Response monitoring in metastatic breast cancer: a comparison of survival times between FDG-PET/CT and CE-CT

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Running title: Survival analysis of PET/CT vs. CE-CT in metastatic breast cancer

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Survival analysis of PET/CT vs. CE-CT in metastatic breast cancer

Abstract

Background: We compared overall survival for metastatic breast cancer (MBC) patients monitored with CE-CT, FDG-PET/CT, or a combination of them in an observational setting.

Methods: Patients with biopsy-verified (recurrent or de-novo) MBC (n=300) who were treated at Odense university hospital (Denmark) and response-monitored with FDG-PET/CT (n=83), CE-CT (n=144), or a combination of these (n=73) were followed until 2019. Survival was compared between the scan groups, and were adjusted for clinico-histopathological variables representing potential confounders in a Cox proportional-hazard regression model.

Results: The study groups were mostly comparable regarding baseline characteristics, but liver metastases were reported more frequently in CE-CT group (38.9%) than in FDG-PET/CT group (19.3%) and combined group (24.7%). Median survival was 30.0 months for CE-CT group, 44.3 months for FDG-PET/CT group, and 54.0 months for Combined group. Five-year survival rates were significantly higher for FDG-PET/CT group (41.9%) and combined group (43.3%), than for CE-CT group (15.8%). Using the CE-CT group as reference, the hazard ratio was 0.44 (95% CI: 0.29-0.68, P=0.001) for the FDG-PET/CT group after adjusting for baseline characteristics. FDG-PET/CT detected the first progression 4.7 months earlier than CE-CT, leading to earlier treatment change.

Conclusions: In this single-center, observational study, patients with metastatic breast cancer who were response-monitored with FDG-PET/CT alone or in combination with CE-CT had longer overall survival than patients monitored with CE-CT alone. Confirmation of these findings by further, preferably randomized clinical trials is warranted.

Keywords: Metastatic breast cancer; FDG-PET/CT; Survival analysis; Response monitoring

Introduction

An increasing number of women are living longer with metastatic breast cancer (MBC), making this a chronic disease with a non-negligible prevalence (1). The prognosis is still poor, however, with five-year overall survival of only 25% (2-4). Shorter survival is observed for patients with triple-negative MBC, and longer survival is associated with bone-only metastases (5, 6). All women with MBC are highly dependent on effective medical treatment along with accurate response assessment. Response monitoring by imaging is widely used to guide treatment decisions, but no specific recommendations for imaging procedures can be found in international MBC guidelines (7-10). Contrast-enhanced computed tomography (CE-CT) and the corresponding Response Evaluation Criteria in Solid Tumors (RECIST 1.1) have traditionally been used for response monitoring of MBC and are based on changes in the morphological size of metastases (11). However, CE-CT has low sensitivity for detecting bone metastases (11), low specificity for detection of liver metastases (12), and may also have some limitations for response monitoring in MBC patients (13, 14).

[^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) computed tomography (FDG-PET/CT) has proven highly accurate in detecting MBC and has the potential to provide valid information on tumor metabolic activity by distinguishing active tumor from post-therapeutic changes (15, 16). Changes in tumor activity potentially occur long before morphological changes appear, and clinical application of FDG-PET/CT for response monitoring may adopt treatment at an earlier time point than with conventional imaging (16-18).

Previous studies have shown that disease-specific survival could be better predicted by the response on FDG-PET/CT than on CE-CT (19), but the patient benefit from using FDG-PET/CT for longitudinal response monitoring in patients with MBC is still unknown.

We hypothesized that FDG-PET/CT would improve clinical decision-making and thereby lead to prolonged survival for patients with MBC. Therefore, we aimed to compare the overall survival for patients with metastatic breast cancer response monitored with FDG-PET/CT, CE-CT, or a combination of both modalities in an observational setting. Our objectives were i) to provide a detailed description of the baseline characteristics to determine if the groups were roughly comparable, ii) to describe patient management in each group during the response monitoring, and iii) to investigate the survival in each group and in subgroups of triple-negative patients and patients with bone-only metastases.

Material and Methods

This was a single-centre, retrospective study based on prospective registration of patients. The study was conducted at the Department of Nuclear Medicine at Odense University Hospital, Denmark, in 2018-2020. The study protocol was approved by the Danish Patient Safety Authority (Ethics permission code: 3-3013-2448/1), including permission to register data from the patients' electronic medical files until 10.08.2019.

Patient selection and study groups

Women diagnosed with MBC in 2004-2018 were eligible for the study. All patients were treated at the Department of Oncology, and imaging for response assessment was performed at the Departments of Radiology and/or Nuclear Medicine at Odense University Hospital. Inclusion criteria were distant relapsed MBC (biopsy-verified) or de novo breast cancer (biopsy verification of primary tumor and disseminated disease at baseline scan); baseline and at least one follow-up scan for response monitoring; use of either FDG-PET/CT, CE-CT, or

a combination of the two as the main response monitoring modality; standard response monitoring protocol with imaging intervals of 9-12 weeks (20); and regular clinical follow-up. As monitoring by CE-CT or FDG-PET/CT was required, patients mainly monitored with magnetic resonance imaging (MRI) were not considered in the population. Exclusion criteria were other known disseminated malignancy, brain metastasis at baseline scan, acute cardiovascular disease or severe dementia at the time of MBC diagnosis, missing clinical data at follow-up, lost to follow-up due to emigration, and refusal of treatment.

The modality used for response monitoring was generally decided by the oncologist who met the patient at the initial visit when MBC was diagnosed. No internal algorithm was available to guide the decision about the choice of response monitoring modality, and the choice was thus mainly at the discretion of the oncologist. Patients were allocated arbitrarily to the treating oncologists, with no distinctions due to clinical or performance status. Patients typically saw the same oncologist for each of their follow-up visits, minimizing the risk of a change in monitoring modality.

Visual assessment was used for response evaluation without further criteria, i.e. the RECIST were not used regularly for the CE-CT, and the PET Response Criteria in Solid Tumors (PERCIST) were not applied at all. The scan reports typically suggested response (complete/partial response), stable disease, or progressive disease. The oncologists based their clinical decisions on the scan report, the patient's clinical performance status, the patient's wishes, and the potential toxicity of ongoing treatment.

Patients were categorized into three groups based on the imaging modality used for response monitoring: FDG-PET/CT, CE-CT, and the combined group. One scan performed on the opposite imaging modality during the treatment period was considered acceptable in the FDG-PET-CT and CE-CT groups, and patients were allocated to the combined group if they were monitored by both scan types more than once. The scans were performed according to the standard guidelines for FDG-PET/CT and CE-CT (Supplementary Material 1) (11, 21).

Data Collection and Variables

From the patients' medical files, we extracted age, performance status on the World Health Organization scale (22), clinical and histopathological data, referring doctor for the baseline scan, type of treatments received, cause of death, and date of death or last clinical visit. All extracted information was located in the routine patient documentation. For patients with more than one primary breast cancer, we used the data for the primary cancer that had most likely led to the metastasis (i.e. had the same molecular profile as the metastasis). In some cases of de novo MBC, where the metastases had not been biopsied, we used information from the initial breast biopsy.

The overall survival time was defined as the time from the metastasis confirmation until death, with end of study period (10th August 2019) as censoring event. Time to the first treatment change was defined as the time between the baseline scan and first progression leading to treatment change. The patients with detected first progression were followed-up until detection of the subsequent progression, leading to a second treatment change in the clinic, and the time in between was considered as the time to detection of the second progression. The follow-up period was defined as the time interval between the baseline scan and the date of the last clinical visit for survivors and the date of death for non-survivors.

Statistical Analyses

Continuous data were presented using the median (interquartile range) and mean ± standard deviation. Frequencies and respective percentages were given for categorical variables. The primary endpoint of this study was overall survival. Median two-year, five-year, and ten-year survival were evaluated for all study groups with 95% confidence intervals (95% CI). Kaplan-Meier survival curves were used for visualization (23). Quantification of the group difference by a hazard ratio (HR) from a Cox regression model was restricted to the two groups of patients solely monitored by FDG-PET/CT or CE-CT as survival in the combined group was affected by immortality bias, i.e. to experience monitoring by both modalities, patients would have to survive for some time. The HR was adjusted for a wide range of baseline and treatment characteristics to take account of any differences between the groups.

A time-varying HR based on Schoenfeld residuals was used to depict the change in the HR over follow-up time. The significance level was set at 0.05. All statistical analyses were conducted with STATA/IC (version 16.1, StataCorp, College Station, USA).

Results

Of 333 eligible patients, 33 were excluded due to the reasons shown in Figure 1, and the analysis was conducted on 300 patients divided into the CE-CT group (n = 144), the FDG-PET/CT group (n = 83), and the combined group (n = 73). Median follow-up time was 33.0 (3.6-130.6) months. Clinical and histopathological characteristics of the primary and metastatic breast cancer are summarized in Table 1 and Table 2, respectively. The study groups were mostly comparable on baseline characteristics, apart from more biopsy-verified liver metastasis in the CE-CT group and more biopsy-verified lung metastasis in the FDG-PET/CT group.

Information on treatment and performed scans is shown in Table 3 for the three groups. Comparing the FDG-PET/CT and CE-CT groups, the main difference between them was that fewer patients in the FDG-PET/CT group received chemotherapy at least once. The number of scans was significantly higher in the combined group (P<0.001), but after adjusting for the number of performed scans per follow-up time (Number of scans / 3 months of response monitoring), there was no statistically significant difference between the study groups (P=0.40).

Information on mortality and median survival is presented in Table 4. Of the 215 patients who died within the follow-up period, the cause of death was MBC in 209 (97.2%) patients and unknown in six (2.8%). Median survival time was longer in the FDG-PET/CT and combined groups than in the CE-CT group. Survival curves are shown in the Kaplan-Meier plot in Figure 2. An extended Kaplan-Meier survival curve including pointwise 95% CI can be found in Supplementary Material 2. Two-year survival probabilities differed only slightly between the groups, but five-year survival for the FDG-PET/CT and combined groups were considerably higher (advantage of 26.1% and 27.5%, respectively) than for the CE-CT group.

The FDG-PET/CT and combined groups had statistically significantly longer survival with HR of 0.56 (95% CI: 0.40-0.80, P=0.001) and 0.41 (95% CI: 0.29-0.59, P<0.001), respectively, when using the CE-CT group as reference in univariate survival analyses. When considering only the FDG-PET/CT and CE-CT groups and adjusting for baseline characteristics (selected variables from Table 1 and Table 2), there was a statistically significantly longer survival for the FDG-PET/CT group with HR of 0.44 (P=0.001, Table 5). The results of the multivariable analysis also showed a negative prognostic value of short time until relapse, negative estrogen and

HER-2 receptors in the metastasis, and bone and liver metastases at the baseline scan. A visual display of HR over time corroborated the increasing difference between groups over time as already visible in the survival curve (Supplementary Material 3). Adding a time x group interaction term to the model supported this visual finding (P<0.001).

Information on the duration of treatment during follow-up is summarized in Table 6 for the three groups. Patients in the FDG-PET/CT group received fewer treatment lines, experienced longer duration of treatment courses, and had shorter time on chemotherapy than patients in the CE-CT group. The first progression leading to treatment change occurred on average 4.7 months earlier in the FDG-PET/CT group than in the CE-CT group, while the second progression was detected on average 4.0 months later in the FDG-PET/CT group compared with the CE-CT group (12.1 vs. 8.1 months, P=0.0001). Sensitivity analyses showing the effect of excluding patients who received one scan from the other scan modality and who received protocolled experimental treatments are presented in Supplementary Material 4 and Supplementary Material 5, respectively. Furthermore, sensitivity analysis of replacing region of metastases by the number of metastatic organs is presented in Supplementary Material 6.

Discussion

This study revealed a survival benefit of 14-24 months for patients with metastatic breast cancer who were response-monitored with FDG-PET/CT alone or in combination with CE-CT compared with patients monitored with CE-CT alone. Increased survival was confirmed for patients response-monitored by FDG-PET/CT (HR: 0.44) in a multivariable Cox regression analysis using the CE-CT group as a reference controlled for relevant baseline factors. The five-year survival rate was considerably higher in the FDG-PET/CT group and the combined group than in the CE-CT group, and the difference in survival increased over time. FDG-PET/CT detected the first progression dictating treatment change approximately five months earlier than CE-CT, which may have had an impact on the effect and tolerability of subsequent treatment lines. Earlier detection of progression leading to treatment change could be a potential reason for the achievement of a more efficacious next treatment line in the FDG-PET/CT group, as we observed a longer time to experience the second progression in this group. Overall, patients in the FDG-PET/CT group received a lower number of treatment lines over a longer time than patients in the CE-CT group. We could consider the overall survival equal to disease-specific survival in this study as 97% of the mortality was due to metastatic breast cancer.

The results of this study suggest that FDG-PET/CT-based response monitoring may improve the clinical management of MBC patients through earlier termination of ineffective treatment which result in longer survival. A reduction of false positive decisions implying stop of efficient treatment when using CT may also contribute to this effect although this could not be analysed in this observational study. Deducing intervention effects from observational data should only be interpreted cautiously. However, the present study had some favourable circumstances in that the choice of response modality probably reflected a preference by the treating oncologist, and major prognostic patient characteristics seem to be rather balanced or do not systematically favour one group.

We found that liver metastasis at the baseline scan was predictive of poor prognosis, which is in line with the results of a Danish registry-based cohort study (24). Actually, the incidence of liver metastasis at baseline scan was higher in the CE-CT group than in the FDG-PET/CT group (38% vs. 19%). We conjecture that this reflects

the lower specificity of CE-CT for diagnosing liver metastasis compared to FDG-PET/CT (12), and not a true difference between the two groups. However, the overall distribution of biopsy-verified liver/lung metastases, known as negative prognostic factors (25), was almost the same between CE-CT (34.8%) and FDG-PET/CT (36.1%) groups. In any case, we adjusted the multivariable analysis for the region of metastasis at baseline scan to take the potential differences between the groups into account.

It has already been demonstrated that MBC patients with bone-only metastasis have better long-term survival than patients with metastases in other regions (5). In the subgroup of patients with bone-only metastasis (n = 27), however, we still observed longer survival in the FDG-PET/CT group compared with the CE-CT group (82.6 vs. 33.9 months). In contrast, patients with triple-negative MBC have a poor prognosis with a reported median survival of approximately 12 months (26, 27); this was the same in our study regardless of whether monitoring with CE-CT or FDG-PET/CT. Patients with such aggressive tumor types may not benefit from response monitoring to guide treatment decisions.

Previous reviews and smaller studies have suggested that an FDG-PET/CT approach for monitoring distant metastases in MBC could improve treatment decisions by detecting non-response earlier than conventional methods and preventing patients from receiving ineffective, potentially toxic treatments (15, 16, 20). In one larger study, FDG-PET/CT could identify non-responders earlier than CE-CT (17). These results are supported by our findings indicating that FDG-PET/CT might prolong the survival of MBC patients through earlier detection of the first progression and hence sparing non-responding patients for ineffective treatment. However, effective medical treatment and clinicopathological features have the main role in improved long-term survival of MBC patients (25), and response monitoring could only guide clinical management of patients through improved prognostic stratification (28).

A few studies have proposed that FDG-PET/CT could play a role in predicting overall survival or progression-free survival when evaluating response to chemotherapy or endocrine treatment (29, 30). In a study on 65 MBC patients who underwent FDG-PET/CT and CE-CT as their response evaluation after initial treatment line, it was concluded that responders on PERCIST (FDG-PET/CT) had significantly better progression-free and disease-specific survival than responders on RECIST (CE-CT) (19). This corresponds well with the results of the current study that favor FDG-PET/CT for guiding treatment decisions.

Novel treatments such as CDK4/6 inhibitors have improved survival in MBC patients (31-34). Evaluation of the effects of costly new treatments might be improved by adding FDG-PET/CT for response monitoring, or even by using more dedicated PET tracers that are currently under development in pre-clinical trials (35, 36). Our data did not reflect the effects of this new generation of treatments, which were only sparsely administered in the current retrospective setting.

The overall economic burden of managing MBC patients will increase as the number of women with MBC increases (37-41). Most of the cost is due to treatment costs as expenses related to imaging and diagnostic tests are approximately one-sixth of the treatment costs (39). It is thus important to select the most accurate method for treatment response monitoring to improve long-term survival of MBC patients and potentially decrease costs to the healthcare system by reducing treatment intensity.

A limitation of the current study was the single-centre, observational retrospective design, meaning that patients were not randomly allocated to the study groups. A multivariable Cox-regression model was used to adjust for a variety of clinico-histopathological variables representing potential measured confounders (e.g. a higher rate of

liver metastases in the CT group), but we cannot exclude the existence of further unmeasured confounders. Further, FDG-PET/CT is a newer modality, and patients diagnosed more recently had a higher chance to be followed by this modality and to have the advantage of new anti-cancer therapy. However, year of diagnosis was included as a potential confounder in the multivariable analysis, and hence this difference was taken into account. The RECIST criteria were only applied sporadically for CE-CT, and no standardized evaluation was used for FDG-PET/CT. We allowed one of the opposite scan types to be performed in each of the CE-CT and the FDG-PET/CT groups, which may have affected our results to some degree. However, in a sensitivity analysis of 'pure' FDG-PET/CT and CE-CT groups (where patients having one of the opposite scan types were excluded), the superiority of FDG-PET/CT was unchanged (Supplementary Material 4). We have to mention that participation of patients in an experimental protocol during the follow-up period, influenced group membership, as Food and Drug Administration and European Medicines Agency required response evaluation based on RECIST. In total, 28 patients participated at some time point during follow-up in such a protocol, and in 13 of them, such participation implied a change from the FDG-PET/CT group to the combined group, which resulted in an excellent survival (median survival of 85 months) among them.

Strengths of the current study were that: it was conducted in a relatively large patient population representative of daily clinical practice and with a long follow-up time (median of 33 months) that allowed us to analyze long-term survival probabilities. All included patients had biopsy-verified metastatic disease and were treated and monitored using the same equipment in a single university hospital. The data quality was high due to regular and careful registration of patients' electronic files. As Danish residents, the patients had equal access to the healthcare services, and all were covered by the same national insurance system (42).

Our results require confirmation in prospective multicenter studies with extended follow-up times to allow further insights into the long-term consequences of using these modalities. These may be randomized studies or studies monitoring a systematic change from one modality to another with routine application of RECIST and PERCIST.

Conclusion

In this single-center, observational study, we found improved patient management and prolonged overall survival for patients with metastatic breast cancer when FDG-PET/CT was used alone or in combination with CE-CT for response monitoring as compared with using CE-CT alone. Using FDG-PET/CT for response monitoring provided earlier detection of the first progression, leading to change or termination of ineffective treatment, and longer effective next treatment line. The advantage of using FDG-PET/CT increased clearly over time, as we expect from an effective response strategy. Our results indicate that using FDG-PET/CT for response monitoring in patients with metastatic breast cancer may improve clinical decision-making and patient survival. This potential advantage requires confirmation in prospective trials, preferable using a randomized design.

Additional Information:

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Authors' contributions:

- **Study concept and design:** Mohammad Naghavi-Behzad, Marianne Vogsen, Kristian Kidholm, Annette Raskov Kodahl, Wolfgang Weber, Malene Grubbe Hildebrandt
- **Data collection:** Mohammad Naghavi-Behzad, Marianne Vogsen, Rasmus Mølgård Vester, Maiken MB Olsen, Hjalte Oltmann
- **Statistical analyses:** Mohammad Naghavi-Behzad, Oke Gerke, Werner Vach
- **Interpretation of data:** Mohammad Naghavi-Behzad, Marianne Vogsen, Poul-Erik Braad, Jon Thor Asmussen, Oke Gerke, Werner Vach, Annette Raskov Kodahl, Malene Grubbe Hildebrandt
- **Critical revision of the manuscript:** All of the authors
- **Approval of final draft:** All of the authors

Ethics approval: The study protocol was approved by the Danish Patient Safety Authority (Ethics permission code: 3-3013-2448/1), including permission to register data from the patients' electronic medical files until 10.08.2019.

Consent for publication: Not applicable

Data availability: The datasets generated during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Figure Legends

Figure 1. Flowchart of patient' selection and study groups (CE-CT: contrast-enhanced computed tomography, FDG-PET/CT: Fluorodeoxyglucose positron emission tomography with integrated computed tomography, MRI: Magnetic resonance imaging).

Figure 2. Kaplan-Meier plot and risk table showing survival of metastatic breast cancer patients according to response monitoring method (CE-CT: contrast-enhanced computed tomography, FDG-PET/CT: Fluorodeoxyglucose positron emission tomography with integrated computed tomography)

Table Legends

Table 1. Clinicopathological characteristics of primary breast cancer

Table 2. Clinicopathological characteristics of metastatic diseasea

Table 3. Treatment types and imaging information in response monitoring

Table 4. Survival among study groups according to Kaplan-Meier estimates

Table 5. Multivariable COX regression analyses of baseline clinical and histopathological characteristics on patient survival

Table 6. Received treatment according to study group

Table 1. Clinicopathological characteristics of primary breast cancer

Characteristics[a]	Study Groups			*p*-value
	CE-CT (n = 144)	FDG-PET/CT (n = 83)	Combined (n = 73)	
Primary tumor size (mm)	20 (3-70)	24 (1-80)	20 (9-60)	0.69
Bilateral cancer	12 (8.3)	9 (10.8)	6 (8.2)	0.81
Histopathology				
Ductal	111 (77.1)	57 (68.7)	50 (68.5)	
Lobular	19 (13.2)	15 (18.1)	7 (9.6)	0.13
Adenocarcinoma	6 (4.2)	2 (2.4)	6 (8.2)	
Unknown	8 (5.6)	9 (10.8)[b]	10 (13.7)	
Surgery of primary tumor				
No surgery	27 (18.8)	13 (15.7)	15 (20.6)	
Lumpectomy	50 (34.7)	22 (26.5)	31 (42.5)	0.13
Mastectomy	66 (45.8)	46 (55.4)	25 (34.3)	
Unknown	1 (0.7)	2 (2.4)	2 (2.7)	
Estrogen receptor status				
Positive	122 (84.7)	59 (71.1)	51 (69.9)	**0.02**
Negative	16 (11.1)	12 (14.4)	11 (15.1)	
Unknown	6 (4.1)	12 (14.4)	11 (15.1)	
Human epidermal growth factor receptor-2 status				
Positive	17 (11.8)	7 (8.4)	12 (16.4)	0.10
Negative	87 (60.4)	55 (66.3)	33 (45.2)	
Unknown	40 (27.8)	21 (25.3)	28 (38.4)	
Tumor grade				
Grade 1	20 (13.9)	15 (18.1)	9 (12.3)	
Grade 2	63 (43.8)	24 (28.9)	23 (31.5)	0.16
Grade 3	30 (20.8)	24 (28.9)	16 (21.9)	
Unknown	31 (21.5)	20 (24.1)	25 (34.3)	
Ki-67 proliferation (%)	30 (1-100)	40 (1-95)	30 (5-90)	0.54
Lymph node involvement				
None	30 (20.8)	23 (27.7)	18 (24.7)	
Single cell / Micro-metastasis	8 (5.6)	5 (6.0)	3 (4.1)	0.16
Macro-metastasis	75 (52.1)	31 (37.4)	26 (35.6)	
Unknown	31 (21.5)	24 (28.9)	26 (35.6)	
Treatment protocol				
Neo-adjuvant treatment	21 (14.6)	8 (9.6)	11 (15.1)	
Adjuvant treatment[c]	104 (72.2)	51 (61.5)	46 (63.0)	0.17
Both of the above	8 (5.6)	12 (14.5)	5 (6.9)	
None of protocols	8 (5.6)	9 (10.8)	7 (9.6)	
Unknown	3 (2.1)	3 (3.6)	4 (5.5)	
Radiotherapy protocol				
None	66 (45.8)	40 (48.2)	34 (46.6)	
Breast only	23 (16.0)	8 (9.6)	13 (17.8)	0.62
Breast + axilla	55 (38.2)	35 (42.2)	26 (35.6)	

CE-CT contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography

[a]Data shown as median (interquartile range) and frequency (%).

[b]The histopathology of one patient in FDG-PET/CT group was granular cell tumor.

[c]Adjuvant treatment included both endocrine and chemotherapy.

Table 2. Clinicopathological characteristics of metastatic disease[a]

Characteristics	Study Groups			*p*-value
	CE-CT (n = 144)	**FDG-PET/CT** (n = 83)	**Combined** (n = 73)	
Year of diagnosis	2013 (2007-2017)	2015 (2009-2018)	2013 (2004-2017)	**<0.001**
Age at diagnosis (years)	66.1 (28.4-84.5)	64.7 (28.2-86.7)	60.4 (31.0-95.3)	**0.003**
Performance status				
0	71 (49.3)	40 (48.2)	35 (48.0)	0.08
1	40 (28.8)	26 (31.3)	18 (24.7)	
2	11 (7.6)	6 (7.2)	1 (1.37)	
≥3	5 (3.5)	3 (3.6)	0 (0)	
Unknown	17 (11.8)	8 (9.6)	19 (26.0)	
Time until relapse[b] (months)	69.8 (0-271.4)	59.3 (0-313.2)	78 (0-364.0)	0.94
De novo metastatic cancer	31 (21.5)	17 (20.5)	20 (27.4)	0.56
Histopathology				
Ductal	36 (25.0)	14 (16.9)	14 (19.2)	0.69
Lobular	16 (11.1)	9 (10.8)	5 (6.9)	
Adenocarcinoma	58 (40.3)	36 (43.4)	35 (48.0)	
Unknown	34 (23.6)	24 (28.9)	19 (26.0)	
Estrogen receptor status				
Positive	118 (81.9)	69 (83.1)	55 (75.3)	0.24
Negative	17 (11.8)	13 (15.7)	14 (19.2)	
Unknown	9 (6.6)	1 (1.2)	4 (5.5)	
Human epidermal growth factor receptor-2 status				
Positive	13 (9.0)	8 (9.6)	18 (24.7)	**0.02**
Negative	103 (71.5)	64 (77.1)	44 (60.3)	
Unknown	28 (19.4)	11 (13.3)	11 (15.1)	
Ki-67 proliferation (%)	32.5 (1-95)	30 (5-95)	40 (5-80)	0.83
Origin of biopsy				
Bone	41 (28.5)	24 (28.9)	19 (26.0)	**0.03**
Liver	27 (18.8)	4 (4.8)	7 (9.6)	
Lung	16 (11.1)[c]	13 (15.7)	9 (12.3)	
Pleural fluid	7 (4.9)	13 (15.7)	4 (5.5)	
Lymph nodes	18 (12.5)	12 (14.5)	13 (17.8)	
Breast	21 (14.6)	11 (13.3)	11 (15.1)	
Skin	8 (5.6)	3 (3.6)	5 (6.9)	
Others	6 (4.2)	3 (3.6)	5 (6.9)	
Triple-negative[d]	12 (8.3)	8 (9.6)	5 (6.9)	0.78
Detected metastatic lesions at baseline scan				
Oligometastatic cancer[e]	18 (12.5)	8 (9.6)	15 (20.6)	0.14
Bone	95 (66.0)	59 (71.1)	45 (61.6)	0.47
Liver	56 (38.9)	16 (19.3)	18 (24.7)	**0.005**
Lung / pleural effusion	53 (36.8)	37 (44.6)	21 (28.8)	0.12
Lymph nodes (locoregional/distant)	80 (55.6)	60 (72.3)	48 (65.8)	**0.04**
Breast / local recurrence	31 (21.5)	17 (20.5)	14 (19.2)	0.95
Soft tissue	9 (6.3)	8 (9.6)	3 (4.1)	0.39
Bone-only metastasis	19 (13.2)	7 (8.4)	11 (15.1)	0.41
Bone and/or soft tissue dominant	31 (21.5)	15 (18.1)	20 (27.4)	0.38
Organ-specific metastasis (according to baseline scan)				
Single organ metastasis	42 (29.2)	13 (15.7)	22 (30.1)	0.06
Two-four organs metastases	101 (70.1)	68 (81.9)	49 (67.1)	
Five-organs metastases	1 (0.7)	2 (2.4)	2 (2.7)	

CE-CT contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography

[a]Data shown as median (interquartile range) and frequency (%).

[b]Time until relapse for patients with primary disseminated disease was considered zero.

[c]One patient was diagnosed with metastatic breast cancer and primary lung cancer at the same time.

[d]Negative for excess HER2 protein, estrogen, and progesterone receptors.

[e]Oligometastatic cancer refers to patients with fewer than five metastatic lesions in a single organ.

Table 3. Treatment types and imaging information in response monitoring

Characteristics[a]	Study Groups			
	CE-CT (n = 144)	**FDG-PET/CT** (n = 83)	**Combined** (n = 73)	***p*-value**
Exposure of patients to treatment categories				
Endocrine therapy	107 (74.3)	61 (73.5)	53 (72.6)	0.97
Chemotherapy	99 (68.8)	45 (54.2)	57 (78.1)	**0.006**
Palliative radiotherapy	32 (22.2)	9 (10.9)	12 (16.4)	0.09
Anti-HER2 therapy[b]	13 (9.0)	7 (8.4)	17 (23.3)	**0.009**
CDK4/6 inhibitors	19 (13.2)	19 (22.9)	12 (16.4)	0.18
Bone-target therapy	105 (72.9)	60 (72.3)	52 (71.2)	0.98
No treatment / Unknown	0 (0)	1 (1.2)	0 (0)	0.52
Protocolled experimental treatments	15 (10.4)	0 (0)	13 (17.8)	**<0.001**
Imaging information during follow-up period				
Total number of scans	11 (3-36)	11 (3-36)	18 (5-51)	**<0.001**
Number of scans per 3 months	1.2 (0.4-3.6)	1.1 (0.3-5.8)	1.2 (0.2-2.7)	0.40
Patients experienced switch to opposite modality (once)	37 (25.7)	39 (47.0)	-	**0.001**
Performed MRI scans	1 (0-8)	1 (0-10)	1 (0-9)	0.26

CE-CT contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography, *MRI* magnetic resonance imaging, *HER2* human epidermal growth factor receptor 2

[a]Data shown as frequency (%) at the patient level and as median (interquartile range) for performed scans.

[b]Anti-HER2 therapies consisted of Trastuzumab, Pertuzumab, and T-DM1.

Table 4. Survival among study groups according to Kaplan-Meier estimates

Characteristics	Study groups		
	CE-CT (n = 144)	**FDG-PET/CT** (n = 83)	**Combined** (n = 73)
Total number of deaths[a]	123 (85.4)	45 (54.2)	47 (64.4)
Survival probabilities[b] (%)			
Two-year survival	63.9 (55.4-71.1)	69.3 (58.0-78.1)	87.7 (77.6-93.4)
Five-year survival	15.8 (9.8-23)	41.9 (29.0-54.2)	43.3 (30.6-55.4)
Ten-year survival	-	20.9 (7.4-39.1)	23.0 (12.3-35.7)
Survival time[b] (months)			
All patients	30.0 (25.4-36.0)	44.3 (29.7-80.2)	54.0 (44.3-80.1)
Triple-negative patients[c]	12.4 (8.4-31.6)	12.2 (4.2-20.5)	44.3 (7.4 - ∞)
Patients with bone-only metastasis	33.9 (17.5-52.9)	82.6 (15.5 - ∞)	58.0 (31.2-80.1)
Patients with oligometastatic cancer	40.3 (29.1-54.4)	94.0 (46.5 - ∞)	87.1 (44.3 - ∞)
Patients received experimental treatments	31.8 (12.0-48)	-	85.0 (33.9-90.9)

CE-CT Contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography

[a]Data shown as frequency (%)

[b]Data shown as median (95% confidence interval)

[c]Negative for estrogen receptors, progesterone receptors, and excess HER2 protein.

Table 5. Multivariable COX regression analyses of baseline clinical and histopathological characteristics on patient survival*

	Variable	HR	95% CI	*p*-value
Arm	***CE-CT (Reference)***			
	FDG-PET/CT	0.44	0.29-0.68	**0.001**
Primary Breast Cancer (Clinical & surgical parameters)	**Tumor size**	0.99	0.999-1.002	0.19
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	1.54	0.77-3.06	0.22
	Adenocarcinoma	1.65	0.61-4.48	0.33
	Unknown	1.004	0.36-2.78	0.99
	Estrogen receptor status ***(Positive as reference)***			
	Negative	1.58	0.72-3.50	0.26
	Unknown	0.73	0.29-1.83	0.50
	HER-2 receptor status ***(Positive as reference)***			
	Negative	0.82	0.36-1.84	0.63
	Unknown	1.40	0.55-3.52	0.48
	Tumor grade ***(Grade 1 as reference)***			
	Grade 2	0.88	0.51-1.51	0.65
	Grade 3	1.10	0.60-2.01	0.76
	Unknown	0.72	0.36-1.45	0.36
	Lumpectomy / Mastectomy	1.30	0.57-3.00	0.53
	Lymph node involvement ***(No involvement as reference)***			
	Single cell / Micro-metastasis	0.69	0.31-1.51	0.35
	Macro-metastasis	1.09	0.71-1.69	0.68
	Unknown	1.13	0.51-2.52	0.76
	Receiving adjuvant therapy	1.26	0.70-2.26	0.44
	Receiving radiotherapy	0.91	0.60-1.38	0.66
	Time until relapse (months)	0.992	0.988-0.996	**<0.001**

	Variable	HR	95% CI	*p*-value
Metastatic Cancer (Clinico-histopathological parameters)	**Year of metastasis diagnosis**	1.15	1.06-1.26	**0.001**
	Age at metastasis (years)	0.994	0.979-1.010	0.48
	Performance status ≥ 2	1.32	0.77-2.27	0.31
	Primary disseminated disease	0.71	0.33-1.51	0.37
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	0.61	0.26-1.43	0.26
	Adenocarcinoma	0.63	0.39-1.04	0.07
	Unknown	0.51	0.29-0.90	0.02
	Estrogen receptor status ***(Positive as reference)***			
	Negative	3.02	1.38-6.62	**0.006**
	Unknown	1.07	0.44-2.61	0.89
	HER-2 receptor status ***(Positive as reference)***			
	Negative	3.62	1.44-9.08	**0.006**
	Unknown	8.21	2.99-22.60	**<0.001**
	Referral Oncologist ***(Oncologist A as reference)***			
	Oncologist B	1.34	0.79-2.28	0.28
	Oncologist C	0.65	0.36-1.18	0.15
	Oncologist D	1.88	0.94-3.74	0.07
	Other oncologists	0.91	0.54-1.53	0.71
	Tumor characteristics & region of metastasis at baseline scan			
	Oligometastases	0.47	0.24-0.89	**0.02**
	Bone	1.71	1.09-2.69	**0.02**
	Liver	2.73	1.82-4.10	**<0.001**
	Lung / Pleural	0.97	0.66-1.41	0.86
	Regional / distant lymph node	0.97	0.65-1.42	0.86

HR hazard ratio, *CI* confidence interval, *CE-CT* contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography, *HER2* human epidermal growth factor receptor-2

*Variables considered in this model included baseline characteristics that are assumed to have potentially a prognostic value and in particular those which showed some imbalance between the groups.

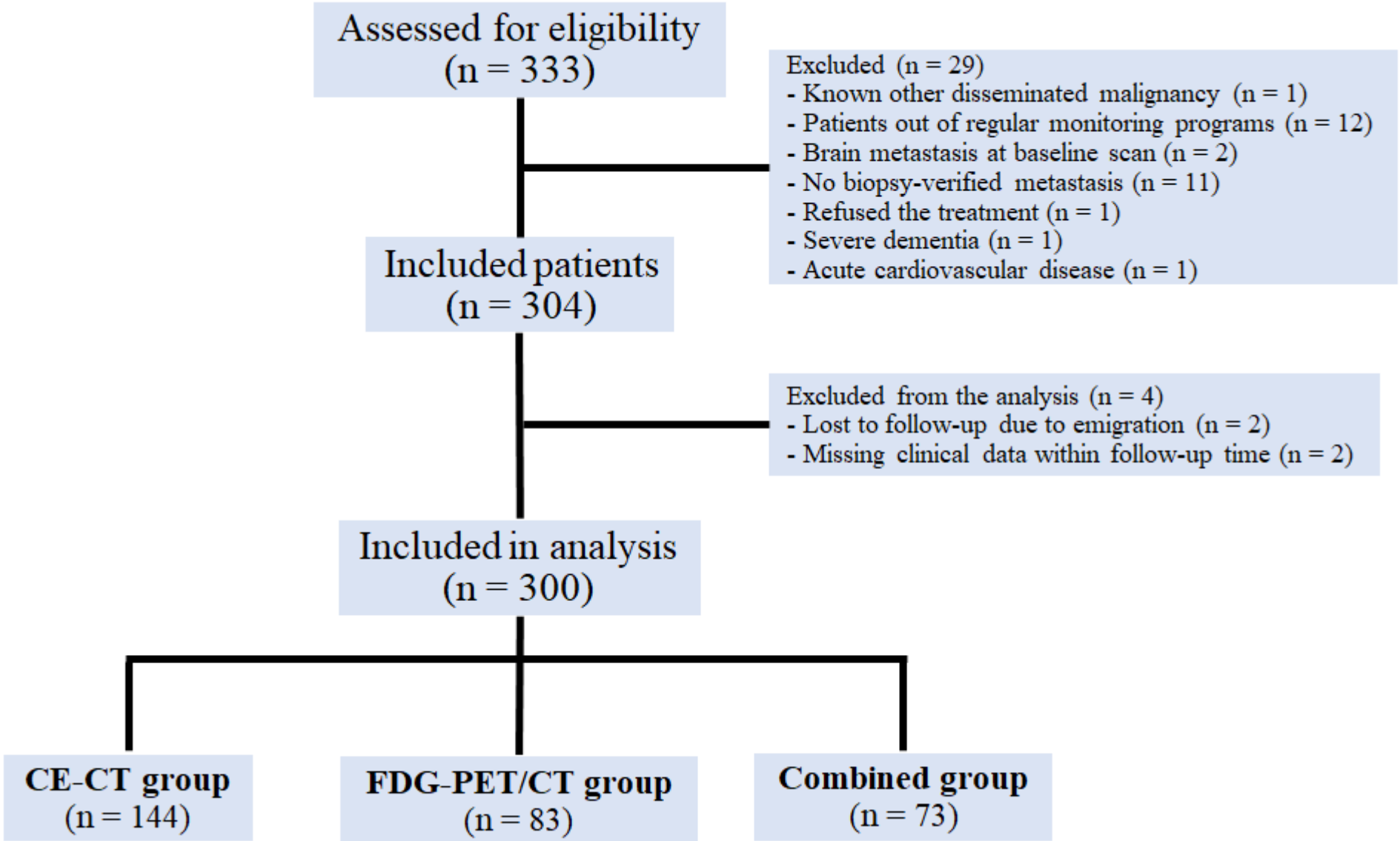
Table 6. Received treatment according to study group

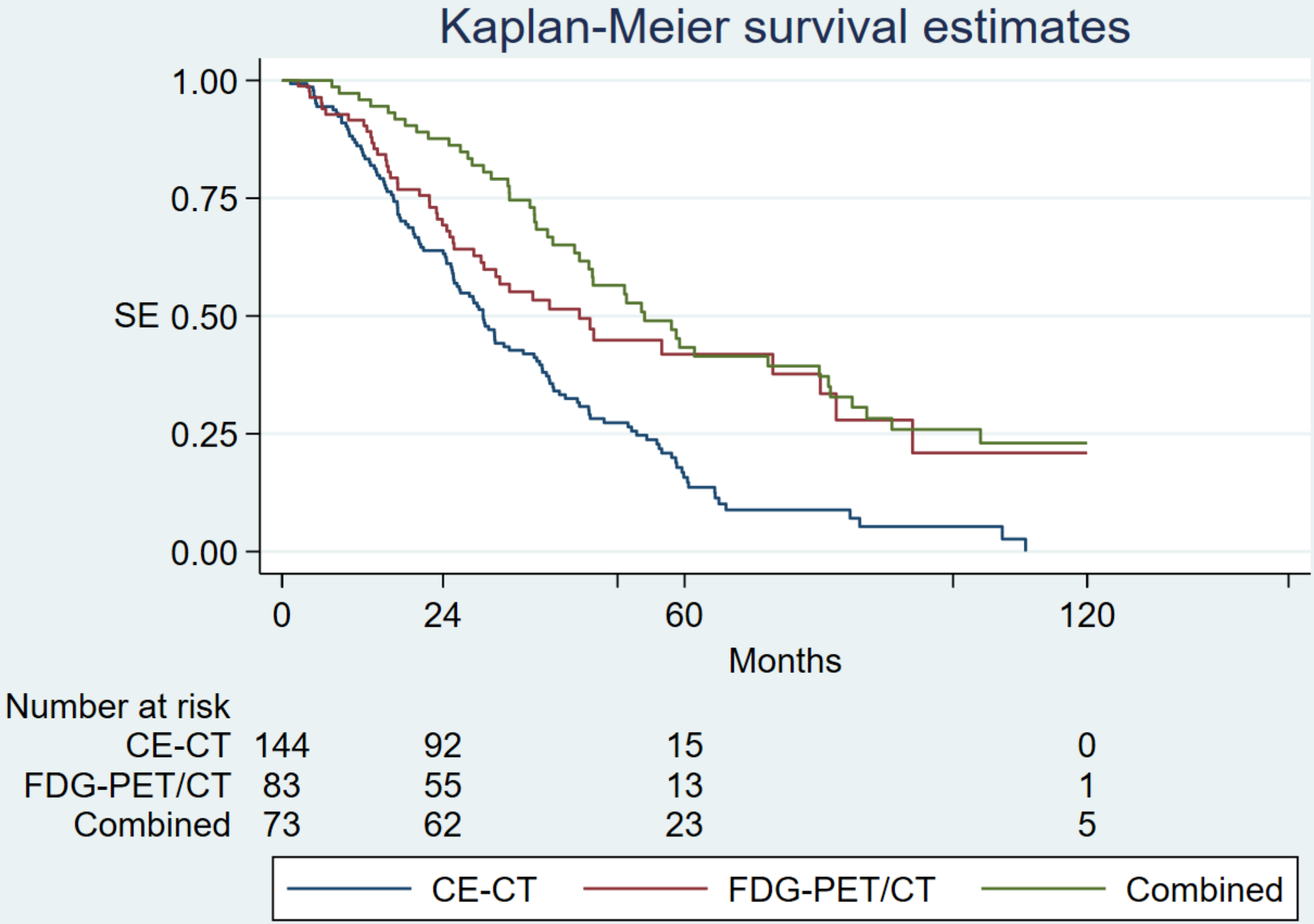
Characteristics	Study Groups			
	CE-CT (n = 144)	**FDG-PET/CT** (n = 83)	**Combined** (n = 73)	***p*-value**
Number of treatment lines				
Mean ± standard deviation	3.1 ± 1.6	2.5 ± 1.5	3.6 ± 2.0	**<0.001**
Median (interquartile range)	3 (1-8)	2 (0-8)	3 (1-9)	
Duration of treatment courses (months)				
Mean ± standard deviation	10.3 ± 9.5	13.9 ± 14.5	15.9 ± 15.9	**0.01**
Median (interquartile range)	6.8 (0.50-49.3)	7.7 (0.50-76.7)	9.3 (1.4-105)	
Time to first treatment change[a] (months)				
Mean ± standard deviation	17.6 ± 13.5	12.9 ± 11.6	16.0 ± 15.3	**0.03**
Median (interquartile range)	13.6 (2.4-61.7)	10.1 (1.8-61.3)	11.4 (1.5-77.1)	
Time to detect second progression[b] (months)				
Mean ± standard deviation	8.1 ± 7.9	12.1 ± 8.1	14.7 ± 15.8	**0.0001**
Median (interquartile range)	5.6 (1-42.7)	10.4 (2.8-33.5)	11 (1.6-106.2)	
Time period receiving treatment (months)				
Mean ± standard deviation	26.7 ± 20.1	27.0 ± 23.8	43.5 ± 31.2	**<0.001**
Median (interquartile range)	22.2 (0.9-84.8)	19.3 (0-112.6)	33.5 (2.8-135.3)	
Time period receiving chemotherapy (months)				
Mean ± standard deviation	12.6 ± 11.6	8.9 ± 7.2	19.2 ± 20.7	**0.005**
Median (interquartile range)	8.6 (0.1-61.9)	7.2 (0.2-26.9)	12.5 (0.1-123.9)	

CE-CT contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography

[a]Time period between baseline scan and first detected progression leading treatment change.

[b]Time period between first and second detected progressions leading treatment change.


Assessed for eligibility
(n = 333)
Excluded (n = 29)
- Known other disseminated malignancy (n = 1)
- Patients out of regular monitoring programs (n = 12)
- Brain metastasis at baseline scan (n = 2)
- No biopsy-verified metastasis (n = 11)
- Refused the treatment (n = 1)
- Severe dementia (n = 1)
- Acute cardiovascular disease (n = 1)
Included patients
(n = 304)
Excluded from the analysis (n = 4)
- Lost to follow-up due to emigration (n = 2)
- Missing clinical data within follow-up time (n = 2)
Included in analysis
(n = 300)
CE-CT group
(n = 144)
FDG-PET/CT group
(n = 83)
Combined group
(n = 73)


Kaplan-Meier survival estimates
1.00
0.75
SE 0.50
0.25
0.00
0
24
60
120
Months
Number at risk
CE-CT 144 92 15 0
FDG-PET/CT 83 55 13 1
Combined 73 62 23 5
CE-CT
FDG-PET/CT
Combined

Supplementary Material 1. Imaging techniques of performed scans.

FDG-PET/CT

Patients fasted for six hours before the scan. The tracer 18F-FDG was administered intravenously in a dose of 4 MBq/kg, and patients then rested and rehydrated with 800 ml of water. Scans were performed approximately 60 min (± 15 min) after FDG injection. A low-dose CT scan was performed from the skull to the proximal femora, immediately followed by a PET scan of the same area. FDG-PET/CT scans were performed using either General Electric Discovery STE or Discovery RX (GE Medical Systems, Milwaukee, USA) with the following settings: CT-scan 140 kV and 30-110 mA Smart mA, rotation time 0.8 sec, pitch 1.375:1, Noise Index 25, detector coverage 40 mm. Transverse images were reconstructed using filtered back projection with standard filter, slice thickness 3.75 mm, interval 3.27 mm. PET scans were performed in 3D with a scan time of 2.5 min/frame for one-hour images. Images were reconstructed iteratively, OSEM, 2 iterations, 21 or 28 subsets, slice thickness 3.3 mm (1).

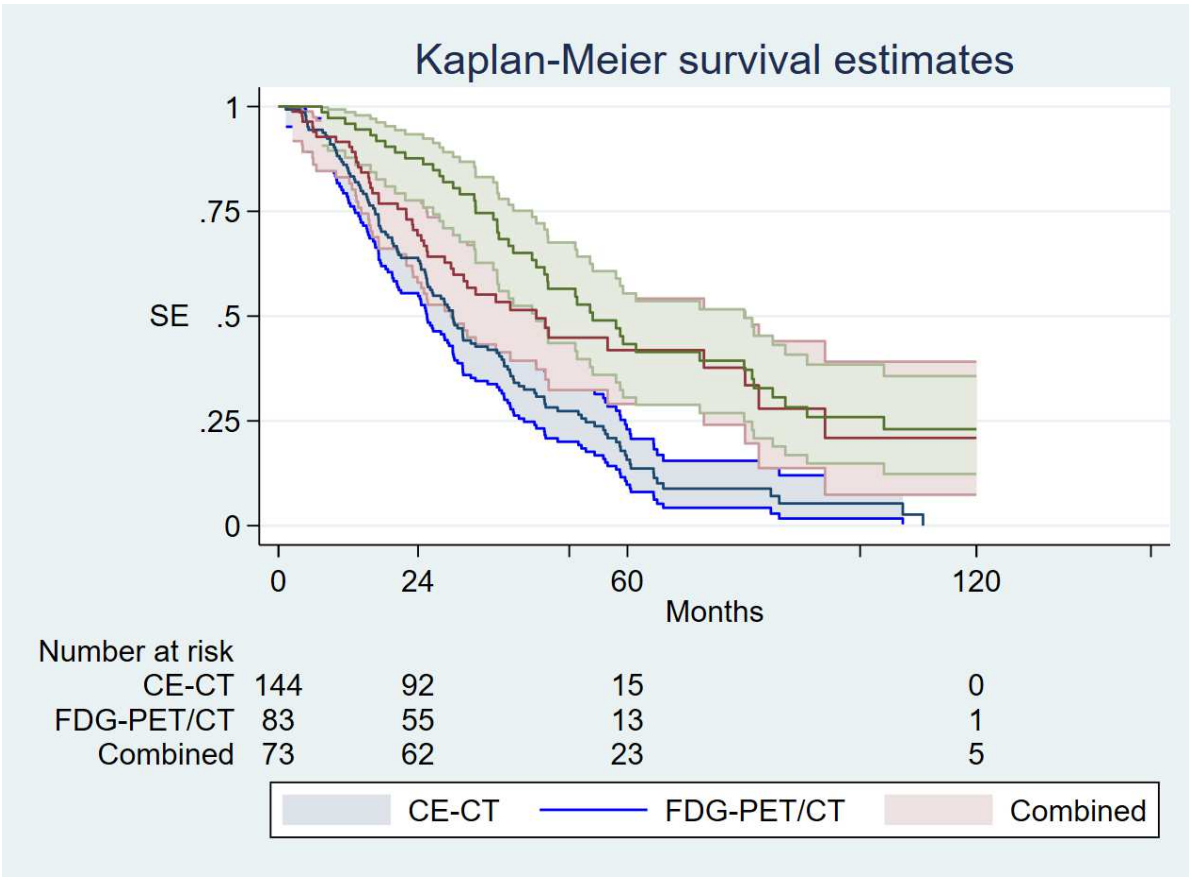
CE-CT

The diagnostic CE-CT scans were obtained on either GE VCT, GE VCT XT, GE HD 750HD, Siemens Somatom Definition Flash, or Siemens Somatom Force. The settings for the GE scanners were 120 kV and 100-750 mA Smart mA, Auto mA, rotation time 0.5 sec, pitch 0,984:1, Noise Index from 40 to 47 depending on the scanner type either HD 750 or VCT due to detector specification. The ASiR level was set to 40%, detector coverage 40 mm. Three reconstructions were made using Soft, Standard, and Lung algorithms. Soft was used for 0.625 mm axial slices and 5 mm coronal and sagittal slices. Standard and Lung were reconstructed in 5 mm axial slices. The settings for the Siemens Flash scanner were 120 kV, ref mas 150, rotation time 0.5 sec, Pitch 0.9. The detector coverage was 40 mm, 0.6 mm x 128, SAFIRE level 3. The

settings for the Siemens FORCE scanner were 120 kV, ref mas 110, rotation time 0.5 sec, pitch 0.6. The detector coverage was 60 mm, 0.6 mm x 192, ADMIRE level 2. Reconstructions for the Flash scanner were made with I31f medium Smooth and I50f medium Sharp ASA kernels. I31f was used for 0.625 mm and 5 mm axial, coronal, and sagittal slices. Lung window was reconstructed with I50f medium Sharp ASA in 5 mm axial slices. Reconstructions for the Force scanner were made with Br40 and Bl57 kernels. Br40 was used for 0.625 mm and 5 mm axial, coronal, and sagittal slices. Lung window was reconstructed with Bl57 in 5 mm axial slices (2).

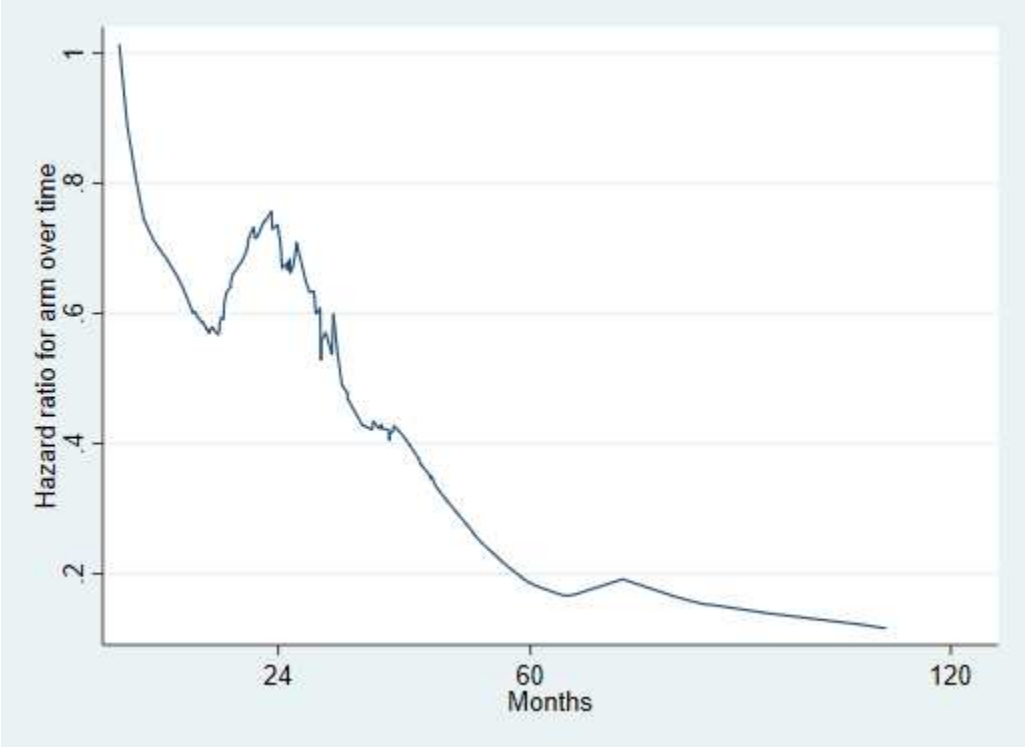
References:

1. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. European journal of nuclear medicine and molecular imaging. 2015;42(2):328-54.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.

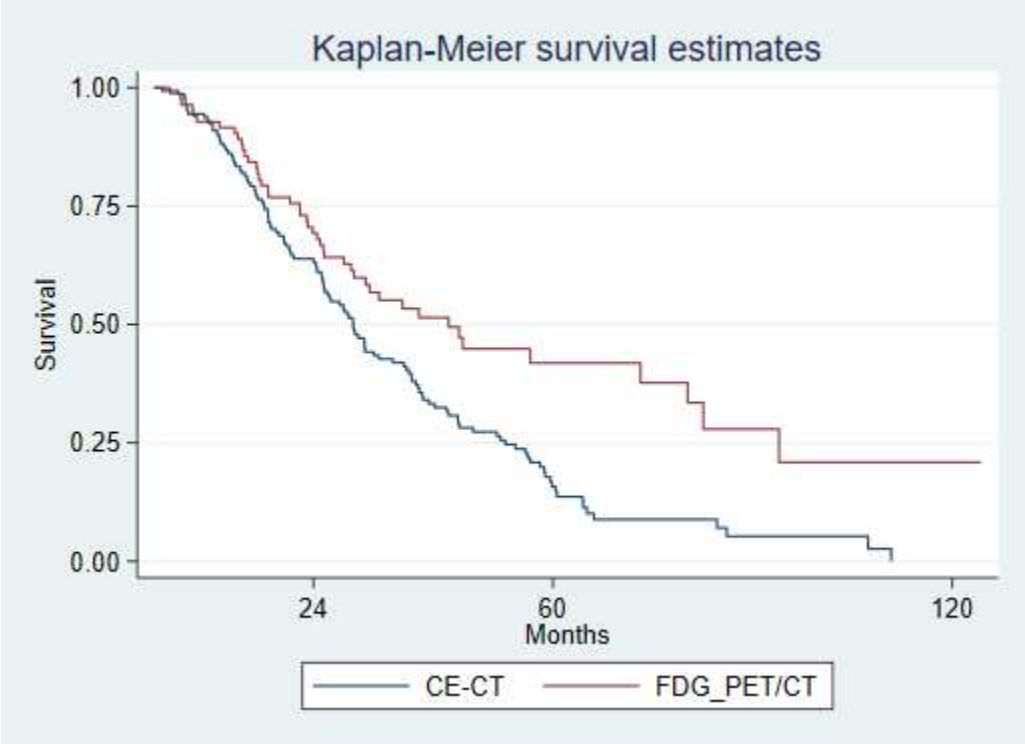


Supplementary Material 2. Kaplan-Meier plot and risk table showing overall survival of metastatic breast cancer patients including pointwise 95% confidence intervals (CE-CT: contrast-enhanced computed tomography, FDG-PET/CT: Fluorodeoxyglucose positron emission tomography with integrated computed tomography).

Supplementary Material 3a. Hazard ratio for group variable (FDG-PET/CT compared to CE-CT) based on Schoenfeld residuals



Supplementary Material 3b. Kaplan-Meier plot for survival of metastatic breast cancer patients (CE-CT vs. FDG-PET/CT)



Supplementary Material 4a. Univariate survival analysis after changing study groups without allowing CE-CT and FDG-PET/CT groups to have one scan from opposite modality.

Study groups	Hazard Ratio	Standard Error	*p*-value	Confidence Interval
CE-CT (Reference)				
FDG-PET/CT	0.45	0.1078	**0.001**	0.277-0.716
Combined	0.59	0.0861	**<0.001**	0.444-0.787

Supplementary Material 4b. Multivariable Cox regression analysis after changing study groups without any scan from opposite modality (CE-CT vs. FDG-PET/CT)*

	Variable	HR	95% CI	*p*-value
Primary Breast Cancer (Clinical & surgical parameters)	**Arm**			
	CE-CT (N = 107)		***(Reference)***	
	FDG-PET/CT (N = 44)	0.20	0.10-0.40	**<0.001**
	Tumor size	0.99	0.998-1.005	0.38
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	3.07	1.01-9.30	0.05
	Adenocarcinoma	1.85	0.60-5.70	0.28
	Unknown	1.97	0.56-6.95	0.29
	Estrogen receptor status ***(Positive as reference)***			
	Negative	0.72	0.20-2.57	0.61
	Unknown	0.69	0.22-2.13	0.52
	HER-2 receptor status ***(Positive as reference)***			
	Negative	1.22	0.44-3.38	0.70
	Unknown	2.60	0.83-8.20	0.10
	Tumor grade ***(Grade 1 as reference)***			
	Grade 2	0.45	0.21-0.97	0.05
	Grade 3	0.71	0.29-1.72	0.45
	Unknown	0.40	0.16-0.99	0.05
	Lumpectomy / Mastectomy	2.01	0.55-7.44	0.29
	Lymph node involvement ***(No involvement as reference)***			
	Single cell / Micro-metastasis	0.58	0.21-1.60	0.29
	Macro-metastasis	1.06	0.55-2.03	0.85
	Unknown	0.39	0.13-1.13	0.08
	Receiving adjuvant therapy	0.45	0.20-1.05	0.06
	Receiving radiotherapy	0.53	0.28-0.99	0.05
	Time until relapse (months)	0.989	0.984-0.995	**<0.001**
Metastatic Cancer (Clinico-histopathological parameters)	**Year of metastasis diagnosis**	1.21	1.08-1.35	**0.001**
	Age at metastasis (years)	0.990	0.968-1.012	0.38
	Performance status ≥ 2	3.17	1.38-7.28	**0.007**
	Primary disseminated disease	0.37	0.12-1.16	0.09
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	0.49	0.15-1.60	0.24
	Adenocarcinoma	0.61	0.33-1.13	0.11
	Unknown	0.42	0.20-0.89	**0.02**
	Estrogen receptor status ***(Positive as reference)***			
	Negative	4.73	1.37-16.32	**0.01**
	Unknown	1.61	0.51-5.07	0.42
	HER-2 receptor status ***(Positive as reference)***			
	Negative	1.34	0.50-3.58	0.57
	Unknown	2.65	0.80-8.75	0.11
	Referral Oncologist ***(Oncologist A as reference)***			
	Oncologist B	1.08	0.54-2.16	0.84
	Oncologist C	0.59	0.27-1.29	0.19
	Oncologist D	1.10	0.36-3.39	0.87
	Other oncologists	0.63	0.31-1.28	0.20
	Tumor characteristics & region of metastasis at baseline scan			
	Oligometastases	0.50	0.22-1.13	0.09
	Bone	1.50	0.83-2.69	0.18
	Liver	3.12	1.84-5.31	**<0.001**
	Lung / Pleural	1.09	0.65-1.84	0.73
	Regional / distant lymph node	1.38	0.80-2.37	0.25

HR hazard ratio, *CI* confidence interval, *CE-CT* contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography, *HER2* human epidermal growth factor receptor-2

*Variables considered in this model included baseline characteristics that are assumed to have potentially a prognostic value and in particular those which showed some imbalance between the groups.

Supplementary Material 5a. Univariate survival analysis after excluding patients who received experimental protocolled treatments.

Study groups	Hazard Ratio	Standard Error	*p*-value	Confidence Interval
CE-CT (Reference)				
FDG-PET/CT	0.57	0.10	**0.001**	0.40-0.81
Combined	0.43	0.09	**<0.001**	0.30-0.64

Supplementary Material 5b. Multivariable Cox regression analysis after excluding patients who received experimental protocolled treatments (CE-CT vs. FDG-PET/CT)*

	Variable	HR	95% CI	*p*-value
Arm	***CE-CT (Reference)***			
	FDG-PET/CT	0.49	0.32-0.77	**0.002**
Primary Breast Cancer (Clinical & surgical parameters)	**Tumor size**	0.99	0.999-1.002	0.15
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	1.81	0.88-3.73	0.11
	Adenocarcinoma	1.79	0.61-5.19	0.29
	Unknown	0.87	0.31-2.45	0.79
	Estrogen receptor status ***(Positive as reference)***			
	Negative	1.57	0.70-3.55	0.28
	Unknown	0.68	0.26-1.77	0.43
	HER-2 receptor status ***(Positive as reference)***			
	Negative	1.07	0.50-2.52	0.87
	Unknown	1.94	0.73-5.17	0.19
	Tumor grade ***(Grade 1 as reference)***			
	Grade 2	0.75	0.42-1.33	0.32
	Grade 3	1.02	0.54-1.91	0.96
	Unknown	0.69	0.33-1.46	0.33
	Lumpectomy / Mastectomy	1.23	0.53-2.85	0.63
	Lymph node involvement ***(No involvement as reference)***			
	Single cell / Micro-metastasis	0.78	0.35-1.74	0.54
	Macro-metastasis	1.12	0.71-1.77	0.62
	Unknown	1.16	0.52-2.60	0.71
	Receiving adjuvant therapy	1.28	0.70-2.36	0.43
	Receiving radiotherapy	0.92	0.59-1.44	0.73
	Time until relapse (months)	0.992	0.987-0.996	**<0.001**

	Variable	HR	95% CI	*p*-value
Metastatic Cancer (Clinico-histopathological parameters)	**Year of metastasis diagnosis**	1.14	1.04-1.25	**0.004**
	Age at metastasis (years)	0.996	0.980-1.013	0.65
	Performance status ≥ 2	1.41	0.81-2.45	0.22
	Primary disseminated disease	0.77	0.36-1.66	0.51
	Tumor histopathology ***(Invasive ductal carcinoma as reference)***			
	Invasive lobular carcinoma	0.62	0.25-1.54	0.30
	Adenocarcinoma	0.72	0.42-1.23	0.23
	Unknown	0.67	0.36-1.24	0.20
	Estrogen receptor status ***(Positive as reference)***			
	Negative	2.95	1.30-6.66	**0.009**
	Unknown	1.52	0.59-3.95	0.39
	HER-2 receptor status ***(Positive as reference)***			
	Negative	2.67	1.06-6.73	**0.04**
	Unknown	5.89	2.11-16.42	**0.001**
	Referral Oncologist ***(Oncologist A as reference)***			
	Oncologist B	1.42	0.81-2.47	0.22
	Oncologist C	0.68	0.37-1.24	0.21
	Oncologist D	1.76	0.83-3.73	0.14
	Other oncologists	1.05	0.60-1.82	0.88
	Tumor characteristics & region of metastasis at baseline scan			
	Oligometastases	0.49	0.24-1.00	0.05
	Bone	1.78	1.09-2.91	**0.02**
	Liver	2.94	1.92-4.52	**<0.001**
	Lung / Pleural	1.02	0.69-1.51	0.92
	Regional / distant lymph node	0.96	0.64-1.45	0.86

HR hazard ratio, *CI* confidence interval, *CE-CT* contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography, *HER2* human epidermal growth factor receptor-2

*Variables considered in this model included baseline characteristics that are assumed to have potentially a prognostic value and in particular those which showed some imbalance between the groups.

Supplementary Material 6. Multivariable COX regression analyses of baseline clinical and histopathological characteristics on patient survival after replacing region of metastasis by number of metastatic organs (CE-CT vs. FDG-PET/CT)*

	Variable	HR	95% CI	*p*-value
Arm	***CE-CT (Reference)***			
	FDG-PET/CT	**0.35**	**0.23-0.54**	**<0.001**
Primary Breast Cancer (Clinical & Surgical information)	**Tumor size**	0.99	0.998-1.006	0.79
	Tumor histopathology *(Invasive ductal carcinoma as reference)*			
	Invasive lobular carcinoma	1.38	0.72-3.66	0.34
	Adenocarcinoma	1.40	0.51-3.86	0.52
	Unknown	1.44	0.54-3.84	0.46
	Estrogen receptor status *(Positive as reference)*			
	Negative	1.03	0.49-2.18	0.93
	Unknown	0.76	0.31-1.84	0.55
	HER-2 receptor status *(Positive as reference)*			
	Negative	0.71	0.33-1.50	0.37
	Unknown	1.22	0.51-2.91	0.65
	Tumor grade *(Grade 1 as reference)*			
	Grade 2	1.05	0.62-1.78	0.86
	Grade 3	1.20	0.65-2.23	0.56
	Unknown	0.86	0.44-1.67	0.66
	Lumpectomy / Mastectomy	1.84	0.81-4.21	0.15
	Lymph node involvement *(No involvement as reference)*			
	Single cell / Micro-metastasis	0.77	0.35-1.69	0.51
	Macro-metastasis	1.02	0.66-1.58	0.93
	Unknown	1.03	0.46-2.29	0.95
	Receiving adjuvant therapy	1.28	0.73-2.70	0.39
	Receiving radiotherapy	0.92	0.61-1.39	0.69
Metastatic Cancer (Clinico-histopathological information)	**Metastasis year**	1.19	1.09-1.31	**<0.001**
	Age at metastasis	0.989	0.974-1.004	0.15
	Performance status ≥ 2	1.45	0.85-2.45	0.17
	Time until relapse	0.991	0.987-0.995	**<0.001**
	Primary disseminated disease	0.56	0.27-1.18	0.13
	Tumor histopathology *(Invasive ductal carcinoma as reference)*			
	Invasive lobular carcinoma	0.77	0.33-1.77	0.54
	Adenocarcinoma	0.54	0.33-0.89	**0.02**
	Unknown	0.46	0.26-0.80	**0.006**
	Estrogen receptor status *(Positive as reference)*			
	Negative	2.62	1.24-5.55	**0.01**
	Unknown	0.92	0.38-2.25	0.86
	HER-2 receptor status *(Positive as reference)*			
	Negative	3.49	1.45-8.40	**0.005**
	Unknown	5.87	2.29-15.08	**<0.001**
	Referral Oncologist *(Oncologist A as reference)*			
	Oncologist B	1.15	0.67-1.98	0.21
	Oncologist C	0.65	0.35-1.21	0.18
	Oncologist D	1.66	0.84-3.26	0.14
	Other oncologists	0.79	0.46-1.33	0.37
	Oligometastatic cancer	0.36	0.18-0.73	**0.005**
	Number of metastatic organs** *(single organ as references)*			
	Two-four involved organs	0.81	0.50-1.31	0.39
	Five involved organs	4.61	1.09-19.44	**0.04**

HR hazard ratio, *CI* confidence interval, *CE-CT* contrast-enhanced computed tomography, *FDG-PET/CT* Fluorodeoxyglucose positron emission tomography with integrated computed tomography, *HER2* human epidermal growth factor receptor-2

*Variables considered in this model included baseline characteristics that are assumed to have potentially a prognostic value and in particular those which showed some imbalance between the groups.

**Number of involved metastatic organs according to baseline scan