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

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, 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. 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 $I^2$-based Q-test and P 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.17,18 If publication bias existed, the “trim and fill” method19 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.15,20–23 The cancer categories included head and neck cancer (8 studies),20,21,23–27 breast cancer (18 studies),15,28–44 prostate cancer (5 studies),14,45–48 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.
| Author, year | Country | Ethnicity | Disease | SNP | Sample size (N) | Adverse effect | Assessment criteria | RT dose | CT involved | Study design | Genotyping method |
|-------------|---------|-----------|---------|-----|----------------|---------------|-------------------|---------|-------------|--------------|------------------|
| Alsheih et al. 2010 | Saudi Arabia | Caucasian | NPC | rs25487 | 60 | Late: fibrosis | RTOG/EORTC ≥ G2 | 66–70 Gy | Yes | Case–control | PCR |
| Andreassen et al. 2003 | Denmark | Caucasian | Breast | rs25487 | 41 | Late: fibrosis | LENT-SOMA ≥ G3 | 36.6–51.4 Gy | No | Cohort | PCR |
| Andreassen et al. 2005 | Denmark | Caucasian | Breast | rs25487 | 52 | Late: breast appearance | Photograph ≥ G2 | 50 Gy/25f, 42.9 Gy/13f, 39 Gy/13f | NA | Case–control | PCR |
| Andreassen et al. 2006 | Denmark | Caucasian | Breast | rs25487, rs25489, rs1799782 | 120 | Late: fibrosis | LENT-SOMA ≥ G3 | 41 Gy | Yes | Cohort | PCR |
| Azria et al. 2008 | France | Caucasian | Breast, HNC | rs25489 | 34 | Late: fibrosis | RTOG/EORTC ≥ G2 | NA | Yes | Case–control | PCR |
| Brem et al. 2006 | France | Caucasian | Breast | rs3213245 | 247 | Acute and Late | CTC v3.0 ≥ G3 | EORTC | 50 Gy, tumor bed boost 10 Gy | NA | Case–control | PCR-RFLP |
| Burri et al. 2008 | America | Mixed | Prostate | rs25487, rs25489, rs1799782 | 135 | Late: rectal bleeding, urinary morbidity, erectile dysfunction | RTOG/EORTC ≥ G2 | 125i: 160 Gy | 103 Pd: 124 Gy | 103 Pd: 100 Gy | NA | Cohort | PCR |
| Changclaude et al. 2005 | Germany | Caucasian | Breast | rs25487, rs25489, rs1799782 | 446 | Acute: skin reaction | CTCAE v2.0 ≥ G2c | Mean 54.0±4.8 Gy (35.5–64.5 Gy) | No | Cohort | PCR-RFLP |
| Changclaude et al. 2009 | Germany | Caucasian | Breast | rs25487, rs25489, rs1799782, rs3213245 | 409 | Late: telangiectasia | RTOG/EORTC ≥ G2 | Mean 61.8±4.10 Gy (51–71 Gy) | No | Cohort | PCR-RFLP |
| Cheuk et al. 2014 | Hong Kong | Asian | NPC | rs25487, rs1799782 | 120 | Late: fibrosis | RTOG ≥ G1 | 66–76 Gy | Yes | Cohort | PCR-RFLP |
| Damaraju et al. 2006 | Canada | Mixed | Prostate | rs25489, rs1799782 | 83 | Late: bladder or rectal toxicity | RTOG ≥ G2 | Mean 77.1 Gy (68.3–82.1 Gy) | No | Cohort | PCR |
| De Ruyck et al. 2005 | Belgium | Caucasian | Cervical, endometria | rs25487, rs25489, rs1799782 | 62 | Late | CTCAE v3.0 ≥ G2 | EBRT: 45–66 Gy | 192i: 15–35 Gy | Yes | Cohort | PCR-RFLP |
| De Ruyck et al. 2013 | Belgium | Caucasian | HNC | rs3213245 | 189 | Acute: dysphagia | CTCAE v3.0 ≥ G3 | 66–70 Gy | Yes | Cohort | PCR-RFLP |
| Duldualo et al. 2013 | USA | Caucasian | Rectal | rs25487 | 132 | Acute: gastrointestinal toxicity | CTCAE v3.0 ≥ G3 | NA | Yes | Cohort | PCR, direct sanger sequencing |
| Falvo et al. 2011 | Italy | Caucasian | Breast | rs1799782 | 57 | Acute: erythema | CTCAE v3.0 ≥ G1 | 21 Gylf | Yes | Cohort | PCR |
| Falvo et al. 2012 | Italy | Caucasian | Breast | rs25487 | 57 | Late: fibrosis, fat necrosis | CTCAE v3.0 ≥ G2 | 21 Gylf | Yes | Cohort | PCR |
| Study          | Location | Ethnicity   | Tumor Type | SNP | Cohort | Tumor BED | Boost BED | Toxicity Description | Toxicity Measure | Dosage | Coefficient | Cohort | Methodology       |
|---------------|----------|-------------|------------|-----|--------|-----------|-----------|----------------------|------------------|--------|-------------|--------|-----------------|
| Giotopoulos et al. (2007) | UK       | Mixed       | Breast     | rs25487 | Cohort | 167       | Yes       | Late: telangiectasia  | RTOG LENT-SOMA ≥G2 | 40–50 Gy, tumor bed boost of 15 Gy/5f | Yes   | Cohort | PCR-RFLP |
| Ishikawa et al. (2011) | Japan | Asian       | Cervical   | rs25487 | Cohort | 208       | Yes       | Acute: diarrhea               | CTCAE v2.0 ≥G2 | EBRT 50.6 Gy | Yes   | Cohort | PCR   |
| Langenlehner et al. (2011) | Austria | Caucasian | Prostate   | rs25487, rs25489, rs1799782 | Cohort | 579       | Yes       | Late: bladder or rectal toxicity | RTOG/EORTC ≥G2 | Brachytherapy 24.0 Gy | 66–70.4 Gy | No    | Cohort | PCR   |
| Li et al. (2013) | China    | Asian       | NPC        | rs25487, rs1799782 | Cohort | 114       | Yes       | Acute: mucositis, dermatitis | CTCAE v3.0 ≥G3 | 50–70 Gy | Yes   | Cohort | PCR-RFLP |
| Mangoni et al. (2011) | Italy | Caucasian   | Breast     | rs25487, rs1799782 | Cohort | 87        | Yes       | Acute: skin reaction         | CTCAE v2.0 ≥G2c | 50 Gy/25f, 44 Gy/16f | Yes   | Cohort | PCR   |
| Moullian et al. (2003) | France  | Caucasian   | Breast     | rs25487, rs25489, rs1799782 | Cohort | 254       | Yes       | Acute and Late              | EORTC | 50 Gy, tumor bed boost 10 Gy | NA    | Cohort | PCR   |
| Mumbrekar et al. (2017) | India   | Asian       | Breast     | rs25487 | Cohort | 126       | Yes       | Acute: skin reaction         | RTOG ≥G2 | 50 Gy, tumor bed boost 10 Gy for 26 patients | Yes   | Cohort | PCR   |
| Popanda et al. (2009) | Germany | Caucasian | Prostate   | rs25487, rs25489, rs1799782 | Cohort | 405       | No        | Acute: proctitis cystitis    | CTCAE v2.0 ≥G3 | 61–72 Gy | No    | Cohort | Sequence-specific hybridization probes PCR-RFLP |
| Pratesi et al. (2011) | Italy   | Caucasian   | HNC        | rs25487 | Cohort | 101       | Yes       | Acute: mucositis, skin erythema | CTCAE v3.0 ≥G2 | Mean 62 Gy (54–70 Gy) | Yes   | Case–control | PCR-RFLP |
| Raabe et al. (2012) | Germany | Caucasian   | Breast     | rs25487 | Cohort | 83        | NA        | Acute: erythema              | RTOG ≥G2 | 50–50.4 Gy | NA    | Cohort | PCR-RFLP, MALDI-TOF |
| Såkano et al. (2010) | Japan   | Asian       | Bladder    | rs25487 | Cohort | 95        | Yes       | Acute: gastrointestinal toxicity | CTCAE v3.0 ≥G2 | Median 48.6 Gy (30.0–60.4 Gy) | Yes   | Cohort | PCR-RFLP |
| Smith et al. (2017) | America | Mixed       | Rectal     | rs25487 | Cohort | 165       | Yes       | Acute: gastrointestinal and genitourinary toxicity (diarrhea, proctitis, cystitis) | CTCAE v3.0 ≥G3 | Median 50.4 Gy | Yes   | Cohort | PCR, MALDI-TOF |
| Suga et al. (2007) | Japan   | Asian       | Breast     | rs25487 | Cohort | 399       | Yes       | Acute: skin reaction         | CTCAE v2.0 ≥G2 | 46–60 Gy | Yes   | Cohort | PCR   |
| Terrazzino et al. (2012) | Italy   | Caucasian   | Breast     | rs25487, rs1799782, rs3213245 | Cohort | 286       | Yes       | Acute: skin reaction         | RTOG ≥G2 | 50–50.4 Gy, tumor bed boost 9–16 Gy | Yes   | Cohort | PCR-RFLP |
| Terrazzino et al. (2012) | Italy   | Caucasian   | Breast     | rs25487, rs1799782 | Cohort | 237       | Yes       | Late: fibrosis               | LENT-SOMA ≥G2 | 50–50.4 Gy, tumor bed boost 9–16 Gy | Yes   | Cohort | PCR-RFLP |
| Tucker et al. (2013) | USA     | Caucasian   | NSCLC      | rs25487 | Cohort | 141       | Yes       | Late: radiation pneumonitis | CTCAE v3.0 ≥G3 | Median 63 Gy (50.4–72 Gy) | Yes   | Cohort | PCR-RFLP |
| Usmani et al. (2014) | Canada  | Caucasian   | Prostate   | rs25487 | Cohort | 217       | No        | Late: urinary toxicity        | RTOG ≥G2 | 125±145 Gy | No    | Cohort | PCR   |

(Continued)
| Author, year | Country | Ethnicity | Disease | SNP                      | Sample size (N) | Adverse effect                              | Assessment criteria | RT dose | CT involved | Study design | Genotyping method |
|----------------|----------------|-----------|---------|--------------------------|-----------------|---------------------------------------------|---------------------|---------|-------------|--------------|------------------|
| Venkatesh et al. 2014 | India | Caucasian | HNC | rs25487, rs25489, rs1799782, rs3213245 | 183            | Acute: mucositis, skin reaction              | RTOG ≥ G3           | 60–70 Gy | Yes         | Cohort       | PCR-RFLP        |
| Yin et al. 2011 | USA | Mixed | NSCLC | rs25487 | 165            | Late: radiation pneumonitis                   | CTCAE v3.0 ≥ G2     | Median 63 Gy (50.4–84.0 Gy) | Yes         | Cohort       | PCR-RFLP        |
| Yoon et al. 2011 | USA | Mixed | Esophageal adenocarcinoma | rs25487 | 60            | Acute: dysphagia                             | CTCAE v2.0 ≥ G3     | 45 Gy    | Yes         | Cohort       | PCR, MALDI-TOF  |
| Xian et al. 2015 | China | Asian | Esophageal squamous cell carcinoma | rs25487 | 118           | Acute: esophagitis                           | CTCAE ≥ G3          | Median 60 Gy (45–66 Gy) | Yes         | Cohort       | PCR             |
| Zhai et al. 2016 | China | Asian | NPC | rs25487 | 60            | Acute and Late: skin, mucosa, salivary gland | RTOG ≥ G2           | 66–76 Gy | Yes         | Cohort       | PCR-LDR         |
| Zhou et al. 2010 | China | Asian | Breast | rs25487, rs25489, rs1799782, rs3213245 | 119           | Acute: skin reaction                         | CTCAE v3.0 ≥ G2     | 46–54 Gy | No          | Cohort       | PCR-RFLP        |
| Zschenker et al. 2010 | Germany | Caucasian | Breast | rs25487 | 69            | Late: fibrosis                              | LENT-SOMA ≥ G2      | 54–55 Gy | Yes         | Cohort       | PCR-RFLP, MALDI-TOF |

**Abbreviations:** CTC, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, external beam radiotherapy; 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),49,50 bladder cancer (1 study),51 rectal cancer (2 studies),52-53 non-small-cell lung cancer (NSCLC; 2 studies),54,55 esophageal cancer (2 studies),22,56 and one mixed cancers (mainly breast cancer and head and neck cancer).57 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, \( \text{OR} = 1.29, 95\% \text{ CI: } 1.10–1.52, P = 0.002 \); 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 (\( \text{OR} = 1.91, 95\% \text{ CI: } 1.17–3.11, P = 0.01 \)) and acute gastrointestinal and genitourinary toxicity (\( \text{OR} = 1.49, 95\% \text{ CI: } 1.04–2.11, P = 0.03 \); 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 (\( \text{OR} = 1.46, 95\% \text{ CI: } 1.12–1.90, P = 0.005 \)), whereas the correlation was not significant for breast or pelvic irradiation (breast, \( \text{OR} = 1.13, 95\% \text{ CI: } 0.95–1.33, P = 0.18 \); pelvic, \( \text{OR} = 1.20, 95\% \text{ CI: } 0.94–1.54, P = 0.14, \text{ respectively} \); 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 (\( \text{OR} = 0.78, 95\% \text{ CI: } 0.58–1.06, P = 0.11 \)), especially in acute adverse effects (\( \text{OR} = 0.66, 95\% \text{ CI: } 0.38–1.14, P = 0.14 \); Figure 6) or in breast irradiation area (\( \text{OR} = 0.71, 95\% \text{ CI: } 0.47–1.06, P = 0.10 \); 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 (\( \chi^2 = 79\%, P = 0.14 \)), late side effect (\( \chi^2 = 55\%, P = 0.05 \)), and pelvic irradiation (\( \chi^2 = 48\%, P = 0.03 \)) 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.58 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.
| 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 |
|------------------|------------|-------|---------------|-------|------------|-----------------------------|-----------------------------|
| **Acute adverse effects** |
| Changalwala et al.2005 (a1) |
| Duldulao et al.2013 (a3) |
| Ishikawa et al.2014 (a3-2) |
| Li et al.2013 (a1) |
| Li et al.2013 (a2) |
| Mangoni et al.2011 (a1) |
| Mumbrekar et al.2017 (a1) |
| Popandopoulou et al.2004 (a3) |
| Pratesi et al.2011 (a1) |
| Pratesi et al.2011 (a2) |
| Pratesi et al.2011 (a4) |
| Raabe et al.2012 (a1) |
| Sakamoto et al.2010 (a3-1) |
| Sakano et al.2010 (a3-2) |
| Smith et al.2017 (a3) |
| Suga et al.2007 (a1) |
| Terrazano et al.2012 (a1) |
| Venkatesh et al.2014 (a1) |
| Venkatesh et al.2014 (a2) |
| Yoon et al.2011 (a4) |
| Xian et al.2015 (a4) |
| Zhao et al.2015 (a1) |
| Zhao et al.2016 (a1) |
| Zhao et al.2016 (a2) |
| Zhao et al.2016 (a5) |
| Zhou et al.2010 (a1) |
| **Subtotal (95% CI)** |
| 944 | 2,665 | 50.4 | 1.29 (1.10–1.55) |

| **Heterogeneity:** $\chi^2=21.80$, df=24 (P=0.59); I²=0%
| **Test for overall effect:** Z=3.04 (P=0.002) |

| **Late adverse effects** |
| Alsaheb et al.2010 (b1-1) |
| Andreassen et al.2003 (b1-1) |
| Andreassen et al.2006 (b1-16) |
| Andreassen et al.2006 (b1-1) |
| Burri et al.2008 (b2-1) |
| Burri et al.2008 (b2-2) |
| Burri et al.2008 (b3) |
| Changalwala et al.2009 (b1) |
| Cheuk et al.2014 (b1-1) |
| De Roy et al.2005 (b) |
| Falvo et al.2012 (b1-1) |
| Girotopoulo et al.2007 (b1) |
| Langsenlehner et al.2011 (b2) |
| Terrazano et al.2012 (b1-1) |
| Tucker et al.2013 (b3) |
| Uomana et al.2014 (b2-2) |
| Yin et al.2011 (b3) |
| Zhao et al.2016 (b1) |
| Zhao et al.2016 (b1-1) |
| Zhao et al.2016 (b4) |
| Zhao et al.2016 (b5) |
| Zschonker et al.2010 (b1-1) |
| **Subtotal (95% CI)** |
| 762 | 2,209 | 45.8 | 1.05 (0.87–1.26) |

| **Total events:** 449 | 1,311 |
| **Heterogeneity:** $\chi^2=23.01$, df=21 (P=0.34); I²=9%
| **Test for overall effect:** Z=0.50 (P=0.62) |

| **Acute and late mixed** |
| Moullan et al.2003 (a+b) |
| **Subtotal (95% CI)** |
| **Total events** |
| **Heterogeneity:** not applicable
| **Test for overall effect:** Z=1.71 (P=0.09) |

| **Total (95% CI)** |
| 1,776 | 5,058 | 100 | 1.19 (1.06–1.35) |
| **Total events** |
| 1,049 | 2,868 |
| **Heterogeneity:** $\chi^2=43.90$, df=47 (P=0.40); I²=4%
| **Test for overall effect:** Z=2.90 (P=0.004) |

**Test for subgroup differences:** $\chi^2=4.05$, df=2 (P=0.13); I²=50.7%

**Figure 2** Forest plot for the association between rs25487 and radiation-induced adverse effects.

**Notes:** A fixed-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 "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, obstipation, bleeding and proctitis); a4, dysphagia; a5, 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.

**Abbreviations:** M–H, Mantel–Haenszel; OR, odds ratio.
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, obstipation, bleeding and prolactis); a4, dysphagia; a5, salivary gland; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangietasia 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. 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. A positive association between rs25487 Arg399Gln polymorphism and acute side effect in breast cancer patients, and a negative association between rs25489 Arg280His variant and late side effect in breast cancer and prostate cancer patients have been reported in these meta-analyses.

In our meta-analysis, more specific evidences were provided. For rs25487 Arg399Gln polymorphism, significant associations with serious 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. XRCC1 SNPs appear to be more likely to correlate with acute RT-induced side effects, but the reason is unclear. Radiation causes DNA strand breaks in normal cells, most of the cells die and cannot renew in time leading to acute side effects, accompanied by responses of DNA damage repair. Late side effects refer to the cells unable to regenerate after exhausted by radiation and eventually lead to fibrosis instead. The XRCC1 protein 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 al16 and Mangoni et al43 indicated that the rs1799782194Trp variant was associated with an increased risk of RT-induced adverse response when analyzed in combination with the rs25487 399Gln 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.

### Table: Predictive value of SNPs in XRCC1

| Study or subgroup | Case GA+AA | Control GA+AA | Total Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI |
|------------------|------------|---------------|------------------|-----------------------------|-----------------------------|
| **Breast**       |            |               |                  |                             |                             |
| Andreassen et al.20 2003 (b1-1) | 4 | 70 | 3 | 50 | 3.4 | 0.95 (0.20–4.44) |
| Changlaude et al.25 2006 (a1) | 6 | 74 | 44 | 368 | 14.3 | 0.62 (0.26–1.52) |
| Changlaude et al.25 2009 (b1) | 9 | 127 | 32 | 276 | 19.1 | 0.58 (0.27–1.26) |
| Moullan et al.26 2003 (a+b) | 10 | 70 | 30 | 184 | 14.5 | 0.86 (0.39–1.86) |
| Zhou et al.10 2010 (a1) | 14 | 69 | 8 | 33 | 8.8 | 0.80 (0.30–2.14) |
| **Subtotal (95% CI)** | 413 | 911 | 60 | 0.71 (0.47–1.06) |
| **Total events** | 43 | 117 |  |  |  |
| **Pelvic**       |            |               |                  |                             |                             |
| Burri et al.44 2008 (b2-1) | 0 | 6 | 11 | 129 | 1.1 | 0.79 (0.04–14.99) |
| Burri et al.44 2008 (b2-2) | 1 | 13 | 10 | 122 | 1.8 | 0.93 (0.11–7.93) |
| Burri et al.44 2008 (b2-3) | 4 | 17 | 2 | 43 | 0.9 | 6.31 (1.03–38.48) |
| Damaraju et al.46 2006 (b2) | 3 | 28 | 3 | 55 | 1.8 | 2.08 (0.39–11.05) |
| De Ruyck et al.47 2005 (b) | 6 | 22 | 4 | 40 | 2.1 | 3.38 (0.84–13.62) |
| Langsenlehner et al.48 2011 (b2) | 3 | 91 | 57 | 487 | 17.7 | 0.26 (0.08–0.84) |
| Popanda et al.49 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 |  |  |  |
| **Head and neck** |            |               |                  |                             |                             |
| Venkatesh et al.50 2014 (a1) | 38 | 39 | 127 | 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 |  |  |  |
| **Mixed**       |            |               |                  |                             |                             |
| Azria et al.51 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 |  |  |  |
| **Total (95% CI)** | 699 | 2,283 | 100 | 0.78 (0.58–1.06) |

**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.
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 occur months to years later. Furthermore, different RT-induced side effects may occur in the same irradiation field distension or prostatectomy, which may cause different toxic effects on the surrounding tissue. In addition, differences in the types of RT may contribute to the heterogeneity. Consequently, the risk of late toxicity should be considered when selecting the treatment strategy for patients with different cancer types.
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**

1. Chen Y, Trotti A, Coleman CN, et al. Adverse event reporting and developments in radiation biology after normal tissue injury: International Atomic Energy Agency consultation. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1442–1451.

2. Pignon JP, le Maitre A, Maillard E, Bourhis J; Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92(1):4–14.

3. Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. *Oncologist*. 2010;15(4):360–371.

4. Bentzen SM, Saunders MI, Dische S, Bond SJ. Radiotherapy-related early morbidity in head and neck cancer: quantitative clinical radiobiology as deduced from the CHART trial. *Radiother Oncol*. 2001;60(2):123–135.

5. Gruber S, Dorr W. Tissue reactions to ionizing radiation-Oral mucosa. *Mutat Res*. 2016;770(Pr B):292–298.

6. Andratschke N, Maurer J, Molls M, Trott KR. Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention. *Radiother Oncol*. 2011;100(2):160–166.

7. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol*. 2003;4(9):529–536.

8. Andreassen CN. Searching for genetic determinants of normal tissue radiosensitivity—are we on the right track? *Radiother Oncol*. 2010;97(1):1–8.

9. Andreassen CN, Dikomey E, Parliament M, West CM. Will SNPs be useful predictors of normal tissue radiosensitivity in the future? *Radiother Oncol*. 2012;105(3):283–288.

10. Barnett GC, Coles CE, Elliott RM, et al. Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study. *Lancet Oncol*. 2012;13(1):65–77.

11. Nakano T, Xu X, Salem AMH, Shoulkamy MI, Ide H. Radiation-induced DNA-protein cross-links: mechanisms and biological significance. *Free Radic Biol Med*. 2017;107:136–145.

12. Tomkinson AE, Sallmyr A. Structure and function of the DNA ligases encoded by the mammalian LIG3 gene. *Gene*. 2013;531(2):150–157.

13. Seibold P, Behrens S, Schmeper P, et al. XRCC1 polymorphism associated with late toxicity after radiotherapy in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2015;92(5):1084–1092.

14. Curioni C, Stock RG, Cesaretti JA, et al. Association of single nucleotide polymorphisms in SOD2, XRCC1 and XRCC3 with susceptibility for the development of adverse effects resulting from radiotherapy for prostate cancer. *Radiat Res*. 2008;170(1):49–59.

15. Zhou L, Xia J, Li H, Dai J, Hu Y. Association of XRCC1 variants with acute skin reaction after radiotherapy in breast cancer patients. *Cancer Biother Radiopharm*. 2010;25(6):681.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.

17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101.

18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.

19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463.

20. Cheuk IW, Yip SP, Kwong DL, Wu VW. Association of XRCC1 and XRCC3 gene haplotypes with the development of radiation-induced fibrosis in patients with nasopharyngeal carcinoma. *Mol Clin Oncol*. 2014;2(4):553.

21. Li H, You Y, Lin C, et al. XRCC1 codon 399 Gln polymorphism is associated with radiotherapy-induced acute dermatitis and mucositis in nasopharyngeal carcinoma patients. *Radiother Oncol*. 2013;8(1):31.

22. Xian Y, He X, Baojian Z, Xu Z, Ge W. DNA repair gene ERCC1 C118T polymorphism predicts sensitivity of recurrent esophageal cancer to radiochemotherapy in a Chinese population. *Thorac Cancer*. 2015;6(6):741–748.

23. Zhai XM, Hu QC, Gu K, Wang JP, Zhang JN, Wu YW. Significance of XRCC1 Codon399 polymorphisms in Chinese patients with locally advanced nasopharyngeal carcinoma treated with radiation therapy. *Asia Pac J Clin Oncol*. 2016;12(1):e125–e132.

24. Alsbeih G, Al-Harbi N, Al-Hadyan K, El-Sebaie M, Al-Rajhi N. Association between normal tissue complications after radiotherapy and polymorphic variations in TGFBI and XRCC1 genes. *Radiat Res*. 2010;173(4):505–511.

25. De Ruyck K, Duprez F, Werbrouck J, et al. A predictive model for dysphagia following IMRT for head and neck cancer: introduction of the EMLasso technique. *Radiother Oncol*. 2013;107(3):295–299.

26. Pratesi N, Mangoni M, Mancini I, et al. Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer. *Radiother Oncol*. 2011;99(3):356–361.

27. Venkatesh GH, Manjunath VB, Mumbrekar KD, et al. Polymorphisms in radio-responsive genes and its association with acute toxicity among head and neck cancer patients. *PLoS One*. 2014;9(3):e89079.
28. Andreassen CN, Alsner J, Overgaard J, et al. TGFβ1 polymorphisms are associated with risk of late normal tissue complications in the breast after radiotherapy for early breast cancer. *Radiother Oncol*. 2005;75(1):18–21.

29. Andreassen CN, Alsner J, Overgaard M, Overgaard J. Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes. *Radiother Oncol*. 2003;69(2):127–135.

30. Andreassen CN, Alsner J, Overgaard M, Sorensen FB, Overgaard J. Risk of radiation-induced subcutaneous fibrosis in relation to single nucleotide polymorphisms in TGFβ1, SOD2, XRCC1, XRCC3, APEX and ATM—a study based on DNA from formalin fixed paraffin embedded tissue samples. *Int J Radiat Biol*. 2006;82(8):577–586.

31. Brem R, Cox DG, Chapot B, et al. The XRCC1 -77T→C variant: haplotypes, breast cancer risk, response to radiotherapy and the cellular response to DNA damage. *Carcinogenesis*. 2006;27(12):2469–2474.

32. Changclaude J, Ambrosone CB, Lilia C, et al. Genetic polymorphisms in DNA repair and damage response genes and late normal tissue complications of radiotherapy for breast cancer. *Br J Cancer*. 2009;100(10):1680.

33. Changclaude J, Popanda O, Kropp S, et al. Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and acute side effects of radiotherapy in breast cancer patients. *Clin Cancer Res*. 2005;11(13):4802–4809.

34. Falvo E, Strigari L, Citro G, et al. SNPs in DNA repair or oxidative stress genes and late subcutaneous fibrosis in patients following single shot partial breast irradiation. *J Exp Clin Oncol*. 2012;31(1):7.

35. Giotopoulos G, Symonds RP, Fowleraker K, et al. The late radiotherapy normal tissue injury phenotypes of telangectasia, fibrosis and atrophy in breast cancer patients have distinct genotype-dependent causes. *Br J Cancer*. 2007;96(6):1001–1007.

36. Moullan N, Cox DG, Angéle S, Romestaing P, Gerard JP, Hall J. Polymorphisms in the DNA repair gene XRCC1, breast cancer risk, and response to radiotherapy. *Cancer Epidemiol Biomarkers Prev*. 2003;12(11 Pt 1):1168–1174.

37. Mumbrekar KD, Bola Sadashiva SR, Kabekkodu SP, et al. Genetic variants in CD44 and MAT1A confer susceptibility to acute skin reaction in breast cancer patients undergoing radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;97(1):118.

38. Sugà T, Ishikawa A, Koho M, et al. Haplotype-based analysis of genes associated with risk of adverse skin reactions after radiation therapy in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2007;69(3):685–693.

39. Terrazino S, La MP, Gambaro G, et al. Common variants of GSTP1, GSTA1, and TGFβ1 are associated with the risk of radiation-induced fibrosis in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2012;83(2):504–511.

40. Terrazino S, Mattina PL, Masini L, et al. Common variants of eNOS and XRCC1 genes may predict acute skin toxicity in breast cancer patients receiving radiotherapy after breast conserving surgery. *Radiother Oncol*. 2012;103(2):199–205.

41. Zschenderle R, Raabe A, Boecckelmann IK, et al. Association of single nucleotide polymorphisms in ATM, GSTP1, SOD2, TGFβ1, XPD and XRCC1 with clinical and cellular radiosensitivity. *Radiother Oncol*. 2010;97(1):26–32.

42. Falvo E, Strigari L, Citro G, et al. Dose and polymorphic genes xrc1, xrc3, gst play a role in the risk of article developing erythema in breast cancer patients following single shot partial breast irradiation after conservative surgery. *BMC Cancer*. 2011;11:291.

43. Mangoni M, Bisani S, Carozzi F, et al. Association between genetic polymorphisms in the XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, and MGMT genes and radiosensitivity in breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2011;81(1):52–58.

44. Raabe A, Derda K, Reuther S, et al. Association of single nucleotide polymorphisms in the genes ATM, GSTP1, SOD2, TGFβ1, XPD and XRCC1 with risk of severe erythema after breast conserving radiotherapy. *Radiother Oncol*. 2012;7:65.

45. Damaraju S, Murray D, Dufour J, et al. Association of DNA repair and steroid metabolism gene polymorphisms with clinical late toxicity in patients treated with conformal radiotherapy for prostate cancer. *Clin Cancer Res*. 2006;12(8):2545–2554.

46. Langsenlehner T, Renner W, Gerger A, et al. Association between single nucleotide polymorphisms in the gene for XRCC1 and radiation-induced late toxicity in prostate cancer patients. *Radiother Oncol*. 2011;98(3):387–393.

47. Popanda O, Marquardt JU, Chang-Claude J, Schmeizer P. Genetic variation in normal tissue toxicity induced by ionizing radiation. *Mutat Res*. 2009;667(1–2):58–69.

48. Usmani N, Leong N, Martell K, et al. Single-nucleotide polymorphisms studied for associations with urinary toxicity from (125)I prostate brachytherapy implants. *Brachytherapy*. 2014;13(3):285–291.

49. De Ruyck K, Van EM, Claes K, et al. Radiation-induced damage to normal tissues after radiotherapy in patients treated for gynecologic tumors: association with single nucleotide polymorphisms in XRCC1, XRCC3, and OGG1 genes and in vitro chromosomal radiosensitivity in lymphocytes. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1140.

50. Ishikawa A, Suga T, Sjöhi Y, et al. Genetic variants of NPAT-ATM and AURKA are associated with an early adverse reaction in the gastrointestinal tract of patients with cervical cancer treated with pelvic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;81(4):1144–1152.

51. Sakano S, Hinoda Y, Sasaki M, et al. Nucleotide excision repair gene polymorphisms may predict acute toxicity in patients treated with chemoradiotherapy for bladder cancer. *Pharmacogenomics*. 2010;11(10):1377–1387.

52. Dudluao MP, Lee W, Nelson RA, et al. Gene polymorphisms predict toxicity to neoadjuvant therapy in patients with rectal cancer. *Cancer*. 2013;119(5):1106–1112.

53. Smith JJ, Wasserman I, Milgrom SA, et al. Single nucleotide polymorphism TGFβ1 R25P correlates with acute toxicity during neoadjuvant chemoradiotherapy in rectal cancer patients. *Int J Radiat Oncol Biol Phys*. 2017;97(5):924.

54. Tucker SL, Li M, Xu T, et al. Incorporating single-nucleotide polymorphisms into the Lyman model to improve prediction of radiation pneumonitis. *Int J Radiat Oncol Biol Phys*. 2013;85(1):251–257.

55. Ying M, Liao Z, Liu Z, et al. Functional polymorphisms of base excision repair genes XRCC1 and APEX1 predict risk of radiation pneumonitis in patients with non-small cell lung cancer treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;81(3):e67–e73.

56. Yoon HH, Catalano P, Gibson MK, et al. Genetic variation in radiation and platinum pathways predicts severe acute radiation toxicity in patients with esophageal adenocarcinoma treated with cisplatin-based preoperative radiochemistry: results from the Eastern Cooperative Oncology Group. *Cancer Chemother Pharmacol*. 2011;68(4):863–870.

57. Azria D, Ozsahin M, Kramar A, et al. Single nucleotide polymorphisms, apoptosis, and the development of severe late adverse effects after radiotherapy. *Clin Cancer Res*. 2008;14(16):6284–6288.

58. Horton JK, Watson M, Stefanick DF, Shaughnessy DT, Taylor JA, Wilson SH. XRCC1 and DNA polymerase beta in cellular protection against cytotoxic DNA single-strand breaks. *Cell Res*. 2008;18(1):48–63.

59. Andreassen CN, Alsner J. Genetic variants and normal tissue toxicity after radiotherapy: a systematic review. *Radiother Oncol*. 2009;92(3):299–309.

60. Rattay T, Talbott CJ. Finding the genetic determinants of adverse reactions to radiotherapy. *Clin Oncol (R Coll Radiol)*. 2014;26(5):301–308.

61. West CM, Barnett GC. Genetics and genomics of radiotherapy toxicity: towards prediction. *Genome Med*. 2011;3(8):52.

62. Ghazali N, Shaw RJ, Rogers SN, Risk JM. Genomic determinants of normal tissue toxicity after radiotherapy for head and neck malignancy: a systematic review. *Oral Oncol*. 2012;48(11):1090–1100.

63. Andreassen CN. Can risk of radiotherapy-induced normal tissue complications be predicted from genetic profiles? *Acta Oncol*. 2005;44(8):801–815.
64. Zhou Y, Zhou W, Liu Q, et al. XRCC1 R399Q polymorphism and risk of normal tissue injury after radiotherapy in breast cancer patients. *Tumour Biol*. 2014;35(1):21–25.

65. Xie XX, Ouyang SY, Jin HK, Wang H, Zhou JM, Hu BQ. Predictive value of XRCC1 gene polymorphisms for side effects in patients undergoing whole breast radiotherapy: a meta-analysis. *Asian Pac J Cancer Prev*. 2012;13(12):6121–6128.

66. Barnett GC, Thompson D, Fachal L, et al. A genome wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity. *Radiother Oncol*. 2014;111(2):178–185.

67. Andreassen CN, Barnett GC, Langendijk JA, et al. Conducting radiogenomic research—do not forget careful consideration of the clinical data. *Radiother Oncol*. 2012;105(3):337–340.