

Safety of concurrent immune checkpoint inhibitor therapy during postoperative radiotherapy for triple-negative breast cancer: A preliminary retrospective analysis

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Abstract. Immune checkpoint inhibitors (ICIs) have recently been approved as part of a neoadjuvant therapy plan for triple-negative breast cancer (TNBC). Consequently, the concurrent use of radiotherapy (RT) and ICIs is becoming increasingly common in clinical practice. Combining RT with ICIs may increase the risk of radiation pneumonitis. However, evidence remains limited regarding whether concurrent ICIs administered during postoperative RT increase the risk of radiation pneumonitis in patients with TNBC. The aim of the present preliminary, single-centre, retrospective, hypothesis-generating study was to evaluate the incidence of radiation pneumonitis in patients with TNBC treated with concurrent ICIs and RT. Patients with TNBC, who were treated at Hubei Cancer Hospital (Wuhan, China) between 2022 and 2024, were retrospectively enrolled. The inclusion criteria were receipt of neoadjuvant chemotherapy with or without ICIs, followed by postoperative adjuvant RT. Patients were divided into two groups: Postoperative RT with concurrent ICIs (ICIs-RT) and postoperative RT alone (RT-alone group). Baseline clinical characteristics, treatment responses, RT parameters and

follow-up CT scans for the assessment of radiation pneumonitis were documented. The χ^2 test and Student's t-test were used for the statistical analyses. A total of 132 patients with TNBC were enrolled. The pathological complete response rate following neoadjuvant therapy was significantly higher in patients who subsequently received postoperative ICIs-RT than in those who received RT alone (46.7 vs. 22.5%; $P=0.01$). Of the 132 patients, 30 received ICIs-RT and 102 received RT alone. In the ICIs-RT group, 5 patients received pembrolizumab, 22 received tislelizumab, 1 received camrelizumab and 2 received toripalimab. Follow-up assessments, including contrast-enhanced CT scans, were performed every 3 months for 1 year. The incidence of grade 1 radiation pneumonitis was 63.3% (19/30) in the ICIs-RT group and 46.1% (47/102) in the RT-alone group, with no statistically significant difference between the groups. No grade 2 or higher radiation pneumonitis occurred in either group. Hypothyroidism was observed in 33.3% (10/30) of patients in the ICIs-RT group, which was significantly higher than the 11.8% (12/102) observed in the RT-alone group ($P=0.01$). The incidence of grade 1 radiation dermatitis was 10.0% (3/30) in the ICIs-RT group and 9.8% (10/102) in the RT-alone group, whereas the incidence of grade 2 radiation dermatitis was 90.0% (27/30) and 90.2% (92/102), respectively, with no significant difference between the groups. In patients with TNBC previously treated with neoadjuvant ICIs, the addition of concurrent ICIs to postoperative RT did not significantly increase the incidence of radiation dermatitis. Regarding radiation pneumonitis, no statistically significant increase was observed; however, a clinically meaningful trend toward a higher incidence of grade 1 radiation pneumonitis cannot be excluded. An increased risk of hypothyroidism was observed, likely attributable to immune-related adverse effects of ICIs. These preliminary findings require validation in larger prospective trials.

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Introduction

Triple-negative breast cancer (TNBC) is a biologically aggressive subtype of breast cancer defined by the absence of

estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) expression. It accounts for 15-20% of all breast cancers worldwide and is disproportionately diagnosed in younger women, with a median age at diagnosis of ~53 years and a particularly high incidence among premenopausal women and those under 40 years of age (1). Clinically, TNBC often presents as a rapidly growing palpable mass and, due to its high proliferative rate, it is more likely to manifest as an interval cancer between screening mammograms (1). The disease is characterized by substantial biological heterogeneity, with the basal-like molecular subtype predominating, and is associated with poor histological differentiation, aggressive clinical behavior, and an elevated risk of early recurrence and visceral metastasis (1,2). Unlike hormone receptor-positive or HER2-positive breast cancers, TNBC lacks established molecular targets, and until recently, cytotoxic chemotherapy remained the only systemic treatment option. This therapeutic limitation, combined with its aggressive natural history, has historically resulted in a poorer prognosis, with a 5-year overall survival rate of 60-65% for patients with locally advanced disease (1).

The treatment landscape for early-stage TNBC has been transformed by the introduction of immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis. The landmark KEYNOTE-522 phase III trial demonstrated that the addition of pembrolizumab to standard neoadjuvant chemotherapy significantly improved the pathological complete response (pCR) rate from 51.2 to 64.8% and prolonged event-free survival (3). Based on these results, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab has become the standard of care for high-risk, early-stage TNBC. In patients who achieve pCR after neoadjuvant therapy, the decision to administer postoperative radiotherapy (RT) is typically guided by the initial clinical stage and other risk factors, including tumor size and lymph node involvement at presentation (4). For patients with residual disease after neoadjuvant therapy, postoperative RT is routinely indicated. Consequently, an increasing number of patients with TNBC are receiving adjuvant ICIs concurrently with postoperative RT, raising important clinical questions regarding the safety of this combined approach.

Radiotherapy exerts its antitumor effects not only through direct DNA damage but also through the induction of immunogenic cell death, which can prime systemic antitumor immune responses (5). Preclinical studies have demonstrated that RT upregulates PD-L1 expression on tumor cells and enhances the presentation of tumor-associated antigens, thereby providing a mechanistic rationale for combining RT with ICIs (6,7). This synergy has been shown to enhance local tumor control and, in some instances, mediate abscopal effects, where distant, non-irradiated tumors also regress (7). However, this immunostimulatory activity also raises concerns that the combination of RT and ICIs could potentiate immune-mediated injury in normal tissues within the radiation field. Evidence from multiple studies in lung cancer has shown that the addition of ICIs to thoracic RT is associated with an increased risk of serious adverse events, particularly radiation pneumonitis (8,9). In the PACIFIC trial of durvalumab following chemoradiotherapy for stage III non-small-cell

lung cancer, the incidence of any-grade pneumonitis was 33.9% in the durvalumab group compared with 24.8% in the placebo group, and grade 3-4 pneumonitis occurred in 3.4% of patients receiving durvalumab (9). In severe cases, radiation pneumonitis can be life-threatening, and this toxicity has become a major consideration in the clinical implementation of combined RT-ICI regimens.

Despite these concerns, data on the safety of concurrent RT and ICIs in patients with breast cancer, and particularly in those with TNBC, remain limited. Compared with thoracic RT for lung cancer, RT fields for breast cancer typically involve smaller lung volumes and lower doses to critical organs. Furthermore, the patient population differs substantially in terms of baseline pulmonary function and comorbidities. A recent real-world study specifically evaluating the safety of concurrent pembrolizumab and RT in patients with TNBC reported that the combination was generally well tolerated, but the evidence base remains limited by small sample sizes and short follow-up (10). Therefore, the safety of concurrent postoperative RT and maintenance ICIs in patients with TNBC remains poorly understood.

To address this uncertainty, the present study retrospectively evaluated the safety and tolerability of concurrent postoperative RT and ICIs following neoadjuvant ICIs in patients with TNBC treated at Hubei Cancer Hospital (Wuhan, China). The findings of the present study may help guide the concurrent use of ICIs and postoperative RT in this patient population.

Materials and methods

Patient population. This retrospective study included a total of 132 female patients with TNBC who received neoadjuvant chemoimmunotherapy or chemotherapy alone at Hubei Cancer Hospital between 2022 and 2024. All patients were female, with a median age of 45 years (range, 33-69 years). The inclusion criteria were as follows: i) Histologically confirmed TNBC; ii) prior treatment with neoadjuvant chemotherapy or chemoimmunotherapy; and iii) receipt of postoperative RT to the chest wall and/or regional lymph nodes. Patients who underwent breast-conserving surgery received whole-breast irradiation only. The exclusion criteria were as follows: i) Presence of distant metastasis; ii) severe comorbid medical conditions; and iii) intolerance to local RT. This study was conducted in accordance with the requirements of the Ethics Committee of Hubei Cancer Hospital (approval no. LLHBCH2026YN-106). Written informed consent was obtained from all patients who received off-label immunotherapy.

Treatment protocol. The treatment protocol for all enrolled patients consisted of three phases: Neoadjuvant systemic therapy, surgery, and postoperative RT with or without adjuvant ICI therapy. During the neoadjuvant phase, patients received chemotherapy with either an anthracycline-cyclophosphamide regimen followed by a taxane (AC-T) or docetaxel plus carboplatin (TCb), with or without concurrent ICIs (pembrolizumab, tislelizumab, camrelizumab or toripalimab), at the discretion of the treating medical oncologist. Following completion of neoadjuvant therapy, all patients underwent either breast-conserving surgery or radical mastectomy with

axillary lymph node dissection or sentinel lymph node biopsy. During the postoperative phase, patients who had received neoadjuvant ICIs continued the same ICI concurrently with adjuvant RT, and comprised the ICIs-RT group. Patients who had not received neoadjuvant ICIs proceeded to adjuvant RT without immunotherapy and comprised the RT-alone group. No postoperative adjuvant chemotherapy was administered to any patient in either group.

Assessment of pathological response. pCR was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0) upon histopathological examination of surgical specimens, consistent with the criteria used in the KEYNOTE-522 trial (3). All surgical specimens were evaluated by dedicated breast pathologists at Hubei Cancer Hospital. The pCR status was determined according to standardized institutional protocols, consistent with current international guidelines for the pathological assessment of breast cancer specimens (3).

Methods of radiation therapy. All patients received postoperative RT. The RT technique was based on previously published methods (11). Volumetric modulated arc therapy was delivered using 6 MV photons from a linear accelerator (Elekta Infinity or Elekta Axeses; Elekta Instrument AB). For patients who underwent breast-conserving surgery, the prescribed dose was 40–42 Gy in 15–16 fractions to the whole breast, followed by a sequential boost to the tumor bed of 8.7–10 Gy in 3–5 fractions. For patients who underwent radical mastectomy, RT was delivered at a dose of 50 Gy in 25 fractions. Target volumes and organs at risk (OARs) were contoured according to the Radiation Therapy Oncology Group breast cancer atlas (12). Supraclavicular fossa irradiation was administered to patients with positive axillary lymph nodes, whereas no patient received intentional internal mammary lymph node irradiation. The dose constraints were as follow: i) Ipsilateral volume of lung receiving at least 20 Gy (V20)<30% and V5<60%; ii) mean heart dose <8 Gy for left-sided tumors and <4 Gy for right-sided tumors; and iii) maximum dose to the spinal cord planning organ-at-risk volume (PRV) <45 Gy.

Follow-up. Patients were categorized into two groups: Postoperative RT with concurrent ICIs (ICIs-RT) and postoperative RT alone (RT-alone group). RT planning parameters, including planning target volume (PTV) and mean target dose, were collected. To evaluate target dose homogeneity, the volume of the PTV receiving $\geq 106\%$ (V53) of the prescribed dose of 50 Gy was assessed. Total lung volume was also recorded. Lung dosimetric parameters, including V5, V20 and V30 and the mean lung dose were analyzed. The mean heart dose and the maximum dose to the spinal cord PRV were also recorded.

Follow-up chest CT imaging was performed every 3 months after RT. Radiation pneumonitis in the ipsilateral lung was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (13). Radiation dermatitis was graded using the same criteria. Complete blood counts and thyroid function test results obtained before and after immunotherapy were documented. During follow-up, event-free survival (EFS), local control and overall survival

(OS) were evaluated. Notably, grade 1 radiation pneumonitis was defined according to CTCAE version 4.0, as asymptomatic radiological changes were detected on chest CT without clinical symptoms.

Definition of events. For the evaluation of EFS, events were defined as local recurrence (histologically confirmed or radiologically evident disease in the ipsilateral chest wall, breast or regional lymph nodes), distant metastasis (radiologically or histologically confirmed tumor spread beyond the locoregional region) or death from any cause; whichever occurred first. Patients who were alive and free of any of these events at the last follow-up were censored.

Statistical analysis. All statistical analyses were performed using GraphPad Prism version 5.0 (Dotmatics). The normality of continuous data was assessed using the Shapiro-Wilk test. As the dosimetric parameters were normally distributed, parametric tests were applied. Continuous variables were compared between the two groups using the unpaired (independent samples) Student's t-test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. $P < 0.05$ was considered to indicate a statistically significant difference. EFS was estimated using the Kaplan-Meier method and between-group comparisons were performed using the log-rank test. A univariate Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals. The proportional hazards assumption was assessed using Schoenfeld residuals and no violation was identified.

Results

Baseline patient characteristics. A total of 132 patients with TNBC were enrolled in this study. Baseline patient characteristics are summarized in Table I. Among these patients, 30 were assigned to the ICIs-RT group and 102 to the RT-alone group. Age, T stage, N stage, histological subtype and surgical procedure were well balanced between the two groups, with no statistically significant differences. The proportion of patients receiving platinum-based regimens (TCb) was significantly higher in the ICIs-RT group than in the RT-alone group (90.0 vs. 56.8%; $P < 0.001$). In addition, patients in the ICIs-RT group had a significantly higher pCR rate after neoadjuvant therapy than those in the RT-alone group (46.7 vs. 22.5%; $P = 0.01$). Regarding immunotherapy agents, 22 of the 30 patients (73.3%) in the ICIs-RT group received tislelizumab.

RT dosimetric parameters. Postoperative RT was administered to all patients in both groups (Table II). RT dose regimens were determined based on the surgical approach. Target volumes were comparable between the two groups, with no statistically significant differences observed. The mean target dose and dosimetric parameters for the OARs were also similar between the groups. Overall, the RT dosimetric parameters were well balanced between the two groups.

Treatment toxicity. As shown in Table III, no patient developed grade ≥ 2 radiation pneumonitis or grade ≥ 3 radiation dermatitis. Grade 1 radiation pneumonitis occurred in 63.3% (19/30) of patients in the ICIs-RT group and 46.1% (47/102)

Table I. Baseline characteristics of patients receiving concurrent radiotherapy and immunotherapy for triple-negative breast cancer.

Factors	ICIs-RT group (n=30)	RT-alone group (n=102)	P-value
Age			
Mean age, years (range)	45 (33-68)	46.5 (42-69)	0.91
<65 years	28 (93.3%)	99 (97.1%)	0.96
T Stage			0.90
T1/T2	12 (40%)	42 (41.2%)	
T3/T4	18 (60%)	60 (58.8%)	
N Stage			0.55
Positive	27 (90%)	97 (95.1%)	
Negative	3 (10%)	5 (4.9%)	
Pathological type			0.54
Infiltrating ductal carcinoma	29 (96.7%)	100 (98%)	
Micropapillary carcinoma	1 (3.3%)	2 (2%)	
Neoadjuvant chemotherapy drugs			0.01 ^a
AC-T	3 (10%)	44 (43.2%)	
TCb	27 (90%)	58 (56.8%)	
Immune checkpoint inhibitors			-
Pembrolizumab	5 (16.7%)		
Tislelizumab	22 (73.3%)		
Camrelizumab	1 (3.3%)		
Toripalimab	2 (6.7%)		
Tumour laterality			0.80
Left	14 (46.7%)	45 (44.1%)	
Right	16 (53.3%)	57 (55.9%)	
Surgery approach			0.94
Breast-conserving	6 (20%)	21 (20.6%)	
Radical mastectomy	24 (80%)	81 (79.4%)	
Pathological response			0.01 ^a
pCR	14 (46.7%)	23 (22.5%)	
NonPCR	16 (53.3%)	79 (77.5%)	

^aP<0.01. Data are presented as n (%) unless shown otherwise. ICIs-RT, postoperative RT with concurrent immune checkpoint inhibitors; RT-alone group, postoperative RT alone; AC-T, Doxorubicin and Cyclophosphamide followed by Docetaxel; TCb, Docetaxel and Carboplatin; pCR, pathological complete response.

of patients in the RT-alone group, a difference that was not statistically significant. Radiation dermatitis rates were not statistically significant. Hypothyroidism was more frequent in the ICIs-RT group than in the RT-alone group (33.3 vs. 11.8%; $P=0.01$). All patients had normal baseline thyroid function before ICI initiation. The proportion of patients receiving supraclavicular fossa irradiation was comparable between the two groups (86.7 vs. 85.3%); however, the thyroid dose was not systematically analyzed as a dosimetric parameter in this study. Hematological toxicities and lymphocyte parameters were similar between the groups. Concurrent immunotherapy was not associated with a statistically significant increase in radiation pneumonitis; however, a clinically meaningful trend toward a higher incidence of grade 1 radiation pneumonitis cannot be excluded. No increase in radiation dermatitis was observed.

Clinical outcomes. With a median follow-up of 12 months, events occurred in 6.7% of patients in the ICIs-RT group and 3.9% of patients in the RT-alone group (Table IV; $P>0.05$). The 1-year EFS rates were 93.3 and 96.1%, respectively (Fig. 1; $HR=1.71$; 95% CI, 0.31-9.38; $P=0.89$). Local recurrence (3.3 vs. 1.0%) and distant metastasis (3.3 vs. 2.9%) occurred at similar rates in the two groups. No deaths occurred during follow-up, therefore the 1-year OS rate was 100% in both groups and the median OS was not estimable. The median EFS was not estimable because of the limited number of events.

Discussion

The present study revealed that concurrent immunotherapy was not associated with a statistically significant increase in the risk of radiation pneumonitis during postoperative RT

Table II. Radiotherapy dosimetric parameters of patients receiving concurrent radiotherapy and immunotherapy for triple-negative breast cancer.

Factors	ICIs-RT group (n=30)	RT-alone group (n=102)	P-value
Radiotherapy dose			
Breast-conserving	48-50.7 Gy in 18-21 fractions	48-50.7 Gy in 18-21 fractions	-
Radical mastectomy	50 Gy in 25 fractions	50 Gy in 25 fractions	-
Target volume, cm ³			
Breast-conserving	497.5±23.1	473.2±25.3	0.93
Radical mastectomy	1241.2±156.3	1123.5±178.7	0.08
Mean target dose, Gy			
Breast-conserving	43±2.1	42.9±3.1	0.97
Radical mastectomy	51.5±0.8	51.9±1.1	0.99
V53 of Target, %			
Breast-conserving	-	-	
Radical mastectomy	33±8.1	37±10.4	0.98
Ipsilateral lung V20, %			
Breast-conserving	16.84±3.2	15.89±4.7	0.94
Radical mastectomy	26.5±2.2	25.4±3.2	0.87
Ipsilateral lung V5, %			
Breast-conserving	32.5±4.2	33.7±3.7	0.89
Radical mastectomy	52.3±6.2	51.2±5.2	0.91
Ipsilateral lung V30, %			
Breast-conserving	12.36±3.1	11.2±4.2	0.95
Radical mastectomy	18.3±3.2	17.7±2.1	0.97
Mean heart dose, Gy			
Left breast tumor	6.2±1.2	5.9±2.3	0.96
Right breast tumor	2.3±1.2	2.1±2.4	0.93
Maximum spinal cord dose, Gy			
Breast-conserving	1.91±1.2	2.4±1.4	0.99
Radical mastectomy	19.3±3.2	18.6±3.7	0.95

Values are presented as mean ± standard deviation unless otherwise shown. P-values for heart dose were calculated separately for left-sided and right-sided tumors using Student's t-test. ICIs-RT, postoperative RT with concurrent immune checkpoint inhibitors; RT-alone group, postoperative RT alone; V53, the volume of the planning target volume (PTV) receiving ≥106% of the prescribed dose of 50 Gy; V5, V20 and V30, percentage of lung volume receiving ≥5 Gy, ≥20 Gy and ≥30 Gy, respectively.

for TNBC; however, a clinically meaningful trend toward a higher incidence of grade 1 radiation pneumonitis cannot be excluded. This finding is consistent with the results of the KEYNOTE-522 trial, which reported a low incidence of radiation pneumonitis in patients receiving immunotherapy (3). However, hypothyroidism was observed more frequently in patients treated with concurrent immunotherapy, likely attributable to ICI-associated adverse events. Therefore, ICI-related immune thyroiditis remains the most likely explanation for the increased incidence of hypothyroidism.

RT has traditionally been considered a localized cytotoxic treatment. However, emerging evidence suggests that RT can induce immunogenic cell death, particularly with hypofractionated regimens (14). Irradiated tumor cells release damage-associated molecular patterns (for example, high mobility group box 1, ATP and calreticulin), which act as danger signals to promote dendritic cell maturation and antigen

presentation (15). When combined with immune checkpoint blockade, these newly exposed antigens stimulate tumor-specific T-cell responses, converting bystander T cells into active effector cells and ultimately triggering systemic antitumor immunity; the abscopal effect (16). In postoperative breast cancer RT, local elimination of microscopic residual disease may be accompanied by enhanced systemic immune surveillance, which could reduce the risk of recurrence and metastasis (17).

RT can reduce the infiltration of myeloid-derived suppressor cells and M2-polarized tumor-associated macrophages within the tumor microenvironment. Concurrently, RT upregulates programmed death-ligand 1 (PD-L1) expression on tumor cells, thereby providing a direct target for ICIs (18). RT also improves tumor vascular structure and perfusion, facilitating the infiltration and persistence of effector T cells within tumors. In the setting of postoperative RT for breast cancer, in which treatment is typically administered following chemotherapy

Table III. Treatment toxicity of patients receiving concurrent radiotherapy and immunotherapy for triple-negative breast cancer.

Toxicity	Grade	ICIs-RT group (n=30)	RT-alone group (n=102)	P-value
Radiation pneumonitis				0.10
	1	19 (63.3%)	47 (46.1%)	
	2	0	0	
	3	0	0	
	4	0	0	
Radiation dermatitis	5	0	0	0.75
	1	3 (10%)	10 (9.8%)	
	2	27 (90%)	92 (90.2%)	
	3	0	0	
	4	0	0	
Hypothyroidism	Any	10 (33.3%)	12 (11.8%)	0.01 ^a
Leukopenia				0.85
	1	17 (56.7%)	58 (56.9%)	
	2	10 (33.3%)	41 (40.2%)	
	3	1 (3.3%)	3 (2.9%)	
	4	0	0	
Anemia				0.68
	1	12 (40%)	32 (31.4%)	
	2	3 (10%)	13 (12.7%)	
	3	0	0	
	4	0	0	
Thrombocytopenia				0.99
	0	29 (96.7%)	99 (97.1%)	
	1	1 (3.3%)	3 (2.9%)	
	2	0	0	
	3	0	0	
	4	0	0	
Lymphocyte percentages, %		35.8±5.2	37.7±8.2	0.99
Lymphocyte count, 10 ⁹ /l		2.54±1.2	2.86±1.1	0.98

^aP<0.01. Continuous variables are presented as mean ± standard deviation (SD) and were compared using Student's t-test. Categorical variables were compared using the chi-square test, except for hypothyroidism, leukopenia, anemia and thrombocytopenia, where Fisher's exact test was used. ICIs-RT, postoperative RT with concurrent immune checkpoint inhibitors; RT-alone group, postoperative RT alone.

Table IV. Clinical outcomes of patients receiving concurrent radiotherapy and immunotherapy for triple-negative breast cancer.

Event	ICIs-RT group (n=30)	RT-alone group (n=102)	P-value
Any recurrence or metastasis	2 (6.7%)	4 (3.9%)	0.89
Local recurrence	1 (3.3%)	1 (1.0%)	0.41
Distant recurrence	1 (3.3%)	3 (2.9%)	0.99
Dead	0	0	-

P-values were calculated using Fisher's exact test. No deaths occurred in either group. ICIs-RT, postoperative RT with concurrent immune checkpoint inhibitors; RT-alone group, postoperative RT alone.

and/or neoadjuvant immunotherapy, immune memory may already be established. Postoperative RT may further reshape the tumor microenvironment, thereby enhancing the local execution of immune memory responses (15).

Although the present study did not observe a statistically significant increase in radiation pneumonitis, RT and immunotherapy may exert additive toxic effects on normal tissues from a mechanistic perspective. Radiation-induced lung injury

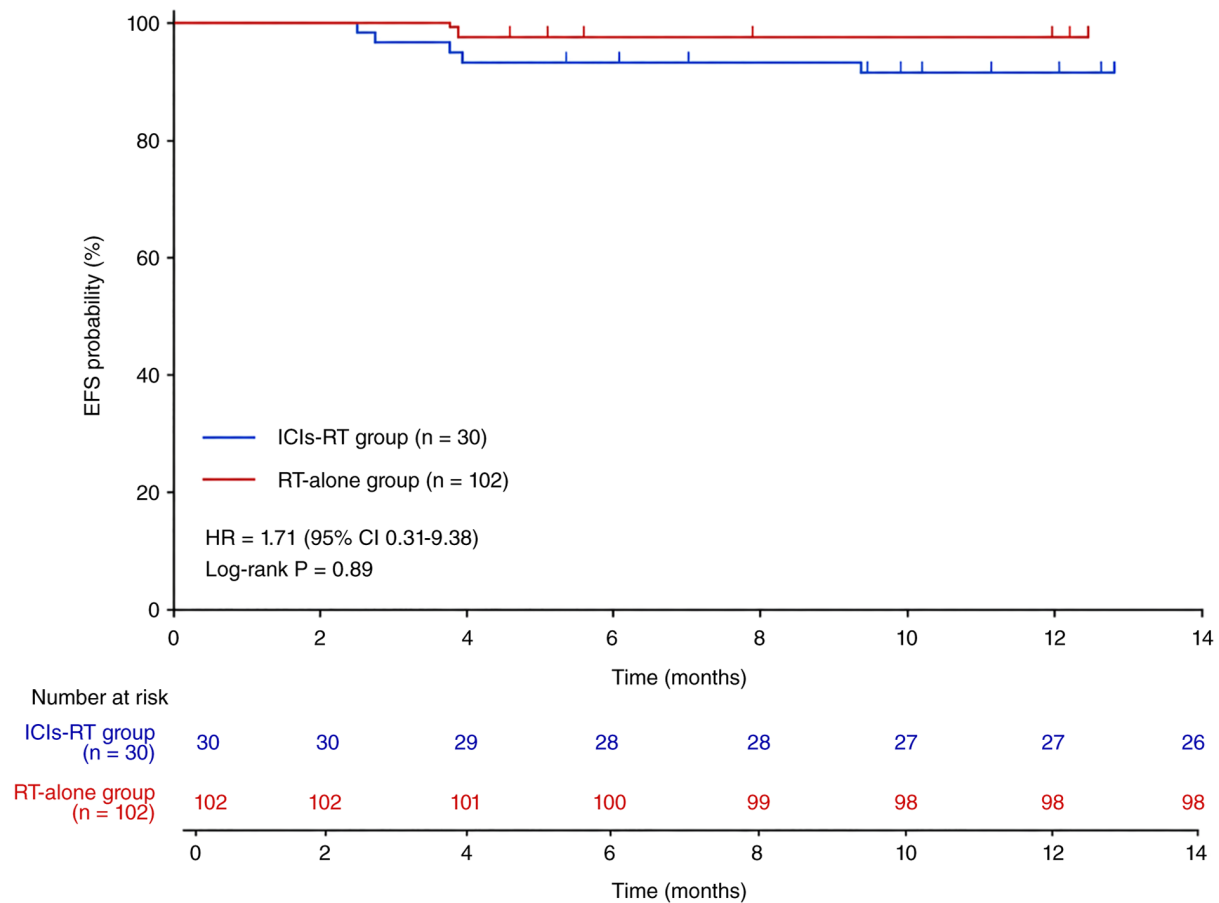


Figure 1. Kaplan-Meier estimates of event-free survival in patients receiving ICIs-RT vs. RT-alone. EFS, event-free survival; ICIs-RT, concurrent ICIs and radiotherapy; RT-alone, radiotherapy alone.

is mediated by inflammatory cytokines such as transforming growth factor- β and tumor necrosis factor- α , whereas immune checkpoint blockade may activate T cells which also target normal tissues (5,19,20). Clinically, the relatively low incidence of pneumonitis in patients with breast cancer may be attributable to smaller radiation field sizes and specific fractionation schedules. Notably, the relatively high incidence of grade 1 radiation pneumonitis observed in the present study (63.3% in the ICIs-RT group and 46.1% in the RT-alone group) may partially reflect the sensitivity of routine contrast-enhanced CT imaging performed every 3 months, which could detect subtle, asymptomatic radiological changes that might otherwise remain unnoticed. By contrast, the risk of pneumonitis is substantially higher in patients with lung or esophageal cancer, warranting careful monitoring in these settings. In patients with left-sided breast cancer, postoperative RT may expose the heart to radiation. Although immune-mediated myocarditis is rare, it can be life-threatening; therefore, stricter cardiac dose constraints should be considered when combining RT with immunotherapy (21).

The choice of PD-1 inhibitor (pembrolizumab, tislelizumab, camrelizumab or toripalimab) was based on physician preference and local drug availability, and was not determined by patient or disease-specific factors. Given the small number of patients receiving each agent, formal subgroup analyses were not feasible. No obvious differences in toxicity profiles were observed across agents; however,

agent-specific effects cannot be excluded and should be examined in larger cohorts.

The present study has several limitations. First, as a single-center retrospective analysis, potential selection bias cannot be excluded. Notably, the significantly higher proportion of patients receiving platinum-based chemotherapy in the ICIs-RT group (90.0 vs. 56.8%; $P < 0.001$) reflects real-world clinical practice, as ICIs in the neoadjuvant setting for TNBC are predominantly combined with platinum-containing regimens according to the KEYNOTE-522 protocol. This imbalance may have contributed to the higher pCR rate observed in the ICIs-RT group, and the relative contributions of platinum agents and ICIs cannot be disentangled within the current retrospective study design. Due to the small number of patients in the ICIs-RT group ($n=30$), propensity score matching and multivariable regression analyses were not feasible for adjusting baseline imbalances. Second, the follow-up duration was limited (median, 12 months); therefore, the data from the current study support conclusions regarding acute and early subacute toxicities only. Late effects, such as radiation fibrosis, cardiac toxicity and long-term survival outcomes, require extended follow-up. Furthermore, the small sample size resulted in insufficient statistical power. With only 30 patients in the intervention group and a low event count, the study was underpowered to detect uncommon but clinically meaningful toxicities, such as grade ≥ 2 radiation pneumonitis. Therefore, the absence of a statistically significant difference

in grade 1 radiation pneumonitis should not be interpreted as evidence of equivalent safety. Future prospective studies with larger sample sizes and longer follow-up are warranted to validate these findings and to employ appropriate methodologies for adjusting baseline confounding. Multiple ongoing trials are currently evaluating combined RT and immunotherapy strategies in the neoadjuvant, adjuvant and metastatic settings. Radiation dose and fractionation schedules may modulate immunologic synergy (22). Notably, hypofractionated RT may enhance immune activation (23). However, the optimal timing and sequencing; whether concurrent, sequential or sandwich, remain undefined. Finally, the identification of predictive biomarkers such as PD-L1 expression and tumor-infiltrating lymphocyte levels, will be crucial for identifying patients most likely to benefit from combined therapy (24,25).

In summary, concurrent immunotherapy during postoperative RT was not associated with a significant increase in radiation dermatitis or a statistically significant increase in radiation pneumonitis; however, a clinically meaningful trend toward a higher incidence of grade 1 radiation pneumonitis cannot be excluded. Concurrent immunotherapy did not appear to adversely affect short-term clinical outcomes; however, the limited follow-up duration and small number of events preclude definitive conclusions. These findings support the safety of the combined approach but highlight the need for continued vigilance.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GL conceived and designed the study, performed the investigation, prepared the figure and tables, and drafted and revised the manuscript. QZ provided study materials and patient resources, supervised the formal statistical analysis, and contributed to data interpretation. MY collected and managed the clinical data, and assisted with data visualization. GY collected and curated the data, and participated in the investigation. FY obtained funding, contributed to the conception and design of the study, supervised the project and critically revised the manuscript for important intellectual content. GL and FY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

This retrospective study was approved by the Ethics Committee of Hubei Cancer Hospital, Tongji Medical College,

Huazhong University of Science and Technology (approval no. LLHBCH2026YN-106). All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its subsequent amendments. Written informed consent for participation in the study was obtained from all living patients who were able to provide consent. For patients who were deceased or lost to follow-up, the requirement for informed consent was waived by the Ethics Committee, and all data were anonymized to protect patient privacy. Written informed consent for the off-label use of immunotherapy was also obtained from all patients who received such treatment, in accordance with institutional and regulatory requirements.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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