PET/CT and dedicated PET in breast cancer: Implications for classification, staging, and response monitoring
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SUMMARY AND DISCUSSION

SAMENVATTING

RESUMEN

LIST OF PUBLICATIONS

DANKWOORD

CURRICULUM VITAE
Progressive insight in breast cancer and its various appearances has changed generalized breast cancer treatment to today's individualized or patient-tailored therapy, which is guided by a combination of patient and tumor characteristics. It is important to assign a patient to the appropriate treatment regimen at once. In order to select patients optimally benefiting from the assigned therapy, several imaging procedures and clinical/pathological assessments are currently available.

The core of this thesis is dedicated to the value of PET/CT and dedicated PET in breast cancer, particularly aiming for an improvement in patient selection and care by increasing personalized management. The use of PET/CT and dedicated PET is mainly investigated in large and/or node-positive breast cancer treated with neoadjuvant chemotherapy (NAC); a smaller proportion of this thesis addresses its use in early-stage breast cancer.

The general outline of this thesis consists of three parts. What is the value and accuracy of 18F-FDG PET/CT for primary tumor visualization and regional/distant staging in primary breast cancer (part 1)? How and when could PET/CT be used for response monitoring during NAC and how accurate is the combination of PET/CT and MRI for response prediction (part 2)? Could whole-body PET/CT and/or a dedicated breast PET be used for improved primary tumor characterization (part 3)?

In the following chapter, a summary of our main findings per chapter is provided for all three topics. Thereafter, relevant aspects for clinical practice are discussed and directives for future research are suggested.

PART ONE | PET/CT

Classification and staging

The first part of this thesis describes the value of pretreatment PET/CT for primary tumor visualization and staging. Chapter 2 reports on primary tumor visualization with PET/CT in breast cancer patients before treatment with NAC. Primary tumor FDG uptake was sufficient for response monitoring in 203 (95%) of 214 stage II-III breast cancer patients. No subgroup of patients with consistently low tumor FDG uptake could be identified, thereby not allowing us to select a group of patients unlikely to benefit from pretreatment PET/CT based on tumor characteristics associated with low tumor FDG uptake. Univariable analysis showed a significantly higher primary tumor SUVmax in patients with unfavorable tumor characteristics: non-lobular carcinomas, tumors with negative hormone receptors, triple negative tumors, grade 3 tumors, tumors with high Ki-67, and in case of distant metastases. This improves the accuracy of PET/CT for tumor detection and optimizes its use for staging or response monitoring in this particular population. After multiple linear regression analysis, triple negative and grade 3 tumors were significantly associated with a higher SUVmax.

Chapter 3 describes the value of PET/CT in T1 breast cancer. Whereas several papers report that the sensitivity for visualization of small (≤2 cm) breast carcinomas is low, we showed that the primary tumor was visible with PET/CT in 54 (87%) of 62 T1 breast cancer patients when using the hanging breast technique in prone position. Visualization
increased from 59% in tumors ≤10 mm to 98% in tumors over 10 mm. Sensitivity and specificity in the detection of axillary metastases were 73% and 100%, respectively. The excellent positive predictive value (100%) indicates that an immediate axillary lymph node dissection (ALND) instead of a sentinel lymph node biopsy (SLNB) is reasonable in case of an FDG-avid axillary node. However, sensitivity was low, requiring an SLNB in case of absence of FDG-avid nodes. Of 12 FDG-avid distant lesions, one was confirmed to be a lung metastasis, three were false positive findings, and eight were new primary proliferative lesions. Based on this study we do not recommend its standard use for staging in these patients because of the suboptimal sensitivity regarding the axilla and the low yield regarding distant metastases.

The optimal method for locoregional staging in patients treated with NAC remains subject of debate. Especially the preferred time-point of SLNB (pre- or post-chemotherapy) is yet to be determined. Therefore, the accuracy of hanging breast PET/CT for detecting locoregional lymph node metastases before NAC is analyzed in chapter 4. In 311 stage II-III breast cancer patients scheduled for NAC axillary FDG uptake was compared with pathology (ultrasound with fine needle aspiration (FNA) or, in case of negative FNA, SLNB). Sensitivity and negative predictive value were suboptimal (82 and 53%, respectively), but positive predictive value was excellent (98%), indicating that an FDG-avid node is highly predictive of axillary metastasis. The proportion of missed metastases with PET/CT was significantly lower in patients with unfavorable tumor characteristics: triple negative tumors, high Ki-67, high grade, and a higher N-stage. Further, occult N3-disease in the internal mammary chain (IMC) and periclavicular area was detected in 26 (8%) and 32 (10%) patients, respectively. This resulted in changed radiotherapy planning in 50 (16%) patients. New N3-nodes were significantly more often detected in patients with a larger primary tumor and a higher TNM-stage. In chapter 5 we describe how often pre-chemotherapy PET/CT upstages nodal stage in the same cohort of patients. Due to treatment with NAC the number of tumor-positive nodes, an important risk factor for locoregional recurrence (LRR) and selection factor for postoperative regional irradiation, can no longer reliably be determined. Based on the high positive predictive value of FDG-avid nodes in breast cancer, pre-chemotherapy PET/CT may offer a surrogate for assessing the number of tumor-positive nodes before start of treatment, thereby changing risk for LRR and guiding decisions on postoperative irradiation. PET/CT detected occult N3-disease in 5 (11%) of 47 low-risk patients. In 144 intermediate-risk patients, PET/CT detected ≥4 FDG-avid axillary nodes in 24 (17%) patients and occult N3-disease in 22 (15%) patients, thereby finally upstaging 38 (26%) intermediate-risk patients. Of 43 (23%) upstaged patients, 18 were eventually ypN0, 12 were ypN1, and 13 were ypN2-3. Chapter 6 demonstrates that PET/CT is superior to conventional imaging techniques for the detection of distant metastases. In 154 stage II-III breast cancer patients forty-two additional distant lesions were seen in 25 patients with PET/CT. These lesions could be confirmed in 20 (13%) patients. PET/CT was false positive for 8 additional lesions and misclassified the presence of metastatic disease in 5 (3%) patients. In 16 (80%) of 20 patients, additional lesions were exclusively seen with PET/CT, leading to a change in treatment in 13 (8%) of 154 patients. In 129 patients with a negative staging PET/CT, no
metastases developed during the follow-up of 9.0 months. Sensitivity and specificity of PET/CT for detecting distant metastases were 100 and 96%, respectively. In contrast, sensitivity of chest radiography was 11%, whereas sensitivity and positive predictive value of bone scintigraphy were 57 and 20%, respectively.

PART TWO | HANGING BREAST PET/CT
Response monitoring of primary tumor and axillary metastases

In the second part of this thesis we evaluate the use of hanging breast PET/CT during NAC for prediction of complete pathological response (pCR) in breast and/or axilla after NAC. Chapter 7 underlines the relevance of breast cancer subtypes for monitoring of therapy response during NAC with PET/CT. We found that (near)pCR was significantly associated with clinical subtype and change in FDG uptake. Further, multivariate regression indicated a significant interaction between the change in FDG uptake and breast cancer subtype. Receiver operating characteristic (ROC) analyses for prediction of (near)pCR with PET/CT were employed, generating an area under the ROC curve (ROC-AUC) of 0.35 for HER2-positive, 0.90 for ER-positive/HER2-negative, and 0.96 for triple negative tumors. Thus, PET/CT response monitoring during NAC is most likely to be useful in ER-positive/HER2-negative and triple negative tumors.

In Chapter 8 we evaluate the value of combined breast and axilla response monitoring with PET/CT during NAC, since absence of tumor cells in both breast and axilla is associated with longest survival. Further, we compared the accuracy of PET/CT response prediction at two time-points during NAC. ROC-AUCs increased when using the change in SUVmax in both breast and axilla as compared with breast or axilla only. In triple negative tumors a PET/CT after six weeks seemed more accurate than after two, whereas in HER2-positive patients neither PET/CT2 nor PET/CT3 appeared useful for response prediction.

The combined value of PET/CT and MRI for response monitoring during NAC is presented in chapter 9. Since PET/CT response monitoring seemed inaccurate in HER2-positive tumors and MRI appeared less accurate in ER-positive/HER2-negative tumors, we hypothesized that both devices might have a complimentary value. For prediction of (near)pCR the ROC-AUC increased from 0.78 for PET/CT and 0.81 for MRI to 0.86 for both modalities combined. The additional value of PET/CT to MRI was predominantly seen in ER-positive/HER2-negative tumors: all patients having >25% decrease on MRI (favorable response according to current institutional guidelines) but <40% decrease on PET/CT did not achieve (near)pCR at pathology and might benefit from a switch in chemotherapeutic regimen.

If all pre-chemotherapy node-positive patients undergo ALND after NAC, overtreatment may occur in complete responders. Chapter 10 focuses on the value of sequential PET/CTs during NAC for axillary response monitoring. In 30 (38%) of 80 patients an axillary pCR was perceived. The relative decrease in SUVmax was significantly higher in patients achieving pCR than in those who did not (PET/CT2 p<0001, PET/CT3 p=0.025). ROC-
AUCs for PETCT2 and PET/CT3 were 0.80 and 0.65, respectively. A relative decrease ≥60% on PET/CT2 had an excellent specificity (35/37, 95%), a high positive predictive value (12/14, 86%), and a sensitivity of 48%; i.e., accurately identifying pCR in 12 of 25 responders, in whom less invasive axillary treatment may be appropriate (for instance, axillary radiotherapy).

PART THREE | HANGING BREAST IMAGING WITH PET/CT AND DEDICATED BREAST PET

Improving primary tumor characterization

In the third and final part of this thesis we address the value of hanging breast molecular imaging for improved primary tumor characterization. In chapter 11 we report on the correlation between the core biopsy location and the area with highest metabolic activity before NAC. Based on intratumor heterogeneity, PET/CT information may enable tumor sampling from the most aggressive part of the tumor (area with highest degree of FDG uptake). This chapter describes how often non-correspondence between the tumor sampling location and SUVmax area is seen. A distance ≥2 cm and a relative difference ≥25% in SUV between core biopsy location (depicted by a marker) and the SUVmax area were considered clinically relevant and a combination of both was defined as non-correspondence, which was seen in 28 (14%) of 203 tumors. Non-correspondence was significantly more often seen in tumors with a higher T-stage, in diffuse (non-mass) and multifocal tumors on MRI, diffuse and multifocal tumors on PET/CT, tumors >3 cm, and lobular carcinomas, in which PET/CT information and possibly FDG-guided biopsies are most likely to improve pretreatment tumor sampling.

The use of PET/CT is currently not recommended for primary tumor detection,6,7 based on limitations due to limited spatial resolution, breast tissue compression, blurring due to the breathing motion of the thorax, and the long path from source to detector. Nevertheless, there is increased interest in visualization and quantification of primary tumors with PET or PET/CT based on lower accuracy of MRI in dense breasts,8 the correlation between FDG uptake and prognostic characteristics,9 and promising results regarding PET/CT response monitoring during NAC.10 Chapter 12 describes the first clinical experience with the MAMMI PET, a high-resolution dedicated breast PET for hanging breast molecular imaging, developed to improve primary tumor detection and characterization. In this first feasibility study MAMMI PET visualized 31 (97%) of 32 tumors, including lesions close to the pectoral muscle (smallest distance 3.3 mm). Agreement in FDG uptake with whole body PET/CT was high, but SUVmax on MAMMI PET was consistently higher (average ratio 2.7).

Chapter 13 contains a review of currently available dedicated breast PETs. Dedicated breast PETs can be classified according to positioning of breast and patient, being a compressed breast with upright patient positioning or a hanging breast in prone position. The positron emission mammography (PEM) is the most extensively investigated device using compression. It allows for image comparison with mammography, has a high
sensitivity and specificity for the detection of breast cancer, yields comparable accuracy as MRI for presurgical planning, and allows FDG-guided biopsies. However, used FDG doses are high, images are acquired in 2D, and lesions close to the pectoral muscle are more frequently missed. The MAMMI PET is the most used device for hanging breast imaging, generating 3D images, directly comparable with MRI. It visualized most tumors in stage II-III breast cancer patients, including those close to the pectoral muscle. A biopsy system is currently in the final stage of development. The additional value of dedicated breast PETs should mainly be sought in dense breast imaging, screening in high-risk patients, tumor visualization in case of an occult or inconclusive lesion on conventional imaging, accurate FDG uptake determination, response monitoring, or FDG-guided biopsies.

In chapter 14 we evaluated heterogeneity of primary tumor FDG uptake using MAMMI PET and whole body PET/CT. In thirty-five patients mean FDG uptake intensity score was similar on both devices (p=0.439), but heterogeneity scores on MAMMI images were significantly higher (p=0.005). MAMMI showed a higher heterogeneity score in 11 (31%) of 35 patients. Heterogeneity scores on both PET/CT and MAMMI were significantly higher in large tumors and in tumor with a high degree of FDG uptake.

GENERAL DISCUSSION AND FUTURE PROSPECTS

Breast cancer is a heterogeneous disease with several distinct entities and related prognoses. The different behavior of several breast cancer subtypes on PET/CT is a common theme throughout this thesis and underlines its heterogeneous nature. Both in future research and clinical practice, knowledge of clinical and pathological characteristics is essential for accurate review of PET/CT images.

PART ONE | PET/CT

Classification and staging

Based on preoperative treatment with NAC or radiotherapy, surgical specimens of breast and axilla are no longer available as pathology standard. Instead, MRI and core biopsies are used as standards for primary tumor visualization (T-stage, size) and histologic assessments, respectively. Clearly, these methods suffer from imperfection. However, in clinical practice information from the whole surgery specimen is not available at the time of therapy planning in these patients either. Therefor the real added value of PET/CT at this time-point is demonstrated in this thesis.

In accordance with several other papers we found an association between the degree of primary tumor FDG uptake and prognostic characteristics. Future studies should point out if SUVmax could be used as (independent) predictor of recurrence or survival; not only primary tumor FDG uptake, but also FDG uptake in axillary nodes or a combination of both should be further explored as prognosticators. Based on the
presumed association between FDG uptake in the primary tumor and metastases\textsuperscript{16,17} and the fact that tumors with prognostically unfavorable characteristics show highest SUVmax,\textsuperscript{9} sensitivity of locoregional and distant staging with PET/CT will be optimal in patients with highest likelihood of metastasis at diagnosis.

Axillary evaluation with PET/CT generated an excellent positive predictive value (98%) for axillary metastases, but a moderate negative predictive value (53%). Based on the association between degree of FDG uptake and prognostic characteristics, missed metastases (without FDG uptake) may be prognostically favorable lymph node metastases in which standard postoperative therapy (i.e., hormonal or HER2-targeted therapy) may be sufficient. In the context of the debate on pre- or post-chemotherapy SLNB, PET/CT may be a helpful tool for patient selection: in US/FNA- and PET/CT-negative axillae a post-chemotherapy SLNB could be performed, whereas in US/FNA- and/or PET/CT-positive nodes some form of axillary response monitoring is appropriate.

Based on the results described in this thesis, part of this hypothesis has been translated to clinical practice in our institute, since a pre-chemotherapy SLNB is no longer performed in ER-positive/HER2-negative and HER2-positive US/FNA- and PET/CT-negative axillae.

The assessment of number of FDG-avid axillary nodes suffers from the suboptimal sensitivity as well. However, based on the excellent positive predictive value, the proportion of upstaged patients will probably even be an underestimation. Further, regional irradiation in patients treated with NAC or in intermediate-risk patients treated with primary surgery remains controversial.\textsuperscript{18,19} Although PET/CT has been shown to be useful, final classifications and recommendations regarding upstaging, risk for locoregional recurrence, and irradiation are yet to be determined and confirmed.

The detection of occult infra- or supraclavicular disease was also based on the high positive predictive value of FDG-avid regional nodes. Although pathological verification was not available in most patients, our institutional guidelines consider them to be patients with N3-disease in whom radiotherapy planning should be adapted. Follow-up of these patients should give a decisive answer on this approach. Second, the involvement of internal mammary nodes has been shown to be prognostically significant, but up to now no clear benefit from elective surgical or radiotherapeutic treatment has been found.\textsuperscript{20,21} Although follow-up should be performed, PET/CT may help selecting patients for postoperative internal mammary chain radiotherapy.

In agreement with our findings several other studies have been published reporting on outperformance of conventional staging by PET/CT.\textsuperscript{22-24} Since detection of distant metastases on PET/CT resulted in a changed treatment plan, we don’t know if these metastases would have become clinically evident without PET/CT; in other words, are we now detecting small metastases that could have been curatively treated with systemic therapy, thereby causing unnecessary patient distress and withdrawing them from treatment with curative intent? Subsequently, what should be done in case of a PET-positive lesion without an anatomical substrate? In our studies we did not classify these lesions as metastases, but they might also be eligible for treatment modification. In current practice, based on the small number of false positives, we recommend...
pathological confirmation of FDG-avid distant metastases and ignorance/follow-up of lesions without anatomical substrate.

From the societal perspective, reducing costs of healthcare while maintaining (or even improving) quality is very relevant nowadays. The beneficial effect on cost-effectiveness of PET/CT in primary breast cancer needs to be addressed in a future study. Although a PET/CT scan is expensive, it may allow omission of SLNB or ALND in selected patients, may prevent a costly and intense treatment with chemotherapy and surgery in patients with metastases, and may prevent patients from receiving ineffective chemotherapy with accompanying toxicity.

Finally, future research should clarify the obscurities regarding visualization of lytic and/or sclerotic bone metastases. It is reported that the detection rate of bone metastases was significantly lower in sclerotic metastases or in case of pretreatment with chemotherapy. In our patient population, however, PET/CT was able to detect both lytic and sclerotic bone metastases. A large trial, evaluating PET/CT accuracy in all patients with bone metastases, should elucidate this issue and determine in what group of patients sensitivity is suboptimal.

PART TWO | HANGING BREAST PET/CT
Response monitoring of primary tumor and axillary metastases

The definite position of PET/CT for response prediction during NAC remains to be determined, but this thesis underlines that its accuracy largely depends on breast cancer subtype. PET/CT seems a promising tool for both primary tumor and axillary lymph node response monitoring and may be a valuable addition to MRI, particularly in ER-positive/HER2-negative and triple negative tumors.

Several articles have reported on the use of PET and PET/CT in the prediction of response to NAC, consistently showing promising results. Conclusive recommendations, however, have not been made yet, based on several limitations of the existing literature. First, in most studies analyses have not been done for the three subtypes separately. Also, study protocols differ greatly regarding inclusion criteria, chemotherapeutic regimens, time-point of second PET/CT, and patient positioning, limiting comparability between different studies. Finally, there is a great variability across centers regarding scanners, image reconstruction, and data analysis, prohibiting exchange and/or reproducibility of SUV values. So, the first step is standardization of PET/CT performance and reporting. Future trials should use standardized protocols and analyze data per subtype for determination of robust cut-off points and optimal scanning time-points.

Although a pCR of the primary tumor and lymph nodes is associated with improved survival, pathological response is a dichotomous variable. Especially in ER-positive/HER2-negative tumors, of which only a very small proportion will achieve pCR, this is an inconvenient end point. The decrease in SUVmax during NAC is a continuous variable, which may be correlated with survival as well. This could be particularly useful as an outcome predictor for ER-positive/HER2-negative tumors, in which varied decreases in SUVmax were noted.
On the reasons why PET/CT for response monitoring of HER2-positive patients is inaccurate can only be speculated. PET/CT2 seemed superior to PET/CT3 in predicting pCR, but both scans suffered from imperfect accuracy. It is purely speculative, but the addition of trastuzumab could facilitate chemotherapeutic action by inducing an inflammatory or immunologic response, causing a rise in glucose uptake and increased SUVmax in responders. This needs to be investigated in future trials. Also, HER2-positive tumors have been shown to be a heterogeneous group. Possibly, results for PET/CT response monitoring of HER2-positive tumors may improve when analyzing subgroups based on ER-status or microarrays.

Finally, PET/CT response monitoring was found to be particularly accurate in triple negative tumors, both for the primary tumor as the axillary nodes. Since sequential PET/CTs visualize changes in glucose metabolism rather than anatomic changes, it is thought that response prediction could be performed early after start of NAC. This was indeed found in some trials, reporting that response monitoring could be performed after the first cycle. Our findings suggest that the early application of PET/CT in triple negative cancers is not sufficient for adequate response monitoring.

Most published studies aim for prediction of pCR, which is an important marker of survival. Perhaps more important could be the determination of a cut-off point for detection of non-responders. In these patients, continuation of the first chemotherapeutic regimen would cause drug toxicity without pathological response and they might benefit from switching therapy to a non-cross-resistant regimen.

Axillary staging and treatment before or after NAC remains subject of debate. Although it required an additional surgical procedure, in our institute a pre-chemotherapy SLNB was performed for accurate assessment of initial axillary stage in clinically node-negative patients. However, if all initially node-positive patients undergo ALND after NAC, overtreatment may occur in complete responders. We have shown that axillary response monitoring could accurately detect 48% of histologic complete responders, in whom an ALND might possibly be spared. Marking the cytology-proven tumor-positive node before NAC with an iodine seed (MARI procedure) is another promising technique. A combination of both modalities may generate even better results, particularly in patients with a tumor-positive MARI-node in whom the remaining lymph nodes were found to be tumor-negative. Further research on axillary PET/CT response monitoring should focus on the analysis per subtype, since these interactions and different behavior of subtypes could not be addressed yet.

The complimentary value of PET/CT and MRI, described in chapter 9, should be further addressed after final inclusion (target accrual 300 patients). These results should be confirmed before translation to clinical practice, in which decision rules for each modality and tumor subtype will be needed. Again, cost-effectiveness plays an important role. Finally, a prospective trial could be envisaged in which PET/CT and/or MRI are used for switching chemotherapy in non-responders. This trial should validate the first results and investigate if higher response percentages could be obtained. Such studies could generate a rationale for the use of new PET/MRI devices.
PART THREE | HANGING BREAST IMAGING WITH PET/CT AND DEDICATED BREAST PET

Improving primary tumor characterization

In this part we have shown that molecular imaging may eventually improve primary tumor characterization before NAC by detection of heterogeneity and guidance of pretreatment tumor sampling to the area with highest proliferation. Further, dedicated breast PETs may enable FDG-guided biopsies and could be useful in selective groups of patients.

Clearly, the studies on detection of heterogeneity and of non-correspondence between tumor sampling location and area with highest degree of FDG uptake are observational. Both findings should be confirmed pathologically, preferably using FDG-guided biopsies. Nonetheless, PET/CT information might improve pretreatment tumor sampling by providing the radiologist with information on the location with highest FDG uptake from which a core biopsy should be performed.

As compared with positron emission mammography (PEM), we found a higher sensitivity for detection of lesions close to the pectoral muscle with the MAMMI PET. This is most likely to be caused by the difference in breast and patient positioning: upright patient positioning and compression of the breast with PEM, prone position with hanging breast with MAMMI. Although we detected the majority of breast cancers with MAMMI PET, in five (13%) patients the tumor was located close to the thoracic wall and incompletely visualized. Since only partial tumor information was returned, SUVmax calculation in these patients was less reliable.

Incorporation of the MAMMI PET in breast cancer diagnosis and treatment is not (yet) established. This thesis describes its feasibility only, whereas future trials should address its value in comparison with MRI regarding detection of (small) primary tumors, the accuracy in dense breasts, the additional value in inconclusive lesions on conventional imaging, its use in response monitoring of the primary tumor during NAC, and the possibility of performing FDG-guided biopsies. Also, the effects of a decrease in FDG dose and performing a scan 60 min after injection of FDG should be addressed.

CONCLUDING REMARKS

Previous studies have reported low yield of PET/CT in early breast cancer and promising but not yet conclusive results regarding detection of distant metastases in (locally) advanced tumors and response monitoring during NAC. Therefore, current international guidelines recommend performing a PET/CT only for the detection of local recurrence or distant metastases in suspected patients, in which its value has been clearly described. The results described in this thesis expand our knowledge on the use of PET/CT in breast cancer and have provided a rationale for extending the use of PET/CT to primary breast cancer patients. Based on these results, we recommend performing a PET/CT before NAC in all stage II-III breast cancer patients for staging purposes.
The involvement of several medical departments underlines the multidisciplinary approach of this thesis, but also the benefit of a PET/CT for each involved medical specialist. PET/CTs before and during NAC are supportive to surgeons, medical oncologists, radiation oncologists, pathologists, and radiologists and facilitate individualized treatment planning. Most important, patients will benefit from PET/CTs because of improved staging, the installation of optimal treatment at once, and provision of correct information before start of therapy.


