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LETTER

Impact of pre-neoadjuvant radioactive iodine seed marking on pathologic complete response and survival in early-stage breast cancer patients

Yihao Geng[1]*, Qi Zhang[1]*, Zhao Bi[1]*, Zhiqiang Shi[1], Qiuchen Zhao[2], Xiaowei Qi[3], Rongrong Zhao[1], Yongsheng Wang[1], Pengfei Qiu[1]

[1]Breast Cancer Center, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China; [2]Cancer Research UK Cambridge Centre and Department of Oncology, University of Cambridge, Cambridge CB2 0XZ, UK; [3]Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University, Chongqing 400038, China

Neoadjuvant therapy (NAT) has become the standard treatment for patients with locally advanced breast cancer and stage II–III HER2-positive (HER2+) or triple-negative breast cancer (TNBC)[1,2]. It is essential to accurately mark the primary breast tumor and positive axillary lymph nodes (ALNs) prior to NAT to ensure precise surgical excision, guide axillary downstaging, and guarantee reliable lesion retrieval for pathologic evaluation[3]. The false-negative rate of sentinel lymph node biopsy (SLNB) after NAT can be reduced to < 10% by applying modalities, such as the identification of ≥ 3 sentinel lymph nodes (SLNs) with dual-mapping techniques or removal of the marked lymph node with target axillary dissection (TAD) according to the ASCO, NCCN, and CBCS guidelines[3-5]. However, there is a lack of consensus regarding the optimal methods and materials for accurate marking[6,7]. Conventional techniques include clip placement, guidewire localization, and carbon or ink tattooing, whereas wireless technologies, such as Magseed®, radiofrequency identification tags, SAVI SCOUT®, and radioactive iodine-125 (^{125}I) seeds, have also been adopted. Traditional marking techniques have a localization failure rate of approximately 10%. In contrast, the use of ^{125}I seeds (with a radiation dose of 0.1–0.3 mCi) has significantly improved localization accuracy[8,9]. Nevertheless, owing to radioactive properties, concerns have been raised regarding the potential impact of ^{125}I seed marking on assessing the pathologic complete response (pCR) after NAT[10]. Moreover, whether the influence of ^{125}I seed marking on pCR could lead to suboptimal adjuvant treatment decisions and potentially compromise long-term oncologic outcomes has not been established. To investigate the potential impact of ^{125}I seed placement on the pCR rate and long-term outcomes in breast cancer patients receiving NAT, we conducted a retrospective cohort study utilizing propensity score matching (PSM).

Clinicopathologic characteristics

A total of 1594 breast cancer patients who received NAT followed by surgery between January 2017 and December 2024 were eligible for this study. A total of 1103 patients with complete clinicopathologic and follow-up data were included after applying inclusion and exclusion criteria (see **Supplementary methods** for details), as follows: 216 patients (19.6%) underwent ^{125}I seed marking; 887 patients (80.4%) did not undergo ^{125}I seed marking. This study was approved by the Ethics Committee of Shandong Cancer Hospital (Approval No. SDZLEC2025-477-01). The study flowchart, study population, NAT regimens, surgical procedures, pathologic evaluation, follow-up care, and statistical analysis methods are detailed in the **Supplementary material**.

^{125}I seed marking protocol

Preoperative axillary ultrasound (US) was performed by two radiologists with 12 and 8 years of experience in breast US, respectively. Following whole-breast US, the same radiologists

*These authors contributed equally to this work.
Correspondence to: Rongrong Zhao, Yongsheng Wang and Pengfei Qiu
E-mail: zhaorongrong2002@126.com, yswang@sdfmu.edu.cn and qiu.pf@outlook.com
ORCID ID: https://orcid.org/0009-0006-8721-8986, https://orcid.org/0009-0002-1134-1815 and https://orcid.org/0000-0001-6784-410X
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routinely assessed axillary US and documented any suspicious sonographic features involving the ALNs. If multiple suspicious ALNs were identified, the largest node was selected for US-guided fine-needle aspiration (FNA) biopsy based on the shared decisions of the radiologists and patients. Repeated negative pressure aspiration was performed targeting the abnormal regions of the ALN and the collected specimens were subsequently subjected to cytologic evaluation. ^{125}I seeds were simultaneously marked in the FNA-positive ALNs. ALNs were retrieved intraoperatively using gamma probe. The ^{125}I seed implantation process and the parameters set are shown in **Figure 1A and 1B**.

Logistic regression analyses of pCR and cohort construction *via* PSM

Univariate logistic regression analysis of pCR showed that the Ki-67 index (P = 0.001), pathologic subtype (P < 0.001), initial clinical T stage [cT] (P = 0.011), and ^{125}I seed marked (P < 0.001) were significantly associated with pCR. Multivariate logistic regression analysis demonstrated that all four variables were independent predictors of total pCR (tpCR), which was defined as ypT0/is ypN0 (i.e., no residual invasive carcinoma in both the breast and ALNs). The Ki-67 index (OR = 2.35, 95% CI = 1.60–3.44, P < 0.001), pathologic subtype (OR = 1.88, 95% CI = 1.57–2.26, P < 0.001), cT (OR = 0.79, 95% CI = 0.63–0.98, P < 0.015), and ^{125}I seed marking (OR = 1.66, 95% CI = 1.19–2.32, P = 0.003) are displayed in **Table S1**. To minimize bias and balance confounding factors between the groups, PSM was performed on the enrolled patients at a 2:1 ratio. The matching variables included age, menopausal status, histologic findings, Ki-67 index, clinical T/N stage, and pathologic subtype. After matching, 648 patients were included in the final analysis, including 432 in group A (no ^{125}I seed marking) and 216 in group B (^{125}I seed-marked). The demographic and clinicopathologic characteristics before and after PSM are summarized in **Table 1**.

pCR outcomes with ^{125}I seed marking in the matched cohort

Breast pCR (bpCR) was defined as no histologic evidence of invasive tumor cells in the breast with or without ductal carcinoma *in situ* (ypT0/is). Axillary pCR (apCR) is defined as the absence of micro- and macro-metastases in ALNs (ypN0). Patients with ^{125}I seed marking in the matched cohort had significantly higher rates of bpCR, apCR, and tpCR. (tpCR: 55% *vs.* 46%, P = 0.030; bpCR: 63% *vs.* 53%, P = 0.016; apCR: 71% *vs.* 60%, P = 0.009; **Figure 1C**). Subgroup analysis based on pathologic subtype revealed that among the HR+/HER2− subgroup, the ^{125}I seed-marked group had a significantly higher tpCR rate than group A (tpCR: 26% *vs.* 8%, P = 0.028; **Figure 1D**). By contrast, no significant differences were detected in tpCR, bpCR, and apCR rates (tpCR: 60% *vs.* 57%; bpCR: 70% *vs.* 62%; apCR: 77% *vs.* 73%, P > 0.05; **Figure 1E**) in HER2+ patients. The ^{125}I seed-marked group in TNBC patients had significantly higher tpCR and bpCR rates compared to group A (tpCR: 59% *vs.* 39%, P = 0.033; bpCR: 66% *vs.* 48%, P = 0.021; **Figure 1F**). These findings suggested that ^{125}I seed marking may enhance pCR following NAT in patients with breast cancer.

Correlation between ^{125}I seed marking and long-term prognosis

As of the final follow-up in December 2024, the median duration of follow-up was 36.7 months. A total of 50 recurrence/metastasis events were recorded [50/648 (7.7%)]: 8 in the ^{125}I seed-marked group (3 local/axillary recurrences and 5 distant metastases); and 42 in the unmarked group (13 local/axillary recurrences and 29 distant metastases). The invasive disease-free survival (iDFS) was defined as the interval between the first postoperative day and the first occurrence of local recurrence or distant metastasis. Kaplan–Meier survival analysis showed that the ^{125}I seed-marked group had a significantly higher 3-year iDFS compared to patients without ^{125}I seed marking (96% *vs.* 90%, P = 0.02; **Figure 1G**). The survival curves for each subtype are provided in the **Figures S2 and S3**.

Kaplan–Meier survival analysis stratified by ^{125}I seed-marked status was performed among patients with pCR. The analysis demonstrated that in both group A and B, patients achieving pCR had significantly better iDFS and lower risk of recurrence compared to those without pCR (group A: 96% *vs.* 85%, P = 0.021; group B: 99% *vs.* 83%, P = 0.003). Patients who achieved pCR exhibited similarly favorable prognosis, irrespective of ^{125}I seed marked status (99% *vs.* 96%, P = 0.875; **Figure 1H**).

Discussion

Recent studies have reported that there were no significant differences in recurrence rates and survival outcomes between TAD and SLNB groups[9,11,12]. ^{125}I seeds have been increasingly utilized due to enhanced accessibility and cost-effectiveness. In the current study, the ^{125}I seed-marked group exhibited significantly higher tpCR, bpCR, and apCR rates (P < 0.05) compared to the group that did not undergo ^{125}I seed marking. Notably, this benefit was more pronounced among patients

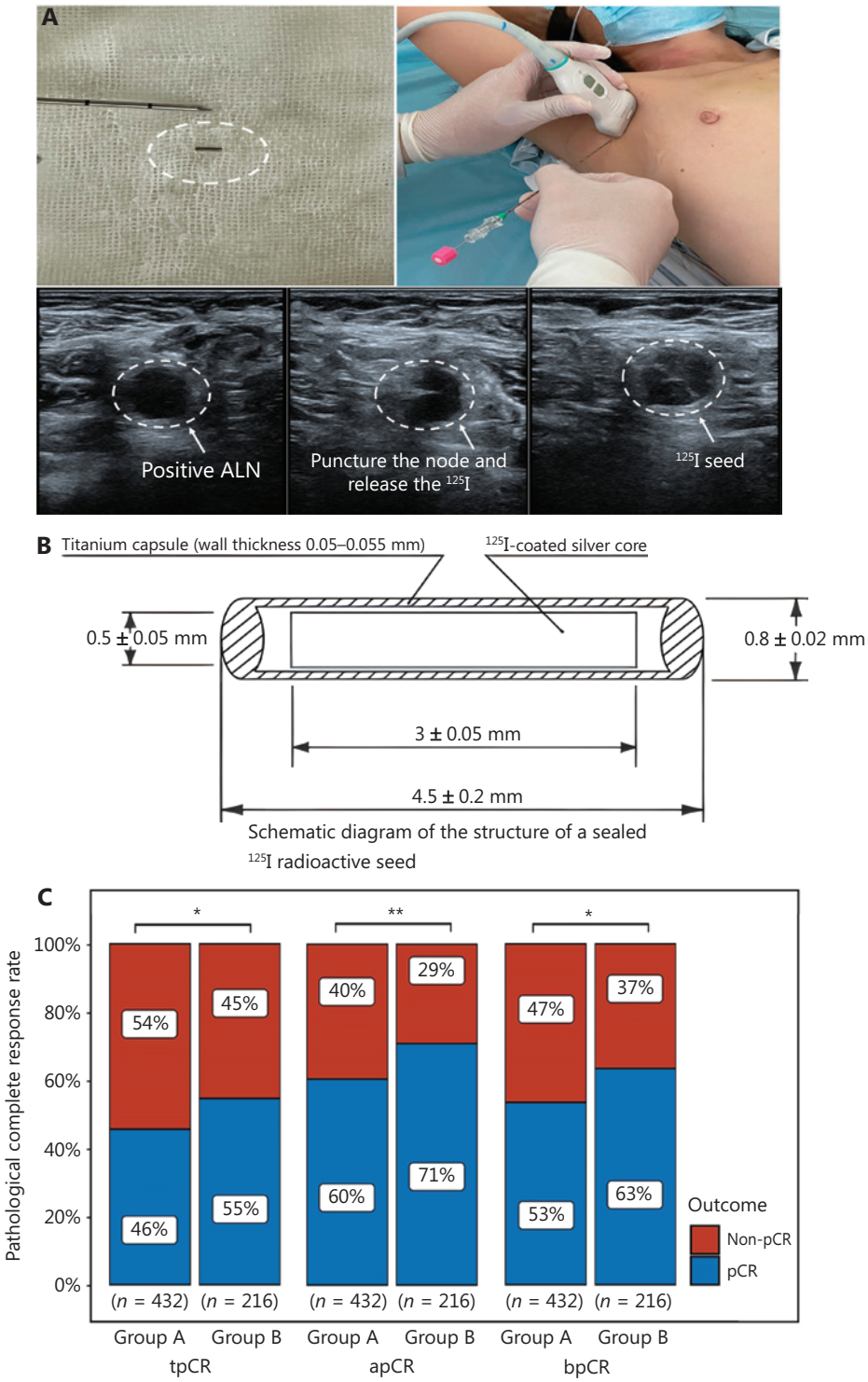


Figure 1 Continued

with TNBC. These findings suggested that radioactive seed marking may enhance pCR following NAT in patients with breast cancer.

In the era of molecular subtype-guided precision therapy, the pCR after NAT serves as a crucial prognostic indicator for patients with breast cancer[13]. Adjuvant escalation strategies

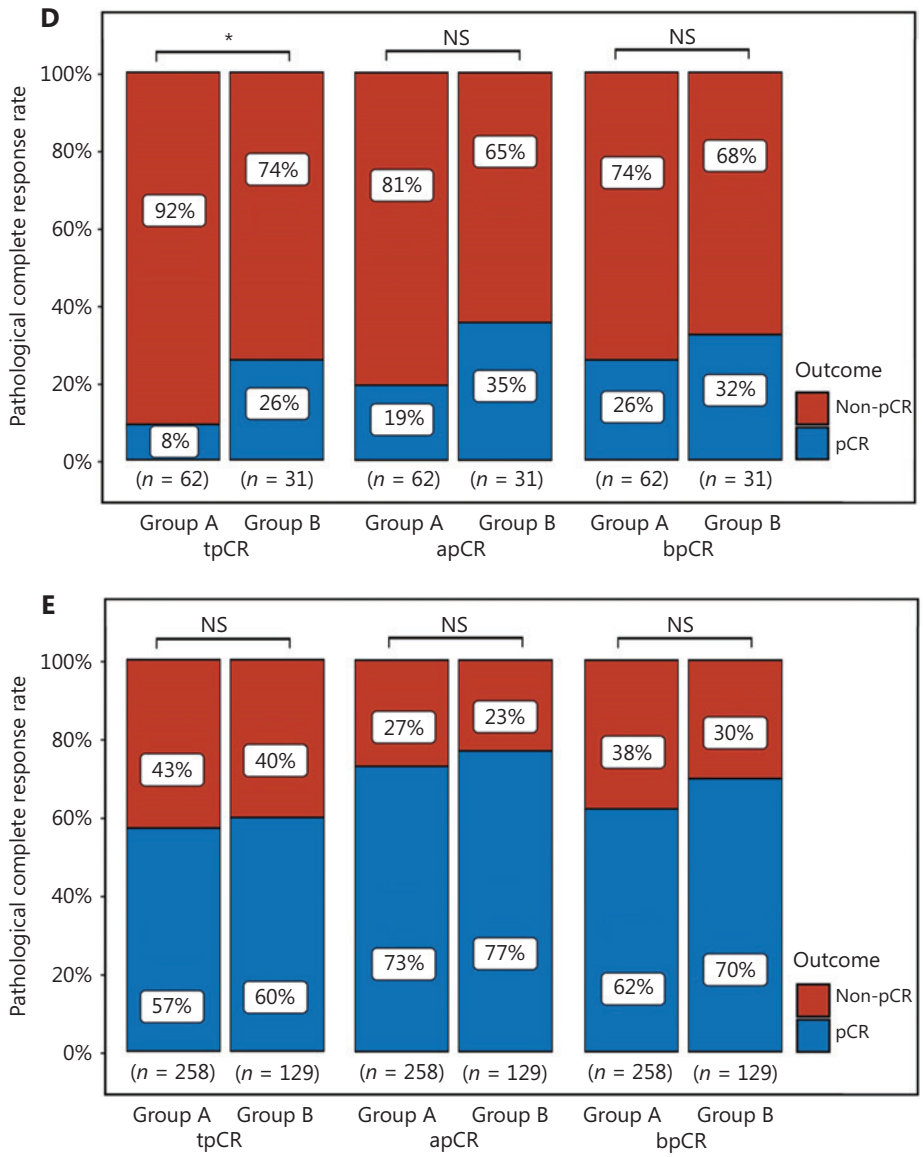


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can improve overall survival for patients who do not achieve pCR[14,15]. Consequently, accurate assessment of the treatment response following NAT is essential. A key concern is whether pCR associated with ^{125}I seed marking reflects genuine therapeutic response or artifact of local radiation exposure. Low-dose rate brachytherapy using ^{125}I seed has long served as a radical treatment modality for malignant tumors[16]. Although the therapeutic dose is significantly higher than the pre-NAT marked dose (0.1–0.3 mCi) the potential impact of these low doses on pCR and subsequent adjuvant treatment strategies remains an open question with little published evidence linking marking dose to therapeutic efficacy. In the current study, none of the patients who achieved pCR received subsequent adjuvant intensification therapy. Notably, the results herein indicated that patients who underwent ^{125}I seed marking and achieved pCR had comparable iDFS to patients who achieved pCR without ^{125}I seed marking (99% *vs.* 96%, P = 0.875), suggesting that pCR induced by ^{125}I seed marking may carry biological significance equivalent to that achieved with NAT alone. This finding addresses the concern regarding the prognostic validity of pCR in the context of seed marking[17]. Furthermore, the current study revealed that the iDFS in the ^{125}I seed-marked group was significantly superior to that in the group without ^{125}I seed marking (P = 0.018), indicating that the increased pCR rate associated with radioactive seed marking may translate into improved survival outcomes.

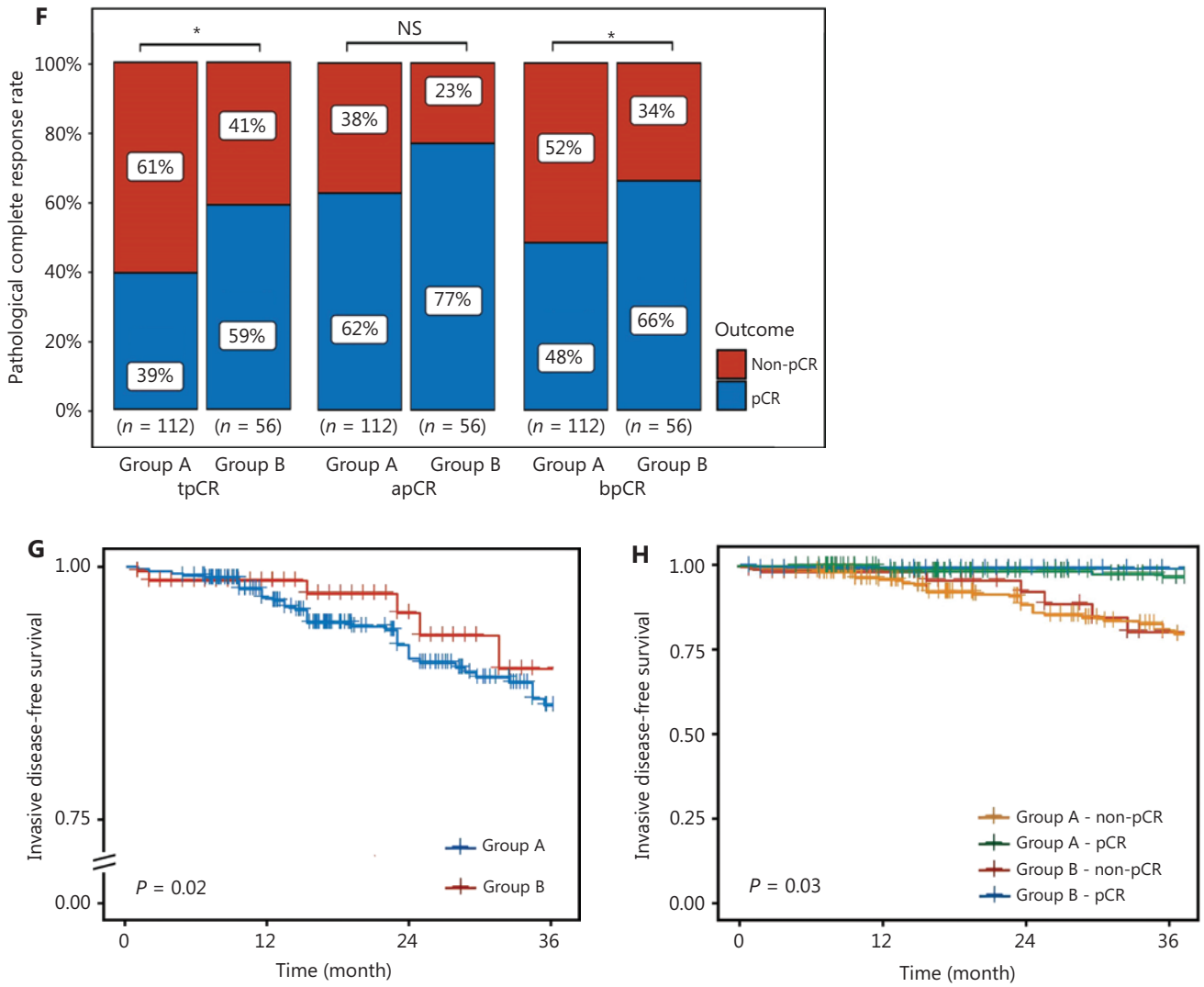


Figure 1 Impact of ^{125}I seed marking on neoadjuvant therapeutic efficacy and postoperative disease recurrence. (A) Schematic of key procedural details for ^{125}I seed implantation. (B) The key parameters of ^{125}I seed marking. (C) Intergroup differences in pCR rates among the overall population. (D) Intergroup differences in pCR rates among the HR+/HER2− subgroup. (E) Intergroup differences in pCR rates among the HER2+ subgroup. (F) Intergroup differences in pCR rates among the TNBC subgroup. (G) The impact of ^{125}I seed marking on the 3-year iDFS in the overall population. (H) Kaplan–Meier curves of 3-year iDFS stratified by ^{125}I seed marking and pCR status. Group A = without ^{125}I seed-marked group. Group B = ^{125}I seed-marked group. *P < 0.05; **P < 0.01; ***P < 0.001; NS, no statistically significant difference. pCR, pathological complete response; HR+, hormone receptor positive; HER2−, human epidermal growth factor receptor 2 negative; HER2+, human epidermal growth factor receptor 2 positive; TNBC, triple-negative breast cancer; iDFS, invasive disease-free survival.

These results suggested that radioactive seed marking may have unique clinical value in facilitating surgical de-escalation as well as improving long-term prognosis.

This study had several limitations. First, the potential for selection bias cannot be entirely eliminated despite the use of PSM. Second, the relatively short follow-up (median follow-up time = 36.7 months) constitutes another limitation of this study. Third, the findings lack multicenter external data validation, and the precise radiobiologic and immunologic mechanisms are incompletely understood because the precise radiobiologic effects of ^{125}I seed marking have not been fully elucidated. Furthermore, there is a need for further in-depth research on the mechanism underlying ^{125}I action. Future multi-center, large-sample, prospective randomized controlled studies are required to validate this conclusion.

In conclusion, this study demonstrated that pre-neoadjuvant radioactive ^{125}I seed marking (0.1–0.3 mCi) significantly increased the pCR rates in breast cancer patients undergoing NAT, with the greatest benefit occurring in

Table 1 Baseline characteristics of patients before and after PSM

Characteristics	Before PSM			After PSM		
	Group A[#] (*n* = 833)	Group B[#] (*n* = 216)	*P* value	Group A[#] (*n* = 432)	Group B[#] (*n* = 216)	*P* value
Age, years			0.499			0.911
≤ 50	411 (49.34)	101 (46.76)		204 (47.22)	101 (46.76)	
> 50	422 (50.66)	115 (53.24)		228 (52.78)	115 (53.24)	
Menopausal status			0.360			0.824
Premenopausal	431 (51.74)	104 (48.15)		212 (49.07)	104 (48.15)	
Menopausal	402 (48.26)	112 (51.85)		220 (50.93)	112 (51.85)	
Histopathologic type			0.100			0.604
Ductal	805 (96.64)	214 (99.07)		430 (99.54)	214 (99.07)	
Lobular or mixed	12 (1.44)	2 (0.93)		2 (0.46)	2 (0.93)	
Other	16 (1.92)	0 (0)		0 (0)	0 (0)	
Ki-67			0.001*			0.999
< 20%	106 (12.73)	11 (5.09)		21 (4.86)	11 (5.09)	
≥ 20%	727 (87.27)	205 (94.91)		411 (95.14)	205 (94.91)	
Location			0.211			0.399
Outside	498 (59.78)	119 (55.09)		253 (58.56)	119 (55.09)	
Central/inside	335 (40.22)	97 (44.91)		179 (41.44)	97 (44.91)	
Clinical T stage at presentation			< 0.001*			0.906
T1	117 (14.05)	48 (22.22)		86 (19.91)	48 (22.22)	
T2	532 (63.87)	146 (67.59)		298 (68.98)	146 (67.59)	
T3	95 (11.40)	17 (7.87)		38 (8.80)	17 (7.87)	
T4	89 (10.68)	5 (2.32)		10 (2.32)	5 (2.32)	
Clinical N stage at presentation			0.007*			0.616
N0	75 (9.00)	26 (12.04)		47 (10.88)	26 (12.04)	
N1	550 (66.03)	158 (73.15)		303 (70.14)	158 (73.15)	
N2	135 (16.21)	25 (11.57)		63 (14.58)	25 (11.57)	
N3	73 (8.76)	7 (3.24)		19 (4.40)	7 (3.24)	
Subtype			< 0.001*			0.086
HR+/HER2−	316 (37.94)	31 (14.35)		70 (16.20)	31 (14.35)	
HER2+	339 (40.70)	129 (59.72)		219 (50.69)	129 (59.72)	
TNBC	178 (21.36)	56 (25.93)		143 (33.10)	56 (25.93)	
Breast surgery			0.463			0.857
Mastectomy	612 (73.47)	164 (75.93)		330 (76.39)	164 (75.93)	
BCS	221 (26.53)	52 (24.07)		101 (23.61)	52 (24.07)	

Table 1 Continued

Characteristics	Before PSM			After PSM		
	Group A$^{\#}$ (n = 833)	Group B$^{\#}$ (n = 216)	P value	Group A$^{\#}$ (n = 432)	Group B$^{\#}$ (n = 216)	P value
Axillary surgery			0.583			0.692
SLNB	330 (39.62)	90 (41.67)		173 (40.05)	90 (41.67)	
ALND	503 (60.38)	126 (58.33)		259 (59.95)	126 (58.33)	
Radiotherapy			0.175			0.529
Yes	347 (41.66)	79 (36.57)		169 (39.12)	79 (36.57)	
No	486 (58.34)	137 (63.43)		263 (60.88)	137 (63.43)	

PSM, propensity score matching; HR+/HER2−, hormone receptor-positive/HER2-negative breast cancer; HER2+, HER2-positive breast cancer; TNBC, triple-negative breast cancer; BCS, breast-conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection. *Difference was statistically significant. Group A$^{\#}$ = without ^{125}I seed-marked group, Group B$^{\#}$ = ^{125}I seed-marked group.

patients with TNBC. The observed improvement in pCR was associated with a measurable benefit in iDFS, indicating that the increased pCR conferred a meaningful clinical advantage.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Pengfei Qiu, Yongsheng Wang, Rongrong Zhao, Xiaowei Qi.
Collected the data: Yihao Geng, Qi Zhang, Zhiqiang Shi.
Analyzed the data: Qi Zhang, Qiuchen Zhao.
Wrote the paper: Yihao Geng, Zhao Bi.

Data availability statement

The data generated in this study are available upon reasonable request from the corresponding author.

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