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ORIGINAL ARTICLE

The Potential Utilization of DNA Repair Protein XRCC1 as a Predictive Biomarker for Radiotherapy Response in Iraqi Women with Breast Cancer

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ABSTRACT

This study sought to elucidate whether the XRCC1 protein could serve as a predictive biomarker for treatment response in breast cancer (BC) women undergoing radiotherapy (RT). Between July 2024 and January 2025, 180 blood samples from 60 newly diagnosed BC patients, aged 34–56 years, before and after RT at the Al-Amal National Hospital for Cancer Management and the Baghdad Center for Nuclear Medicine and Radiotherapy, as well as 60 age- and sex-matched controls (30 RT workers and 30 healthy women), were tested. A made-on-request enzyme immunoassay measured XRCC1 levels. Serum XRCC1 levels in BC patients significantly increased after RT, followed by RT workers, compared to pre-RT patients and healthy controls (438.42±105.18 vs 348.58±104.56 vs 53.36±13.97 vs 93.71±27.56 pg/ml, $P<0.001$). In BC patients receiving RT, XRCC1 levels were higher in the 15-fraction and 30-fraction groups than the 20- and 25-fraction groups (449.95±105.48 vs 538.59±4.63 vs 336.18±3.01 vs 368.12±80.16 pg/ml, $P<0.05$). XRCC1 levels were elevated significantly with RT doses of ≥ 50 Gy and 45 Gy (570.33±45.07 and 472.47±66.92 pg/ml). RT at 6 and 10 MV did not significantly affect BC patients (449.39±101.35 vs. 428.83±109.11 pg/ml, $P>0.05$). The XRCC1 ROC curve showed a high AUC (0.801, 95% CI= 0.70-0.88) with 74.5% sensitivity and 89.7% specificity. Additionally, XRCC1 predicted RT response with 81% accuracy (95% CI= 71.48-88.52). In BC patients and RT workers, high XRCC1 levels were linked to RT parameters, suggesting that XRCC1 may predict RT responsiveness and DNA repair efficacy. XRCC1 may also predict radiation-induced DNA damage in RT workers and encourage greater radiation protection.

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1- INTRODUCTION

Breast cancer (BC) refers to the unregulated proliferation and modification of cells in breast tissue, resulting in tumor development [1]. Breast cancer remains a leading cause of cancer-related mortality in women, underscoring notable disease heterogeneity, metastatic potential, and resistance to treatment [2]. Thus, early detection has been linked

to reduced mortality rates [3]. In Iraq, BC is identified as the predominant malignancy, representing a quarter of cancer cases [4]. The lifestyle, genetic, and environmental variables might contribute to the development of BC plus around thirty percent of cases may be influenced by changeable variables [5].

Radiotherapy (RT) is a targeted intervention applying high-energy photons or particles to eradicate malignant cells [6]. After a mastectomy or lumpectomy, patients often get adjuvant RT to lessen the likelihood of cancer returning [7]. The responses of patients to RT can vary markedly, highlighting the basic processes that regulate the body's reactivity to radiation-induced damage [8]. Radiation resistance presents a significant challenge to improving therapy results, leading to the failure of RT, the persistence of tumors, and unfavorable prognoses [9]. Tumor heterogeneity, the local microenvironment, and genetic alterations are potential causes of this resistance. One significant change is the existence of the XRCC1 protein [10].

The XRCC1 gene, which is found on the long arm of chromosome 19, encodes the DNA repair protein known as X-Ray Repair Cross-Complementing 1 (XRCC1) in humans [11]. XRCC1 is a scaffolding protein that participates in the base excision repair (BER) pathway and interacts with several DNA repair enzymes, including DNA polymerase-β and DNA ligase III [12], to effectively repair DNA single-strand breaks (SSBs) caused by exposure to ionizing radiation (IR) [13]. As the XRCC1 protein has a crucial role in genomic stability, its dysregulation has been linked to the development of several human malignancies. However, the association between XRCC1 variants and BC risk remains controversial [14]. XRCC1 deficiency results in hypersensitivity to IR. However, limited studies revealed a significant association between XRCC1 overexpression and increased risk of poor overall survival and RT-induced side effects in cancer patients, indicating its prognostic significance for those undergoing radiation therapy [15, 16]. Accordingly, this study aimed to reveal the potential role of the XRCC1 protein as a predictive biomarker for therapeutic response in Iraqi BC women receiving RT.

2- MATERIALS AND METHODS

2.1 Study design and subject

This follow-up case-control research included 60 newly diagnosed Iraqi BC females aged 34 to 56 who attended the Al-Amal National Hospital for Cancer Management and the Baghdad Center for Nuclear Medicine and Radiation Therapy between July 2024 and January 2025. The consulting medical staff and pathologist/oncologist committee determined the selection and recognition of patients based on clinical examination, mammography, CT scan, and histological results. Except for surgery, no patients got chemotherapy or RT. The same sixty patients then received RT and were followed up to finish the treatment. This study included 60 age- and sex-matched control participants, divided into two groups: 30 workers from the RT department with ≥ 5 years of duration and 30 healthy women without medical history.

2.2 Radiotherapy administration

The RT protocol administered to the BC patients was the 3D-conformal radiation therapy (CRT) with 40-50 Gray units (Gy) for 15-30 fractions (5 sessions/week) at 6 or 10 megavolts (MV).

2.3 Exclusion criteria

The exclusion criteria comprised patients with BC undergoing chemo or radiotherapy prior to the initial blood collection; patients with missed sampling following RT; patients with other chronic illnesses or supplying insufficient information; those with pregnancy or lactation; and individuals not meeting the inclusion criteria.

2.4 Sample collection

Blood samples from BC patients were collected prior to the initiation of RT fractions. Subsequently, patients were monitored, and additional blood samples were obtained following the final RT fraction. A total of 180 blood samples were collected from participants, centrifuged, and stored at -20℃ for the subsequent estimation of serum XRCC1 levels.

2.5 Serum estimation of XRCC1

A quantitative dual antibody-Sandwich ELISA kit (FineTest®), manufactured upon request, was utilized to measure the blood levels of human XRCC1 protein in both patient and control groups [17]. An anti-XRCC1 antibody-coated microplate was included. Standards and samples were added. After incubation and washing, biotinylated antibodies detected the precoated antibody-bound XRCC1. Next, the enzyme conjugate (HRP) was added. Then, the substrate (TBM) was followed. The Stop solution rendered the color yellow. The microplate reader at 450nm and a standard curve were used for XRCC1 concentration calculation.

2.6 Ethical statement

The research received approval from the Medical Ethics Committees at Middle Technical University (MEC no. 64) and the Iraqi Ministry of Health (no. 22, 2024). Participants' verbal consent for involvement in this study was obtained.

2.7 Statistical analysis

Data were analyzed using SPSS software (version 27.0) and presented as mean ± standard deviation (SD) and, when applicable, as a percentage. A one-way ANOVA and an independent t-test were performed, when applicable, to compare groups. The receiver operating characteristic (ROC) curve was employed to ascertain the area under the curve (AUC) and compute cutoff values, sensitivity, specificity, plus positive and negative predictive values. Significant differences were observed at $p<0.05$.

3- RESULTS

As illustrated in Figure 1, BC patients after RT had significantly higher levels of serum XRCC1 (438.42±105.18 pg/ml) compared to those pre-RT (53.36±13.97 pg/ml), control workers (348.58±104.56 pg/ml), and healthy people (93.71±27.56 pg/ml). Additionally, RT workers had higher levels of XRCC1 compared to healthy controls and BC patients before RT (348.58±104.56 vs. 93.71±27.56 vs. 53.36±13.97 pg/ml, P<0.001).

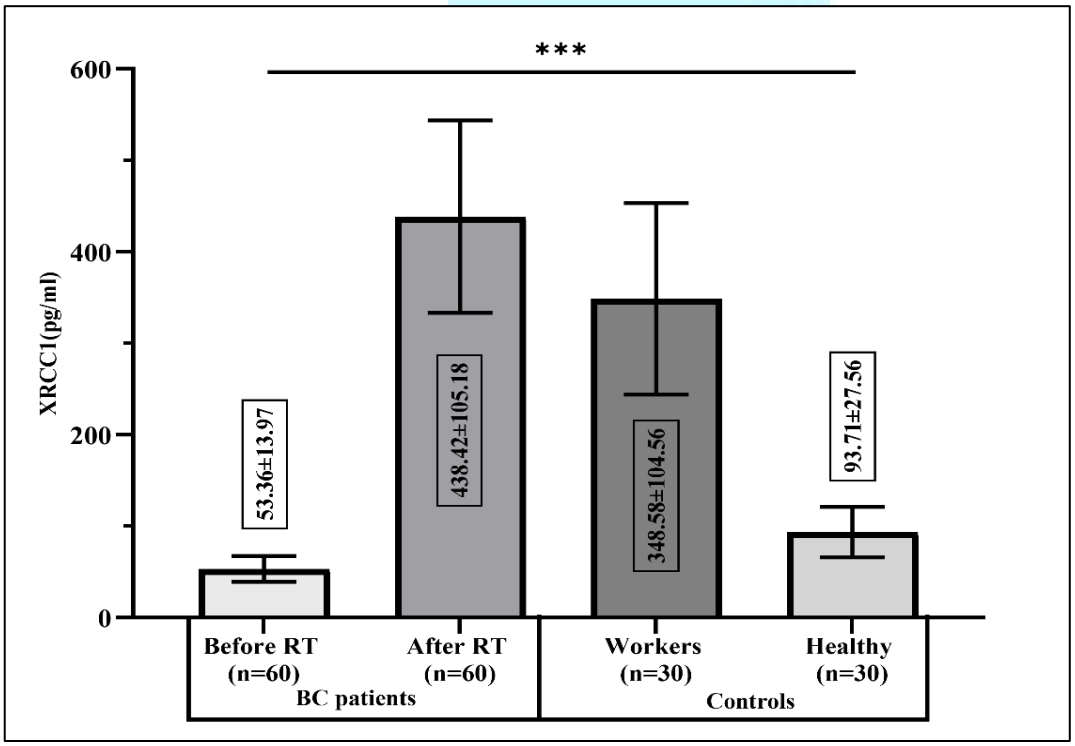

Figure (1): Distribution of mean XRCC1 levels among the studied groups

In BC patients, XRCC1 levels were significantly higher in the 15-fraction group (449.95±105.48 pg/ml) compared to the 20-, 25-, and 30-fraction groups (336.18±3.01, 368.12±80.16, and 538.59±4.63 pg/ml). BC patients who got 30 fractions had greater XRCC1 levels than those who received 20 or 25 fractions (538.59±4.63 vs. 336.18±3.01 vs. 368.12±80.16 pg/ml, P<0.05). No significant difference in XRCC1 levels was observed between the 20- and 25-fraction groups (336.18±3.01 vs. 368.12±80.16 pg/ml, P>0.05) as displayed in Figure 2.

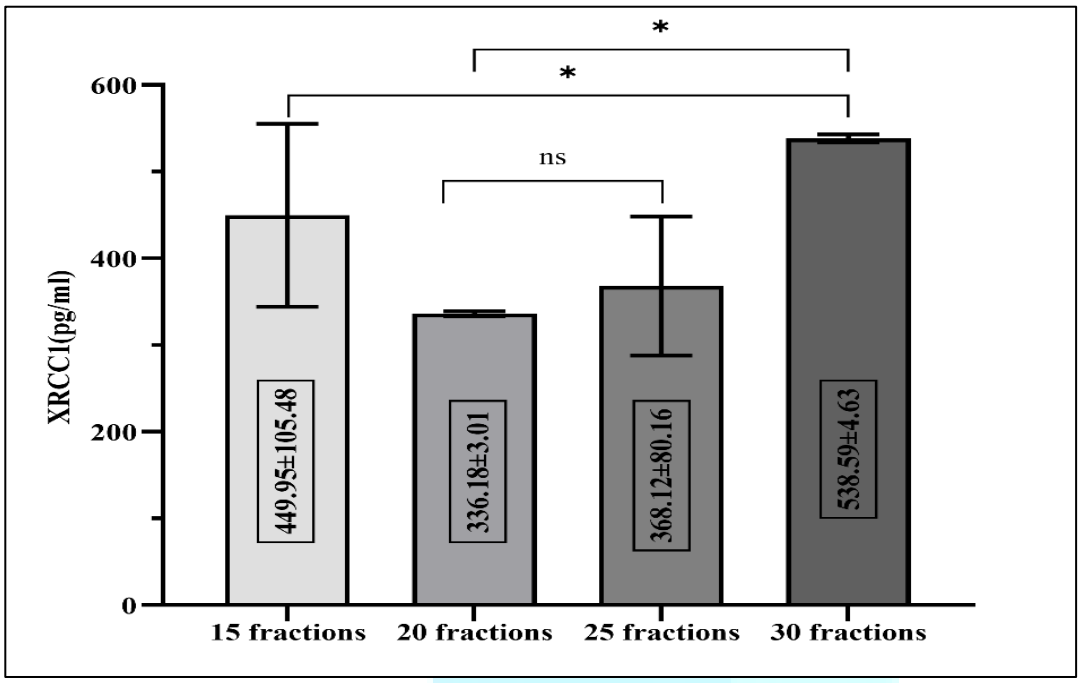

Figure (2): Distribution of XRCC1 levels according to radiotherapy fractions

Figure 3 shows that the XRCC1 levels in BC patients were significantly elevated in individuals who underwent RT of 50 Gy or more, in comparison to those receiving 45 or 40 Gy (570.33±45.07 vs. 472.47±66.92 vs. 371.76±86.86 pg/ml, P<0.001). Furthermore, patients administered 45 Gy demonstrated higher XRCC1 levels than those in the 40 Gy cohort (472.47±66.92 vs. 371.76±86.86 pg/ml, P<0.001).

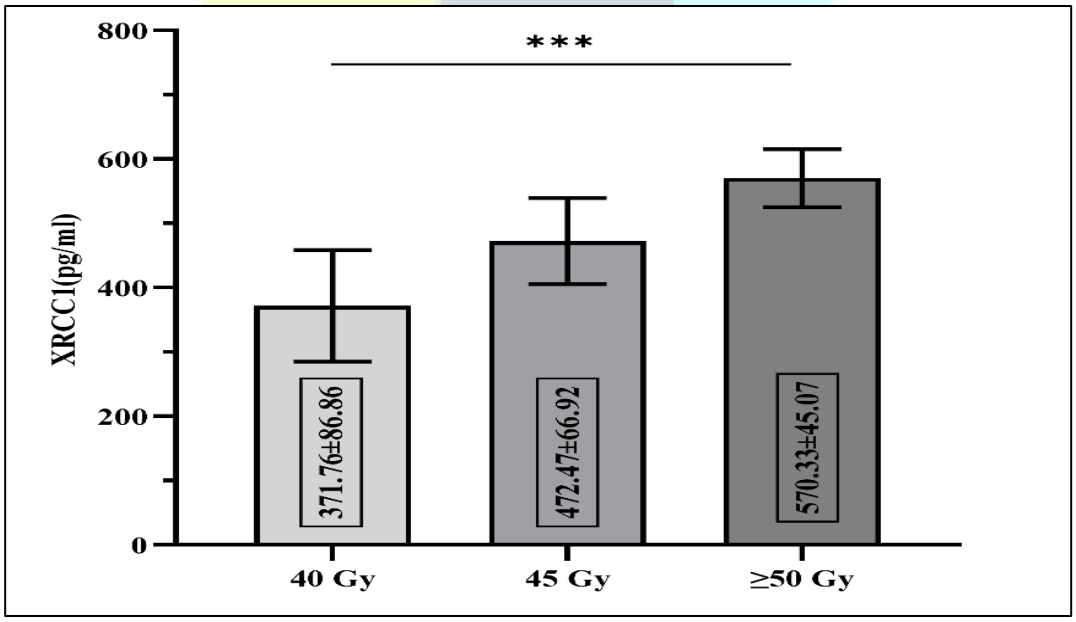

Figure (3): Distribution of XRCC1 levels according to radiotherapy doses

As presented in Figure 4, the BC patients who received RT at 6 MV demonstrated elevated XRCC1 levels in comparison to those administered at 10 MV, even though this difference had no statistical significance (449.39±101.35 vs. 428.83±109.11 pg/ml, P>0.005).

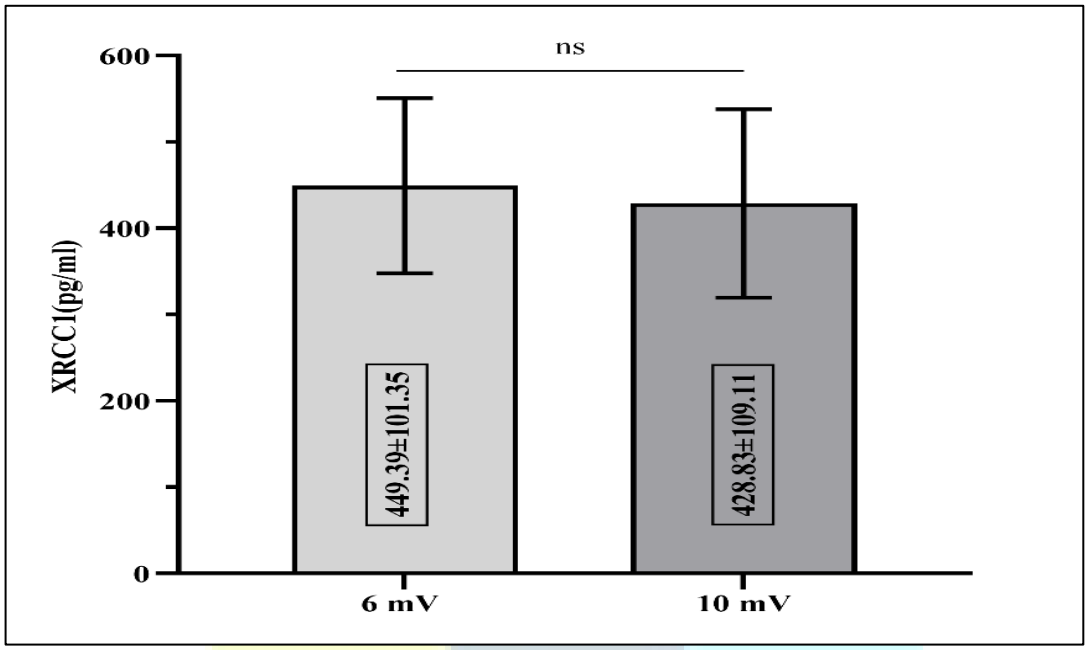

Figure (4): Distribution of XRCC1 levels according to radiotherapy volt

The ROC curve for XRCC1 in BC patients and controls demonstrated a significant AUC (0.801, 95% CI= 0.70-0.88), as illustrated in Table 1 and Figure 5. The optimal cutoff value of XRCC1 to prognose RT response was >134.9 pg/ml, exhibiting 74.5% sensitivity and 89.7% specificity. Furthermore, the positive predictive value, negative predictive value, and accuracy of XRCC1 were 90.5%, 72.9%, and 81% (95% CI= 71.48-88.52), respectively.

Table (1): The predictive performance of the XRCC1 in the studied groups

Biomarker	**ROC curve characteristics**							
	AUC (95%CI)	***P*-value**	**Cutoff**	**Sens**	**Spec**	**PPV**	**NPV**	**Accu (95% CI)**
XRCC1 (pg/ml)	0.801 (0.70 -0.88)	0.012	>134.9	74.5%	89.7%	90.5%	72.9%	81.1% (71.48-88.52)

ROC: Receiver operating characteristic, AUC: area under the curve, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, Accu: accuracy.

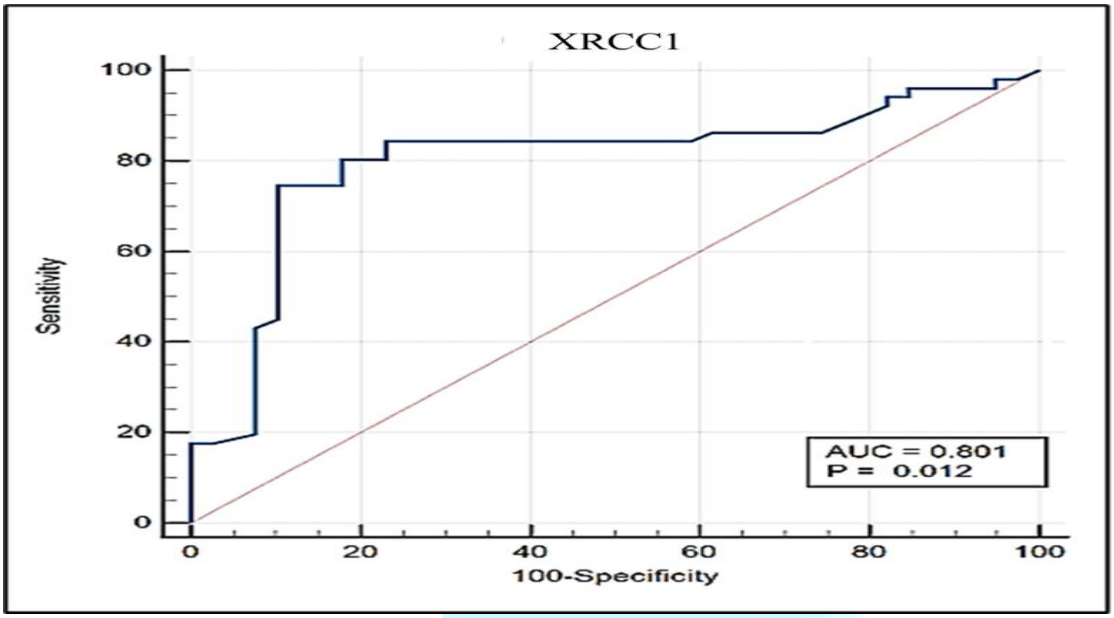

Figure (5): ROC curve analysis of the XRCC1

4- DISCUSSION

Given the increasing global prevalence of BC and the possibility of patients developing resistance to RT, it is essential to evaluate RT's effectiveness before completing its fractions. As far as we know, locally, this study is the first to estimate serum levels of the XRCC1 in BC patients pre- and post-RT and compared them to RT department's workers and healthy controls. Among the studied groups, BC patients after RT exhibited the highest significant levels of XRCC1, followed by the RT workers, compared to those patients before RT and healthy controls. The findings largely align with those of Wright *et al*., who reported elevated XRCC1 levels and expression in BC patients subjected to RT [18]. These patients exhibited increased survival rates; however, XRCC1 overexpression may be associated with late radiation toxicity. Few studies have examined DNA-repair genes in RT staff and the associated radiotoxicity. Surniyantoro *et al*. identified that 40% of RT workers exhibited elevated XRCC1 levels, correlating with an increased risk of DNA damage repair inefficiency, which may elevate cancer risk [19]. The results indicate that XRCC1 may serve as both a predictive and prognostic marker for radiation-induced DNA damage and the effectiveness of RT in cancer patients. Still, Zheng *et a*l. articulated their dissent regarding our findings. They asserted that no link exists between radiation-induced detrimental effects in cancer patients and XRCC1 [20]. This signified that XRCC1 had lower prognostic efficacy. The discrepancies in results may be ascribed to differences in patient ethnicity, sample size, cancer stage and grade, and study design. XRCC1's elevated levels are associated with its function as a DNA repair protein necessary for SSB repair. Therefore, its increased expression is a normal physiological reaction to DNA damage caused by RT [13].

In BC patients undergoing RT, the 15-fraction group had a significantly higher distribution of XRCC1 levels than the 20- and 25-fraction groups, followed by the 30-fraction group. These results were exclusive to this study, as the RT implemented for the BC patients was tailored to their tumor grade, stage, mastectomy type, and ethnicity. Nonetheless, our findings resembled those by Nowicka *et al*. [21] and Gupta *et al*. [22], regardless of tumor type. They found that the RT fractions for tumors post-excision ranged from 15 to 30; although the use of 30 or more fractions was effective and common, treatment typically ceased at 20 fractions because of acute radiotoxicity. This indicates that hypofractionated radiotherapy is effective and safe.

XRCC1 levels in BC patients rose significantly with 50 Gy or higher of RT, then 45 Gy. These findings indicated that higher radiation doses increase XRCC1 levels and DNA repair, implying that XRCC1 might be utilized to predict RT response. These findings were somewhat similar to Marazzi *et al*. and Gudur *et al*., who found XRCC1 overexpression in cancer patients who had >15 fractions of radiation dose >50 Gy [23, 24]. It appears that larger radiation doses boost DNA repair capacity, enhancing responsiveness. However, radiotoxicity often rises.

Although not statistically significant, BC patients getting 6 MV radiation had higher XRCC1 levels than those receiving 10 MV. This study suggests that low-voltage RT can upregulate the XRCC1 gene with less radiotoxicity compared to high-voltage radiation, which can harm nearby healthy tissues. Thus, this protein could predict RT response. Few studies

connect RT volts with XRCC1 levels in tumor patients; however, Lu *et al*. [25] discovered a positive correlation between XRCC1 expression and low-voltage (≤6 MV) radiation throughout consecutive fractions, and noted that XRCC1 knockdown was associated with resistance to RT.

At a cutoff value of >134.9 pg/ml, XRCC1 predicts outcomes with 74.5% sensitivity and 89.7% specificity. It had 90.5% PPV and 72.9% NPV. The response of RT in BC patients was predicted with 81% accuracy using that cutoff value. More investigations showed that XRCC1 had a significant AUC of 0.85, 68% sensitivity, and 75% specificity, suggesting that it could predict cancer risk and treatment response [26, 27]. Wei *et al*. reported that XRCC1 effectively predicted cancer patients' treatment response with an AUC of 0.8 [28].

5- CONCLUSION

This study demonstrated elevated XRCC1 levels in BC patients after RT, as well as in RT workers, and their association with RT parameters. This suggests that XRCC1 could be a biomarker to predict RT response and DNA repair effectiveness in these patients. Additionally, XRCC1 could help predict the risk of radiation-induced DNA damage in RT workers and highlight the need for better protection against radiation exposure.

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