (*39,40*). Despite the fact that these women were heavily pretreated, further treatment options remain, which promise to improve their prognosis.

CONCLUSION

The present study showed that ^{18}F-FDG PET using SUV_{max} is able to predict survival of breast cancer patients with hepatic metastases treated with SIRT independently of their hormone or Her-2/*neu* receptor status, hepatic tumor burden, response as assessed with CT or MRI, and the presence of extrahepatic disease.

DISCLOSURE STATEMENT

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