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Treatment planning

Is contrast enhancement required to visualize a known breast tumor in a pre-operative CT scan?

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ABSTRACT

Background and purpose: A pre-operative CT scan with contrast enhancement (CE) has recently been proposed to improve tumorbed delineation in breast conserving therapy. However, it is not clear whether CE is required for visualization of a known breast tumor. The main aims of this study were to compare the sensitivity of a CE-CT scan with a native CT scan (*i.e.* without CE) and to identify characteristics predictive for the requirement of CE.

Patients and methods: Both a CE-CT and a native CT were made in 58 breast cancer patients (age 37–75 yr), prior to breast conserving surgery. Visibility of the tumor on CT was scored by three observers (clearly visible/doubtful/not visible). Age, tumor size, palpable tumor yes/no, histology, and visibility on mammography were analyzed with respect to the visibility of the tumor on the native CT.

Results: The sensitivity for tumor detection was better for CE-CT (95%) than for native CT (83%) ($p < 0.001$). Only mammographic visibility scores appeared to be significantly correlated with the visibility of the tumor on the native CT ($p = 0.013$).

Conclusion: In most patients CE is not required to visualize a known breast tumor. Mammographic visibility is a good parameter to decide on the use of CE.

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Introduction

Several studies have shown that application of a boost dose to the tumorbed in patients treated with breast conserving therapy (BCT) reduces the local recurrence rate with almost a factor 2 [1–3] for all age groups. Nevertheless, the majority of local recurrences still occurs in the tumorbed [1]. This may partly be explained by the fact that delineation of the tumorbed for applying the boost is associated with a large interobserver variation [4–8]. This uncertainty in tumorbed delineation may not only be important for delivering an adequate boost irradiation, but may also hamper the feasibility of partial breast irradiation if delivered with post-operative external beam radiotherapy. Consequently, there is a need for improved tumorbed delineation.

Several approaches have been described to improve tumorbed delineation, such as the use of clips, placed according to strict guidelines [9,10], and the use of ultrasound and/or MRI [10,11]. Kirova et al. [12] suggested to make a pre-operative CT scan with contrast enhancement (CE-CT) made in radiation treatment position, and to register this CT-scan with the post-operative planning-CT scan, to improve localization of the tumorbed. Although this image registration may be quite challenging due to surgery-induced changes of the breast, we also wondered whether the pre-operative CT was sufficiently sensitive to visualize the tumor. Kirova et al. [12] reported that the tumor was visible in 20 out of the 20 patients. Our group performed a pilot study using PET-CT in 29 patients with advanced breast cancer or with recurrent breast cancer [13]. Analysis of the CE-CT-data only, without taking into account the PET data, showed that the breast tumors were visible on CT in 13 out of 17 patients (76%); including the knowledge of the PET-data increased the detection rate by CT to 100%. In literature several other studies also reported a good sensitivity for CE-CT [14–17]. Ternier et al. [14] found a 90% sensitivity and 90% specificity for a CE-CT to detect a breast cancer recurrence, whereas Uematsu et al. [15] even found a sensitivity of 100% in breast tumors. Furthermore, Akashi-Tanaka et al. [16,17] claimed that CE-CT was very good in detecting extensive intraductal components, with a sensitivity of 82–88% and a specificity of 75–89%. These data thus suggest that breast tumors may indeed be visible on a CE-CT. It is however, not clear from the literature whether a known breast tumor may also be visible on a native CT-scan, *i.e.* without CE. Since a native CT is obviously more easy to acquire, without the risk of

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adverse reactions, this is to be preferred if sufficiently sensitive. The issue of sensitivity of the CT with or without CE is not only relevant for improving tumorbed delineation, but may be even more relevant when considering pre-operative radiotherapy.

The aim of the current study was, therefore, first to compare the sensitivity of a CE-CT scan with a native CT scan, in patients with a known breast tumor, eligible for breast conserving therapy. The second aim was to investigate whether we could identify factors that can predict whether CE is required, such that CE only has to be given in selected cases. Finally, an elementary comparison of tumor size or volume was made between all imaging modalities and pathology. The impact of a pre-operative CT on interobserver-variation in tumorbed delineation will be reported in a separate paper.

Patients and methods

Patient characteristics

Between September 2008 and October 2009, 60 female cT1-2N0-1 breast cancer patients were included in a study aimed at investigating the impact of a pre-operative CT scan on interobserver variation in the tumorbed delineation [NCT00721058]. Fifty-eight of the 60 patients underwent both a pre-operative CT scan with and without CE, and are subjects of investigation in the current report. All patients were referred for pre-operative consultation to the radiotherapy department (MAASTRO clinic), from four different hospitals in the region. The patients were on average 59 years old (range 37–75 yrs). Eighteen out of the 58 tumors were clearly palpable; 40 tumors were detected by the screening program for detection of early breast cancer. In all patients regular mammography and ultrasound of the tumor was available, with tumor sizes on ultrasound varying from 0.4 to 2.6 cm. Thirteen patients had a conventional mammography, whereas 45 patients had a digital mammography (Table 1).

All patients had a histologically proven breast cancer, a visible mass on mammography or ultrasound and were eligible for breast conserving therapy. All patients had a kreatinine clearance >60 mL/min needed for intravenous contrast.

Patients were included in the study after giving written informed consent. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, according to the Dutch law and regulations.

Acquisition of the CT data

Both a contrast-enhanced (CE)-CT and a native CT were made with the patient in radiation treatment position. The patients were scanned lying in supine position with the arms above the head in an arm-support (Sinmed, Posirest-2), and the legs resting on a Kneefix (Sinmed). The palpable breast tissue (*i.e.* the Clinical Target Volume (CTV)) was marked with a radio-opaque wire. In addition, if a palpable tumor was present, this was marked as well. CT-images were obtained at 3-mm slice thickness from the level of the mandible down to the diaphragm (Siemens Somatom Sensation).

First, a native CT-scan was made; immediately thereafter, 100 mL intravenous contrast (Xenetix 300) was injected, and another CT was made 120 s after injection.

Table 1
Patient characteristics ($N = 58$).

Average tumor size on ultrasound in cm (range)	1.29 (0.4–2.6)
Median age in yrs (range)	58.3 (37–75)
# of patients with digital mammography available (%)	45 (78%)
# of patients with a palpable tumor (%)	18 (31%)
# of patients with screen-detected tumor (%)	40 (70%)
# of patients with infiltrating ductal carcinoma (%)	50 (86%)
# of patients with infiltrating lobular carcinoma (%)	5 (9%)
# of patients with other histology than infiltrating lobular or ductal carcinoma (%)	3 (5%)

Analysis of the CT-data

The visibility of the tumor on the CT was scored by three trained radiation oncologists till consensus was reached for each individual patient. The observers had full knowledge of all available diagnostic information: physical examination, mammography and ultrasound. For each patient, the native CT was analyzed prior to analysis of the CE-CT, to prevent that knowledge of the CE-CT influenced the judgment of the native CT. The visibility was scored on a 3 point scale: clearly visible, doubtfully visible, not visible (Fig. 1).

In addition, the tumor volumes were delineated of those patients with a clearly visible lesion on the native CT, first on the native CT, and thereafter on the CE-CT. All delineations were performed by one observer (BH), who also had complete knowledge of the diagnostic information.

Analysis of the mammography

The visibility of the tumor on mammography was scored by a panel of three radiation-oncologists. The visibility was classified on a three-point scale: clearly visible, doubtfully visible and not visible (Fig. 2).

Statistical analysis

The first aim of the current study was to compare the sensitivity for tumor detection of the native CT with that of the CE-CT. Sensitivity is usually defined as the proportion (or percentage) of only the patients with the condition under study that are correctly identified by the test. Since all the patients in this study have a breast tumor, sensitivity refers to the proportion of all patients in this study that are identified with either the native CT or the CE-CT.

All patients were included in a study aimed at investigating the impact of a pre-operative CT scan on interobserver variation in the tumorbed delineation [NCT00721058]. This number is sufficient to compare the sensitivity of the native CT and CE-CT with the following assumptions. Assuming a 95% sensitivity of the CE-CT [14,15], we could detect a 8.5% decrease in sensitivity of the native CT compared to the CE-CT, with a power of 80% and an alpha of 0.05, with the available data of the 58 included patients. To determine the sensitivity for tumor detection, patients with either a visible or a doubtfully visible tumor on CT were classified as visible.

Secondly, a univariate analysis (independent samples *t*-test for continuous variables and a chi-square test for discrete variables) was performed to test whether age, tumor size on ultrasound, palpable tumor yes/no, histology, or visibility on mammography were related to the visibility on the native CT. Visibility on CT was dichotomized as yes or no. For this purpose, patients with a doubtful visible tumor on CT were classified as visible. In addition, a backward multivariate analysis was performed using logistic regression analysis (SPSS package, version 17.0® for Windows (SPSS INC 2009)) to control for confounding of predictor variables.

Finally, the tumor volumes as delineated on the CE-CT and on the native CT were compared using a paired samples *t*-test, and the Pearson correlation-coefficient was calculated. Furthermore, the largest diameter on the native CT was measured and compared to the same measure on ultrasound and pathology, again using a paired samples *t*-test and a Pearson correlation coefficient.

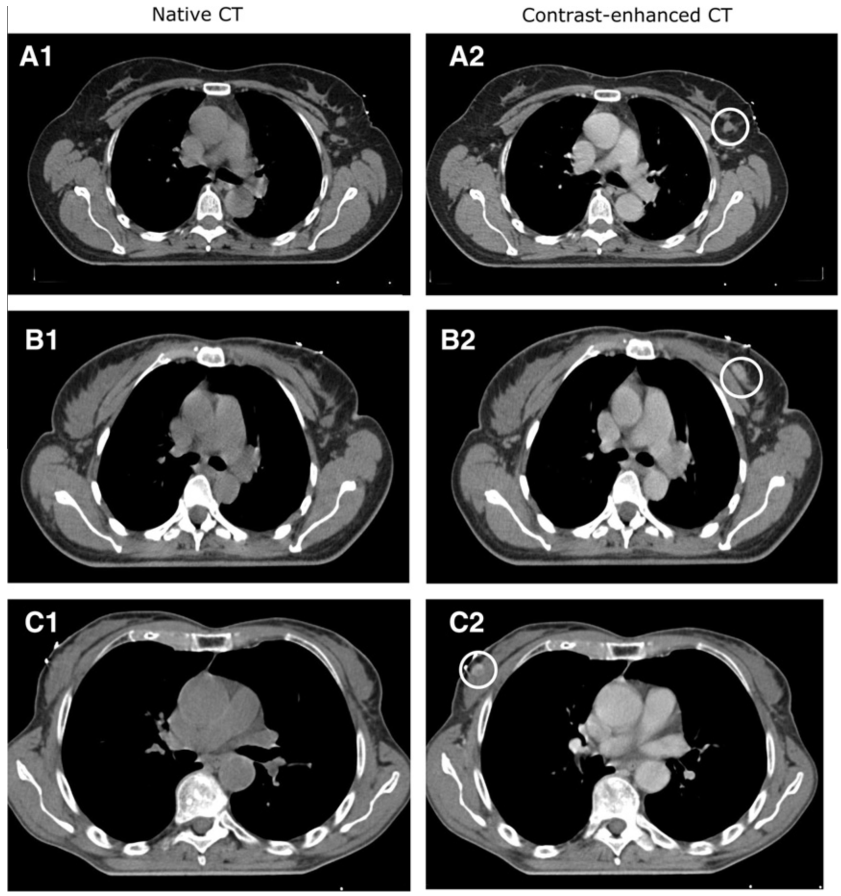

Fig. 1. Example of a clearly visible (A), doubtfully visible (B) or invisible tumor (C) on the native CT (A1–C1), with the corresponding CE-CT (A2–C2).

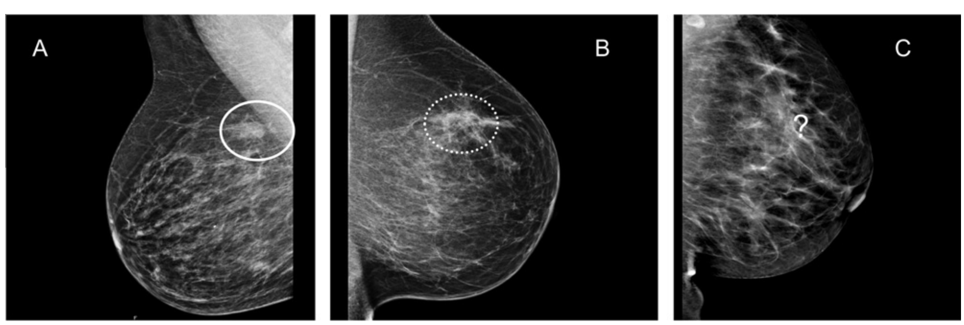

Fig. 2. Example of a clearly visible (A), doubtfully visible (B) or invisible (C) tumor on the mammography.

Results

Sensitivity of the CE-CT the native CT

Of the 58 patients with a native CT, 41 (71%) tumors were clearly visible, 10 (17%) tumors were not visible, and 7 (12%) were doubtfully visible. For the CE-CT these figures were 54 (93%), 3 (5%) and 1 (2%), respectively (Table 2).

To determine the sensitivity for tumor detection, patients with a doubtfully visible tumor on CT were classified as visible. This resulted in a sensitivity of the native CT of 83% versus a sensitivity for the CE-CT of 95% ($p < 0.001$).

Predictive factors

The tumor was clearly visible on mammography in 34 of the patients (59%), doubtful in 17 patients (29%), and not visible in 7 patients (12%). Univariate analysis showed that neither age, nor tumor size, nor tumor palpable yes/no, nor histology showed a significant relation with the visibility of the tumor on the native CT. The only factor that was significantly related to the visibility of the tumor on the native CT was the visibility of the tumor on mammography ($p = 0.013$). The same was found when analyzing the data with a backward multivariate analysis: only visibility of the tumor on mammography appeared to be significantly related to the visibility of the tumor on the native CT ($p < 0.01$). This meant that in 32 of the 34 patients (94%) with a clearly visible tumor on mammography, the tumor was visible ($N = 29$) or doubtfully visible ($N = 3$) on the native CT as well. Out of the two patients with a tumor that was not visible on the native CT, in only one patient the tumor was visible on the CE-CT. The positive predictive value of the mammography for the visibility of the tumor on the native CT was thus 85% (29/34) if only clearly visible tumors on CT were

Table 2
Visibility of the tumor on the CT with and without CE.

	Visible on native CT	Doubtfully visible on native CT	Not visible on native CT	Total
Visible on CE-CT	41	6	7	54
Doubtfully visible on CE-CT	0	1	0	1
Not visible on CE-CT	0	0	3	3
Total	41	7	10	58

Table 3
Visibility of the tumor on the native CT (Table 3A) and on the CE-CT (Table 3B) in relation to the visibility on mammography.

Number (%)	Visible on native CT	Doubtfully visible on native CT	Not visible on native CT	Total
A				
Visible on mammography	29 (50%)	3 (5%)	2 (3%)	34 (58%)
Doubtfully visible on mammography	9 (16%)	2 (3%)	6 (10%)	17 (29%)
Not visible on mammography	3 (5%)	2 (3%)	2 (3%)	7 (12%)
Total	41 (71%)	7 (12%)	10 (17%)	58 (100%)
B				
Visible on mammography	33 (57%)	0 (0%)	1 (2%)	34 (59%)
Doubtfully visible on mammography	15 (26%)	1 (2%)	1 (2%)	17 (29%)
Not visible on mammography	6 (10%)	0 (0%)	1 (2%)	7 (12%)
Total	54 (93%)	1 (2%)	3 (5%)	58 (100%)

counted, and raised to (32/34) 94% if patients with a clearly and doubtfully visible tumor on CT were taken together (Table 3).

Of the 24 patients with a doubtfully or invisible tumor on the mammography, the tumor was nevertheless visible on the native CT in 16 patients (66%). Out of these 16 patients, in 12 patients the tumor was clearly visible and in four only doubtfully visible (Table 3).

Tumor volumes

The tumor volumes delineated on the CT with and without CE were on average 1.6 cc (SD 1.7) and 1.7 cc (SD 2.0), respectively ($p > 0.05$, paired samples *t*-test). The correlation between these volumes was quite high, with a correlation coefficient of 0.87 (Fig. 3A).

The average maximum tumor diameter on the native CT was larger than on ultrasound and pathology (1.47 cm (SD 0.6) *vs.* 1.28 cm (SD 0.5) and 1.30 cm (SD 0.7), respectively. Only the difference between native CT and ultrasound showed a statistically significant difference of 0.31 cm ($p < 0.001$, paired samples *t*-test). In addition, the maximum tumor diameter on the native CT only poorly correlated with the maximum tumor diameter on ultrasound and pathology (Fig. 3B), with correlation coefficients of 0.53 and 0.18 for the ultrasound and pathology, respectively.

Discussion

To our knowledge this is the first study comparing the visibility of a known breast tumor on a CT with and without contrast enhancement (CE). We showed a clear superior sensitivity of CE-CT, but even in the native CT, the sensitivity was reasonable (71–83%). Consequently, CE is clearly not always required to visualize the tumor. Minimizing the use of CE is obviously associated with lower costs, more convenience for both the patient and logistics, and without risk of adverse reactions. On the other hand, if CE is only applied when the tumor is not visible on the native CT, a second CT-scan with CE has promptly to be scheduled, causing troublesome logistic consequences and inconvenience for the patient.

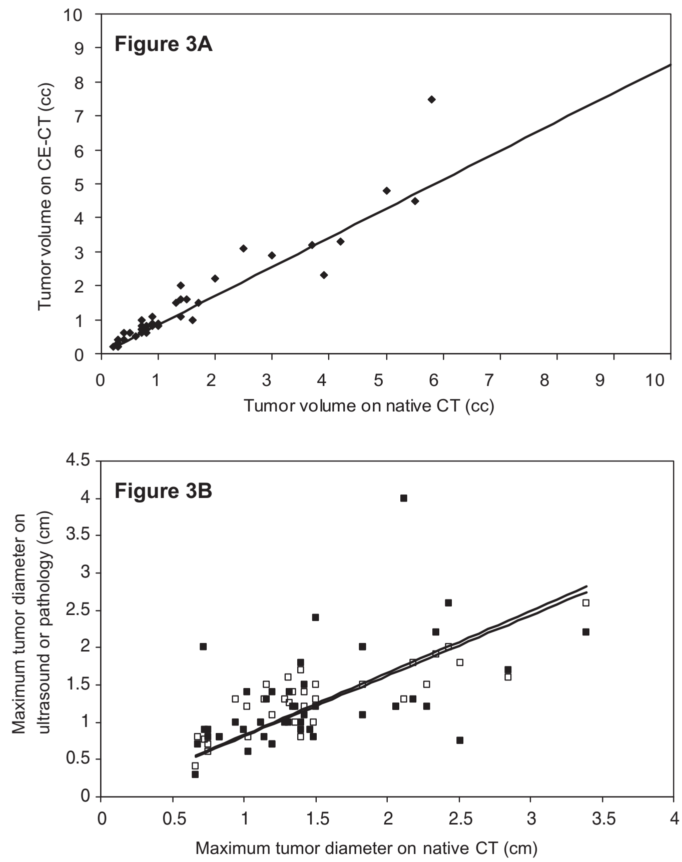

Fig. 3. Tumor volume on the CE-CT versus the native CT, $r^2 = 0.87$ (Figure 3A), and maximum tumor diameter on the native CT, versus the maximum diameter on ultrasound (open squares) and pathology (closed squares) ($r^2 = 0.53$ and 0.18, respectively), Figure 3B).

Below, we compared the consequences for three strategies for selecting patients for contrast-enhancement (Table 4):

- Strategy 1: All patients receive CE. In our patient population, we would have made 58 CTs, all with CE. Forty-one of these 58 (71%) patients would, however, not have needed CE, because the tumor was (doubtfully) visible on the native CT as well.
- Strategy 2: Only patients with an invisible tumor on the native CT receive CE. In that case, only 10 of the 58 patients (17%) would need a CE-CT, but they would all have to come in for a 2nd time; in three of these 10 patients (30%) the tumor would not be visible on the CE-contrast either. In total this would result in 68 CTs, 58 native CTs and 10 CE-CTs.
- Strategy 3: Only patients with an invisible or doubtfully visible tumor on mammography receive CE. In that case, 24 of the 58 patients (41%) would receive CE during their first CT, but in 16 of these 24 (67%), CE would not have been required. Two

Table 4
Number of required CE-CTs and of total required CTs, according to the followed strategy to apply contrast-enhancement.

	Native CT only	CE-CT only	Both native and CE-CT	Total # of CTs
Strategy 1: all patients CE-CT	0	58	0	58
Strategy 2: only CE-CT if not visible on native CT	48	0	10	68
Strategy 3: CE-CT if not/poorly visible on mammography	32	24	2	60

patients would still have to come in for a 2nd time for a CE-CT, but in only one of these the tumor would be visible on the CE-CT. In total 60 CTs would be made, 34 native CTs and 26 CE-CTs.

Consequently, although the visibility on mammography had a high positive predictive value, still 2/3 of the patients receiving CE would not have needed it. Therefore, further studies are required to improve selection of patients requiring CE. For example, we only used subjective interpretation of the mammography, instead of objective imaging features. To counterbalance the influence of subjectivity, we used three observers to score the visibility on imaging; nevertheless, further studies could be focused onto trying to derive more objective imaging features e.g. from MRI [18], ultrasound [19] or mammography that might be predictive for visualization on CT. In addition, although we could not demonstrate a difference between the visibility on conventional mammography or digital mammography, one might speculate that the use of digital mammography would improve the predictive value further, especially in pre- and peri-menopausal patients younger than 50 years, with dense breasts [20].

The sensitivity of the CE-CT was quite similar to the sensitivity mentioned in other studies [14–17]. However, we have to keep in mind that in our study patients already had a proven breast cancer, and the observers had all relevant information of other imaging available, which was not the case in the other studies [14–17].

Since the use of CE might influence the delineation of the tumor itself, we also investigated whether a CE-CT would yield different tumor volumes than the CT without CE. We found that if a pre-operative CT is used for tumorbed delineation, the CE-CT and the native CT without CE yielded similar results, provided that the tumor can be visualized. However, it should be kept in mind that the tumor diameter on CT shows a very poor correlation with the pathologic tumor diameter. In general, CT slightly overestimated the diameter on pathology (regression line: $y = 0.83*x$); this might on one hand be explained by tumor shrinkage following fixation, but also by overestimation of the CT-size due to surrounding edema, or maybe even in situ carcinoma. In addition, inaccuracies in the measurements may explain the poor correlation.

Two patients had a severe (>1 cm) underestimation of the tumor on CT. One of these two patients had a lobular carcinoma (the outlier on the graph with a size on pathology of 2 cm), which is known to have a high risk of underestimation in imaging. The other patient (the outlier on the graph, with a 4 cm size on pathology), appeared to have a very fast growing tumor; in the waiting time for surgery the tumor progressed that fast, that neo-adjuvant chemotherapy was advised. If this patient was neglected, the overestimation of CT increased even further (regression line: $y = 0.78*x$). This patient should, therefore, be neglected in the correlation of sizes between pathology and CT.

Current analyses are ongoing to investigate the value of a pre-operative CT-scan with respect to inter-observervariation in tumorbed delineation. The methods and results of that study will be reported in another paper. If pre-operative imaging in treatment position appears to have a positive effect on tumorbed delineation, it may also be worthwhile to investigate the possibility to use an MRI in treatment position, since MRI has cleary been shown to have a much better correlation with pathology than CT [21].

Conclusion

We showed that a CE-CT has a higher sensitivity for visualizing a known breast tumor than a CT without contrast. Nevertheless, by using the visibility of the tumor on mammography as a predictive factor for requiring CE, the use of CE can be prevented in almost 60% of the patients. Further studies are needed to improve the selection of patients with a visible tumor on the native CT.

Conflict of interest statement

The authors declare that potential conflicts of interest do not exist.

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