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Accuracy of cancer diagnostic probe for intra-surgical checking of cavity side margins in neoadjuvant breast cancer cases: A human model study

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Abstract

Background: Background Recently, a real-time system, named cancer diagnostic probe (CDP), has been developed to diagnose the presence of pre-neoplastic/neoplastic cells in breast cavity side margins. Detecting mechanism is real-time determination of the ROS/H_2O_2 released from cancer or atypical cells, through reverse Warburg effect and hypoxia glycolysis pathways.

Aims: Here, we designed a human model study based on real-time checking of 387 internal margins (IM) from 39 neoadjuvant breast cancer cases by CDP.

Materials & Methods: Each lesion was checked by entered needle sensor and electrical scores were recorded. The permanent pathology result of each tested lesion was our gold standard to evaluate CDP scoring. CDP results were compared with permanent pathology of tumour side margins (as a conventional margin evaluation procedure).

Results: Results showed that the sensitivity of CDP in scoring the cavity side margins of those cases is 91%. A total of 18 involved IM which had been detected by CDP were declared as free margins in pathology section of tumour side samples. Just five involved IM were missed by CDP.

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Discussions: Such sensitivity revealed that metabolism based (here: hypoxia glycolysis) tracing of cancer cells show distinct electrochemical responses between clear and involved cavity side margin evaluation.

Conclusion: This human study showed the promising role of CDP to achieve clear margins after BCS of neoadjuvant cases.

KEYWORDS
biopsy, breast, cancer, chemotherapy, margin, micro surgery, nanotechnology, sensors, surgery, tumour

1 | INTRODUCTION

One of the important challenges in breast conserving surgery (BCS) of neoadjuvant cases is intra-operative evaluation of surgical margins with high precision. X-ray from the tumour, intraoperative frozen pathology and finally permanent section of tumour are conventional methods which all just check tumour side margins.[1] We know that the satellite nature of cancer tumours may be resulted in remained positive margins with scattered cancer cells in the cavity side (tumour bed) even if the reciprocal tumour side margins are reported to be free from tumour cells.[2] Hence, evaluating the cavity side margins, other than tumour side margins, would be so promising to shave such residual tumour cells.[3,4]

On the other hand, a meta-analysis of more than 5000 patients who had been treated by neoadjuvant chemotherapy (NAC) revealed that type of surgical procedure (breast-conserving surgery (BCS) vs. mastectomy) has no impact on locoregional recurrence if we achieve negative margins.[5-7]

Some new reports indicated that in NAC treated (NACT) cases with residual disease after chemotherapy, the involved margins which require post BCS re-excision were totally 43% (5% by IDC, 5% by DCIS and 33% focally involved by both IDC and DCIS).[8] Also, pathologic complete response (PCR) just could be achieved in about 28% of NACT cases.[8] It is well known that after the chemotherapy some distortion and shrinkage may limit the quality of frozen sections for evaluation.[9] This indicates the crucial requirement to new intra-operative techniques for evaluation of cavity side margins. Moreover, the occurrence probability of positive margins in NACT cases is higher than adjuvant chemotherapy treated (ACT) cases.[8,10,11]

Recently cancer diagnostic probe (CDP) as a new clinically approved technology[12,13] was introduced for real-time checking of cavity side margins in breast conserving surgeries. The mechanism of the system has been based on electrochemical tracing of hypoxia glycolysis as typical metabolism of neoplastic cells.[14-16] CDP is capable of detecting the presence of neoplastic and high-risk breast cells in cavity side margins. It takes less than 30 s in each sampling.[11] Here, we designed a human model study on BCS of neoadjuvant cases by CDP to evaluate its precision in scoring cavity side margins.

Three hundred 87 margin samples were investigated in this study, and CDP showed more than 91% and 89% sensitivity and specificity based on permanent pathology of the same tested lesions, respectively.

2 | MATERIALS AND METHODS

2.1 | Principle of CDP mechanism

CDP is a recently introduced technology which is capable of detecting pre-neoplastic and cancerous residues in breast cavity side margins with the assistance of electrochemistry.[17] It would trace the H_2O_2/ROS agents released by neoplastic cells (through hypoxia glycolytic metabolism for ATP production) in real-time.[13] Nano-structured disposable needle sensors of CDP would be entered to the margin lesion and ROS level would be electrochemically recorded. The pathologic state of the tissue in correlation with ROS recorded level would be then declared as the response of the system.[17] In this study, cavity side margins of the neoadjuvant cases were checked by CDP during the surgery. Then both negatively and positively scored lesions (with a size of $3 \times 3mm^2$) were excised and evaluated by permanent section to evaluate the precision of CDP scores (Figure 1).

2.2 | Trial design, participants and limitations

The trial designation was part of a registered trial in IRCT (ID: IRCT20190904044697N1) with Ethical Certificate No: IR.TUMS.VCR.REC.1397.355.

Just neoadjuvant breast cancer patients who had been candidates for BCS were recruited randomly. All of the selected patients showed non-complete pathologic responses to chemotherapy. Permanent pathology of tumour side margins was the conventional guidance for the surgeons. The surgeon applied the CDP on cavity side margins after resection of the tumour (the resected tumour was sent for permanent section and pathological evaluation). Surgeons were not biased to the CDP scoring results. So, all negatively and positively scored lesions were re-excised for pathological evaluation. The size of each excised lesion was about $3 \times 3mm^2$. These samples were assumed as 'CDP Samples'. The required time for checking all of the margins by CDP was about 10 min. Among 42 recruited cases (From December 2019 to May 2020), 3 were excluded from the trial. All patients were women. Of these 387 samples from 39 patients were intra-surgically scored by CDP and evaluated by permanent pathology. Also, all of their resected tumour side margins were conventionally checked by permanent pathology evaluation

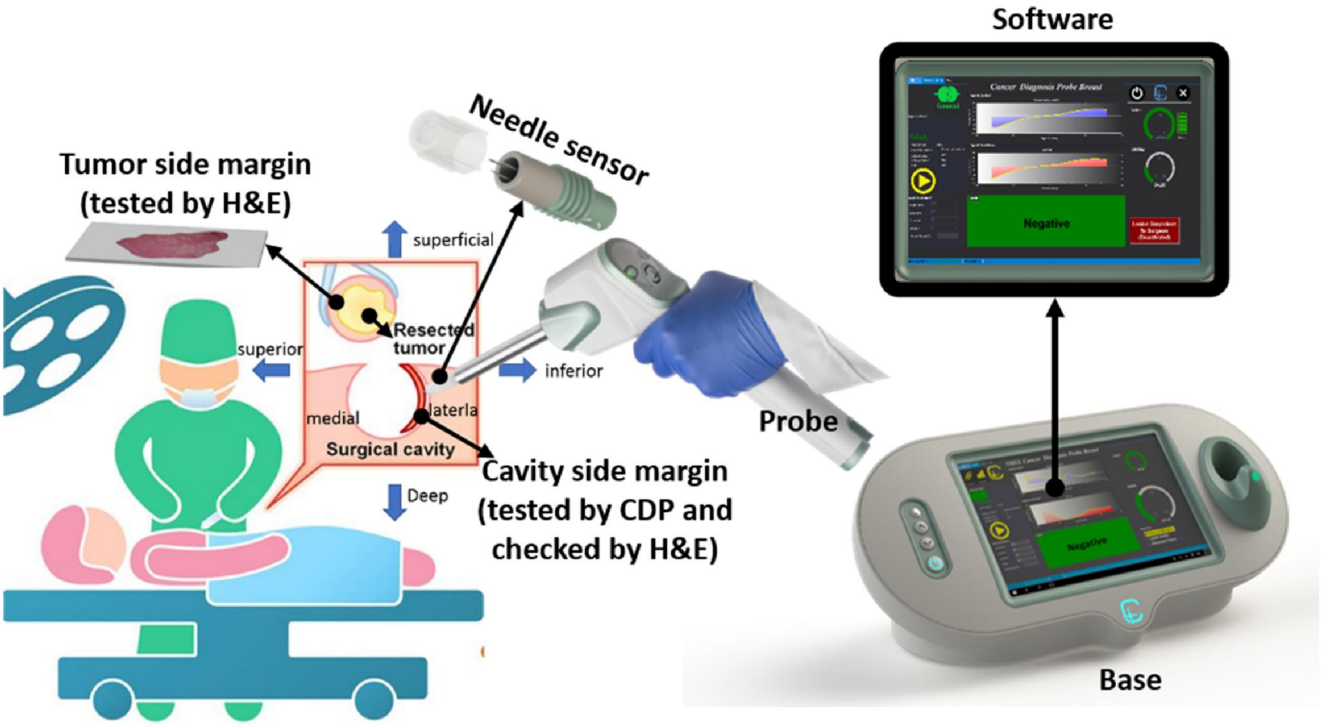


FIGURE 1 Schematic representation of cavity side margin checking in neoadjuvant cases by CDP and checking tumour side margin by conventional permanent pathology, such as H&E. Both lesions, which CDP positively or negatively scored, was checked by H&E

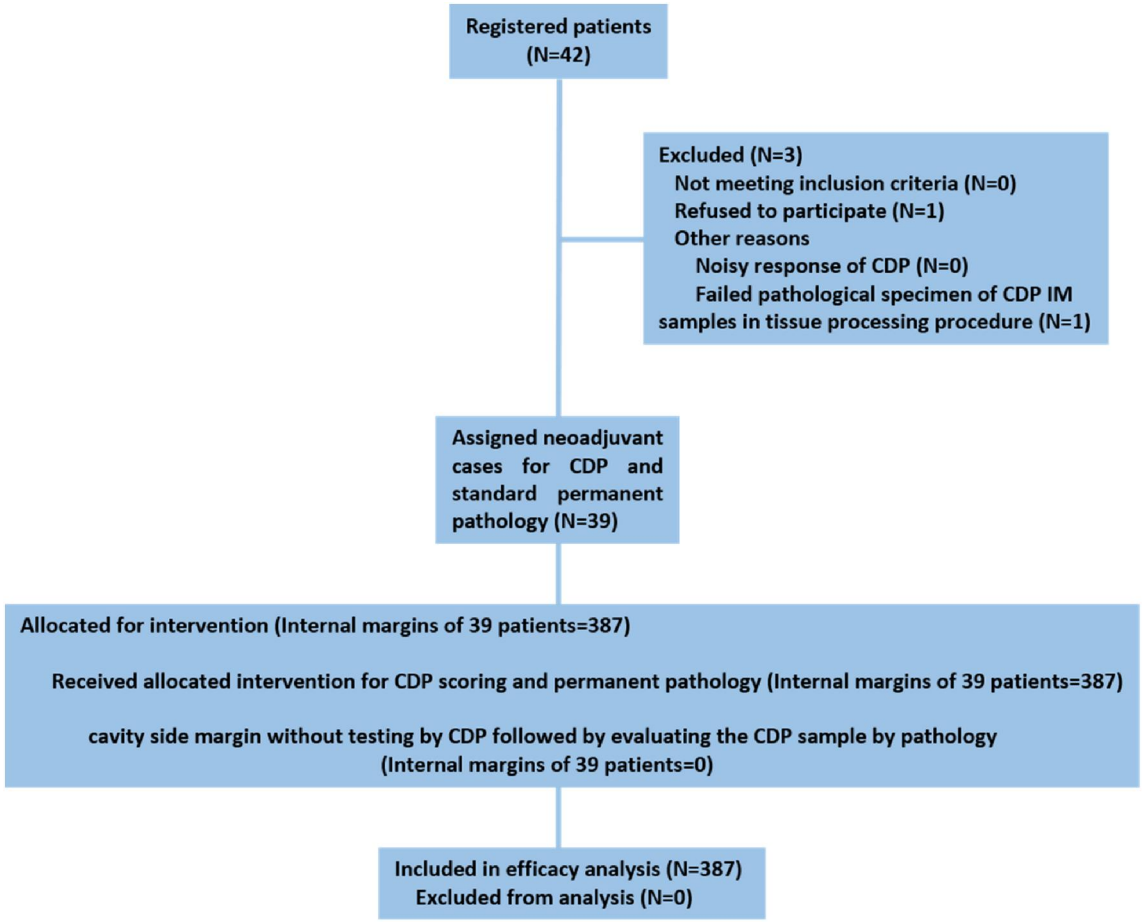


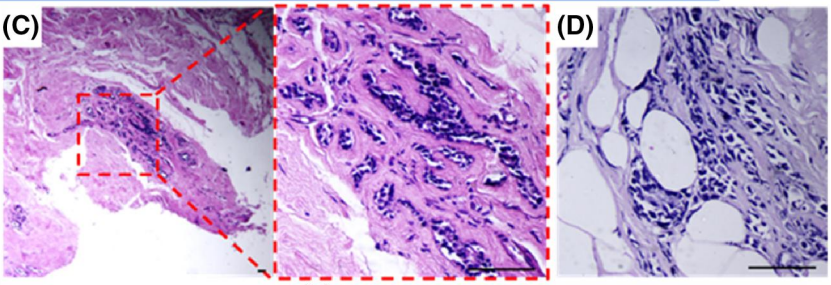
FIGURE 2 CONSORT flow diagram for CDP and standard permanent pathology of IM in neoadjuvant cases in the efficacy analysis

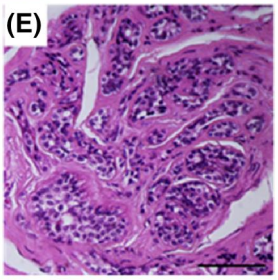
(A)

Patients' details	All Patients (N=39)
Characteristic	
Age	39.7(27-68)
Sex	
Female	39 (100%)
Male	0
Race	White
Type of surgery	
Mastectomy	0
Lumpectomy	39 (100%)
Tumor type	
IDC	39 (100%)
ILC	0
DCIS	0
Atypia	0
Benign	0

(B)

Diagnosis	387 IMs from 39 human cases of breast cancer had been under neoadjuvant therapy before surgery
CDP scores of cavity side margins*	
TP	50
TN	295
FP	37
FN	5
Sensitivity % (99% CI)	91 (81-100)
Specificity % (99% CI)	89 (84-94)
Accuracy % (99% CI)	89 (86-93)
	* Gold standard for scoring evaluation is permanent pathology of CDP scored samples





(F) CDP * Permanent Crosstabulation

			Permanent		
			Negative	Positive	Total
CDP	Negative	Count	295	5	300
		% within CDP	98.3%	1.7%	100.0%
		% within Permanent	88.9%	9.1%	77.5%
	Positive	Count	37	50	87
		% within CDP	42.5%	57.5%	100.0%
		% within Permanent	11.1%	90.9%	22.5%
Total		Count	332	55	387
		% within CDP	85.8%	14.2%	100.0%
		% within Permanent	100.0%	100.0%	100.0%

FIGURE 3 (A) The baseline of the clinical study characteristics of the patients (B) and overall study outcomes, TP: True Positive, TN: True Negative, FP: False Positive, FN: False Negative, cancer type in all of the patients were invasive ductal carcinoma (IDC). All of the cases were neoadjuvant who were under lumpectomy (breast-conserving surgery) after chemotherapy. H&E images of IMs positively scored by CDP: (C) Anterior margin of Patient ID 14 which was reported as free margin in permanent conventional pathology but was confirmed as Fibrocystic change with a focus suggestive for LIN1 (atypical lobular hyperplasia) in permanent pathology of CDP sample. (D) Superior margin of patient ID 68 whilst permanent declared free margin on its reciprocal margin (EM-) but permanent pathology of CDP samples diagnosed margin involvement to invasive carcinoma with a lobular feature on the same IM. (E) FCC with a focus suspicious for lobular neoplasia found in an IM that was positively scored by CDP whilst declared free margin on pathology report of its reciprocal margin (EM-) (Patient ID:151). (F) CDP Permanent Crosstabulation was presented. Based on the permanent pathology of the CDP samples (cavity side lesions scored by CDP and then excised for pathological evaluation), the sensitivity and specificity of CDP were 91% and 89%, respectively

(Figure 2). Hence, the impact of CDP was evaluated as a complementary tool in BCS of neoadjuvant cases.

CDP system and its disposable sensor were produced in the Funder Company (N.H.S.A) under scientific supervision of the Cancer Electronics Research Center at the University of Tehran. Surgeries were done in Shohada Tjarish and Khatamolanbia Hospitals, as well as breast cancer clinics of Motamed Cancer Institute (all these located in Tehran, Iran). Pathological evaluations were also done by pathology labs of the mentioned centres as well as the SEPAS Pathobiology Laboratory (Tehran, Iran).

Recruitments were done under the guidance of Professors M. Abdolahad and M.E. Akbari (supervisors of the study). Patients were informed about the research, and all signed the consent before the surgery. Pathologists were blinded about the results of CDP scoring when they evaluated the CDP samples.

2.3 | CDP operating procedure in the study

About three locations in each cavity side margin named as internal margins (IM) include lateral, medial, etc. would be tested by CDP. One disposable sensor was used for testing each lesion. All of the scored lesions (either positive or negative) were excised, labelled and sent for permanent pathology (named as CDP samples). When the

pathological results of CDP samples were prepared, the CDP scores were checked by their pathological data to evaluate the CDP accuracy. Furthermore, the permanent diagnoses of tumour side margins were compared with pathological results of CDP samples. The detailed procedure is described in the Supporting Infomation.

A total of 387 lesions in IMs from 39 cases were evaluated by CDP (in some margins, the surgeon excised more than one sample due to extended size of the margin or close distance of the margin to the tumour). We considered permanent pathology samples as gold standard for both tumour side and cavity side margins.

2.4 | Statistical analysis

SPSS software (version 26) was applied for statistical analysis of the study. To evaluate the diagnostic accuracy of CDP scoring with respect permanent pathology of CDP samples (as gold standard), the ROC curves and AUC were carried out. Crucial parameters, such as sensitivity, selectivity, accuracy and specificity of the CDP scoring were determined. A *p*-value of less than 0.01 was considered.

3 | RESULTS

First of all, tumour parameters as well as presurgical treatments and evaluations, were all depicted in Table S1 for all recruited patients. Figure 3 showed the characteristics of recruited patients (3-A), CDP scoring data of the patients' IMs (3-B), some examples about pathological results of the scored margins as the gold standard (3C-E) and CDP Crosstabulation results (3-F). Among 55 positive IMs, CDP truly scored 50 of them. Moreover, among 332 negative margins, CDP truly scores 295 of them. Hence, the CDP true positive and negative rates were 91% and 89%, respectively.

It is worth noting that among 387 IMs (from 39 patients), 18 margin samples (from 13 patients) which were truly scored positive by CDP, were not declared as involved margins in permanent pathology reports of tumour side margins (Table 1).

It means that they might be missed in the absence of CDP. These involved cavity side margins were IDC (27%), DCIS (16%) and papilloma with ADH (57%). It may be due to the satellite nature of cancer tumours. Satellite cancer cells in tumour bed cause most recurrences in patients with free tumour side margins. Our study showed that without applying CDP, involved cavity side margins were remained in about 33% of the NACT cases after BCS. However, CDP missed five involved margins in four patients. Figure 4 shows a comparative diagram about scoring values of CDP based on permanent pathology of IMs as the gold standard. It is observable that more than 55 cavity side margins were positive (involved margins), whilst CDP truly scored 50 (90.9%) of them. Moreover, among 332 free IMs, CDP truly scored 295 (88.9%) of them.

Table 2 presented the comparison between pathological diagnoses of tumour side and cavity side margins (tumour side samples vs. CDP samples). It is important to note that 18 (4.6%) free margins on the tumour side were found to be involved in the cavity side, whilst all involved tumour side margins were diagnosed as involved margins in cavity side interface (n = 32, 8.2%). Also, 337 (87.0%) margins were similarly diagnosed as free lesions in both tumour side and cavity side margins.

3.1 | Results of statistical analysis

The permanent pathology is the gold standard test to diagnose the cancerous specimens. To evaluate CDP as a complementary diagnostic tool, the ROC test has been carried out based on permanent pathology gold standard. As it is shown in the ROC curve (Figure 5) and AUC table (Table 3), the area is 0.899 (p-value<0.0001 and CI 99% 0.836-0.962) which shows the diagnostic reliability of the test. Moreover, it shows acceptable balance between sensitivity and specificity.

Hence, CDP can be used as a new cavity side margin diagnostic assay during the BCS of NACT cases.

4 | DISCUSSION

Due to frozen section limitations, advance techniques for real-time checking of cavity side margins during BCS of NACT patients may interestingly reduce the recurrences.

Many studies were focussed on margin assessment of NACT cases.[18,19] All of these methods evaluated tumour side margins. Whilst free tumour margins of >1mm were reported to be required in NACT invasive lobular carcinoma (ILC) cases,[20] other new reports indicated just 'No tumour on ink' is sufficient in NACT cases with PCR.[21] Also recently, it has been reported that a precise margin shaving is so crucial in ER-positive cases.[18] Our study showed that even in tumour side free margins with the distance of>1mm, we may find involved lesions in cavity side margins. Hence evaluating cavity side margins with distinguished technologies would be so helpful. Some techniques such as CDP and Margin Probe[22] may help to do BCS with clear margins for NACT cases. Detecting neoplastic lesions based on a known validated mechanism, hypoxia glycolysis of neoplastic breast cells,[23] is the established mechanism of CDP.

About 33% increment in finding involved cavity side margins, clarified the requirement of CDP in clinics for BCS of NACT cases. In our opinion, a new field in margin evaluation has been started in which not only tumour side margins must be checked by frozen and permanent pathology, but also cavity side margins (margins in tumour bed) are recommended to be checked by advanced systems, such as CDP. Following our proposed trend not only keeps the standard guidelines of BCS in NACT patients but also clarifies the independent role of CDP as a complementary tool in surgery. CDP showed the location of involvement in cavity side margins during BCS

TABLE 1 Detailed data of the 18 involved cavity side margins from 13 patients, which were positively scored by CDP, whilst their tumour side reciprocal was reported as free margins

Patient ID	Sample ID	IHC				Margin name	CDP current (μA)	Permanent H&E/IHC diagnosis of the cavity side involved margin	Permanent H&E/IHC diagnosis of the tumour side margin
		ER	PR	HER2	KI67				
1	8	NEG.	NEG.	POS.	40%	Lateral	582	IDC grade 2	Fibrocystic change
2	6	NEG.	NEG.	POS.	70%	Superomedial	464	Fibrocystic change, a foci suspicious for invasion. After staining for SMMH and P63 myoepithelial staining are not seen so invasion is confirmed.	Non tumoural tissue (proliferative fibrocystic changes with usual ductal hyperplasia, Extensive stromal fibrosis and simple adenosis)
7	5	POS.	POS.	NEG.	30%–35%	Inferior	578	Fibrocystic change with moderate typical ductal hyperplasia (typical/atypical), sclerosing adenosis are also seen. CK5,6/14: After staining no mosaic membranous staining are seen, so atypia is confirmed.	Fibrocystic change
8	1	NEG.	NEG.	POS.	30%–35%	Medial	523	Breast tissue with a focus of tumour emboli	Fibrotic breast tissue
	11					Superolateral	992	Fibrocystic change with microcalcification. Second H&E: Fibrocystic change with florid typical ductal hyperplasia with macrocalcification. CK5,6/14: After staining no mosaic membranous staining are seen, so atypia is confirmed.	Breast tissue with stromal fibrosis
10	6	NEG.	NEG.	NEG.	30%–35%	Medial	718	Fibrocystic change with moderate typical ductal hyperplasia, lobular hyperplasia is also seen. CK5,6/14: After staining no mosaic membranous staining are seen, so atypia is confirmed.	Fibrocystic change with florid typical ductal hyperplasia.
13	5	POS.	POS.	NEG.	55%–60%	Under the nipple	505	Invasive carcinoma with lobular feature	Fibrocystic mastopathy with ductal ectasia and foci of sclerosing adenosis
	12					Superolateral	553	Invasive carcinoma (after staining for pan cytokeratin epithelial cells within fatty tissue are stained, so invasion is confirmed)	Fibrocystic mastopathy with ductal ectasia and foci of sclerosing adenosis fibrofatty tissue
14	14	POS.	POS.	POS.	70%	Inferomedial	574	Haemorrhagic breast tissue with florid typical ductal hyperplasia. Suspicious for atypical invasion.	Non tumoural tissue (proliferative fibrocystic changes, Extensive stromal fibrosis and simple adenosis)
15	4	POS.	NEG.	POS.	30%–35%	Inferomedial	569	Fibrocystic change with florid ductal hyperplasia most probably typical. A focus of invasive component is seen	Breast tissue with stromal fibrosis

TABLE 1 (Continued)

Patient ID	Sample ID	IHC				Margin name	CDP current (μA)	Permanent H&E/IHC diagnosis of the cavity side involved margin	Permanent H&E/IHC diagnosis of the tumour side margin
		ER	PR	HER2	KI67				
16	20	NEG.	NEG.	NEG.	30%–35%	Subareolar	490	Subareolar breast tissue with a focus suggestive for LIN1 atypical lobular hyperplasia, a focus suspicious for pagetoid spread (IHC for E-cad is recommended), Excisional biopsy is recommended.	Non tumoural tissue (proliferative fibrocystic changes and extensive stromal fibrosis)
17	6	NEG.	NEG.	NEG.	30%–35%	Inferomedial	435	Involved by invasive carcinoma	Non neoplastic breast tissue shows fibrocystic changes with intraductal papilloma
25	14	POS.	POS.	NEG.	30%–35%	Suspicious mass in lateral margin (9 o'clock)	600	FCC with a focus suggested for LIN1 (atypical lobular hyperplasia)	Breast tissue with stromal fibrosis
38	2	POS.	NEG.	POS.	30%–35%	Medial	613	FCC with moderate usual ductal hyperplasia, a focus suspicious for LIN1 is also seen.	Breast tissue with stromal fibrosis
39	3	POS.	POS.	POS.	75%	Areolar	620	Florid atypical ductal hyperplasia	Breast tissue with stromal fibrosis
39	6					Areolar	591	Florid atypical ductal hyperplasia (CK5,6/14: membrane staining is not seen, so atypia is double confirmed)	Breast tissue with stromal fibrosis
39	7					Superior	561	Lobular intra-epithelial neoplasia	Breast tissue with stromal fibrosis
39	10					Superomedial	510	Lobular intra-epithelial neoplasia (E-Cad: membrane staining is not seen so neoplastic nature of lobular cells is confirmed)	Breast tissue with stromal fibrosis

Note: Data include pathological evaluation of both positively scored CDP samples and tumour side reciprocal margins.

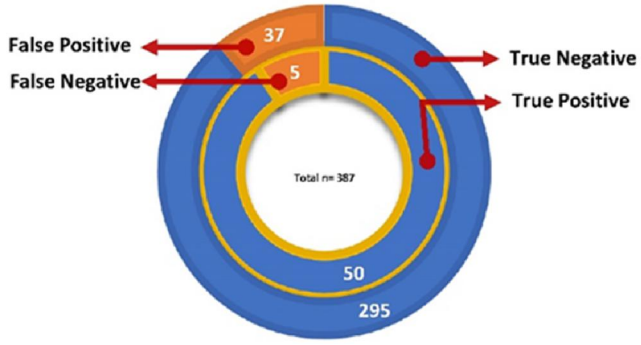


FIGURE 4 The number of IM truly and falsely scored by CDP based on permanent pathology of CDP samples as a gold standard. 90.9% of the involved cavity side margins were truly diagnosed by CDP, whilst 88.9% of pathologically free IM were scored as negative margins by CDP

TABLE 2 The comparative presentation about the number of free and involved margins between tumour side (tumour side sample) and cavity side (CDP Sample) samples evaluated by permanent pathology results

Permanent pathology of tumour side margins (tumour side samples)	Versus	Permanent pathology of same reciprocal margin in cavity side (CDP samples)	*n* = 387 (100%)
Positive	Versus	Positive	*n* = 32 (8.2%)
Positive	Versus	Negative	*n* = 0 (0%)
Negative	Versus	Positive	*n* = 18 (4.6%)
Negative	Versus	Negative	*n* = 337 (87.0%)

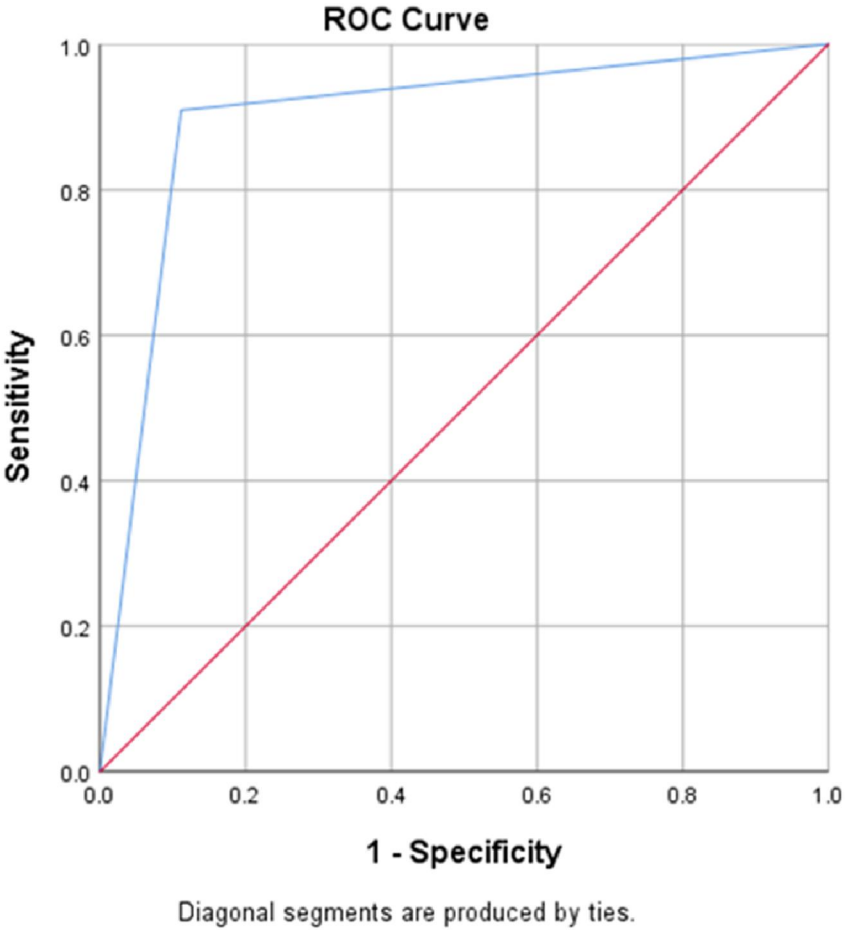


FIGURE 5 ROC diagram for CDP based on permanent results for 387 IM samples from 39 patients

of NACT cases with 91% sensitivity. Real-time scoring, simple use and portable handling to scan all over the tumour bed are other advantages of this system. However, the requirement to margin evaluation by subsequential testing, disposable head probe sensor, cost-effective production and requirement to much more trials are the challenges of using CDP in NACT cases which may be solved in the future.

5 | CONCLUSION

In summary, we experimented the accuracy of CDP during BCS of 39 NACT cases for direct checking of cavity side margins. Standard permanent pathology of tumour margins was carried out for all patients. Results showed 91% sensitivity and 89% specificity for CDP (based on permanent section of tested specimens the samples).

TABLE 3 AUC for CDP results versus permanent for 387 margin samples from 39 patients

Area under the curve				
Test result variable(s): CDP				
			Asymptotic 99% confidence interval	
Area	Standard error[a]	Asymptotic sig.[b]	Lower bound	Upper bound
0.899	0.025	0.000	0.836	0.962

Note: The test result variable(s): CDP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

[a]Under the nonparametric assumption.

[b]Null hypothesis: true area = 0.5.

Tumour side permanent pathology reported 18 (4.6%) of involved cavity side margins as free lesions whilst CDP missed 5 (1.2%) of involved cavity side margins. As the CDP electrochemically detects hypoxia glycolysis, positively scored lesions may be viable neoplastic cells which hadn't been destroyed by chemotherapy. This new technique opened promising lights in better shaving of the margins in NACT cases during the BCS.

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CONFLICT OF INTEREST

The authors declare that they have no financial interests.

AUTHOR CONTRIBUTIONS

Najmeh Dabbagh and Fereshteh Abbasvandi do most of the surgeries in the manner as was designed for the research by Mohammad Abdolahad and Mohammad Esmaeil Akbari. Fereshteh Abbasvandi also helped in performing the experiments. Zohreh Sadat Miripour manufactured the needle sensors for clinical studies, performed the experiments, categorised the tabled data and did the statistical analysis. Parisa Hoseinpour, Afshim Moradi and Mohammad Parniani did the pathological experiments and declared diagnostics. Fahimeh Jahanbakhshi sorting the results. Hooman Riazi and Farid Moradian did some of the surgeries. Fatemeh Shojaeian assisted in performing and validating statistical data. Mohammad Esmaeil Akbari supervised the surgical procedure, managed the clinical samples and helped in designation of the research. Mohammad Abdolahad designed and coordinated the research, supervised the use of CDP and designed its guideline for margin evaluations during the surgeries, analysed the data and wrote the manuscript. All authors and participants reviewed the paper and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The authors declare that all the other data supporting this study are available within the manuscript and its supporting information files. Also, declare that all software codes are available from the corresponding author upon a reasonable request. The authors state that all of the data are available upon request of the journal editor.

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SUPPORTING INFORMATION

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