



Intraoperative digital breast tomosynthesis using a dedicated device is more accurate than standard intraoperative mammography for identifying positive margins



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AIM: To compare a standard intra-operative mammography (IM) device with digital breast tomosynthesis using a dedicated device (Mozart system) in the evaluation of surgical margins at first excision.

MATERIALS AND METHODS: The study received institutional review board approval and written informed consent was obtained from participants. From January 2018 to December 2018, a prospective analysis of the images of IM device and intra-operative digital breast tomosynthesis with a dedicated device (Mozart system) in $n=89$ breast cancer patients (average patients age: 58 years, age range: 35–76 years) was undertaken. Images were evaluated by two expert breast radiologists independently of each other and blinded to each other's interpretation, who indicated the positive cases requiring surgical re-excision intra-operatively.

RESULTS: Mean cancer size was 12.5 ± 4.5 mm. Radiological signs of the lesions were microcalcifications ($n=71$), nodules ($n=10$), and architectural distortions ($n=8$). A total of 20/89 (17%) patients underwent intra-operative re-excision for positive margins. Intra-operative digital breast tomosynthesis with a dedicated device and IM showed discrepancies in 15/89 cases (17%). Mozart system results informed the necessity to perform a re-excision ($n=15$). Overall, receiver operating characteristic (ROC) curve analysis showed an area under the ROC curve (AUC) of 0.82 for the Mozart system versus 0.65 for IM. ROC analysis of radiological findings with microcalcifications showed an AUC of 0.92 for the Mozart system versus 0.74 for IM, whereas AUC in cases with no microcalcifications were 0.87 and 0.75, respectively.

CONCLUSION: Intra-operative digital breast tomosynthesis with a dedicated device provides more information (better accuracy) than IM and facilitated a reduction in re-excision rates.

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Introduction

Breast conservation surgery is the procedure of choice for excision of the primary tumour in most patients with early breast cancer; the main objective for all patients with breast cancer (BC) undergoing conservative breast surgery or oncoplasty is to obtain margins free of malignant neoplasia in a single surgical procedure. Therefore it appears ideal to achieve clear margins at pathology to minimise the risk of local recurrence, and to avoid re-operation or delay in receipt of recommended adjuvant therapies.¹ National and international guidelines recommend mastectomy if adequate margins are not achieved after repeated re-excision²; however, no limits are placed on the number of re-excision procedures undertaken until mastectomy is recommended. The need for multiple re-excision procedures is associated with an increased risk of local recurrence (LR).³ The rate of re-excision for breast cancer after primary conservative therapy with histologically verified carcinoma (histologically B5 and therefore BI-RADS 6) is highly variable, between 10% and 57% in the literature, depending on the defined safety margin.³ Radiography of intra-operative samples is a routine investigation to confirm that non-palpable lesions are correctly excised.⁴ The types of findings, which are most frequently subjected to this intra-operative radiological survey, are represented by micro-calcification clusters or distortions evaluated using stereotactic guidance. Widely adopted clinical practice is to transport the surgical sample from the operating room to the radiology rooms in a suitable container or to perform the radiograph directly in the operating room, where possible.^{5–7}

With the increasing use of tomosynthesis (three-dimensional [3D] mammography), and given the greater definition and enhanced information offered by tomosynthesis images, as demonstrated in the literature,^{5,7,8} a dedicated intra-operative radiological device with 3D images was developed, referred to as Mozart (Kubtec Img, Stratford, USA). In theory, an intra-operative radiological device with 3D images (digital breast tomosynthesis images) should provide more information than standard intra-operative mammography and reduce re-excisions. Previous studies with retrospective reading showed encouraging results in favour of tomosynthesis,^{9,10} therefore, the aim of the present study was to compare the accuracy of a standard intra-operative mammography device with digital breast tomosynthesis with a dedicated device (Mozart system) in the evaluation of surgical margins at first excision.

Material and methods

The study received institutional review board approval, and written informed consent was obtained from participants. The study involved the prospective analysis of the images of a standard intra-operative mammography device (IM) and intra-operative digital breast tomosynthesis using a dedicated device (Mozart system) obtained from the

surgical operative specimen from each patient (Fig 1). N=127 patients with 130 lesions, studied consecutively (with an average age of 58 years, age range: 35–76 years) from January 2018 to December 2018 were included.

Radiological images of IM and the Mozart system (paired images for each surgical specimen) were anonymised and randomised to the “reader”. Then, images were evaluated on the picture archiving and communication system (PACS) at the end of the study by two expert radiologists, with 25 and 18 years of experience in the field of breast imaging (A. Garlaschi and C. Oddone), independently of each other and blinded to each other’s interpretation to indicate the positive cases requiring a surgical re-excision intra-operatively. Negative cases were those with no requirement for surgical re-excision.

All breast cancers in the present studies were diagnosed after vacuum-assisted breast biopsy (VABB) performed with the ATEC (Automatic Tissue Extraction and Collection) device under a stereotactic guide in tomosynthesis (Hologic, Indianapolis, IN, USA) or ultrasound-guided biopsy. For VABB procedure, a 9 G needle with at least 12 samples was used. For the US-guided procedures, a 14 G needle with at least three samples was used.

For the purpose of the study, BI-RADS 3 lesions were not included ($n=41/130$) therefore 89 cases were eligible for inclusion. During surgery, the orthogonal images of the sample were then obtained using the Mozart system; this device provides on all the samples studied a colour frame, a standard radiogram and a re-elaboration in tomosynthesis. Therefore, all patients evaluated present in their iconography both an intra-operative sample radiograph including intra-operative digital breast tomosynthesis using a dedicated device (Mozart system) and standard intra-operative mammography. Images using the Mozart system were obtained using the standard tomosynthesis technique acquiring multiple low-dose projection images over a 30°



Figure 1 Photograph of the intra-operative digital breast tomosynthesis with a dedicated device (Mozart system).

arc and reconstructed into a series of 1-mm sections to create a set of parallel sections. Reference standard was the definitive anatomopathological results of the final surgical specimen after re-excision. The margins of the surgical specimen are considered not “pathology free” when the microcalcifications or spicules of the distortions reach a distance of <1 mm from the surgical margin, requiring in this case an operative re-excision (<https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer>).

Technical parameters of the intra-operative digital breast tomosynthesis with a dedicated device system are reported in Table 1.

Statistical analysis

Diagnostic accuracy of intra-operative digital breast tomosynthesis with a dedicated device (Mozart system) and intra-operative mammography were evaluated using final surgery as the reference standard. The area under the receiver operating characteristic (ROC) curve (AUC) was computed and compared for the two techniques using statistical software (STATA MP and SPSS).

Results

There were 89 patients with lesions classified as BI-RADS 4 or BI-RADS B5 (53 B5a, 26 B5b e10 B5c) in the analysis. The characteristics of the breast cancer patients are reported in Table 2 according to breast cancer subtypes and histology. Mean cancer size was 12.5±4.5 mm. Radiological signs of the lesions were microcalcifications (n=71), nodules (n=10), and architectural distortions (n=8). Table 3 shows breast cancer subtypes and histology according to radiological sign. A total of 20/89 (22%) patients underwent intra-operative re-excision for positive margins.

Intra-operative digital breast tomosynthesis using a dedicated device and standard intra-operative mammography showed discrepancies in 15/89 cases (17%). The results of the Mozart system informed the necessity to perform a re-excision (n=15). Discrepancies were present when the radiological finding was a cluster of microcalcifications or an architectural distortion, whereas for nodules there were no significant differences among intra-operative digital breast tomosynthesis with the dedicated

Table 1
Technical requirements of the intra-operative digital breast tomosynthesis with a dedicated device (Mozart system).

Detector size	12×15 cm
Spatial resolution	10 lp/mm
Energy range	10–50 kV
Tube current	up to 1 mA
Focal spot	50 µm
Window filtration	0.005" beryllium
Integrated optical camera	13 Mp standard
Power	90–250 VAC, 50/60 Hz, 500 VA
Size (W×D×H)	24"×23"×57" (61×58×145 cm)
Whole device size and weight	61×58×145 cm; 136 kg

Table 2
Tumour characteristics of the 89 breast lesions included in the study.

Characteristic	No. of patients
Histological subtype	
Invasive ductal carcinoma	27
Infiltrating lobular carcinoma	2
Ductal carcinoma in situ	55
Tubular carcinoma	3
Infiltrating mucinous	1
Infiltrating cribriform	1
Histological grade (Nottingham scale)	
Low	20
Intermediate	66
High	13

device and standard intra-operative mammography (Figs 2 and 3). Ten re-excisions were required after the anatomopathological results of the first surgical procedure. No radical mastectomy was required. Margin status was positive for those that had a re-excision.

Overall, the ROC analysis showed an AUC of 0.82 for the Mozart system versus 0.65 for standard intra-operative mammography. ROC analysis of the radiological findings with microcalcifications showed an AUC of 0.92 for the Mozart system versus 0.74 for standard intra-operative mammography, whereas the AUC in cases with no microcalcifications were 0.87 and 0.75, respectively. Results of the AUC with 95% confidence intervals are reported in Table 4. No significant variability was found between the two experienced readers and regarding reading time of intra-operative digital breast tomosynthesis using a dedicated device and standard intra-operative mammography.

Discussion

In this prospective study, in which paired intra-operative imaging for breast surgical specimens was obtained, intra-operative digital breast tomosynthesis using a dedicated device (Mozart system) was better than standard intra-operative mammography to identify patients needing re-excision. Indeed, the overall AUC for the Mozart system was 0.826 compared to 0.652 for standard intra-operative

Table 3
Breast cancer subtypes and histology according to radiological sign and grading.

Nodule (n=10)
7 Invasive ductal carcinoma (I, II=5, III)
2 Infiltrating lobular carcinoma (II,III)
1 Infiltrating mucinous (II)
Distortions (n=8)
2 Ductal carcinoma in situ (I)
4 Invasive ductal carcinoma (II)
1 Tubular carcinoma (II)
1 Infiltrating cribriform (II)
Microcalcifications (n=71)
53 Ductal carcinoma in situ (3 low, 45 intermediate, 5 high)
16 Invasive ductal carcinoma (10 I,5 II,1 III)
2 Tubular carcinoma (2 II)

Grade is reported from I to III.

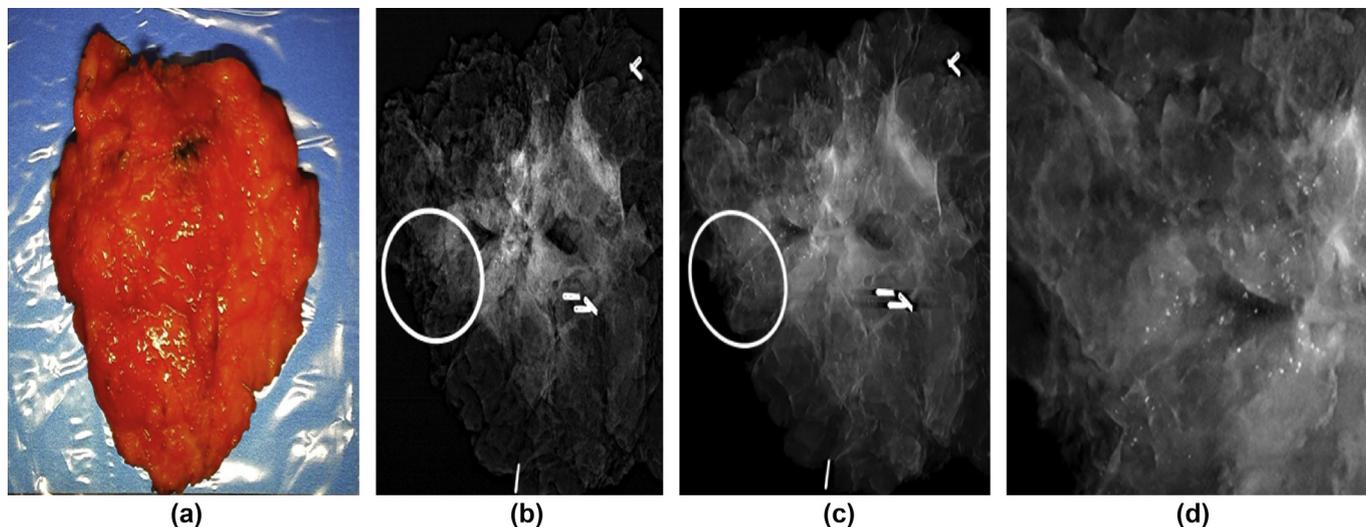


Figure 2 (a) Surgical specimen to be submitted to intra-operative radiological evaluation. (b) The cluster of microcalcifications at the double surgical clip without highlighting suspicious margins (white circle). (c) In addition to the residual cluster, some calcifications are seen at the surgical margin (white circle) using the intra-operative digital breast tomosynthesis dedicated device. (d) Tomosynthesis image showing several microcalcifications that widely affect the surgical margin.

mammography. The number of patients in the present study who may have benefitted by the use of intra-operative tomosynthesis was relatively high (15/89), but is in agreement with the literature¹¹ and the re-excision rate (22.9% re-excision rate in 2220 invasive breast cancers who underwent partial mastectomy) of a large observational study showing substantial surgeon and institutional variation.¹² The high number of patients who received a better treatment due to the application of the dedicated system using intra-operative tomosynthesis during the first

surgical approach is in favour of the adoption of this system directly in the surgical room. Intra-operative digital breast tomosynthesis using a dedicated device performed better than standard intra-operative mammography for breast cancer patients with and without microcalcifications. For patients with microcalcifications, the majority of the cohort, detectable in the surgical specimen by the Mozart system, the AUC reached 0.924. On the contrary, standard intra-operative mammography for patients with microcalcification had a modest AUC of 0.742. This result in favour

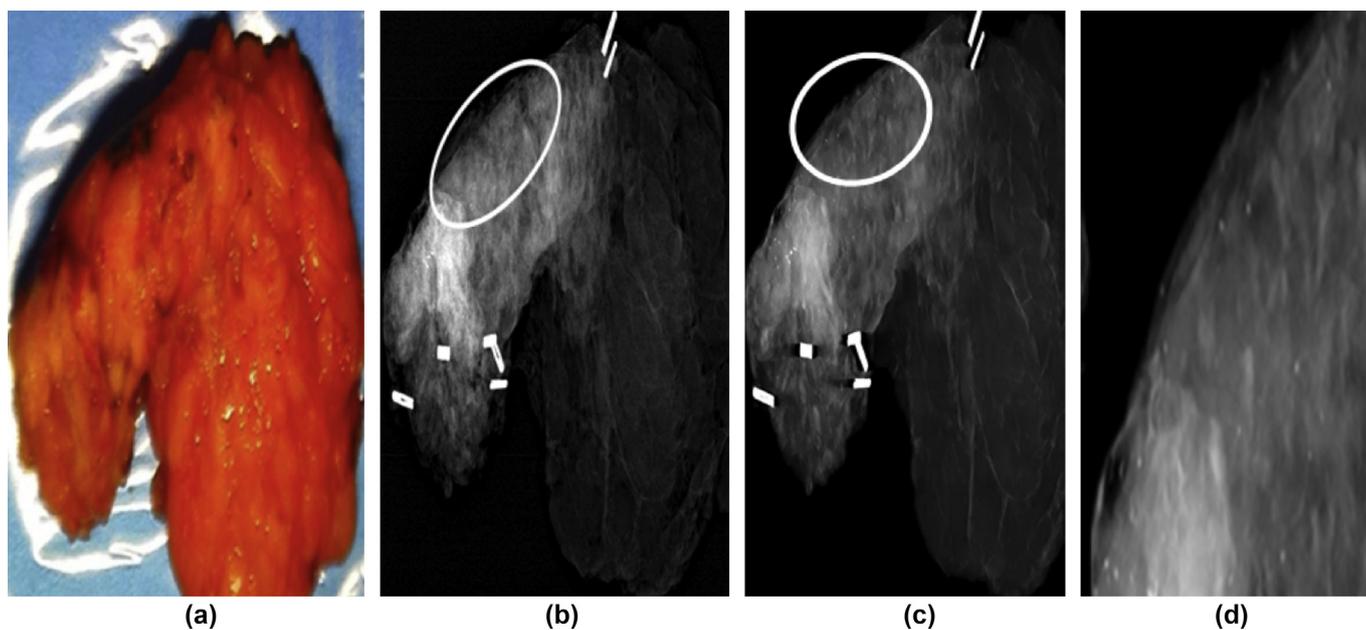


Figure 3 (a) Surgical specimen to be submitted to intra-operative radiological evaluation. (b) The cluster of microcalcifications at the double surgical clip without highlighting suspicious margins (white circle). (c) In addition to the residual cluster, several microcalcifications are seen at the surgical margin at a distance of >1 mm (white circle). (d) Multiple microcalcifications are seen touching the surgical margin.

Table 4

Complete results of area under the receiver operating characteristic curve (AUC) with 95% confidence intervals.

Overall	AUC	Standard error	p-Value	Lower 95% confidence interval	Upper 95% confidence interval
3D	0.826	0.046	0.001	0.736	0.916
2D	0.652	0.058	0.012	0.539	0.766
Only microcalcifications					
3D	0.924	0.038	0.000	0.850	0.998
2D	0.742	0.062	0.001	0.620	0.865
Microcalcification excluded					
3D	0.875	0.134	0.026	0.612	1.000
2D	0.750	0.169	0.137	0.418	1.000

3D: intra-operative digital breast tomosynthesis using a dedicated device (Mozart system); 2D: standard intra-operative digital mammography.

of the Mozart system could be due to the ability of the system to obtain a volumetric evaluation of the whole surgical specimen with better margin delineation, and to provide clear images of targeted lesions reducing the influence of dense tissue and increasing lesion conspicuity.^{11,13–15} In addition, in the present study, digital breast tomosynthesis, which is a pseudo-3D technique, enhanced the images and enabled better appreciation of the edges of the operating specimen even for microcalcifications.

Clear delineation of the surgical margins is clinically relevant, and several studies have shown that positive margins are associated with more than a doubling of risk for local recurrence [10]. Partial mastectomy is optimally performed by achieving adequate surgical margins during the initial surgical resection while maintaining maximum cosmetic appearance of the breast [11]. From the patient's perspective, achieving clear margins at first operation avoids re-excision and additional surgical procedures that can adversely affect psychological and physical health, and even delay use of recommended adjuvant therapies.¹⁶ Indeed, the ultimate goal of using intra-operative digital breast tomosynthesis with a dedicated device was to remove the entire tumour in a single procedure with maximum breast conservation.

A recent study where radiological reading was not available for intra-operative specimen analysis and which did not guide additional tissue excision found that digital breast tomosynthesis was accurate for detecting positive margins in breast cancer patients undergoing segmental mastectomy but digital breast tomosynthesis performed similar to intra-operative standard processing.¹⁰ It is possible that a different definition of margins could explain why the results of the present study are in favour of digital breast tomosynthesis. A positive margin was defined as tumour at ink in the study by Park *et al.*,¹⁰ whereas in the present study a positive margin was considered if a distance of <1 mm from the surgical margin was present.

This study has several limitations. The first is that lesion conspicuity was not compared among the two systems used in this study; however, comparing diagnostic accuracy against a clear and widely accepted reference standard is an

appropriate approach to compare the two systems. The independent evaluation of images obtained by the two system made by different expert radiologists (with blinded interpretation) allowed a real matched within-patient comparison between the two systems in this study with potential to streamline surgery in real-time. A formal cost–benefit analysis was not undertaken, but a reduction in re-excision rates, could be in favour of intra-operative digital breast tomosynthesis using a dedicated device.

In conclusion, the results of the above study show that intra-operative digital breast tomosynthesis using a dedicated device is highly accurate for detecting positive margins intra-operatively in breast cancer patients and can inform necessary wider resection where disease is seen at the specimen margins. Intra-operative digital breast tomosynthesis with a dedicated device provides more information (better accuracy) than standard intra-operative mammography and facilitated a reduction in re-excision rates, which will be beneficial for patients undergoing breast-conserving surgery.

Conflicts of interest

The authors declare no conflict of interest.

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