Replacement of the tumor bed following oncoplastic breast-conserving surgery with immediate latissimus dorsi mini-flap

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Abstract. The aim of the present study was to evaluate the geographic variability of the tumor bed following oncoplastic breast-conserving surgery (OP-BCS), and to assess its relevance for radiotherapy planning. In this prospective study, pre- and postoperative computerized tomography (CT) scans of 22 patients with early-stage breast cancer were fused. The preoperative gross tumor volume or excisional biopsy cavity were contoured under the guidance of preoperative radiological images. Postoperative lumpectomy cavities were contoured under the guidance of surgical clips. The conformity index (CI) was calculated and defined on a scale between 0 and 1, where 0 indicated no overlap and 1 indicated 100% concordance. Associations between CI and the number of clips, time interval between surgery and CT scans, pathological tumor size and age were assessed using independent sample testing. The median CI was 0.07 (in five cases, 1, and in eight cases, 0). The lumpectomy cavity shifted from the primary location in 36.4% of the cases. Median shifts between the isocenters of pre- and postoperative volumes were measured as 1.02 cm (range, 0.4-4.43 cm) in the x, 1.07 cm (range, 0.05-5.67 cm) in the y, and 1.12 cm (range, 0-3.75 cm) in the z directions. Only the clip number was determined to be significantly associated with CI (P=0.017). Pre- and postoperative tumor bed volumes were fully superposed in five of the 22 cases. The present study has shown that the tumor bed is markedly replaced following OP-BCS with latissimus dorsi mini-flap (LDMF) reconstruction. Special care should therefore be taken when defining the lumpectomy cavity following OP-BCS with LDMF reconstruction.

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Introduction

Breast-conservation surgery (BCS), followed by adjuvant irradiation of the intact breast, has been used as a standard treatment for early breast cancer since the mid-1990s (1). Two randomized studies have demonstrated an improved local control, with the addition of a boost to the tumor bed, particularly in younger patients (2,3). Although breast-conserving therapy is now the most favored option of care for early breast cancer, 20% of the patients who undergo BCS have a poor cosmetic result (4). Oncoplastic (OP)-BCS combines a relatively large volume of breast excision with optimized breast remodeling, yielding a desirable cosmetic outcome (5). Immediate plastic remodeling is indicated for patients with an unfavorable tumor to breast ratio or an unfavorable tumor location (medial, inferior or central quadrants), for patients who require re-excision for involved margins, or for patients with free margins who require the correction of defects for cosmetic reasons (6,7). Due to major complications, including infection, wound breakdown, pain, capsular contraction and instability in the excision bed, silicone implants have been shown to be unsuccessful at filling breast defects following a wide excision (8).

Recently, latissimus dorsi mini-flap (LDMF) reconstruction has become a preferred method in OP-BCS, particularly for tumors located in the central, upper inner and upper outer quadrants, where resection of 20-30% of the breast volume is required (9). Another frequent cosmetic complaint may be the discrepancy of the size between the breasts that can be achieved by OP-BCS.

Although the definition of the tumor bed is an important component of breast radiotherapy (RT), a standard technique to delineate or define the tumor bed volume remains to be established (10). The accurate identification of the tumor bed following OP-BCS is more challenging compared with standard BCS due to the rearrangement of breast parenchyma. The aim of present study was to evaluate the replacement of the tumor bed following OP-BCS with LDMF breast reconstruction, and to determinate the most accurate method to delineate the local boost field.

Materials and methods

Patients. This prospective study was conducted between April 2013 and January 2014 with the approval of the Istanbul Bilim University Research Ethics Committee. Patients were operated on by a single surgeon, and RT was planned by a single radiation oncologist. A total of 22 consecutive patients referred from the surgery department prior to OP-BCS with LDMF breast reconstruction were included in the present study, and all patients gave informed consent to be involved in the study.

OP surgical procedures. The surgical technique of LDMF is a one-step procedure, although it was previously described as a two-stage procedure by Dixon *et al* (11). Following a wide local excision of the tumor with clear margins reported by the breast pathologist intraoperatively, sentinel lymph node biopsy and/or axillary dissection is performed. The axillary incision is slightly lengthened and deepened over the lateral margin of the latissimus dorsi (LD) muscle while the patient is held in the lateral decubitus position. The muscle is grasped and retracted from the chest wall to identify the thoracodorsal vessels. The length of muscle required to fill the defect is estimated by measuring from the apex of the axilla to the lower limit of the breast defect. The LD muscle is mobilized from the surrounding structures by using a combination of bipolar scissors and electrocautery. When a sufficient quantity of muscle has been mobilized, the muscle is divided inferiorly and delivered into the axillary wound. Attention is subsequently turned to the superior part of the muscle, which is divided at its insertion into the humerus. At this stage, the LDMF is ready to be transferred into the breast. At this point, the cavity is re-evaluated for any hemorrhaging, and is marked with clips. Depending on the site of the wide local excision, a tunnel is created from the axillary wound into the breast defect. The flap is subsequently passed through the tunnel into the cavity. To remove the tension from the vessels, the flap is secured superolaterally by suturing the tendonous part of the muscle to either the edge of the pectoralis major muscle or to adjacent breast tissue. The muscle is subsequently secured in the breast defect using absorbable sutures to generate a good shape.

Pre- and postoperative computerized tomography (CT) imaging and image registration. All patients underwent two sets of planning CT scans pre- and postoperatively in the treatment position, with a slice thickness of 2.5 mm. Patients were scanned with an Optima CT580 CT scanner (GE Healthcare, Buckinghamshire, UK), which had an 80 cm gantry opening and indexed table (Civco indexed carbon fiber MT-IL4101; Civco Medical Solutions, Kalona, IA, USA), specific for RT. Prior to CT scanning, the margins of palpable glandular breast tissue were marked with a thin CT-compatible Radio Opac wire by the radiation oncologist. Patients were immobilized in the supine treatment position; their shoulders and arms were fixed using a breast board (C-Qual breast inclined plane; Civco Medical Solutions) with knee support. The breast board index parameters were recorded in the patients' chart for the purpose of using the identical parameters in postoperative CT. All CT images were imported to a treatment planning system (Eclipse version 8.1; Varian Medical Systems, Palo Alto, CA, USA). Both CTs were fused using rigid registration on a user-defined region of interest, superposing the sternum and ipsilateral chest wall. During the fusion process, the nipple, skin and parenchymal breast tissue were not assigned priority due to the change in breast configuration following OP-BCS.

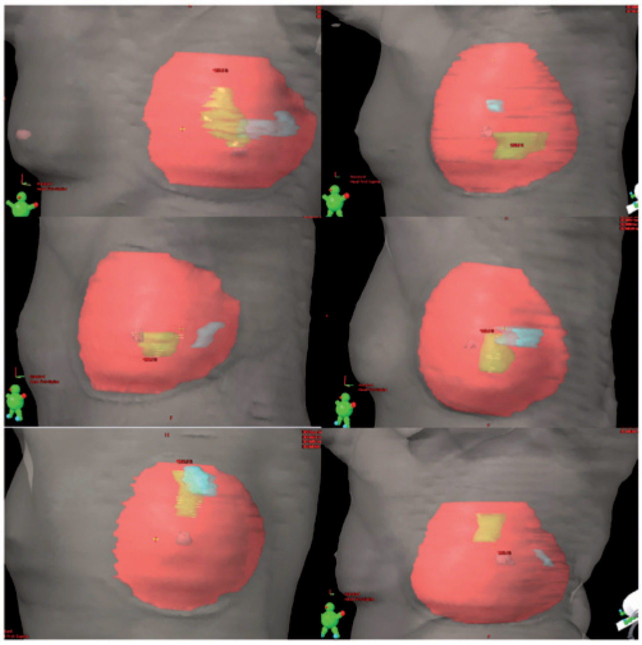

Figure 1. CT image fusion showing the cavity shift. The cyan coloration shows the preoperative gross tumor volume; red, breast clinical target volume; green, lumpectomy cavity; yellow, surgical clips; brown, nipple.

Volume delineation and relative positions. The breast clinical target volume (CTV) in both CTs was delineated by a single radiation oncologist, and a 5 mm section from the skin inwards was excluded. The gross tumor volume (GTV) of the preoperative tumor, or the excisional biopsy cavity, was contoured under the supervision of a radiologist using diagnostic mammography, ultrasonography and/or magnetic resonance images (Fig. 1). All patients were subjected to mammography and breast ultrasound prior to surgery, and 12 patients were also subjected to magnetic resonance imaging (MRI) of the breast. The postoperative lumpectomy cavity was contoured as the area surrounded by the surgical clips. The tumor bed planning target volume (PTV) was created in accordance with the Radiation Therapy Oncology Group (RTOG) 1005 protocol (https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1005), with a 1 cm expansion to the lumpectomy cavity for lumpectomy CTV, and an additional 0.7 cm expansion to the PTV. An electron boost field was generated with a 1 cm set-up margin for the PTV evaluation. Dose-volume histograms were calculated for all delineated volumes. The conformity index (CI) was calculated using the formula defined by Struikmans *et al* (12) as the ratio of overlapping

Table I. Tumor and treatment characteristics (n=22).

Characteristic	n	%	Median	Range
Age, years	22	-	44	29-69
≤40	7	31.8		
>40	15	68.2		
Time from OP-BCS to RT (day)	22	-	90	14-170
Tumor type				
IDC	19	86.3		
ILC	2	9.1		
Other	1	4.6		
Focality				
Unifocal	15	68.2		
Multifocal	7	31.8		
pT stage[a]				
I	11	50.0		
II	10	45.4		
III	1	4.6		
pN stage				
0-mic	14	63.6		
I-III	8	36.4		
p stage				
0	1	4.6		
I	7	31.8		
II	10	45.4		
III	4	18.2		
Primary quadrant location				
Upper outer	16	72.7		
Retroareolar	2	9.1		
Lower outer	3	13.7		
Lower inner	1	4.5		
Chemotherapy				
No	4	18.2		
Anthracyclin-based	3	13.7		
Anthracyclin and taxan-based	15	68.2		
Trastuzumab				
No	17	77.3		
Yes	5	22.7		

[a]According to the TNM cancer staging system. OP-BSC, oncoplastic breast-conserving surgery; pT, primary tumor; pN, regional lymph nodes; RT, radiotherapy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

volume to encompassing total delineated volume. CI was defined between 0 and 1, where a value of 0 indicated no overlap, and 1 indicated 100% concordance. By using coronal, sagittal and axial CT slices of the planning system, the shifts of the isocenter of the volumes were calculated in terms of x, y and z coordinates. Paired sample t-tests were performed to evaluate the changes in volumes. Associations between CI and the number of clips, the time interval between CT scans, pathological tumor size and age were assessed using an independent samples t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient, tumor and treatment characteristics are shown in Table I. The median age was 44 years (range, 29-69 years), seven of the patients were ≤40 years old. The median interval between two CT scans was 90 days (range, 14-170 days). Seven patients had excisional biopsy prior to the preoperative CT. Six of the patients had right-sided cancer, and 16 were left-sided. The tumor was situated in the upper outer, retroareolar, lower outer and lower inner quadrants in 16, 2, 3 and 1 patients, respectively. Tumors were resected with clear

Table II. Volume description.

Patient number	No. of clips	Time interval between CT scans (days)	GTV (cm^3)	Lumpectomy cavity volume (cm^3)	Fused volume (cm^3)	Intersection volume (cm^3)	CI	Preoperative quadrant location	Postoperative quadrant location	Shift directions (cm)		
										x	y	z
1	2	90	1.2	7.4	8.5	0.0	0.0	UOQ	RA	0.47	0.47	3.25
2	4	84	5.2	20.6	25.8	0.0	0.0	UOQ	RA	1.32	4.60	0.76
3	5	127	2.7	21.7	24.4	0.0	0.0	UOQ	LOQ	0.82	2.79	3.75
4	2	148	1.8	6.2	8.0	0.0	0.0	LOQ	RA	2.33	1.22	1.25
5	4	23	24.8	18.4	40.4	0.0	0.0	UOQ	RA	2.44	0.90	2.25
6	2	99	3.4	16.1	19.5	0.0	0.0	UOQ	RA	4.28	5.67	2.76
7	3	14	7.7	31.5	39.2	0.0	0.0	LOQ	RA	2.21	1.96	1.75
8	3	15	0.4	9.5	10.1	0.0	0.0	LOQ	LOQ - RA	1.17	0.70	1.50
9	3	43	5.2	75.8	80.8	0.5	0.0	UOQ	UOQ - LOQ	1.86	2.36	0.0
10	3	30	26.8	51.3	76.1	2.1	0.0	UOQ	RA	4.43	3.69	1.0
11	4	128	8.8	19.7	27.0	1.7	0.0	UOQ	UOQ - LOQ	0.83	2.49	0.67
12	6	170	7.3	62.6	64.8	5.4	0.08	UOQ	UOQ	0.37	0.81	1.25
13	4	48	11.7	9.8	19.9	1.9	0.09	UOQ	UOQ	0.70	0.17	1.42
14	4	119	30.3	60.7	83.7	7.6	0.09	UOQ	UOQ - UIQ	1.86	0.74	0.19
15	2	150	38.8	12.7	45.4	6.5	0.14	UOQ	UOQ	1.06	1.07	2.25
16	5	37	13.6	50.4	54.3	10.1	0.19	UOQ	UOQ	0.51	1.07	1.44
17	3	136	49.2	43.3	74.0	18.9	0.25	LIQ	LIQ	1.41	0.78	0.75
18	5	103	2.4	20.3	20.3	2.4	1.0	RA	RA	0.98	1.20	0.25
19	4	78	3.0	26.0	26.0	3.0	1.0	LOQ	LOQ	0.52	0.63	0.70
20	4	51	18.0	102.2	102.2	18.0	1.0	UOQ	UOQ - LOQ	0.50	1.50	1.0
21	5	42	3.0	48.1	48.1	3.1	1.0	UOQ	UOQ	0.04	0.05	0.50
22	3	120	5.9	24.2	27.4	5.9	1.0	RA	RA	0.24	0.41	1.0

GTV, gross tumor volume; CT, computerized tomography; CI, conformity index; UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; RA, retroareolar.

Table III. Factors associated with CI (n=22).

Factor	n	%	CI mean	P-value
Clip number				0.017
≤3	10	45.4	0.14	
≥4	12	54.6	0.37	
Time between CT scans (day)				0.31
<90	11	50.0	0.30	
≥90	11	50.0	0.23	
Age, years				0.351
≤44	11	50.0	0.31	
>44	11	50.0	0.22	
Tumor size, cm			0.22	
≤2	12	54.6	0.20	
>2	10	45.4	0.34	

CT, computerized tomography; CI, conformity index.

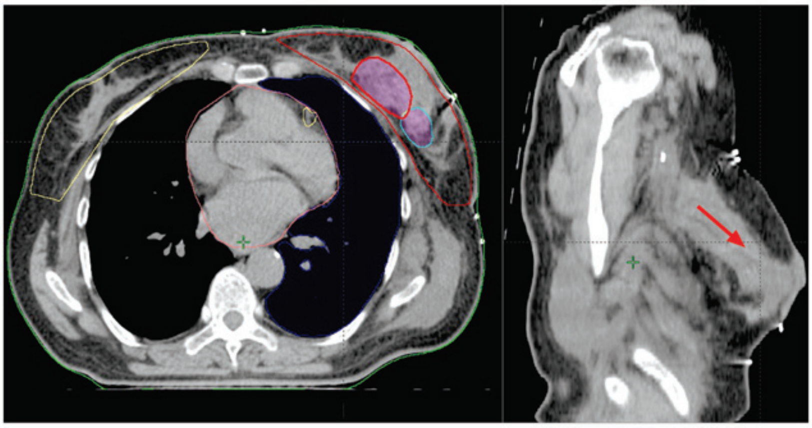

Figure 2. Pre- and postoperative fused volumes with no intersection. Latissimus dorsi mini-flap muscle inside the breast is shown by the arrow.

margins in all patients; in seven cases, multifocality was present.

All patients' volumes are shown in Table II. No significant changes were observed between mean pre- and postoperative whole-breast CTVs [442 cc (range, 276-1,061 cc) vs. 516 cc (range, 243-917 cc); P=0.132]. A median of four surgical clips (range, 2-6) was inserted during the surgery (superposed clips were counted as one). Median pre- and postoperative tumor volumes were 6.6 cc (range, 0.4-49 cc) and 22.95 cc (range, 6.2-102.2 cc), respectively (P=0.001). None of the patients had a seroma or hematoma formation following surgery. Postoperative lumpectomy cavity volumes were identified completely outside of the primary quadrant location in eight (36.4%) of the 22 cases, and were distributed in two quadrants in five (22.7%) cases. Discordance between the volumes was revealed to be high, with a low CI value (median 0.07; range, 0-1). There was an absence of any intersection between the preoperative GTV and postoperative lumpectomy cavity in eight cases (Fig. 2). CI was significantly associated only with the number of clips (≤3 vs. ≥4; P=0.017; Table III). No significant correlation was identified between the time interval between CT scans, pathological tumor size or age and CI (all P>0.05).

The median shifts between the isocenter of volumes were 1.02 cm (range, 0.4-4.43 cm) in the x, 1.07 cm (range, 0.05-5.67 cm) in the y, and 1.12 cm (range, 0-3.75 cm) in the z directions, respectively.

Preoperative GTV was found completely outside of the electron boost field in one of the 22 patients, and partially outside in five of the 22 patients. In those six patients, the median volume of the preoperative GTV receiving 95% of the prescribed dose (V95) was 67.75% (range, 0-86.8%). In the remaining 16 patients, the primary tumor area was inside the electron boost field, and received 100% of the prescribed dose of 60 Gy.

Discussion

Although previously published studies have investigated the accuracy of a boost technique following OP surgery (13-16), to the best of our knowledge, the present study is the only prospective study following LDMF reconstruction, showing a marked tumor bed shift. The shift between pre- and postoperative geometric isocenter coordinates was shown to be >1 cm in all directions (up to 5.67 cm). Postoperative boost volumes were identified completely outside of the primary quadrant location in eight (36.4%) of the 22 patients, and discordance between the volumes was revealed to be high (median CI=0.07). In only five of the 22 patients was the pre- and postoperative volume concordance 100% (CI=1). The tumor bed electron field did not cover the preoperative GTV location in six of the 22 patients following OP-BCS, causing underdosage in this area.

The advantage of using a boost to lower in-breast recurrences has been decisively demonstrated in randomized trials (2,3). However, how to delineate the boost volume remains a matter of controversy in the radiation oncology community (10). Historically, presurgical scars have been used to assist the location of the tumor bed; however, to achieve improved cosmetic results, surgical scars are frequently being placed at a distance from the original site, particularly following OP-BCS. Clinical methods that take account of information on preoperative imaging, clinical palpation of seroma and surgical scars of the tumor bed delineation are not commonly used, due to numerous inaccuracies. In order to overcome the problem of missing the target, postoperative three-dimensional imaging has replaced the clinical methods in planning the boost volumes. However, in the era of OP-BCS, accurate boost volume localization has become more complicated when the tumor is far away from its primary location.

Despite the more widespread use of OP-BCS techniques, few published data have addressed the pitfalls of variability in the postoperative tumor bed shift following these surgical procedures. The use of extensive remodeling for preserving breast shape results in a considerable displacement of breast tissue, which modifies the original position of the tumor bed. In the review of Schaverien *et al* (17), the use of boost RT was reported in 11 of 24 OP-BCS studies, and marking of the tumor bed was discussed in only eight of them. In this review, none of the studies reported on the number of patients where the tumor bed could not be localized.

After OP tissue manipulation, the clips ultimately end up in various different locations within the breast. Two retrospective studies were published in order to analyze tumor cavity replacement following OP-BCS (18,19). In these studies, 43-73% of the patients were shown to have clips outside of the original tumor quadrant, as revealed in the postoperative CT images. The breast quadrant location of the primary tumor was identified retrospectively on the basis of a preoperative diagnostic mammography, breast ultrasound or MRI: A high rate of discordance between the location of the primary tumor and the surgical clips following surgery was demonstrated in the two studies. In the study of Pezner *et al* (18), 11 of 25 patients (26 tumors) had ≥4 clips inserted, and in eight of them (73%) the tumor bed was beyond the original quadrant; in three patients (27%), the CTV was located in two or three separated quadrants. The findings of the present study are consistent with their results, showing quadrant dislocation in eight (36.4%) of the 22 patients, with a distribution in two quadrants for five (22.7%) of the patients.

For an accurate tumor bed definition following plastic breast remodeling, Kirova *et al* (14) described the optimal multidisciplinary approach using pre- and postoperative CT scans, image registration and clips in the tumorectomy region. During surgery, between one and five clips (mean ± standard deviation, 3±1) were inserted into the tumor bed, and a larger discrepancy was observed in the right-left axis (1.4 cm) between the presurgery GTV and postsurgical clips. Their tumor bed PTV included clips in the postoperative CT, GTV in the preoperative CT, and a surgical scar with an overall margin of 5-10 mm in all directions. In a study published by González-Sanchis *et al* (15), including the patients' reconstructive mammoplasty, a total of four or five titanium clips were inserted in all cases, and pre- and postsurgery CT scans were performed in all patients in order to quantify the tumor bed deviation from the original tumor site, and to determine the required margin to cover the tumor bed (15). Variations between the geometric isocenters were identified of between 0.5 and 3 cm, with the largest being in the upper-outer quadrant, of up to 4.5 cm. In the present study, the electron boost fields were created according to RTOG 1005 protocol. However, this protocol requires generous margins for tumor bed delineation, and in six (27.3%) of our patients, the preoperative GTV was outside of the electron field and remained underdosed.

Although the guidelines clearly suggest the use of surgical clips marking the tumor bed, Kirwan *et al* (20) demonstrated that more than one-third of patients do not have tumor bed clips inserted at the time of the surgery. Ideally, it is recommended that at least six surgical clips should be placed prior to closing the cavity (18,21). Studies by Kirova *et al* (14) and Furet *et al* (16) demonstrated that the use of three or more clips during tumorectomy increased the accuracy of tumor bed delineation following image registration. In addition, Pezner *et al* (18) reported that the superposition of the pre- and postoperative volumes was significantly lower in patients with two clips compared with patients with three or more clips (0.73 vs.35.45%; P=0.028). The results of the present study are in line with those studies, showing a positive correlation between the number of clips inserted and the CI (P=0.017). Despite the use of clips, the study by Kirova *et al* (14) and the present study revealed a similar volumetric analysis, demonstrating an intersection between the initial tumor site and the clip zone in 32 and 36.4% of the patients, respectively (18).

Another controversial issue is the image registration. Although rigid pre- and postoperative CT image registration has become standard practice in several clinics, the use of deformable image fusion to allow an improved definition of the boost volume following OP surgery is currently a topic for investigation (22,23). The external soft tissue of the breast would present a deformation following surgery due to postoperative edema, and a changed breast configuration as a result of remodeling. Therefore, a deformable registration would lead to an improved positioning of the preoperative GTV and postoperative clip locations. A Korean study, by Cho *et al* (23), used an initial diagnostic positron emission tomography-CT fusion with a postoperative CT scan for deformable image registration. The mean preoperative ^{18}F-fluorodeoxyglucose-avid tumor volume inside the postoperative tumor bed volume was revealed to be 94.8% (range, 60.9-100%). In contrast with the Korean study, which studied patients who had been subjected to standard BCS, in the present study, following LDMF OP-BCS, the concordance of pre- and postoperative volumes were shown to be very low (median CI=0.07).

In conclusion, the present study has demonstrated that the tumor bed is markedly replaced following OP-BCS with LDMF, with a quadrant dislocation in 36.4% of the patients. Variability in the geometric shift may occur in three dimensions, and the isocenter differed by >1 cm in all directions. Pre- and postoperative CT scans considered in isolation lack accuracy. The use of four or more clips is required to identify changes in the position of tumor bed. Since the lumpectomy cavity may be more extensive and relocated, special care should be taken in terms of defining the tumor bed in RT planning. For an accurate determination of the tumor bed localization, pre- and postsurgery image registration, and marking the lumpectomy cavity with an adequate number of clips following resection and prior to the OP reconstruction, is essential. Therefore, a multidisciplinary approach involving OP breast surgeons and radiotherapists is necessary in order to treat these patients, as was described by Kirova *et al* (13) previously, and as has been supported by the findings in the present study.

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