Predictive value of single nucleotide polymorphisms in XRCC1 for radiation-induced normal tissue toxicity

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Purpose: X-Ray Repair Cross Complementing 1 (XRCC1) functioning in the base excision repair pathway plays an important role in the repair of DNA single-strand breaks caused by ionizing radiation. The relationship between XRCC1 polymorphisms and the risk of radiation-induced side effects on normal tissues remains controversial. Therefore, we performed a comprehensive meta-analysis to elucidate these associations.

Materials and methods: A systematic literature search was carried out in PubMed, Medline (Ovid), Embase, Web of Science, and Cochrane database, and the references of relevant studies. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate the strength of the association.

Results: A total of 40 studies including 6,682 patients were eventually identified in this meta-analysis. Pooled results suggested that rs25487 Arg399Gln polymorphism significantly increased the risk of acute radiation-induced side effects (OR = 1.29, 95% CI: 1.10–1.52, P = 0.002), especially acute mucositis (OR = 1.91, 95% CI: 1.17–3.11, P = 0.01) and acute gastrointestinal and genitourinary toxicity (OR = 1.49, 95% CI: 1.04–2.11, P = 0.03). Furthermore, patients who received head and neck irradiation with rs25487 Arg399Gln polymorphism were more likely to experience radiotherapy (RT)-induced side effects (OR = 1.46, 95% CI: 1.12–1.90, P = 0.005). However, no statistically significant correlations were identified between rs25487 polymorphism and any late side effects and other irradiation areas. Likewise, no significant associations were detected between rs25489, rs1799782, or rs3213245 polymorphism and RT-induced toxicity.

Conclusion: Our meta-analysis demonstrated that XRCC1 rs25487 Arg399Gln polymorphism had a significant predictive value and might predict a risk of severely acute RT-induced adverse effects, especially in acute mucositis and acute gastrointestinal and genitourinary toxicity, or in patients with head and neck irradiation. However, large-scale and well-designed studies are required to further evaluate the predictive value of XRCC1 variations on radiation-induced side effects in order to identify radiosensitive patients and predict radiotoxicity.

Keywords: XRCC1, polymorphism, radiotherapy, side effect

Introduction

Radiotherapy (RT) is a common and indispensable method in cancer treatment, which may result in a spectrum of normal tissue side effects.1 Although improvements in precise RT techniques such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy have increased the possibility of dose escalation in tumor targets,2 the implementation of radiation dose is still limited by the tolerance of normal tissues in and adjacent to the irradiation field.3 However, patients exhibit substantially different degrees of normal tissue toxicity even with the same treatment...
regimen, varying from mild to severe and occasionally lethal. Acute adverse effects may lead to unanticipated RT breaks and then remarkably affect adequate treatment delivery, and late adverse effects markedly influence patients' quality of life. It is important to predict a predisposition of severe RT-induced adverse effects in normal tissues for making personal and optimized treatment decision, particularly in those with "high–intermediate risk".

The severity of RT-induced complication is associated with many factors including irradiated dose, volume of normal tissues, fractionation schedule, combined with chemotherapy, as shown by Stone et al., but they cannot fully explain patient-to-patient differences. Recent studies indicate that genetic component may contribute to the clinical radiosensitivity and radiation adverse effects. DNA is considered to be the main target of RT, which causes cell death by inducing base damage, single-strand breaks (SSBs), and double-strand breaks. So, inter-individual differences in DNA repair capacity may determine varying degrees of the normal tissue response. Extensive researches have been conducted in order to identify some genetic markers such as single nucleotide polymorphisms (SNPs) as predictive factors for the risk of radiation-induced normal tissue toxicity. SNPs in DNA damage and repair genes may alter the amino acid composition of encoded proteins, which play a role in individual's radiation response and capacity of DNA damage repair. The protein encoded by X-Ray Repair Cross Complementing 1 (XRCC1) gene, which functions in the base excision repair (BER) pathway, involves in the efficient repair of DNA SSBs caused by exposure to ionizing radiation. The XRCC1 gene is mapped at human chromosome 19q13.2–13.3. The most common variants of XRCC1 gene are rs25487 Arg399Gln in exon 10, rs25489 Arg280His in exon 9, and rs1799782 Arg194Trp in exon 6.

Although several studies have investigated the association of XRCC1 polymorphisms with clinically observed normal tissue adverse effects, the results are not consistent. It is not sufficient to form a reliable conclusion and consequently limit their clinical applicability as biomarkers. So, we performed a systematic review to investigate these associations. This is, to our knowledge, the first comprehensive meta-analysis of genetics studies on the association between XRCC1 polymorphisms and radiation-related adverse effects.

Materials and methods

Search strategy
A systematic literature search in PubMed, Medline (Ovid), Cochrane, Embase, Web of Science database, and the references of relevant articles was carried out to identify studies involving XRCC1 polymorphisms and the risk of radiation-related normal tissue adverse effects (last search was updated on June 1, 2017). The search terms used were as follows: "XRCC1 or X-Ray Repair Cross Complementing 1" in combination with "SNP or polymorphism or variant or variation or mutation or haplotype" and "radiotherapy or radiation or irradiation" and "side effect or adverse effect or complication or injury or toxicity or reaction or response or radiotoxicity or radiosensitivity or morbidity or normal tissue". All the search terms were restricted to studies in human subjects and in English language.

Inclusion criteria
Studies included in the current meta-analysis met the following inclusion criteria: 1) evaluation of the association between XRCC1 SNPs and radiation-induced normal tissue adverse effects; 2) the design has to be a cohort study or case control study; 3) sufficient published data (genotype distributions of each groups) to estimate an odds ratio (OR) with 95% CI.

Exclusion criteria
Studies were excluded if one of the following existed: 1) data of genotype frequencies of each group were not reported and 2) case reports, reviews, editorials, and repeat studies. If there were more than one study published by the same authors based on the same populations, the one providing the most comprehensive information was included.

Data extraction
Two investigators collected the data independently in duplicate according to the inclusion criteria listed above using a standardized data extraction form. The following items were extracted from each study: first author, publication date, original country, ethnicity, cancer type, subtype of SNP in XRCC1, normal tissue toxicity, sample size, treatment, type of study, genotyping method, genotype number, and total number in cases and controls.

Statistical analysis
ORs and 95% CIs were used to assess the strength of association between genetic polymorphisms and the risk of RT-induced adverse effects. The pooled OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity among eligible studies was measured by $\chi^2$-based Q-test and $I^2$ statistical test. If $Q$-test $P<0.1$ and $I^2$-value $\geq 50\%$, the heterogeneity was considered statistically significant, and the assumption
of homogeneity was deemed invalid and the pooled OR was calculated by random-effects model after exploring the cause of heterogeneity. Otherwise, the fixed-effects model was used. Findings of our meta-analysis are shown in forest plots. The two-tailed \( P<0.05 \) was considered statistically significant. To evaluate the tolerance of different normal tissues and the occurrence time of side effects, subgroup analysis was conducted by early or late adverse effect, special types of side effects, and irradiation area. Sensitivity analysis was performed to confirm the stability and reliability of the pooled results by excluding each study individually and recalculating the pooled ORs and 95% CIs. If the number of included studies were >10, the possible publication bias and the degree of asymmetry were examined by Begg’s funnel plot and Egger’s test. If publication bias existed, the “trim and fill” method was used to estimate the number of missing studies and to adjust the pooled result. Statistical analysis was performed using Revman 5.3 and STATA 14.0 software.

**Results**

**Study characteristics**

A total of 40 studies including 6,682 patients were eventually identified in this meta-analysis for further analysis (Figure 1). The baseline characteristics of each included study are listed in Table 1. These studies were published from 2003 to 2017, and the sample size ranged from 34 to 579. Most of these studies included mainly Caucasian patients, and nine studies included Asian patients, of which five studies are on Chinese. The cancer categories included head and neck cancer (8 studies), breast cancer (18 studies), prostate cancer (5 studies), cervical endometrial

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**Figure 1** Flow diagram of study search and screening for the meta-analysis.

**Abbreviations:** RT, radiotherapy; SNP, single nucleotide polymorphism.
Table 1 Baseline characteristics of the eligible studies

<table>
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<tr>
<th>Author, year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Disease</th>
<th>SNP</th>
<th>Sample size (N)</th>
<th>Adverse effect</th>
<th>Assessment criteria</th>
<th>RT dose</th>
<th>CT involved</th>
<th>Study design</th>
<th>Genotyping method</th>
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<tr>
<td>Alsbeih et al, 2010</td>
<td>Saudi Arabia</td>
<td>Caucasian</td>
<td>NPC</td>
<td>rs25487</td>
<td>60</td>
<td>Late: fibrosis</td>
<td>RT/TOG/EORTC ≥ G2</td>
<td>66–70 Gy</td>
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<td>PCR</td>
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<td>Andreassen et al, 2003</td>
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<td>Breast</td>
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<td>41</td>
<td>Late: fibrosis</td>
<td>LENT-SOMA ≥ G3</td>
<td>36.6–51.4 Gy</td>
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<td>Cohort</td>
<td>PCR</td>
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<td>Denmark, UK</td>
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<td>Breast</td>
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<td>52</td>
<td>Late: breast appearance</td>
<td>Photographic ≥ G2</td>
<td>50 Gy/25 f, 42.9 Gy/13 f, 39 Gy/13 f</td>
<td>NA</td>
<td>Case–control</td>
<td>PCR</td>
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<td>Andreassen et al, 2006</td>
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<td>Caucasian</td>
<td>Breast</td>
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<td>120</td>
<td>Late: fibrosis</td>
<td>LENT-SOMA ≥ G3</td>
<td>41 Gy</td>
<td>Yes</td>
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<td>PCR</td>
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<td>Azria et al, 2008</td>
<td>France</td>
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<td>Breast</td>
<td>rs25489</td>
<td>34</td>
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<td>CTC 3.0 ≥ G3</td>
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<td>Yes</td>
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<td>PCR</td>
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<td>Brem et al, 2006</td>
<td>France</td>
<td>Caucasian</td>
<td>Breast</td>
<td>rs3213245</td>
<td>247</td>
<td>Acute and Late</td>
<td>EORTC</td>
<td>50 Gy, tumor bed boost 10 Gy</td>
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<td>Mixed</td>
<td>Prostate</td>
<td>rs25487, rs25489, rs1799782</td>
<td>135</td>
<td>Late: rectal bleeding, urinary morbidity, erectile dysfunction</td>
<td>RT/TOG/EORTC ≥ G2</td>
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<td>PCR</td>
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<td>Caucasian</td>
<td>Breast</td>
<td>rs25487, rs25489, rs1799782</td>
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<td>Acute: skin reaction</td>
<td>CTCAE v2.0 ≥ G2c</td>
<td>Mean 54.0± 4.8 Gy (35.5–64.5 Gy)</td>
<td>No</td>
<td>Cohort</td>
<td>PCR-RFLP</td>
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<td>Breast</td>
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<td>409</td>
<td>Late: telangiectasia</td>
<td>RT/TOG/EORTC LENT-SOMA ≥ G2</td>
<td>Mean 61.8± 4.10 Gy (51–71 Gy)</td>
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<td>rs25487, rs1799782</td>
<td>83</td>
<td>Late: bladder or rectal toxicity</td>
<td>RT/TOG ≥ G2</td>
<td>Mean 77.1 Gy (68.3–82.1 Gy) EBRT: 45–66 Gy 192i: 15–35 Gy</td>
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<td>De Ruyck et al, 2005</td>
<td>Belgium</td>
<td>Caucasian</td>
<td>Cervical, endometria</td>
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<td>62</td>
<td>Late</td>
<td>CTCAE v3.0 ≥ G2</td>
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<td>rs3213245</td>
<td>189</td>
<td>Acute: dysphagia</td>
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<td>66–70 Gy</td>
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<td>Duldulao et al, 2013</td>
<td>USA</td>
<td>Caucasian</td>
<td>Rectal</td>
<td>rs25487</td>
<td>132</td>
<td>Acute: gastrointestinal toxicity</td>
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<td>NA</td>
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<td>57</td>
<td>Acute: erythema</td>
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<td>21 Gy/f</td>
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<td>Late: fibrosis, fat necrosis</td>
<td>CTCAE v3.0 ≥ G2</td>
<td>21 Gy/f</td>
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<td>Giotopoulos et al.</td>
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<td>167</td>
<td>Late: telangiectasia</td>
<td>RTOG LENT-SOMA ≥G2</td>
<td>40–50 Gy, tumor bed boost of 15 Gy/5f</td>
<td>Yes</td>
<td>Cohort</td>
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<td>Ishikawa et al.</td>
<td>Japan</td>
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<td>Cervical</td>
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<td>208</td>
<td>Acute: diarrhea</td>
<td>CTCAE v2.0 ≥G2</td>
<td>EBRT 50.6 Gy</td>
<td>Yes</td>
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<td>PCR</td>
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<td>Langenlehner et al.</td>
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<td>Caucasian</td>
<td>Prostate</td>
<td>rs25487, rs25489, rs1799782</td>
<td>579</td>
<td>Late: bladder or rectal toxicity</td>
<td>RTOG/EORTC ≥G2</td>
<td>Brachytherapy 24.0 Gy 66–70.4 Gy</td>
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<td>Li et al.</td>
<td>China</td>
<td>Asian</td>
<td>NPC</td>
<td>rs25487, rs1799782</td>
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<td>Acute: mucositis, dermatitis</td>
<td>CTCAE v3.0 ≥G3</td>
<td>50–70 Gy</td>
<td>Yes</td>
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<td>Mangoni et al.</td>
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<td>Breast</td>
<td>rs25487, rs1799782</td>
<td>87</td>
<td>Acute: skin reaction</td>
<td>CTCAE v2.0 ≥G2c</td>
<td>50 Gy/25f, 44 Gy/16f</td>
<td>Yes</td>
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<td>EORTC</td>
<td>50 Gy, tumor bed boost 10 Gy</td>
<td>NA</td>
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<td>PCR</td>
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<td>Mumbrekar et al.</td>
<td>India</td>
<td>Asian</td>
<td>Breast</td>
<td>rs25487</td>
<td>126</td>
<td>Acute: skin reaction</td>
<td>RTOG ≥G2</td>
<td>50 Gy, tumor bed boost 10 Gy for 26 patients</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR</td>
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<td>Popanda et al.</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Prostate</td>
<td>rs25487, rs25489, rs1799782</td>
<td>405</td>
<td>Acute: proctitis cystitis</td>
<td>CTCAE v2.0 ≥G3</td>
<td>61–72 Gy</td>
<td>No</td>
<td>Cohort</td>
<td>Sequence-specific hybridization probes PCR-RFLP</td>
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<td>Pratesi et al.</td>
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<td>101</td>
<td>Acute: mucositis, skin erythema</td>
<td>CTCAE v3.0 ≥G2</td>
<td>Mean 62 Gy (54–70 Gy)</td>
<td>Yes</td>
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<td>RTOG ≥G2</td>
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<td>PCR-RFLP, MALDI-TOF PCR-RFLP</td>
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<td>Sakano et al.</td>
<td>Japan</td>
<td>Asian</td>
<td>Bladder</td>
<td>rs25487</td>
<td>95</td>
<td>Acute: gastrointestinal toxicity</td>
<td>CTCAE v3.0 ≥G2</td>
<td>Median 48.6 Gy (30.0–60.4 Gy)</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR-RFLP</td>
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<td>Smith et al.</td>
<td>America</td>
<td>Mixed</td>
<td>Rectal</td>
<td>rs25487</td>
<td>165</td>
<td>Acute: gastrointestinal and genitourinary toxicity (diarrhea, proctitis, cystitis)</td>
<td>CTCAE v3.0 ≥G3</td>
<td>Median 50.4 Gy</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR, MALDI-TOF</td>
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<td>Terrazzino et al.</td>
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<td>Breast</td>
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<td>Acute: skin reaction</td>
<td>RTOG ≥G2</td>
<td>50–50.4 Gy, tumor bed boost 9–16 Gy</td>
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<td>Cohort</td>
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<td>Terrazzino et al.</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Breast</td>
<td>rs25487, rs1799782</td>
<td>237</td>
<td>Late: fibrosis</td>
<td>LENT-SOMA ≥G2</td>
<td>50–50.4 Gy, tumor bed boost 9–16 Gy</td>
<td>Yes</td>
<td>Cohort</td>
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<td>Tucker et al.</td>
<td>USA</td>
<td>Caucasian</td>
<td>NSCLC</td>
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<td>CTCAE v3.0 ≥G3</td>
<td>Median 63 Gy (50.4–72 Gy)</td>
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<td>Usmani et al.</td>
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<td>Prostate</td>
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<th>Author, year</th>
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<th>Adverse effect</th>
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<th>RT dose</th>
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<td>Venkatesh et al, 2014</td>
<td>India</td>
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<td>183</td>
<td>Acute: mucositis, skin reaction</td>
<td>RTOG ≥ G3</td>
<td>60–70 Gy</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR-RFLP</td>
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<td>Yin et al, 2011</td>
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<td>rs25487</td>
<td>165</td>
<td>Late: radiation pneumonitis</td>
<td>CTCAE v3.0 ≥ G2</td>
<td>Median 63 Gy (50.4–84.0 Gy)</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Yoon et al, 2011</td>
<td>USA</td>
<td>Mixed</td>
<td>Esophageal adenocarcinoma</td>
<td>rs25487</td>
<td>60</td>
<td>Acute: dysphagia</td>
<td>CTCAE v2.0 ≥ G3</td>
<td>45 Gy</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR, MALDI-TOF</td>
</tr>
<tr>
<td>Xian et al, 2015</td>
<td>China</td>
<td>Asian</td>
<td>Esophageal squamous cell carcinoma</td>
<td>rs25487</td>
<td>118</td>
<td>Acute: esophagitis</td>
<td>CTCAE ≥ G3</td>
<td>Median 60 Gy (45–66 Gy)</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR</td>
</tr>
<tr>
<td>Zhai et al, 2016</td>
<td>China</td>
<td>Asian</td>
<td>NPC</td>
<td>rs25487</td>
<td>60</td>
<td>Acute and Late: skin, mucosa, salivary gland</td>
<td>RTOG ≥ G2</td>
<td>66–76 Gy</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR-LDR</td>
</tr>
<tr>
<td>Zhou et al, 2010</td>
<td>China</td>
<td>Asian</td>
<td>Breast</td>
<td>rs25487, rs25489, rs1799782, rs3213245</td>
<td>119</td>
<td>Acute: skin reaction</td>
<td>CTCAE v3.0 ≥ G2</td>
<td>46–54 Gy</td>
<td>No</td>
<td>Cohort</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Zschenker et al, 2010</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Breast</td>
<td>rs25487</td>
<td>69</td>
<td>Late: fibrosis</td>
<td>LENT-SOMA ≥ G2</td>
<td>54–55 Gy</td>
<td>Yes</td>
<td>Cohort</td>
<td>PCR-RFLP, MALDI-TOF</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, chemotherapy; CTc, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, external beam radiation therapy; EORTC, European Organization for Research and Treatment of Cancer; HNC, head and neck cancer; LDR, ligase detection reaction; MALDI-TOF, matrix-assisted laser desorption/ionization time of flight; LENT-SOMA, Late Effects of Normal Tissue-Subjective Objective Management Analytical; NA, not available; NPC, nasopharyngeal carcinoma; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SNP, single nucleotide polymorphism.
cancer (2 studies), bladder cancer (1 study), rectal cancer (2 studies), non-small-cell lung cancer (NSCLC; 2 studies), esophageal cancer (2 studies), and one mixed cancers (mainly breast cancer and head and neck cancer). Four subtypes of SNPs in XRCC1 were analyzed in this meta-analysis. Thirty-six studies were identified for rs25487, 12 studies for rs25489, 17 studies for rs1799782, and 6 studies for rs3213245. Subgroup analyses of radiation-induced adverse effects were performed on acute or late side effects, special types of side effects, and irradiation area. The genotype distributions analyzed in each study were in Hardy–Weinberg equilibrium with \( P > 0.05 \). All the included eligible reports were written in English language.

**Meta-analysis results**

**XRCC1 rs25487 polymorphism**

Overall, XRCC1 rs25487 Arg399Gln G>A polymorphism was significantly associated with acute normal tissue injury after RT. Specifically, rs25487 “Gln” allele increased the risk of acute radiation-induced adverse effects (for GA+AA versus GG, OR=1.29, 95% CI: 1.10–1.52, \( P = 0.002 \); Figure 2).

**Subgroup analysis by specific adverse effect**

Because most studies investigated several different adverse effects, subgroup analysis was conducted by specific adverse effect. The results indicated that rs25487 Arg399Gln “Gln” allele carriers significantly increased acute mucositis (OR=1.91, 95% CI: 1.17–3.11, \( P = 0.01 \)) and acute gastrointestinal and genitourinary toxicity (OR=1.49, 95% CI: 1.04–2.11, \( P = 0.03 \); Figure 3). No statistically significant associations were identified between rs25487 polymorphism and any late radiation-induced adverse effects (Figure 4).

**Subgroup analysis by radiotherapy area**

Subgroup analysis was conducted by different irradiation area irrespective of the type of adverse effect. The rs25487 Arg399Gln polymorphism was significantly associated with a higher risk of adverse effects induced by head and neck irradiation (OR=1.46, 95% CI: 1.12–1.90, \( P = 0.005 \)), whereas the correlation was not significant for breast or pelvic irradiation (breast, OR=1.13, 95% CI: 0.95–1.33, \( P = 0.18 \); pelvic, OR=1.20, 95% CI: 0.94–1.54, \( P = 0.14 \), respectively; Figure 5).

**XRCC1 rs25489, rs1799782, and rs3213245 polymorphisms**

Although no statistically significant associations were identified, the rs25489 Arg280His polymorphism seemed to indicate a protective effect against radiotoxicity (OR=0.78, 95% CI: 0.58–1.06, \( P = 0.11 \)), especially in acute adverse effects (OR=0.66, 95% CI: 0.38–1.14, \( P = 0.14 \), Figure 6) or in breast irradiation area (OR=0.71, 95% CI: 0.47–1.06, \( P = 0.10 \), Figure 7). No significant associations were detected between rs1799782 or rs3213245 polymorphism and RT-induced toxicity (Figures 8 and 9).

**Heterogeneity and sensitivity analyses**

The heterogeneities between studies of most analyses were not significant except for three subgroup analyses, the evaluation on radiation pneumonitis of rs25487 (\( P = 0.98% \), \( \chi^2 P = 0.03 \)), late side effect (\( P = 48% \), \( \chi^2 P = 0.05 \)), and pelvic irradiation (\( P = 55% \), \( \chi^2 P = 0.04 \)) of rs25489. The pooled OR calculated by random-effects model of these subgroup analyses had no statistically significant associations, and the pooled results were stable in the sensitivity analysis.

**Publication bias**

The distribution of all analyzed studies for rs25487 in Begg’s funnel plot was visually asymmetrical and the \( P \)-value of Egger’s test was significantly <0.05. However, we noticed that many included studies assessed several endpoints and different adverse effects, resulting in these studies being evaluated several times in Begg’s funnel plot, which led to an inaccurate result of the publication bias. So, in order to avoid “multiple testing problem”, we reevaluated the publication bias for each subgroup analysis if >10 studies were included based on the results above in the form of one study emerged only one time. The \( P \)-value of Egger’s test of rs25487 for RT-induced acute skin toxicity was 0.245 (Figure 10), which indicates no publication bias. No publication bias was identified in other subgroup analysis of rs25487, and in rs25489, rs1799782, rs3213245 genetic models, and the P-values of Egger’s test were all >0.05, which suggested that there was no obvious risk of publication bias in the meta-analysis.

**Discussion**

The protein encoded by XRCC1 gene functions in the efficient repair of base damage and DNA SSBs formed by ionizing radiation and alkylating agents. This protein interacts with DNA ligase III, polymerase-beta, and poly (ADP-ribose) polymerase to participate in the BER pathway. Polymorphisms in this gene are associated with varying radiosensitivity of cancer patients. Association studies on XRCC1 genetic variations and the risk of RT-induced normal tissue injuries can help us to identify markers predicting occurrence of side effects, but previous studies reported inconsistent findings.
Zhao et al

Figure 2: Forest plots for the association between rs25487 and radiation-induced adverse effects.

Notes: A random-effects model was used. The square with the corresponding horizontal line represents the OR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled OR and 95% CI. The table represents the studies with a significant radiolodide side effects. a) genitourinary toxicity; b1, gastrointestinal toxicity; b2, genitourinary toxicity; b3, erectile dysfunction; b4, radiation pneumonitis; b5, mucosal membrane; b6, salivary gland.

Abbreviations: M–H, Mantel-Haenszel; Or, odds ratio.
Study or subgroup | Case GA+AA Total | Control GA+AA Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI
--- | --- | --- | --- | --- | ---
Skin toxicity | | |
Changglaude et al.²³ 2005 (a1) | 46 | 77 | 219 | 369 | 12.2 | 1.02 (0.62–1.68)
Li et al.²⁷ 2013 (a1) | 14 | 24 | 37 | 90 | 2.6 | 2.01 (0.80–5.00)
Mangoni et al.²¹ 2011 (a1) | 5 | 7 | 26 | 54 | 0.7 | 2.69 (0.48–15.10)
Mumbrek et al.²⁷ 2017 (a1) | 23 | 43 | 44 | 76 | 5.9 | 0.84 (0.39–1.78)
Pratesi et al.²⁶ 2011 (a1) | 18 | 12 | 15 | 33 | 1.1 | 2.40 (0.60–9.56)
Raabe et al.²⁴ 2012 (a1) | 27 | 46 | 20 | 37 | 3.7 | 1.21 (0.50–2.99)
Suga et al.²⁷ 2007 (a1) | 50 | 109 | 122 | 290 | 14.5 | 1.17 (0.75–1.82)
Terrazzini et al.²⁶ 2012 (a1) | 54 | 89 | 118 | 196 | 11.6 | 1.02 (0.61–1.70)
Venkat et al.²⁷ 2014 (a1) | 31 | 39 | 112 | 127 | 4.3 | 0.52 (0.20–1.34)
Zhai et al.²³ 2016 (a1) | 14 | 28 | 13 | 32 | 2.4 | 1.46 (0.53–4.07)
Zhou et al.²³ 2010 (a1) | 30 | 69 | 14 | 33 | 4.3 | 1.04 (0.45–2.41)
Subtotal (95% CI) | 543 | 1,337 | 63.4 | 1.11 (0.90–1.38)
Total events | 302 | 740 |
Heterogeneity: χ²=7.45, df=10 (P=0.68); I²=0%
Test for overall effect: Z=0.97 (P=0.33)

Mucositis
Li et al.²³ 2013 (a2) | 25 | 48 | 26 | 66 | 4.2 | 1.67 (0.79–3.54)
Pratesi et al.²⁶ 2011 (a2) | 15 | 22 | 8 | 23 | 1.0 | 4.02 (1.16–13.90)
Venkatesh et al.²⁴ 2014 (a2) | 48 | 54 | 57 | 66 | 2.3 | 1.26 (0.42–3.86)
Zhai et al.²³ 2016 (a2) | 17 | 30 | 10 | 26 | 1.9 | 2.09 (0.72–6.10)
Subtotal (95% CI) | 154 | 181 | 9.4 | 1.91 (1.17–3.11)
Total events | 105 | 101 |
Heterogeneity: χ²=2.07, df=3 (P=0.56); I²=0%
Test for overall effect: Z=2.58 (P=0.01)

Gastrointestinal and genitourinary toxicity
Duldulao et al.²³ 2013 (a3) | 22 | 24 | 70 | 108 | 0.9 | 5.97 (1.33–26.77)
Ishikawa et al.²³ 2011 (a3-2) | 27 | 58 | 67 | 150 | 8.0 | 1.08 (0.59–1.98)
Popand et al.²³ 2009 (a3) | 37 | 54 | 215 | 351 | 7.2 | 1.38 (0.75–2.54)
Sakano et al.²³ 2010 (a3-1) | 4 | 9 | 32 | 86 | 1.4 | 1.35 (0.34–5.40)
Sakano et al.²³ 2010 (a3-2) | 4 | 13 | 32 | 82 | 2.4 | 0.69 (0.20–2.44)
Smith et al.²³ 2017 (a3) | 12 | 14 | 89 | 151 | 0.9 | 4.18 (0.90–19.33)
Subtotal (95% CI) | 172 | 928 | 20.8 | 1.49 (1.04–2.11)
Total events | 106 | 505 |
Heterogeneity: χ²=7.60, df=5 (P=0.16); I²=34%
Test for overall effect: Z=2.20 (P=0.03)

Dysphagia
Pratesi et al.²⁶ 2011 (a4) | 8 | 12 | 50 | 89 | 1.6 | 1.56 (0.44–5.56)
Yoon et al.²³ 2011 (a4) | 7 | 12 | 24 | 48 | 1.6 | 1.40 (0.39–5.03)
Xian et al.²³ 2015 (a4) | 6 | 10 | 31 | 63 | 1.4 | 1.55 (0.40–6.02)
Subtotal (95% CI) | 34 | 200 | 4.8 | 1.50 (0.71–3.18)
Total events | 21 | 105 |
Heterogeneity: χ²=0.02, df=2 (P=0.99); I²=0%
Test for overall effect: Z=1.06 (P=0.29)

Salivary gland
Zhai et al.²³ 2016 (a5) | 20 | 41 | 7 | 19 | 2.0 | 1.63 (0.54–4.98)
Subtotal (95% CI) | 41 | 19 | 2.0 | 1.63 (0.54–4.98)
Total events | 20 | 7 |
Heterogeneity: not applicable
Test for overall effect: Z=0.86 (P=0.39)

Total events | 944 | 2,665 | 100 | 1.29 (1.10–1.52)
Heterogeneity: χ²=21.80, df=24 (P=0.59); I²=0%
Test for overall effect: Z=3.04 (P=0.002)
Test for subgroup differences: χ²=5.19, df=4 (P=0.27); I²=23.0%

Figure 3 Forest plot for the association between rs25487 and radiation-induced acute adverse effects by specific side effect.

Notes: The “case” represents patients with severe radiation-induced side effects and “control” represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; a3-1, gastrointestinal reactions (nausea and vomiting); a3-2, gastrointestinal reactions (diarrhea, rectal pain, obstipiation, bleeding and proctitis); a4, dysphagia; a5, salivary gland.

Abbreviation: M–H, Mantel–Haenszel.

The present meta-analysis was performed to comprehensively evaluate the influence of XRCC1 polymorphisms on the development of radiation-induced normal tissue adverse effects. Four common SNPs of XRCC1 were analyzed in our meta-analysis: XRCC1 rs25487 (Arg399Gln, G>A), XRCC1 rs25489 (Arg280His, G>A), XRCC1 rs1799782 (Arg194Trp, C>T), and XRCC1 rs3213245 (~77 T>C). Among these, rs25487 (Arg399Gln, G>A) was the most...
Figure 4 Forest plot for the association between rs25487 and radiation-induced late adverse effects by specific side effect.

Notes: The “case” represents patients with severe radiation-induced side effects and “control” represents patients without or with light radiation-induced side effects. b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangiectasia and breast appearance); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction; b3, radiation pneumonitis; b4, mucous membrane; b5, salivary gland.

Abbreviation: M–h, Mantel–Haenszel.
Figure 5 Forest plot for the association between rs25487 and radiation-induced adverse effects by irradiation area.

Notes: The “case” represents patients with severe radiation-induced side effects and “control” represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; a3-1, gastrointestinal reactions (nausea and vomiting); a3-2, gastrointestinal reactions (diarrhea, rectal pain, obstruction, bleeding and proctitis); x4, dysphagia; x5, salivary gland; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangiectasia and breast appearance); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction; b3, radiation pneumonitis; b4, mucous membrane; b5, salivary gland.

Abbreviation: M–H, Mantel-Haenszel.
commonly studied polymorphism of XRCC1 in previous researches. Due to different molecular mechanisms of acute and late radiation effects, we analyzed the acute and late side effects separately.

To date, several systematic reviews have been published on genetic variants and normal tissue toxicities induced by radiation, most of which involved XRCC1 polymorphism.\(^{47,59-63}\) However, due to obvious heterogeneity, it is difficult to draw any definite conclusion. So far, four meta-analyses have been published on XRCC1 polymorphism and the risk of normal tissue injury after RT, three of which were performed only in breast cancer and one in prostate cancer patients; besides, only one to three polymorphisms have been analyzed in each paper.\(^{13,46,64,65}\) A positive association between rs25487 Arg399Gln polymorphism and acute side effect in breast cancer patients,\(^ {64,65}\) and a negative association between rs25489 Arg280His variant and late side effect in breast cancer and prostate cancer patients\(^{56,65}\) have been reported in these meta-analyses.

In our meta-analysis, more specific evidences were provided. For rs25487 Arg399Gln polymorphism, significant associations with seriously acute adverse effects were revealed, especially acute mucositis and acute gastrointestinal and genitourinary toxicity. Subgroup analysis according to irradiated area revealed that rs25487 Arg399Gln significantly correlated with an elevated risk of side effects induced by head and neck irradiation. It indicates that patients with rs25487 variant who receive RT are more likely to experience acute adverse effects, especially in head and neck irradiation. No significant correlation with any late side effects,
or with breast, pelvic, or thoracic irradiation, was observed in rs25487 polymorphism. For rs25489 Arg280His variant, inconsistent with previous results reported, no statistically significant associations were identified, but rs25489 seemed to indicate a protective effect against radiotoxicity, especially in acute adverse effects or in breast irradiation. 

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Case GA+AA Total</th>
<th>Control GA+AA Total</th>
<th>Weight (%)</th>
<th>Odds ratio M–H, fixed, 95% CI</th>
<th>Odds ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andreassen et al, 2003 (b1-1)</td>
<td>4 70 3 50</td>
<td>3.4</td>
<td>0.95 (0.20–4.44)</td>
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<td></td>
</tr>
<tr>
<td>Changlaude et al, 2006 (a1)</td>
<td>6 77 44 368</td>
<td>14.3</td>
<td>0.62 (0.26–1.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changlaude et al, 2009 (b1)</td>
<td>9 127 32 276</td>
<td>19.1</td>
<td>0.58 (0.27–1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moullan et al, 2003 (a+b)</td>
<td>10 70 30 184</td>
<td>14.5</td>
<td>0.86 (0.39–1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou et al, 2010 (a1)</td>
<td>14 69 8 33</td>
<td>8.8</td>
<td>0.80 (0.30–2.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>413 911 60</td>
<td></td>
<td>0.71 (0.47–1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td></td>
<td>117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2=0.75$, df=4 (P=0.94); $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=1.67$ (P=0.10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Pelvic           |                  |                     |            |                               |                               |
| Burri et al, 2008 (b2-1) | 0 6 11 129 | 1.1 | 0.79 (0.04–14.99) |                               |                               |
| Burri et al, 2008 (b2-2) | 1 13 10 122 | 1.8 | 0.93 (0.11–7.93) |                               |                               |
| Burri et al, 2008 (b2-3) | 4 17 2 43 | 0.9 | 6.31 (1.03–38.48) |                               |                               |
| Damaraju et al, 2008 (b2) | 3 28 3 55 | 1.8 | 2.08 (0.39–11.05) |                               |                               |
| De Ruyck et al, 2005 (b) | 6 22 4 40 | 2.1 | 3.38 (0.84–13.62) |                               |                               |
| Langsenlehner et al, 2011 (b2) | 3 91 57 487 | 17.7 | 0.26 (0.08–0.84) |                               |                               |
| Popanda et al, 2009 (a3) | 4 54 35 351 | 8.8 | 0.72 (0.25–2.12) |                               |                               |
| Subtotal (95% CI) | 231 1,227 | 34.3 | 0.88 (0.53–1.45) |                               |                               |
| Total events     | 21               |                     | 122        |                               |                               |
| Heterogeneity: $\chi^2=13.45$, df=6 (P=0.04); $I^2=55%$ |
| Test for overall effect: $Z=0.52$ (P=0.60) |

| Head and neck    |                  |                     |            |                               |                               |
| Venkatesh et al, 2014 (a1) | 38 39 127 | 2.3 | 0.10 (0.00–2.52) |                               |                               |
| Subtotal (95% CI) | 39 127 | 2.3 | 0.10 (0.00–2.52) |                               |                               |
| Total events     | 38               |                     | 127        |                               |                               |
| Heterogeneity: not applicable |
| Test for overall effect: $Z=1.40$ (P=0.16) |

| Mixed           |                  |                     |            |                               |                               |
| Azria et al, 2008 (b1-1) | 8 16 7 18 | 3.4 | 1.57 (0.40–6.14) |                               |                               |
| Subtotal (95% CI) | 16 18 | 3.4 | 1.57 (0.40–6.14) |                               |                               |
| Total events     | 8                |                     | 7          |                               |                               |
| Heterogeneity: not applicable |
| Test for overall effect: $Z=0.65$ (P=0.52) |

| Total (95% CI) | 699 2,283 100 | 0.78 (0.58–1.06) | | | |
| Total events     | 110              |                     | 373        |                               |                               |
| Heterogeneity: $\chi^2=17.60$, df=13 (P=0.17); $I^2=26%$ |
| Test for overall effect: $Z=1.59$ (P=0.11) |
| Test for Subgroup differences: $\chi^2=2.98$, df=3 (P=0.39); $I^2=0%$ |

Figure 7 Forest plot for the association between rs25489 and radiation-induced adverse effects by irradiation area. 

Notes: The “case” represents patients with severe radiation-induced side effects and “control” represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a3, gastrointestinal and genitourinary toxicity; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction. 

Abbreviation: M–H, Mantel-Haenszel.

Functions in the efficient repair of DNA SSBs; thus, we speculate that XRCC1 may participate in the DNA damage repair mainly in the period of RT-induced acute reactions. 

No significant associations were detected between rs1799782 or rs3213245 polymorphism and RT-induced toxicity in the overall or the subgroup analyses. However, Moullan et al and Mangoni et al indicated that the rs1799782 Trpvariant was associated with an increased risk of RT-induced adverse response when analyzed in combination with the rs25487 Gln variant in breast cancer patients. No definite conclusion can be made for rs25489, rs1799782, or rs3213245 polymorphisms, may be due to the relatively small number of identified studies.
Although a series of studies have been made to evaluate the association between SNPs and RT-induced adverse effects, no SNPs have been thoroughly identified to have the predictive power in clinical practice. Moreover, most studies assessed the individual effect of selected SNPs, and the original researches available on combined effect of multiple SNPs are less and not enough to make a meta-analysis. Further studies are needed to elucidate the selection criteria and predictive effect for SNP combinations. In addition, genome-wide association study (GWAS) is more credible due to the comprehensive genetic coverage. Barnett et al presented the largest GWAS in which 1217 breast cancer patients received adjuvant RT and 633 prostate cancer patients received radical RT. Quantile–quantile plot results provided evidence for the true association between common genetic variants and late toxicity, and associations with late toxicity appeared to be tumor site-specific.

The main source of heterogeneity in such meta-analysis is the overall assessment of all kinds of side effects in various cancer types. However, there are two types of RT-induced adverse effects; acute side effects can be observed during RT and within several weeks after RT, while late side effects can be seen in the same irradiation and the original researches available on combined effect of multiple SNPs are less and not enough to make a meta-analysis. Further studies are needed to elucidate the selection criteria and predictive effect for SNP combinations. In addition, genome-wide association study (GWAS) is more credible due to the comprehensive genetic coverage. Barnett et al presented the largest GWAS in which 1217 breast cancer patients received adjuvant RT and 633 prostate cancer patients received radical RT. Quantile–quantile plot results provided evidence for the true association between common genetic variants and late toxicity, and associations with late toxicity appeared to be tumor site-specific.

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area, while the same type of side effect can occur in different irradiation areas with the same histological structure. Hence, it is rational to make subgroup analysis in acute or late side effects, the special type of side effects, and irradiation areas.

The subgroup analyses evaluating the effect of rs25487 on radiation pneumonitis or on thoracic irradiation yielded significant heterogeneity, because the only two identified studies on NSCLC reached contrary conclusions. The evaluations of rs25489 on late side effects and pelvic irradiation as well as rs3213245 on acute side effects also yielded significant heterogeneity. The presence of heterogeneity may be caused by the differences in study characteristics such as treatment regimen, evaluation endpoint, and genotyping method. The results are reliable because the pooled results calculated by random-effects model are stable in the sensitivity analysis.

Limitations

Several limitations of the present meta-analysis should be considered. First, many included studies assessed multiple different endpoints, resulting in the same study being evaluated more than one time in one analysis. The “multiple testing problem” reduced the statistical power. Second, the number of trails in some of the subgroups and the sample sizes of some of the studies were relatively small, which also restricted the statistical power. Third, eight studies without sufficient data could not be evaluated by weight in the pooled result, which may cause some potential bias. Furthermore,
data analyses were not stratified by other confounding factors such as ethnicity, genotyping method, radiation dose, or chemotherapy status because of insufficient information from the primary publications.

Conclusion
The present study, to our knowledge, is the first comprehensive meta-analysis of genetics studies on the association between XRCC1 polymorphisms and radiation-related adverse effects. In conclusion, the meta-analysis suggests that rs25487 Arg399Gln polymorphism is significantly associated with the risk of acute RT-induced adverse effects such as acute mucositis and acute gastrointestinal and genitourinary toxicity. Patients who received head and neck irradiation with rs25487 Arg399Gln polymorphism were more likely to experience RT-induced side effects. The present study also indicates a radioprotective effect for rs25489 polymorphism, especially in acute side effects or in breast irradiation, but without statistical significance. Well-designed studies with large sample size are needed to be performed to assess the value of XRCC1 polymorphisms on radiation-induced adverse effects, which can be used clinically to identify radiosensitive patients and predict radiotoxicity.

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Disclosure
The authors report no conflicts of interest in this work.

References


