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Intra- and inter-observer variability in breast tumour bed contouring and the controversial role of surgical clips

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Abstract

The purpose of this study was to evaluate whether the visualization of surgical clips (SCs) on the same set of planning computed tomography (CT) of breast cancer (BC) patients influences agreement on tumour bed (TB) delineation. Planning CT (CT_{orig}) of 47 BC patients with SCs to visualize the TB was processed in order to blur SCs and create a virtual CT (CT_{mod}). Four radiation oncologists (ROs, 2 juniors and 2 seniors) contoured TB on both the CT sets. Centre of mass distance (CMD), percentage overlap as Dice similarity coefficient (DSC), surface distance as average Hausdorff distance (AHD) and TB volume size were analysed. The intra-observer variability when contouring TB with and without SCs was statistically significant (p-values = 0.016, 0.0002 and $\ll 0.001$ for CMD, AHD and DSC, respectively). Junior ROs showed worse reproducibility compared to seniors. The median DSC was < 0.7. The inter-observer variability with and without SCs was statistically significant ($p < 0.001$) for all metrics, with an increase of 48.7% in DSC and decrease of 50.7% and 57.1% in CMD and AHD, respectively, as relative median values, when SCs were visible. Regarding TB volumes, when SCs were visible, the intra-observer analysis revealed that 3/4 ROs delineated larger volumes, especially juniors. The inter-observer analysis showed that, in presence of visible SCs, the difference in TB volume among all the ROs fell from statistically significant to borderline significance ($p = 0.052$). TB contouring is confirmed to be an observer-dependent task. SCs decreased the intra and inter-observer variability but the overall agreement between ROs remained low.

Keywords Surgical clips · Tumour bed contouring · Breast cancer · Radiotherapy

Abbreviations

AHD	Dice similarity coefficient
BC	Breast cancer
BCS	Breast conservative surgery
CMD	Centre of mass distance
CT	Computed tomography
CT_{mod}	Modified computed tomography
CT_{orig}	Original computed tomography
CTV	Clinical tumour volume
DSC	Average Hausdorff distance
GEC–ESTRO	The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology
IMPORT LOW	Intensity-Modulated Partial Organ Radiotherapy Low
IOERT	Intraoperative RT with electrons
IQR	Interquartile range
PBI	Partial breast irradiation
ROs	Radiation oncologists
RT	Radiotherapy
SCs	Surgical clips
TB	Tumour bed
WBRT	Whole breast radiotherapy

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Introduction

Breast conservative surgery (BCS) and adjuvant radiotherapy (RT) represent the mainstay treatment for early breast cancer (BC) patients [1, 2]. Over the recent years, breast adjuvant RT has emphasized the importance of treating the tumour bed (TB) to deliver either additional dose (boost) or exclusive irradiation (partial breast irradiation, PBI) in selected patients. Additional boost dose to the TB has been proven to be beneficial in increasing local control, in particular in young women and/or high-risk tumour [3], while PBI has become a viable alternative to whole breast RT (WBRT) for low-risk patients, according to National Comprehensive Cancer Network guidelines [4].

The TB delineation is a challenge to radiation oncologists (ROs) and the issue of variability in contouring has been broadly addressed [5–8]. The TB identification can be further complicated by the contribution of oncoplastic surgery, which transposes and displaces the glandular tissue [6] and by volume and shape modifications because of breast tissue non-rigidity both before and during RT [9–11].

As a surrogate to improve the TB localization, surgical clips (SCs) can be put by surgeons to visualize the tumour site. SCs act as fiducial markers to define the TB clinical tumour volume (CTV) in the treatment planning [12–15]. The use of SCs is highly recommended in several guidelines [16, 17]. However, the role of SCs as guidance for TB CTV delineation is controversial. On one hand, SCs may improve TB definition [18–22] and, to some extent, may allow achieving better cosmetic results by sparing the surrounding healthy tissues or improving local control [14], although the latter endpoint has multifaceted causes [23]. On the other hand, changes in TB shape and size affect the target volume [5, 7, 9, 24] so that SCs may mislead the extent and site of TB due to mobility and migration [25, 26]. Moreover, clip insertion technique can vary among surgeons and institutions [17, 27]. Therefore, even in the presence of SCs, an accurate TB delineation is a complex task and requires a number of prerequisites in order to achieve low inter- and intra-observer variability in clinical practice [17].

In this study, we investigated whether the visualization of SCs on the same group of BC patients and on the same set of treatment planning computed tomography (CT) images influences the agreement on TB delineation among ROs with different expertise.

Materials and methods

The study population included BC patients who were operated on with BCS and underwent 12-Gy intraoperative RT with electrons (IOERT) followed by hypofractionated WBRT at the European Institute of Oncology IRCCS (IEO, Milan, Italy). The analysis was conducted within the research project entitled "Adjuvant radiation treatments with intensity-modulated radiotherapy and/or hypofractionated schedules for breast cancer", which was notified to and approved by the IEO Ethics Committee (Milan, Italy) on 26 May 2016. Under the umbrella of the abovementioned breast research project, the review board allowed both retrospective and prospective clinical and dosimetric analyses. All patients gave written informed consent for the treatment and use of their anonymous data for educational and research purposes.

After tumour removal and IOERT boost delivery, surgeons clamped 3 to 5 radio-opaque SCs into the breast parenchyma inside the breast, to visualize resection margins in medial, lateral, cranial and caudal directions, describing the position of SCs on the surgical report.

After about 3 weeks, patients underwent planning CT for WBRT in supine position with arms raised above the head, lying on a Posiboard™ 2-Breastboard (CIVCO Medical Solutions, Orange City, IA, US). CT scans were acquired from the neck to the upper abdomen with an image resolution of $0.94 \times 0.94 \times 2.5$ mm. Dose prescription to the breast planning target volume was 37.05 Gy in 13 daily fractions (dose/fraction 2.85 Gy) using 2 opposed tangential fields and 3-dimensional conformal RT [28]. WBRT started between the 4th and 5th week after surgery. Being the boost already given with IOERT, none of the patients received further dose to the TB.

Image handling and study procedures

The TB contouring was specifically made for the purpose of the study. We modified the original CT scans (CT_{orig}) by hiding the SCs inserted at the time of surgery and IOERT. The image handling was made by an ad hoc procedure, using an in-house developed MATLAB (MathWorks Inc., Natick, MA) script based on manually defined SC contours. In particular, we manually contoured each SC and defined its 3-mm isotropic expansion (i.e. an annulus excluding the clip). Then, for each SC, we defined a normal distribution with mean value and variance equal to the ones of the annulus region. Pseudorandom values obtained from this distribution were assigned to each voxel of the SC contour. The thus obtained modified CT scan, in which SCs were no longer visible, was referred as CT_{mod}.

Four ROs were asked to contour the TB on the CT scans with pre-set soft tissue window with the help of clinical reports, surgery description, histological findings, pre-surgery mammograms and breast photographs at the time of CT simulation. Two ROs were dedicated to BC (MCL and AM, senior ROs), with more than 10-year experience and the other two were senior residents (DR and GF), with 6–12-month training in BC, referred from now on as junior ROs. Due to the closed cavity surgical technique, the TB often appeared as area of increased density, but occasionally a fluid collection could be observed. No wires were placed on the lumpectomy scar. At first, ROs delineated the TB on the CT_{mod} with hidden SCs and then, in a second step, they re-contoured the TB on the CT_{orig} of the same patients where the SCs were visible. In order to be unaware of the previously made contouring, ROs kept a minimum of 4 weeks between the two drawings.

No additional margin was given to the supposed surgical excision site, neither on CT_{mod} nor on CT_{orig}.

Statistics

In order to investigate the impact of SCs in the contouring of TB, we evaluated three positional metrics: the centre of mass distance (CMD), as the distance between the centre of mass of the delineated contours on CT_{mod} and CT_{orig} of the same patient; the average Hausdorff distance (AHD), which is an expression of the distance between surfaces of two volumes to be compared [29]; the Dice similarity coefficient (DSC) [30], which expresses the overlap between the delineated contours as the intersection of the contours normalized to their union and varies from 0 (no overlap) to 1 (perfect overlap). In addition, the volume size of each contour was calculated and the differences between CT_{mod} and CT_{orig} contour size were evaluated.

These metrics were calculated between contours performed in the CT_{mod} and CT_{orig} scans by couples of observers (in order to evaluate the inter-observer variability), thus obtaining 6 two-by-two comparisons, namely AM-MCL, AM-DR, AM-GF, MCL-DR, MCL-GF and DR-GF, and by the same observer (in order to evaluate the intra-observer variability).

The normality assessment was performed through the Jarque–Bera test and a non-parametric statistical analysis (Kruskal–Wallis test) was performed to evaluate the impact of SCs on the performance of the observers.

Results

Forty-seven BC patients were the object of the study. They were treated between December 2010 and June 2011. The median age of the patients at treatment was 49 years (range 33–68).

Simulation CT for WBRT planning took place within the 4th week after surgery and IOERT boost. At the time of WBRT, patients had not started the systemic therapy yet. Before drawing, all the 4 ROs agreed that simulation CT images showed structural changes attributable to BCS.

Most of patients (39/47, 83%) had 4 implanted SCs, whereas 7 (15%) had 3 SCs and 1 had 5 SCs. Overall, 376 contours were obtained and analysed, namely 188 from CT_{orig} with visible SCs and 188 from CT_{mod} with hidden SCs.

Intra-observer variability

The median and interquartile range (IQR) values of CMD, AHD and DSC are reported in Table 1. The intra-observer variability when contouring with or without SCs was high among the ROs involved, and the observed differences were statistically significant ($p = 0.016$, 0.0002 and $\ll 0.001$ for CMD, AHD and DSC, respectively). By grouping ROs by level of expertise, the two junior ROs showed worse reproducibility in TB delineation with and without SCs compared to the two senior ROs. In particular, the senior ROs reached statistically significant superior results for AHD and DSC as compared to the junior ROs. The analysis of CMD was not statistically different between senior and junior ROs ($p = 0.126$) but, on an individual level, for one junior RO (GF), the difference was statistically significant compared to the other 3 ROs. In particular, the same RO (GF) showed higher variability for all the metrics.

Table 1 Intra-observer variability

	MCL (senior) Median ± IQR	AM (senior) Median ± IQR	DR (junior) Median ± IQR	GF (junior) Median ± IQR	*p*-value
CMD [mm]	0.98 ± 0.99	0.88 ± 0.70	1.01 ± 0.81	1.49 ± 1.66	0.0164
AHD [mm]	2.94 ± 2.41	1.87 ± 2.07	3.16 ± 3.16	4.42 ± 5.90	0.0002
DSC	0.58 ± 0.18	0.64 ± 0.17	0.48 ± 0.31	0.38 ± 0.38	≪0.001

Median and interquartile range (IQR) values of centre of mass distance (CMD), average Hausdorff distance (AHD) and Dice similarity coefficient (DSC) between corresponding structures obtained by each observer with and without visible clips (AM-MCL: seniors; DR-GF: juniors)

It is worth noting that for all ROs, the median DSC was lower than the threshold of 0.7, which is usually recognised as the threshold of good overlap [31], and, in particular, for the junior ROs, it was lower than 0.5.

Inter-observer variability

Contours obtained by the 4 ROs on the same CT (with or without SCs) were analysed in two-by-two comparison and the resulting metrics are represented in Fig. 1, showing the boxplot of CMD (Fig. 1a), AHD (Fig. 1b) and DSC (Fig. 1c). The differences between contours obtained with and without SCs were statistically significant ($p < 0.001$) for all the considered metrics, with a relative median increase of 48.7% in DSC (absolute difference 0.21), relative median decrease of 50.7% and 57.1% in CMD and AHD (absolute difference −0.68 mm and −2.21 mm), respectively, when SCs were visible.

The detailed comparisons among couples of observers (AM-MCL, AM-DR, AM-DR, MCL-DR, MCL-GF and DR-GF) for the analysed metrics are shown in Figure S1 Suppl. For each parameter and for each couple considered, the presence of SCs improved consistency of contouring and the differences observed were statistically significant.

Volume analysis

To give a quantitative indication of the volumetric change related to the presence/absence of SCs, the volume size was represented by spheres (Fig. 2).

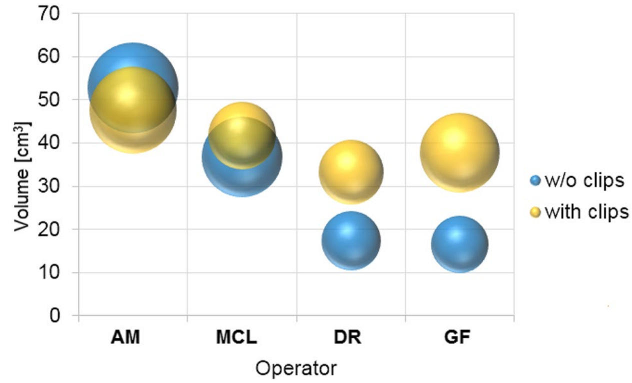

Fig. 2 Analysis of volumes. Tumour bed volumes drawn by seniors (AM-MCL) and juniors (DR-GF). The spheres are centred at the median volume and the dimension corresponds to the variance. Spheres in blue represent tumour bed contoured without—w/o—visible clips. Spheres in yellow represent tumour bed contoured with visible clips. AM-MCL seniors; DR-GF: juniors

Overall, median ± IQR TB volume was 41.1 ± 30.7 cm^3 with visible SCs versus 28.9 ± 34.6 cm^3 with hidden SCs ($p < 0.01$).

At an intra-observer analysis, TB volumes were larger when SCs were visible in all the observers but one senior RO (AM). Individually, TB volumes drawn by the senior ROs were not significantly influenced by SCs (AM: 52.8 ± 42.3 cm^3 vs. 47.6 ± 39.2 cm^3, $p = 0.77$; MCL: 36.8 ± 33.1 cm^3 vs. 41.7 ± 22.9 cm^3, $p = 0.27$). Conversely, the junior ROs were significantly influenced by SCs, both delineating larger volumes in the CT_{orig} than in the CT_{mod}

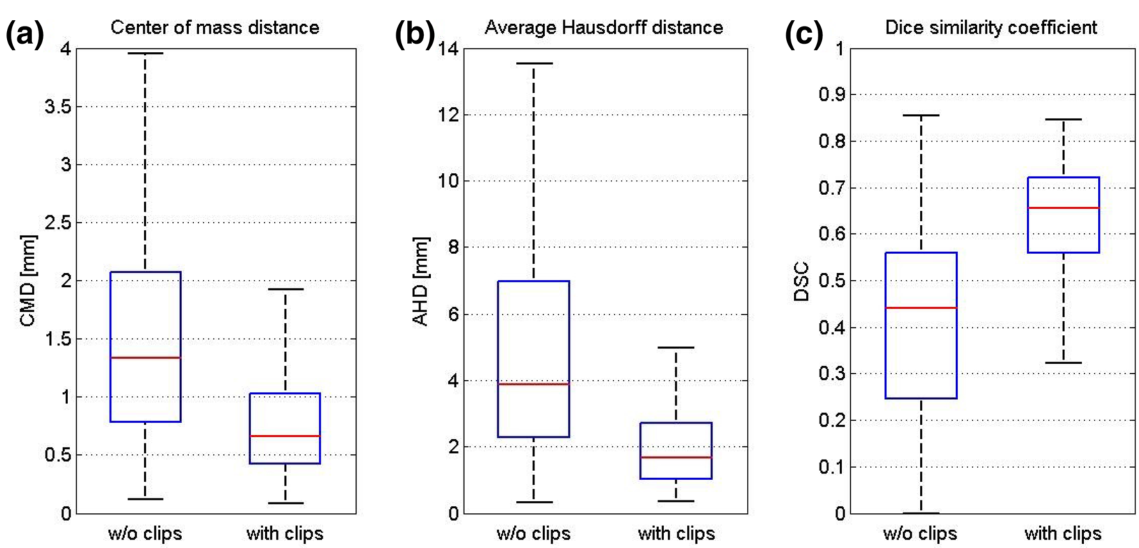

Fig. 1 Inter-observer variability. Boxplot representation of centre of mass distance (CMD) (**a**), average Hausdorff distance (AHD) (**b**) and Dice similarity coefficient (DSC) (**c**) evaluated between corresponding contours segmented by couples of observers. For each metric, the boxplot represents the results obtained from contours segmented on the CT_{mod} (without—w/o—visible clips) and on the CT_{orig} (with visible clips)

(DR: 33.3 ± 21.1 cm^3 vs. 17.4 ± 17.8 cm^3, $p \ll 0.001$; GF: 37.8 ± 32.5 cm^3 vs. 16.5 ± 16.6 cm^3, $p \ll 0.001$).

At an inter-observer analysis, when SCs were visible, the difference in TB volume among all the observers was statistically borderline significant ($p = 0.052$), indicating that SCs helped ROs delineate similar TB volumes and reduce the overall disagreement: for example, considering the 2 ROs (AM, senior and GF, junior) who delineated TB volumes at the two extremes of the range, the median difference of 26.95 ± 30.94 cm^3 obtained when clips were concealed decreased to 5.54 ± 23.84 cm^3 when SCs were visible ($p \ll 0.001$).

Conversely, when SCs were hidden from sight, the inter-observer variability was higher ($p \ll 0.001$, Table 2).

Looking at subgroups with similar level of expertise, the delineated TB volumes were similar between the junior ROs, regardless of SCs ($p = 0.48$ and 0.82 with visible and hidden clips, respectively). Conversely, for the senior ROs, the statistically significant difference in volumes when SCs were blurred ($p = 0.01$) was lost when SCs were visible ($p = 0.22$).

Discussion

Definition of the TB has become an increasingly important aspect of breast RT, especially in the context of PBI, due to the limited treated volume and the high risk of local relapse in the surrounding area [32]. Variability in target volume delineation is a well-recognized problem which occurs very often in RT planning, particularly when small target volumes are in play [33, 34].

To our knowledge, this is the first study in which the variability of TB contouring has been investigated using the same set of CT images in two different scenarios: one allowing the visualization of SCs implanted at the time of surgery to mark the TB, and the other with SCs being hidden. The CT images handling gave a unique opportunity to assess the contouring variability in the same group of BC patients. The results of the study highlighted the importance of SCs in increasing the consistency of contouring across all the ROs involved, regardless of level of expertise. Several authors [19, 20, 35, 36] emphasized the role of SCs in increasing the agreement between observers and improving accuracy of TB delineation. Investigators of the Intensity-Modulated Partial Organ Radiotherapy (IMPORT) LOW trial stressed the importance of SCs to ease the localization of surgical cavity and consequently decrease inter- and intra-observer variability [18]. Although there was not a control group, surgical cavity was localized in 73% of cases in the presence of SCs compared to 27% of cases on the basis of CT information. In the current study, the visualization of SCs on the simulation CT images was helpful for both senior and junior ROs, but especially for juniors. Indeed, regarding the intra-observer variability, our findings demonstrated that senior ROs were less prone to being influenced by the SCs compared to junior ROs. With and without SCs, the median CMD and AHD obtained for the 2 senior ROs did not exceed 1 mm and 3 mm, respectively, in contrast to higher values obtained by the junior ROs. Similarly, median value of DSC was under 0.5 (threshold for moderate agreement) for juniors. However, it should be noted that the contour agreement remained below the optimal threshold of 0.7 even for senior ROs. Failure to achieve a satisfactory level of agreement underlines the difficulty of identifying the target which does not present well-defined boundaries. Moreover, it is well known that DSC is influenced also by the size of the analysed volumes, with smaller volumes obtaining worse results [37], and this might have played a role in the results obtained in the current study. In order to topographically reconstruct the TB, the ROs involved in this study relied on clinical, pathological and radiological information [38]. In particular, they were able to recognize the CT distortion of the surgical area due to short gap between surgery and CT scan acquisition, which prevented the disappearance of postsurgical tissue changes [8, 9]. Also, the inflammatory effect of IOERT itself caused increased soft tissue contrast on CT images. It is well known that the presence of SCs and visible CT signs of architectural distortions can reduce the TB contouring variability [39], even if the standard deviation for the volumes could be as high as 49% [40] with substantial variation in dosimetric planning. Comparing the adequacy of plans, Denham et al. found that 42% of plans derived from clinical information did not properly cover the TB defined by SCs [6].

In our study, not only the degree of contour agreement improved significantly with SCs with respect to all the geometric variables, but also the volumetric differences became less evident. It is interesting to note that the presence of SCs influenced mainly the performance of junior ROs, who tended to contour smaller volumes when there were no visible SCs. In particular, for juniors the median TB volumes

Table 2 Inter-observer variability: analysis of tumour bed volumes drawn by seniors (AM-MCL) and juniors (DR-GF)

	AM (senior) Median ± IQR [cm^3]	MCL (senior) Median ± IQR [cm^3]	DR (junior) Median ± IQR [cm^3]	GF (junior) Median ± IQR [cm^3]	p-value
CT_{mod}	52.8 ± 42.3	36.8 ± 33.1	17.4 ± 17.8	16.5 ± 16.6	≪0.001
CT_{orig}	47.6 ± 39.2	41.7 ± 22.9	33.3 ± 21.1	37.8 ± 32.5	0.052
p-value	0.77	0.27	≪0.001	≪0.001	

without SCs were about half of the median smallest volumes delineated by senior ROs. Conversely, differences in volumes with and without visible SCs were not statistically significant between the 2 senior ROs. Overall, 3 out of 4 ROs drew larger TB volume in the presence of visible SCs, which contrasts other reports [22] describing the association of SCs with smaller RT fields.

A limitation of the study might be the lack of gold standard. However, the purpose of the analysis was not to prove the accuracy of TB identification or its proper coverage. IOERT to the TB was already delivered and the adequacy of the IOERT field is beyond the scope of the study. There was not a rigid protocol to follow for SCs insertion. The number of SCs was not fixed (median 4, range 3–5) and several breast surgeons were involved. We observed that the number of SCs did not influence the intra- and inter-observer variability. The use of a minimum of 3 SCs was shown to be accurate for TB volume delineation [27], even if the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO) experts' panel [17] recommended a greater number when they were clamped into breast parenchyma or fat breast tissue. The panellists also recognized differences among surgeons inserting SCs by hand, as a factor contributing to variability.

It must be recognized that achieving a reproducible and consistent definition of the target, especially with small volumes, is a complex procedure including training, expertise and codified steps. While the findings of the study proved the fundamental role of SCs, it also highlighted the major contribution of the human element: SCs are asymmetrically distributed around the TB and moving from one slice to another the continuity is often lost so that ROs can connect SCs in a different way, leading to different spatial TB representations. The subjective interpretation and personal view are not easy to overcome with the current available tools (contouring guidelines, hands-on delineation workshops, computer-based atlases, etc.), which make contouring an observer-dependent task, even in the same institution and with expert physicians [41].

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

This clinical and dosimetric study has been approved by the institutional Ethics Committee of the IRCCS European Institute of Oncology as part of the research project entitled "Adjuvant radiation treatments with intensity-modulated radiotherapy and/or hypofractionated schedules for breast cancer" (26 May 2016, Milan, Italy).

Informed consent Informed consent was obtained from all individual participants included in the study.

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