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ORIGINAL RESEARCH

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

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Jing Zhao[1,*]
Zheng Zhi[2,*]
Ming Zhang[1]
Qingxia Li[1]
Jing Li[3]
Xiao Wang[4]
Chunling Ma[1]

[1]Department of Oncology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China; [2]Department of Basic Medicine, Hebei University of Chinese Medicine, Shijiazhuang, Hebei 050200, China; [3]Department of Clinical laboratory, Hebei General Hospital, Shijiazhuang, Hebei 050051, China; [4]Department of Plastic Surgery, Hebei General Hospital, Shijiazhuang, Hebei 050051, China

*These authors contributed equally to this work

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

Correspondence: Jing Zhao
Department of Oncology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China
Email zzzjmail@163.com

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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,[4,5] and late adverse effects markedly influence patients' quality of life.[6] 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,[7] 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.[8–10] *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.[11] 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.[10] 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.[12] 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.[13–15]

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 χ^2-based Q-test and I^2 statistical test.[16] If Q-test $P<0.1$ and I^2-value $\geq 50\%$,[16] 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" method[19] 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

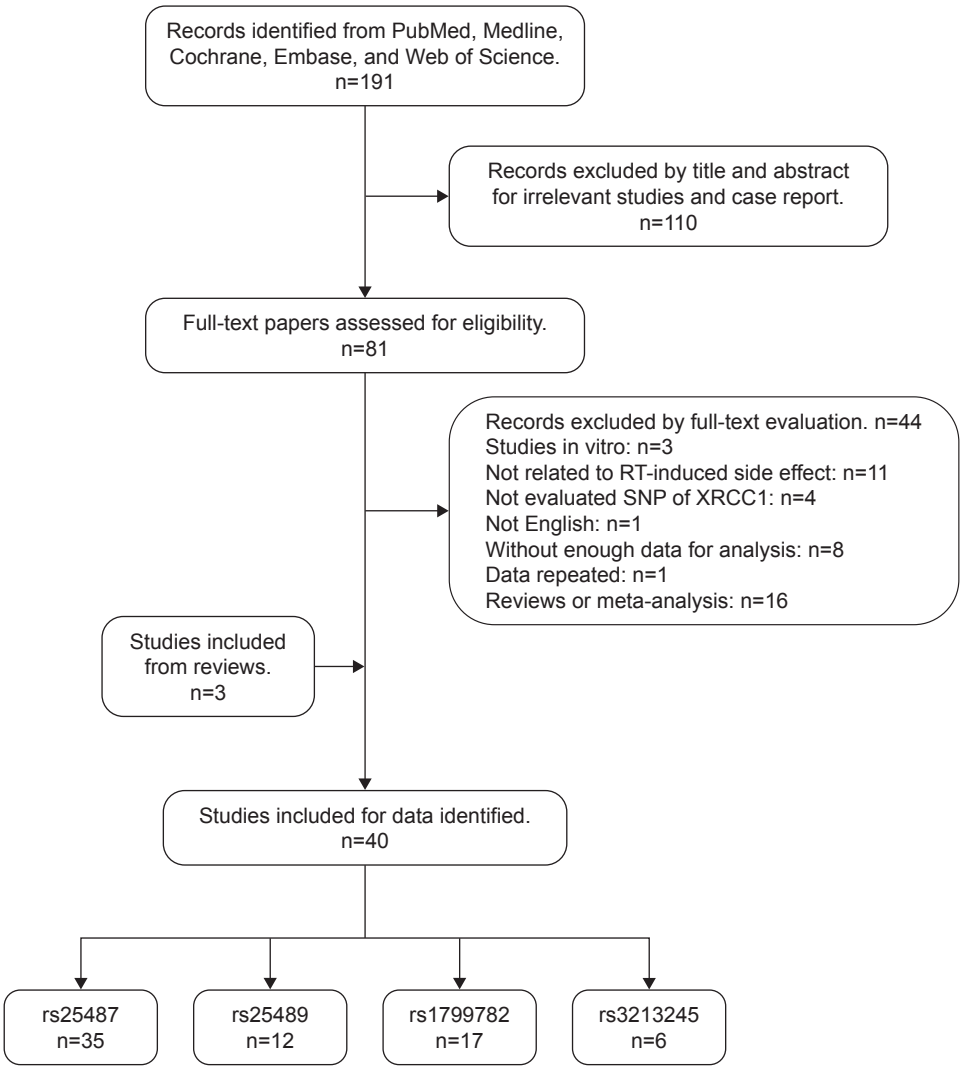

Figure 1 Flow diagram of study search and screening for the meta-analysis.
Abbreviations: RT, radiotherapy; SNP, single nucleotide polymorphism.

Table 1 Baseline characteristics of the eligible studies

Author, year	Country	Ethnicity	Disease	SNP	Sample size (N)	Adverse effect	Assessment criteria	RT dose	CT involved	Study design	Genotyping method
Alsbeih et al,[24] 2010	Saudi Arabia	Caucasian	NPC	rs25487	60	Late: fibrosis	RTOG/EORTC ≥G2	66–70 Gy	Yes	Case–control	PCR
Andreassen et al,[29] 2003	Denmark	Caucasian	Breast	rs25487	41	Late: fibrosis	LENT-SOMA ≥G3	36.6–51.4 Gy	No	Cohort	PCR
Andreassen,[63] 2005	Denmark UK	Caucasian	Breast	rs25487	52	Late: breast appearance	Photographic ≥G2	50 Gy/25f, 42.9 Gy/13f, 39 Gy/13f	NA	Case–control	PCR
Andreassen et al,[30] 2006	Denmark	Caucasian	Breast	rs25487, rs25489, rs1799782	120	Late: fibrosis	LENT-SOMA ≥G3	41 Gy	Yes	Cohort	PCR
Azria et al,[57] 2008	France	Caucasian	Breast, HNC	rs25489	34	Late: fibrosis	RTOG/EORTC CTC v3.0 ≥G3	NA	Yes	Case–control	PCR
Brem et al,[31] 2006	France	Caucasian	Breast	rs3213245	247	Acute and Late	EORTC	50 Gy, tumor bed boost 10 Gy	NA	Case–control	PCR-RFLP
Burri et al,[14] 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+EBRT: 45 Gy	NA	Cohort	PCR
Changclaude et al,[33] 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,[32] 2009	Germany	Caucasian	Breast	rs25487, rs25489, rs1799782, rs3213245	409	Late: telangiectasia	RTOG/EORTC LENT-SOMA ≥G2	Mean 61.8±4.10 Gy (51–71 Gy)	No	Cohort	PCR-RFLP
Cheuk et al,[20] 2014	Hong Kong	Asian	NPC	rs25487, rs1799782	120	Late: fibrosis	RTOG ≥G1	66–76 Gy	Yes	Cohort	PCR-RFLP
Damaraju et al,[45] 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,[49] 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,[25] 2013	Belgium	Caucasian	HNC	rs3213245	189	Acute: dysphagia	CTCAE v3.0 ≥G3	66–70 Gy	Yes	Cohort	PCR-RFLP
Duldulao et al,[52] 2013	USA	Caucasian	Rectal	rs25487	132	Acute: gastrointestinal toxicity	CTCAE v3.0 ≥G3	NA	Yes	Cohort	PCR, direct sanger sequencing
Falvo et al,[42] 2011	Italy	Caucasian	Breast	rs1799782	57	Acute: erythema	CTCAE v3.0 ≥G1	21 Gy/f	Yes	Cohort	PCR
Falvo et al,[34] 2012	Italy	Caucasian	Breast	rs25487	57	Late: fibrosis, fat necrosis	CTCAE v3.0 ≥G2	21 Gy/f	Yes	Cohort	PCR

Giotopoulos et al,[35] 2007	UK	Mixed	Breast	rs25487	167	Late: telangiectasia	RTOG LENT-SOMA ≥G2	40–50 Gy, tumor bed boost of 15 Gy/5f	Yes	Cohort	PCR-RFLP
Ishikawa et al,[50] 2011	Japan	Asian	Cervical	rs25487	208	Acute: diarrhea	CTCAE v2.0 ≥G2	EBRT 50.6 Gy Brachytherapy 24.0 Gy	Yes	Cohort	PCR
Langsenlehner et al,[46] 2011	Austria	Caucasian	Prostate	rs25487, rs25489, rs1799782	579	Late: bladder or rectal toxicity	RTOG/EORTC ≥G2	66–70.4 Gy	No	Cohort	PCR
Li et al,[21] 2013	China	Asian	NPC	rs25487, rs1799782	114	Acute: mucositis, dermatitis	CTCAE v3.0 ≥G3	50–70 Gy	Yes	Cohort	PCR-RFLP
Mangoni et al,[43] 2011	Italy	Caucasian	Breast	rs25487, rs1799782	87	Acute: skin reaction	CTCAE v2.0 ≥G2c	50 Gy/25f, 44 Gy/16f	Yes	Cohort	PCR
Moullan et al,[36] 2003	France	Caucasian	Breast	rs25487, rs25489, rs1799782	254	Acute and Late	EORTC	50 Gy, tumor bed boost 10 Gy	NA	Cohort	PCR
Mumbrekar et al,[37] 2017	India	Asian	Breast	rs25487	126	Acute: skin reaction	RTOG ≥G2	50 Gy, tumor bed boost 10 Gy for 26 patients	Yes	Cohort	PCR
Popanda et al,[47] 2009	Germany	Caucasian	Prostate	rs25487, rs25489, rs1799782	405	Acute: proctitis cystitis	CTCAE v2.0 ≥G3	61–72 Gy	No	Cohort	Sequence-specific hybridization probes
Pratesi et al,[26] 2011	Italy	Caucasian	HNC	rs25487	101	Acute: mucositis, skin erythema	CTCAE v3.0 ≥G2	Mean 62 Gy (54–70 Gy)	Yes	Case–control	PCR-RFLP
Raabe et al,[44] 2012	Germany	Caucasian	Breast	rs25487	83	Acute: erythema	RTOG ≥G2	50–50.4 Gy	NA	Cohort	PCR-RFLP, MALDI-TOF
Sakano et al,[51] 2010	Japan	Asian	Bladder	rs25487	95	Acute: gastrointestinal toxicity	CTCAE v3.0 ≥G2	Median 48.6 Gy (30.0–60.4 Gy)	Yes	Cohort	PCR-RFLP
Smith et al,[53] 2017	America	Mixed	Rectal	rs25487	165	Acute: gastrointestinal and genitourinary toxicity (diarrhea, proctitis, cystitis)	CTCAE v3.0 ≥G3	Median 50.4 Gy	Yes	Cohort	PCR, MALDI-TOF
Suga et al,[38] 2007	Japan	Asian	Breast	rs25487	399	Acute: skin reaction	CTCAE v2.0 ≥G2	46–60 Gy	Yes	Cohort	PCR
Terrazzino et al,[39] 2012	Italy	Caucasian	Breast	rs25487, rs1799782, rs3213245	286	Acute: skin reaction	RTOG ≥G2	50–50.4 Gy, tumor bed boost 9–16 Gy	Yes	Cohort	PCR-RFLP
Terrazzino et al,[40] 2012	Italy	Caucasian	Breast	rs25487, rs1799782	237	Late: fibrosis	LENT-SOMA ≥G2	50–50.4 Gy, tumor bed boost 9–16 Gy	Yes	Cohort	PCR-RFLP
Tucker et al,[54] 2013	USA	Caucasian	NSCLC	rs25487	141	Late: radiation pneumonitis	CTCAE v3.0 ≥G3	Median 63 Gy (50.4–72 Gy)	Yes	Cohort	PCR-RFLP
Usmani et al,[48] 2014	Canada	Caucasian	Prostate	rs25487	217	Late: urinary toxicity	RTOG ≥G2	125I ≥145 Gy	No	Cohort	PCR

(*Continued*)

Table 1 (*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,[27] 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,[55] 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,[56] 2011	USA	Mixed	Esophageal adenocarcinoma	rs25487	60	Acute: dysphagia	CTCAE v2.0 ≥G3	45 Gy	Yes	Cohort	PCR, MALDI-TOF
Xian et al,[22] 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,[23] 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,[15] 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,[41] 2010	Germany	Caucasian	Breast	rs25487	69	Late: fibrosis	LENT-SOMA ≥G2	54–55 Gy	Yes	Cohort	PCR-RFLP, MALDI-TOF

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),[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, 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 ($I^2=79\%$, χ^2 $P=0.03$), late side effect ($I^2=48\%$, χ^2 $P=0.05$), and pelvic irradiation ($I^2=55\%$, χ^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.[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
Acute adverse effects						
Changclaude et al,[33] 2005 (a1)	46	77	219	369	6.2	1.02 (0.62–1.68)
Duldulao et al,[52] 2013 (a3)	22	24	70	108	0.4	5.97 (1.33–26.77)
Ishikawa et al,[50] 2011 (a3-2)	27	58	67	150	4.0	1.08 (0.59–1.98)
Li et al,[21] 2013 (a1)	14	24	37	90	1.3	2.01 (0.80–5.00)
Li et al,[21] 2013 (a2)	25	48	26	66	2.1	1.67 (0.79–3.54)
Mangoni et al,[43] 2011 (a1)	5	7	26	54	0.3	2.69 (0.48–15.10)
Mumbrekar et al,[37] 2017 (a1)	23	43	44	76	3.0	0.84 (0.39–1.78)
Popanda et al,[47] 2009 (a3)	37	54	215	351	3.7	1.38 (0.75–2.54)
Pratesi et al,[26] 2011 (a1)	8	12	15	33	0.5	2.40 (0.60–9.56)
Pratesi et al,[26] 2011 (a2)	15	22	8	23	0.5	4.02 (1.16–13.90)
Pratesi et al,[26] 2011 (a4)	8	12	50	89	0.8	1.56 (0.44–5.56)
Raabe et al,[44] 2012 (a1)	27	46	20	37	1.9	1.21 (0.50–2.89)
Sakano et al,[51] 2010 (a3-1)	4	9	32	86	0.7	1.35 (0.34–5.40)
Sakano et al,[51] 2010 (a3-2)	4	13	32	82	1.2	0.69 (0.20–2.44)
Smith et al,[53] 2017 (a3)	12	14	89	151	0.4	4.18 (0.90–19.33)
Suga et al,[38] 2007 (a1)	50	109	122	290	7.3	1.17 (0.75–1.82)
Terrazzino et al,[39] 2012 (a1)	54	89	118	196	5.9	1.02 (0.61–1.70)
Venkatesh et al,[27] 2014 (a1)	31	39	112	127	2.2	0.52 (0.20–1.34)
Venkatesh et al,[27] 2014 (a2)	48	54	57	66	1.2	1.26 (0.42–3.80)
Yoon et al,[56] 2011 (a4)	7	12	24	48	0.8	1.40 (0.39–5.03)
Xian et al,[22] 2015 (a4)	6	10	31	63	0.7	1.55 (0.40–6.02)
Zhai et al,[23] 2016 (a1)	14	28	13	32	1.2	1.46 (0.53–4.07)
Zhai et al,[23] 2016 (a2)	17	30	10	26	0.9	2.09 (0.72–6.10)
Zhai et al,[23] 2016 (a5)	20	41	7	19	1.0	1.63 (0.54–4.98)
Zhou et al,[15] 2010 (a1)	30	69	14	33	2.2	1.04 (0.45–2.41)
Subtotal (95% CI)		**944**		**2,665**	**50.4**	**1.29 (1.10–1.52)**
Total events	554		1,458			
Heterogeneity: χ^2=21.80, *df*=24 (*P*=0.59); I^2=0%						
Test for overall effect: *Z*=3.04 (*P*=0.002)						
Late adverse effects						
Alsbeih et al,[24] 2010 (b1-1)	5	30	10	30	1.7	0.40 (0.12–1.36)
Andreassen et al,[29] 2003 (b1-1)	11	23	9	18	1.1	0.92 (0.27–3.15)
Andreassen,[63] 2005 (b1)	15	26	16	26	1.4	0.85 (0.28–2.58)
Andreassen et al,[30] 2006 (b1-1)	40	70	32	50	3.2	0.75 (0.36–1.58)
Burri et al,[14] 2008 (b2-1)	3	6	66	129	0.6	0.95 (0.19–4.91)
Burri et al,[14] 2008 (b2-2)	7	13	62	122	1.1	1.13 (0.36–3.55)
Burri et al,[14] 2008 (b2-3)	9	17	27	43	1.5	0.67 (0.21–2.08)
Changclaude et al,[32] 2009 (b1)	77	127	164	276	8.2	1.05 (0.68–1.62)
Cheuk et al,[20] 2014 (b1-1)	14	29	41	91	2.1	1.14 (0.49–2.63)
De Ruyck et al,[49] 2005 (b)	15	22	23	40	1.1	1.58 (0.53–4.73)
Falvo et al,[34] 2012 (b1-1)	14	28	14	29	1.4	1.07 (0.38–3.03)
Giotopoulos et al,[35] 2007 (b1)	13	15	34	67	0.3	6.31 (1.32–30.14)
Langsenlehner et al,[46] 2011 (b2)	52	91	293	484	8.0	0.87 (0.55–1.37)
Terrazzino et al,[39] 2012 (b1-1)	23	41	119	196	3.7	0.83 (0.42–1.63)
Tucker et al,[54] 2013 (b3)	23	28	78	113	1.1	2.06 (0.73–5.88)
Usmani et al,[48] 2014 (b2-2)	35	39	152	178	1.1	1.50 (0.49–4.56)
Yin et al,[55] 2011 (b3)	41	66	75	99	4.6	0.52 (0.27–1.03)
Zhai et al,[23] 2016 (b1)	14	26	13	34	1.1	1.88 (0.67–5.31)
Zhai et al,[23] 2016 (b1-1)	17	36	10	24	1.3	1.25 (0.44–3.55)
Zhai et al,[23] 2016 (b4)	4	6	23	54	0.3	2.70 (0.45–16.00)
Zhai et al,[23] 2016 (b5)	4	6	23	54	0.3	2.70 (0.45–16.00)
Zschenker et al,[41] 2010 (b1-1)	13	17	27	52	0.6	3.01 (0.87–10.46)
Subtotal (95% CI)		**762**		**2,209**	**45.8**	**1.05 (0.87–1.26)**
Total events	449		1,311			
Heterogeneity: χ^2=23.01, *df*=21 (*P*=0.34); I^2=9%						
Test for overall effect: *Z*=0.50 (*P*=0.62)						
Acute and late mixed						
Moullan et al,[36] 2003 (a+b)	46	70	99	184	3.8	1.65 (0.93–2.92)
Subtotal (95% CI)		**70**		**184**	**3.8**	**1.65 (0.93–2.92)**
Total events	46		99			
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: χ^2=48.90, *df*=47 (*P*=0.40); I^2=4%						
Test for overall effect: *Z*=2.90 (*P*=0.004)						
Test for subgroup differences: χ^2=4.05, *df*=2 (*P*=0.13); I^2=50.7%						

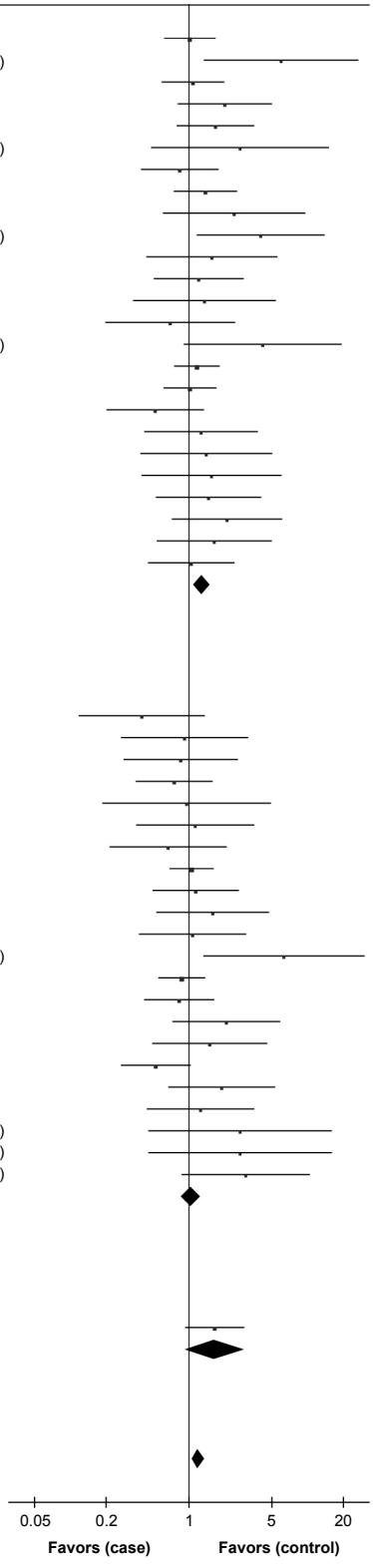

Figure 2 Forest plot for the association between rs25487 and radiation-induced adverse effects.

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.

Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Skin toxicity						
Changclaude et al,[33] 2005 (a1)	46	77	219	369	12.2	1.02 (0.62–1.68)
Li et al,[21] 2013 (a1)	14	24	37	90	2.6	2.01 (0.80–5.00)
Mangoni et al,[43] 2011 (a1)	5	7	26	54	0.7	2.69 (0.48–15.10)
Mumbrekar et al,[37] 2017 (a1)	23	43	44	76	5.9	0.84 (0.39–1.78)
Pratesi et al,[26] 2011 (a1)	8	12	15	33	1.1	2.40 (0.60–9.56)
Raabe et al,[44] 2012 (a1)	27	46	20	37	3.7	1.21 (0.50–2.89)
Suga et al,[38] 2007 (a1)	50	109	122	290	14.5	1.17 (0.75–1.82)
Terrazzino et al,[39] 2012 (a1)	54	89	118	196	11.6	1.02 (0.61–1.70)
Venkatesh 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,[15] 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: χ^2=7.45, *df*=10 (*P*=0.68); I^2=0%						
Test for overall effect: *Z*=0.97 (*P*=0.33)						
Mucositis						
Li et al,[21] 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,[27] 2014 (a2)	48	54	57	66	2.3	1.26 (0.42–3.80)
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: χ^2=2.07, *df*=3 (*P*=0.56); I^2=0%						
Test for overall effect: *Z*=2.58 (*P*=0.10)						
Gastrointestinal and genitourinary toxicity						
Duldulao et al,[52] 2013 (a3)	22	24	70	108	0.9	5.97 (1.33–26.77)
Ishikawa et al,[50] 2011 (a3-2)	27	58	67	150	8.0	1.08 (0.59–1.98)
Popanda et al,[47] 2009 (a3)	37	54	215	351	7.2	1.38 (0.75–2.54)
Sakano et al,[51] 2010 (a3-1)	4	9	32	86	1.4	1.35 (0.34–5.40)
Sakano et al,[51] 2010 (a3-2)	4	13	32	82	2.4	0.69 (0.20–2.44)
Smith et al,[53] 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: χ^2=7.60, *df*=5 (*P*=0.18); I^2=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,[56] 2011 (a4)	7	12	24	48	1.6	1.40 (0.39–5.03)
Xian et al,[22] 2015 (a4)	6	10	31	63	1.4	1.55 (0.40–6.02)
Subtotal (95% CI)		**34**		**200**	**4.6**	**1.50 (0.71–3.18)**
Total events	21		105			
Heterogeneity: χ^2=0.02, *df*=2 (*P*=0.99); I^2=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 (95% CI)		**944**		**2,665**	**100**	**1.29 (1.10–1.52)**
Total events	554		1,458			
Heterogeneity: χ^2=21.80, *df*=24 (*P*=0.59); I^2=0%						
Test for overall effect: *Z*=3.04 (*P*=0.002)						
Test for subgroup differences: χ^2=5.19, *df*=4 (*P*=0.27); I^2=23.0%						

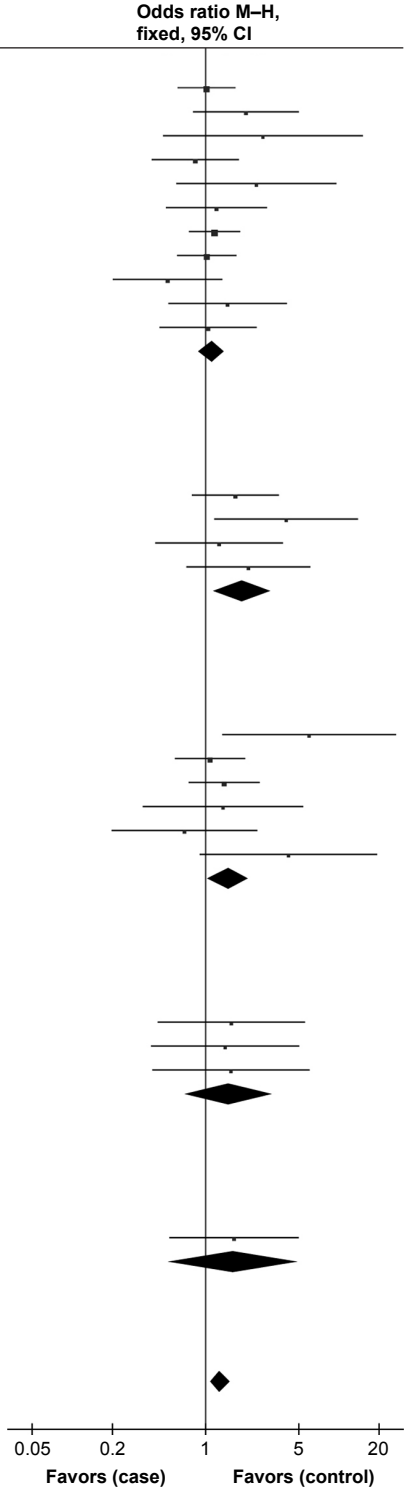

Figure 3 Forest plot for the association between rs25487 and radiation-induced acute adverse effects by specific side effect.
Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute 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, obstipation, 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

Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Skin and subcutaneous toxicity						
Alsbeih et al,[24] 2010 (b1-1)	5	30	10	30	3.7	0.40 (0.12–1.36)
Andreassen et al,[29] 2003 (b1-1)	11	23	9	18	2.3	0.92 (0.27–3.15)
Andreassen,[63] 2005 (b1)	15	26	16	26	3.0	0.85 (0.28–2.58)
Andreassen et al,[30] 2006 (b1-1)	40	70	32	50	7.1	0.75 (0.36–1.58)
Changclaude et al,[32] 2009 (b1)	77	127	164	276	18.0	1.05 (0.68–1.62)
Cheuk et al,[20] 2014 (b1-1)	14	29	41	91	4.5	1.14 (0.49–2.63)
Falvo et al,[34] 2012 (b1-1)	14	28	14	29	3.0	1.07 (0.38–3.03)
Giotopoulos et al,[35] 2007 (b1)	13	15	34	67	0.7	6.31 (1.32–30.14)
Terrazzino et al,[39] 2012 (b1-1)	23	41	119	196	8.0	0.83 (0.42–1.63)
Zhai et al,[23] 2016 (b1)	14	26	13	34	2.3	1.88 (0.67–5.31)
Zhai et al,[23] 2016 (b1-1)	17	36	10	24	2.8	1.25 (0.44–3.55)
Zschenker et al,[41] 2010 (b1-1)	13	17	27	52	1.4	3.01 (0.87–10.46)
Subtotal (95% CI)		**468**		**893**	**56.9**	**1.09 (0.86–1.39)**
Total events	256		489			
Heterogeneity: χ^2=13.02, *df*=11 (*P*=0.29); I^2=15%						
Test for overall effect: *Z*=0.72 (*P*=0.47)						
Gastrointestinal and genitourinary toxicity						
Burri et al,[14] 2008 (b2-1)	3	6	66	129	1.3	0.95 (0.19–4.91)
Burri et al,[14] 2008 (b2-2)	7	13	62	122	2.4	1.13 (0.36–3.55)
Burri et al,[14] 2008 (b2-3)	9	17	27	43	3.2	0.67 (0.21–2.08)
Langsenlehner et al,[46] 2011 (b2)	52	91	293	484	17.6	0.87 (0.55–1.37)
Usmani et al,[48] 2014 (b2-2)	35	39	152	178	2.5	1.50 (0.49–4.56)
Subtotal (95% CI)		**166**		**956**	**27.0**	**0.93 (0.65–1.33)**
Total events	106		600			
Heterogeneity: χ^2=1.23, *df*=4 (*P*=0.87); I^2=0%						
Test for overall effect: *Z*=0.39 (*P*=0.70)						
Radiation pneumonitis						
Tucker et al,[54] 2013 (b3)	23	28	78	113	2.4	2.06 (0.73–5.88)
Yin et al,[55] 2011 (b3)	41	66	75	99	10.1	0.52 (0.27–1.03)
Subtotal (95% CI)		**94**		**212**	**12.5**	**0.83 (0.48–1.42)**
Total events	64		153			
Heterogeneity: χ^2=4.67, *df*=1 (*P*=0.03); I^2=79%						
Test for overall effect: *Z*=0.69 (*P*=0.49)						
Mucous						
Zhai et al,[23] 2016 (b4)	4	6	23	54	0.7	2.70 (0.45–16.00)
Subtotal (95% CI)		**6**		**54**	**0.7**	**2.70 (0.45–16.00)**
Total events	4		23			
Heterogeneity: not applicable						
Test for overall effect: *Z*=1.09 (*P*=0.28)						
Salivary gland						
Zhai et al,[23] 2016 (b5)	4	6	23	54	0.7	2.70 (0.45–16.00)
Subtotal (95% CI)		**6**		**54**	**0.7**	**2.70 (0.45–16.00)**
Total events	4		23			
Heterogeneity: not applicable						
Test for overall effect: *Z*=1.09 (*P*=0.28)						
Mixed late						
De Ruyck et al,[49] 2005 (b)	15	22	23	40	2.3	1.58 (0.53–4.73)
Subtotal (95% CI)		**22**		**40**	**2.3**	**1.58 (0.53–4.73)**
Total events	15		23			
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.82 (*P*=0.41)						
Total (95% CI)		**762**		**2,209**	**100**	**1.05 (0.87–1.26)**
Total events	449		1,311			
Heterogeneity: χ^2=23.01, *df*=21 (*P*=0.34); I^2=9%						
Test for overall effect: *Z*=0.50 (*P*=0.62)						
Test for subgroup differences: χ^2=3.97, *df*=5 (*P*=0.55); I^2=0%						

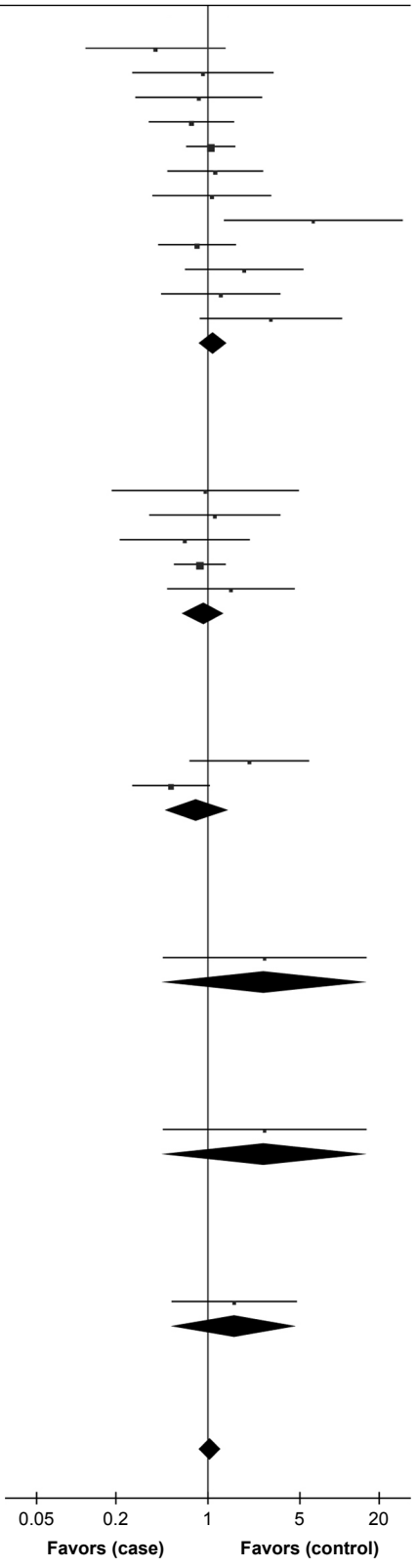

Figure 4 Forest plot for the association between rs25487 and radiation-induced late adverse effects by specific side effect.
Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. b, late 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.

Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Head and neck						
Alsbeih et al,[24] 2010 (b1-1)	5	30	10	30	1.7	0.40 (0.12–1.36)
Cheuk et al,[20] 2014 (b1-1)	14	29	41	91	2.1	1.14 (0.49–2.63)
Li et al,[21] 2013 (a1)	14	24	37	90	1.3	2.01 (0.80–5.00)
Li et al,[21] 2013 (a2)	25	48	26	66	2.1	1.67 (0.79–3.54)
Pratesi et al,[26] 2011 (a1)	8	12	15	33	0.5	2.40 (0.60–9.56)
Pratesi et al,[26] 2011 (a2)	15	22	8	23	0.5	4.02 (1.16–13.90)
Pratesi et al,[26] 2011 (a4)	8	12	50	89	0.8	1.56 (0.44–5.56)
Venkatesh et al,[27] 2014 (a1)	31	39	112	127	2.2	0.52 (0.20–1.34)
Venkatesh et al,[27] 2014 (a2)	48	54	57	66	1.2	1.26 (0.42–3.80)
Zhai et al,[23] 2016 (a1)	14	28	13	32	1.2	1.46 (0.53–4.07)
Zhai et al,[23] 2016 (a2)	17	30	10	26	0.9	2.09 (0.72–6.10)
Zhai et al,[23] 2016 (a5)	20	41	7	19	1.0	1.63 (0.54–4.98)
Zhai et al,[23] 2016 (b1)	14	26	13	34	1.1	1.88 (0.67–5.31)
Zhai et al,[23] 2016 (b1-1)	17	36	10	24	1.3	1.25 (0.44–3.55)
Zhai et al,[23] 2016 (b4)	4	6	23	54	0.3	2.70 (0.45–16.00)
Zhai et al,[23] 2016 (b5)	4	6	23	54	0.3	2.70 (0.45–16.00)
Subtotal (95% CI)		**443**		**858**	**18.5**	**1.46 (1.12–1.90)**
Total events	258		455			
Heterogeneity: χ^2=14.65, *df*=15 (*P*=0.48); I^2=0%						
Test for overall effect: *Z*=2.81 (*P*=0.005)						
Breast						
Andreassen et al,[29] 2003 (b1-1)	11	23	9	18	1.1	0.92 (0.27–3.15)
Andreassen,[63] 2005 (b1)	15	26	16	26	1.4	0.85 (0.28–2.58)
Andreassen et al,[30] 2006 (b1-1)	40	70	32	50	3.2	0.75 (0.36–1.58)
Changclaude et al,[33] 2005 (a1)	46	77	219	369	6.2	1.02 (0.62–1.68)
Changclaude et al,[32] 2009 (b1)	77	127	164	276	8.2	1.05 (0.68–1.62)
Falvo et al,[34] 2012 (b1-1)	14	28	14	29	1.4	1.07 (0.38–3.03)
Giotopoulos et al,[35] 2007 (b1)	13	15	34	67	0.3	6.31 (1.32–30.14)
Mangoni et al,[43] 2011 (a1)	5	7	26	54	0.3	2.69 (0.48–15.10)
Moullan et al,[36] 2003 (a+b)	46	70	99	184	3.8	1.65 (0.93–2.92)
Mumbrekar et al,[37] 2017 (a1)	23	43	44	76	3.0	0.84 (0.39–1.78)
Raabe et al,[44] 2012 (a1)	27	46	20	37	1.9	1.21 (0.50–2.89)
Suga et al,[38] 2007 (a1)	50	109	122	290	7.3	1.17 (0.75–1.82)
Terrazzino et al,[39] 2012 (a1)	54	89	118	196	5.9	1.02 (0.61–1.70)
Terrazzino et al,[39] 2012 (b1-1)	23	41	119	196	3.7	0.83 (0.42–1.63)
Zhou et al,[15] 2010 (a1)	30	69	14	33	2.2	1.04 (0.45–2.41)
Zschenker et al,[41] 2010 (b1-1)	13	17	27	52	0.6	3.01 (0.87–10.46)
Subtotal (95% CI)		**857**		**1,953**	**50.4**	**1.13 (0.95–1.33)**
Total events	487		1,077			
Heterogeneity: χ^2=13.09, *df*=15 (*P*=0.60); I^2=0%						
Test for overall effect: *Z*=1.35 (*P*=0.18)						
Pelvic						
Burri et al,[14] 2008 (b2-1)	3	6	66	129	0.6	0.95 (0.19–4.91)
Burri et al,[14] 2008 (b2-2)	7	13	62	122	1.1	1.13 (0.36–3.55)
Burri et al,[14] 2008 (b2-3)	9	17	27	43	1.5	0.67 (0.21–2.08)
De Ruyck et al,[49] 2005 (b)	15	22	23	40	1.1	1.58 (0.53–4.73)
Duldulao et al,[52] 2013 (a3)	22	24	70	108	0.4	5.97 (1.33–26.77)
Ishikawa et al,[50] 2011 (a3-2)	27	58	67	150	4.0	1.08 (0.59–1.98)
Langsenlehner et al,[46] 2011 (b2)	52	91	293	484	8.0	0.87 (0.55–1.37)
Popanda et al,[47] 2009 (a3)	37	54	215	351	3.7	1.38 (0.75–2.54)
Sakano et al,[51] 2010 (a3-1)	4	9	32	86	0.7	1.35 (0.34–5.40)
Sakano et al,[51] 2010 (a3-2)	4	13	32	82	1.2	0.69 (0.20–2.44)
Smith et al,[53] 2017 (a3)	12	14	89	151	0.4	4.18 (0.90–19.33)
Usmani et al,[48] 2014 (b2-2)	35	39	152	178	1.1	1.50 (0.49–4.56)
Subtotal (95% CI)		**360**		**1,924**	**23.9**	**1.20 (0.94–1.54)**
Total events	227		1,128			
Heterogeneity: χ^2=11.48, *df*=11 (*P*=0.40); I^2=4%						
Test for overall effect: *Z*=1.48 (*P*=0.14)						
Thoracic						
Tucker et al,[54] 2013 (b3)	23	28	78	113	1.1	2.06 (0.73–5.88)
Yin et al,[55] 2011 (b3)	41	66	75	99	4.6	0.52 (0.27–1.03)
Yoon et al,[56] 2011 (a4)	7	12	24	48	0.8	1.40 (0.39–5.03)
Xian et al,[22] 2015 (a4)	6	10	31	63	0.7	1.55 (0.40–6.02)
Subtotal (95% CI)		**116**		**323**	**7.2**	**0.96 (0.06–1.53)**
Total events	77		208			
Heterogeneity: χ^2=5.92, *df*=3 (*P*=0.12); I^2=49%						
Test for overall effect: *Z*=0.17 (*P*=0.86)						
Total (95% CI)		**1,776**		**5,058**	**100**	**1.19 (1.06–1.35)**
Total events	1,049		2,868			
Heterogeneity: χ^2=48.90, *df*=47 (*P*=0.40); I^2=4%						
Test for overall effect: *Z*=2.90 (*P*=0.004)						
Test for subgroup differences: χ^2=3.54, *df*=3 (*P*=0.32); I^2=15.3%						

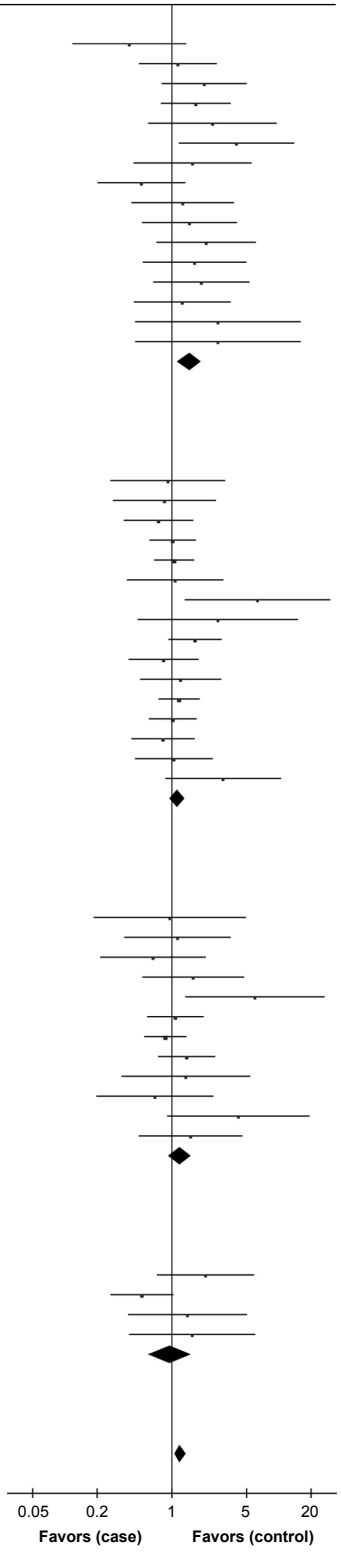

Figure 5 Forest plot for the association between rs25487 and radiation-induced adverse effects by irradiation area.

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 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.

Abbreviation: M–H, Mantel–Haenszel.

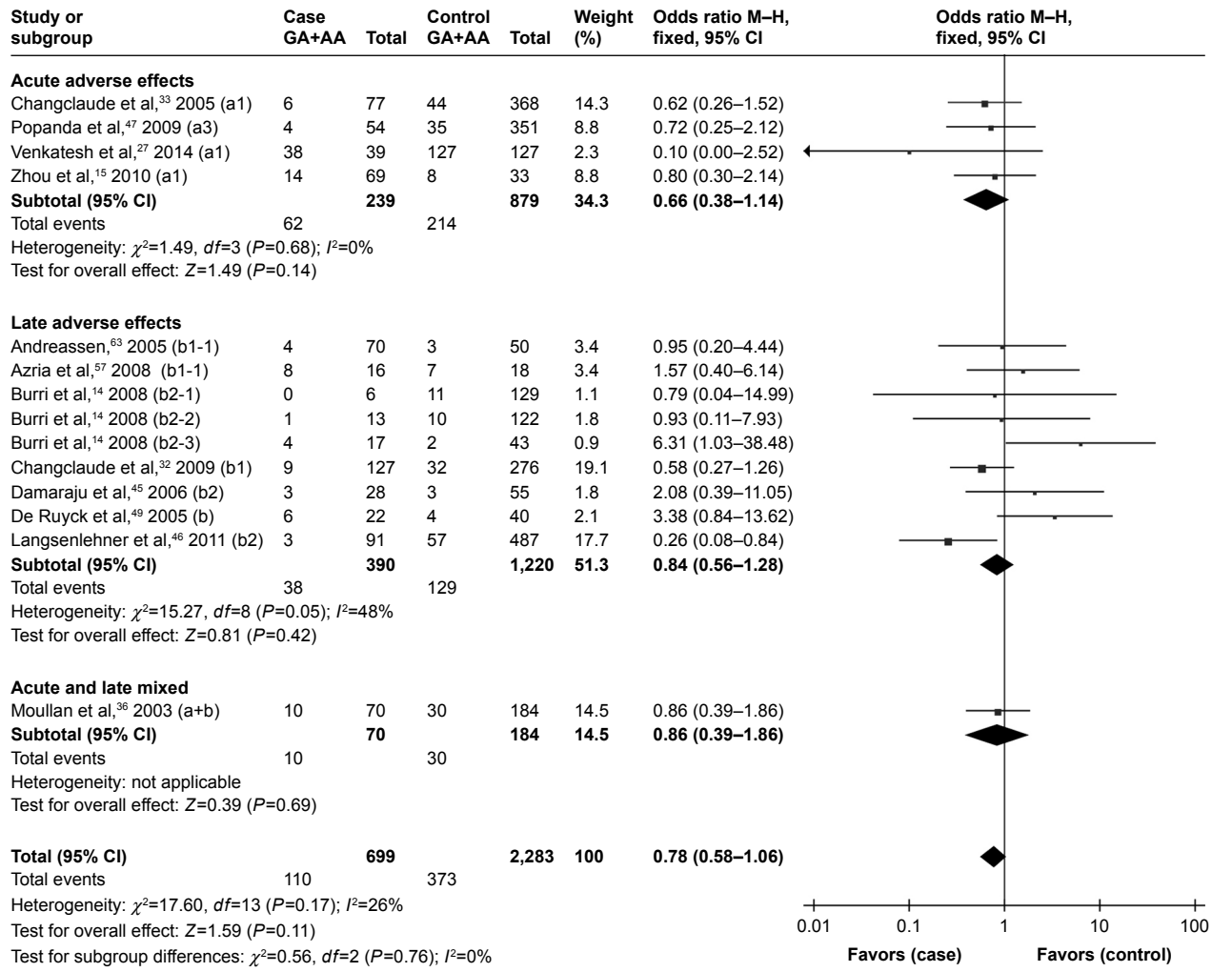

Figure 6 Forest plot for the association between rs25489 and radiation-induced adverse effects.
Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (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.

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[46,65] 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,

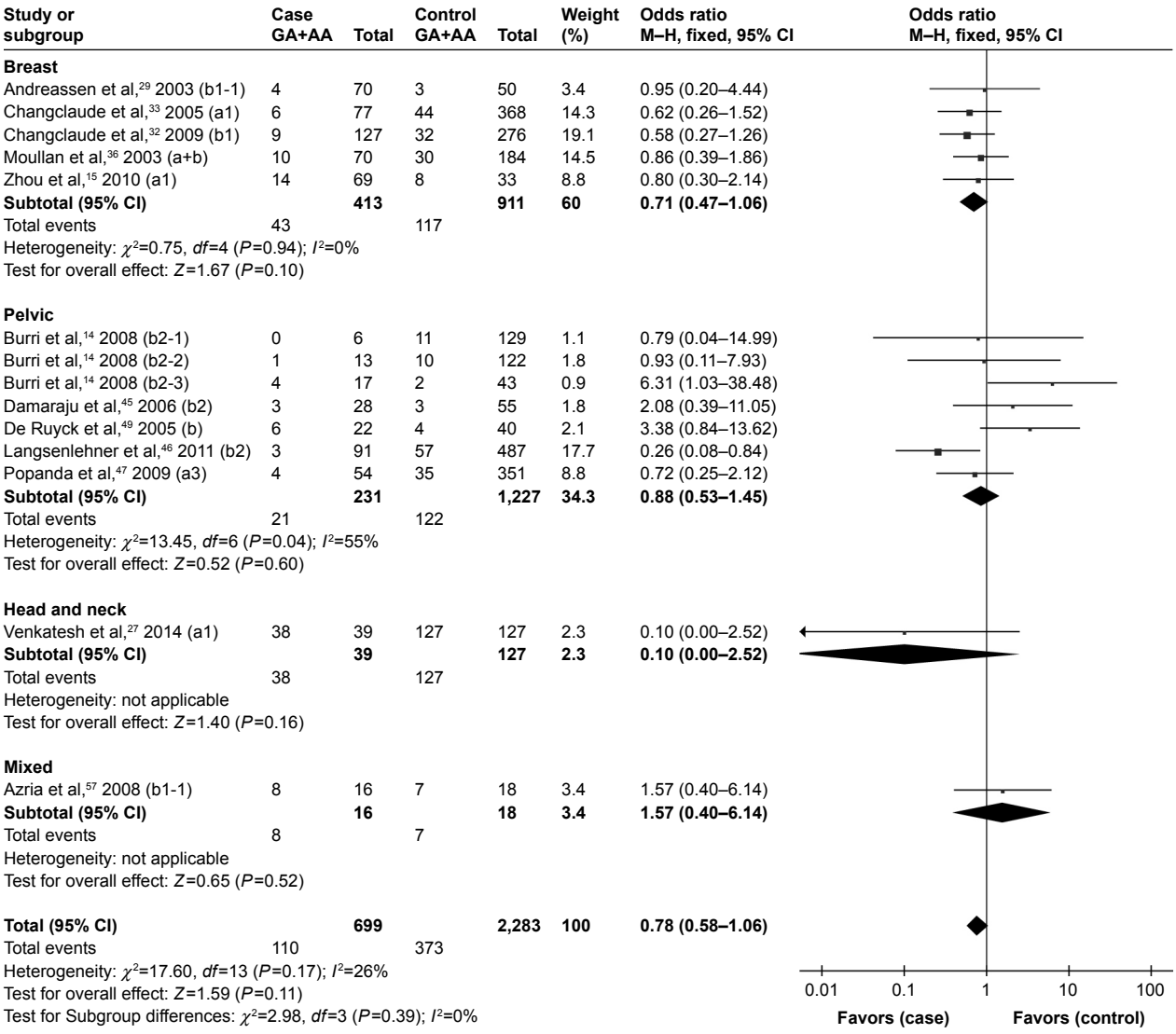

Figure 7 Forest plot for the association between rs25489 and radiation-induced adverse effects by irradiation area.

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.

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 al[36] and Mangoni et al[43] 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.

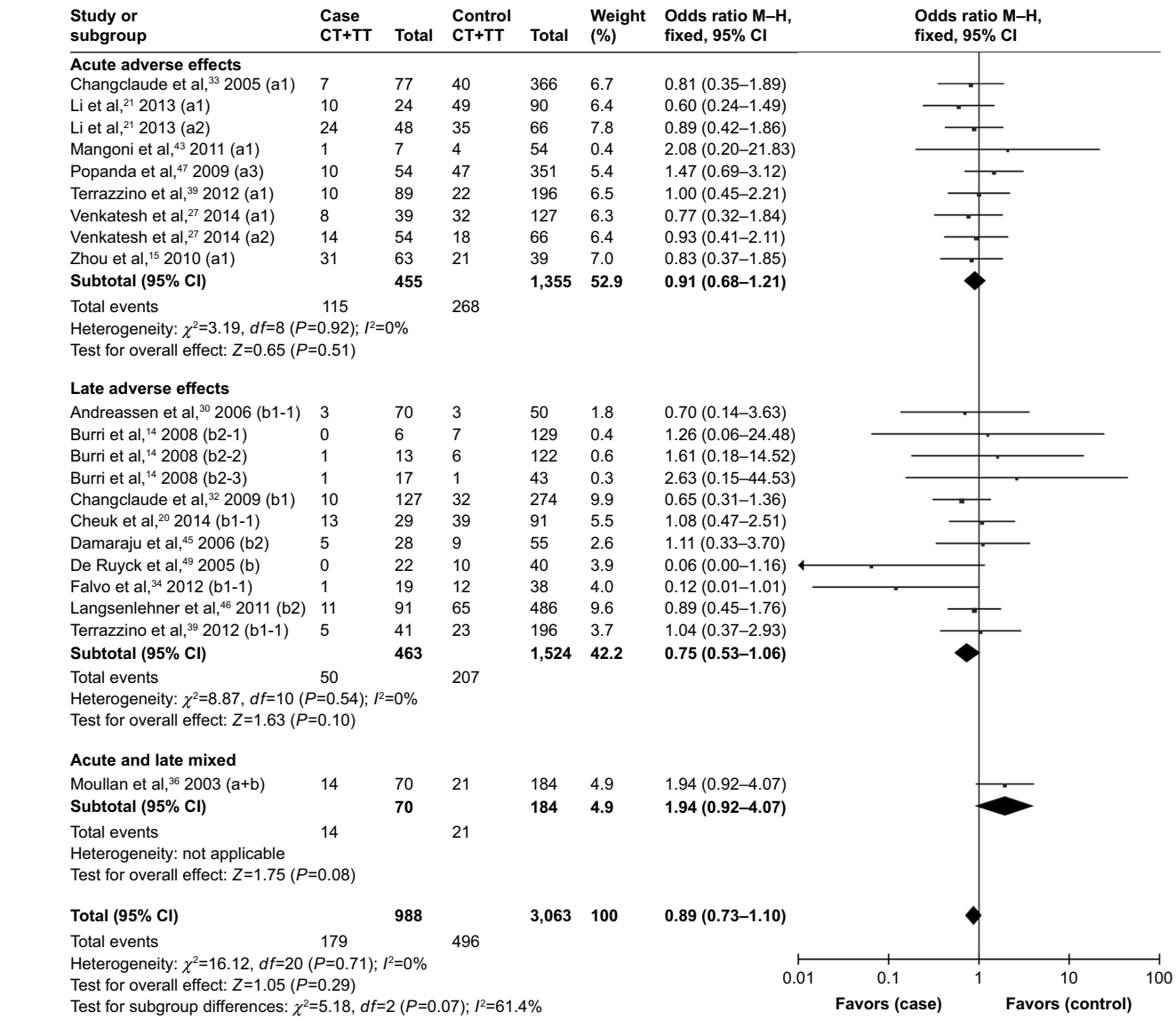

Figure 8 Forest plot for the association between rs1799782 and radiation-induced adverse effects.
Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; 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,[59,61–63] 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[66] 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.[3] Furthermore, different RT-induced side effects may occur in the same irradiation

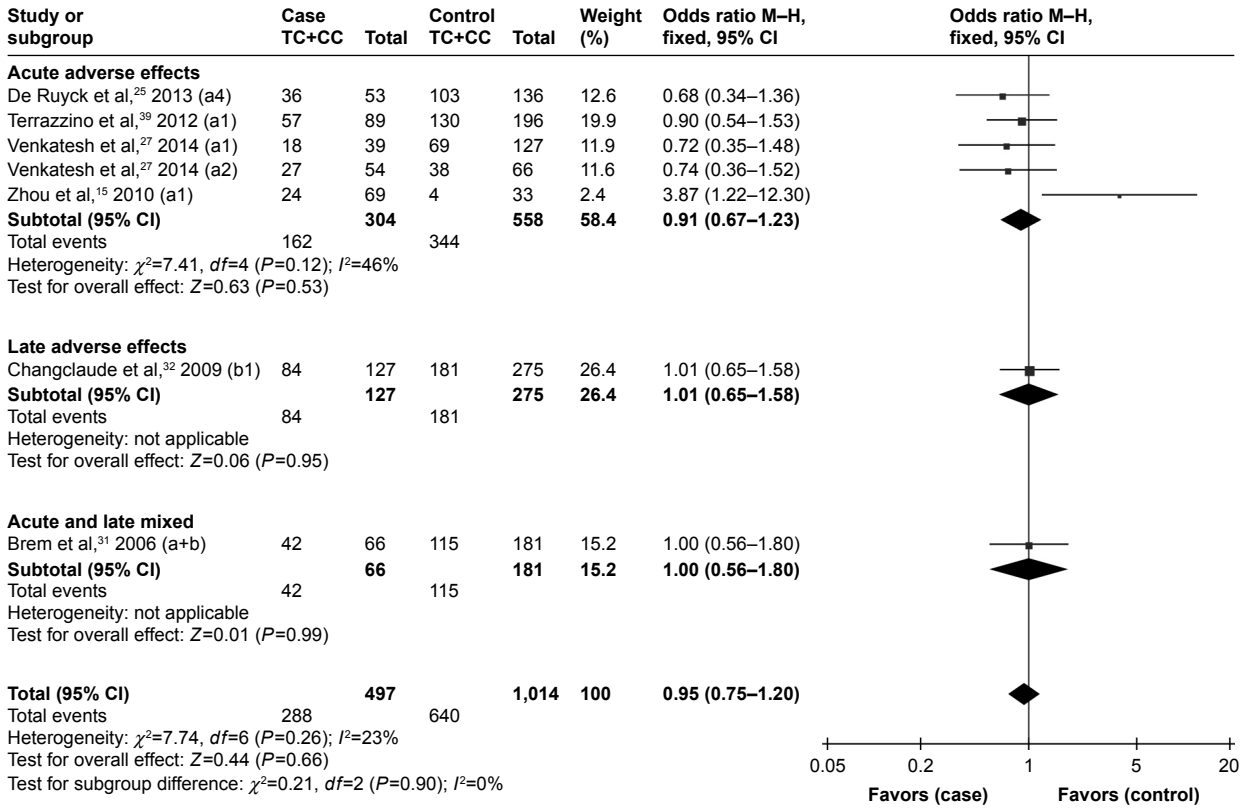

Figure 9 Forest plot for the association between rs3213245 and radiation-induced adverse effects.
Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a4, dysphagia; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia).
Abbreviation: M–H, Mantel–Haenszel.

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.[67] 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.

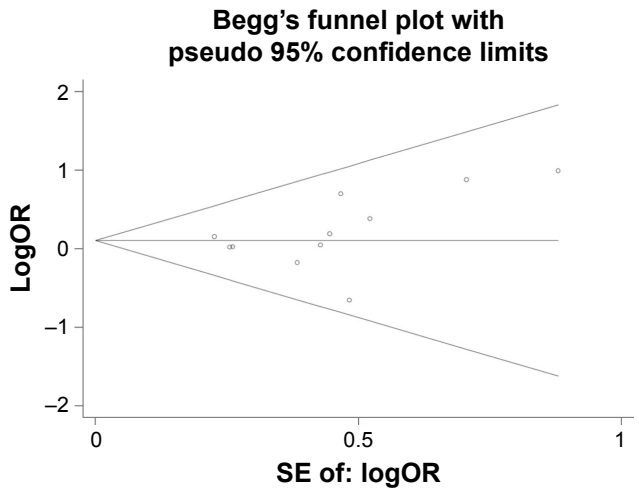

Figure 10 Begg's funnel plot for the effect of rs25487 on radiation-induced skin toxicity.
Note: Circles represent the actually included studies.
Abbreviations: OR, odds ratio; SE, standard error.

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.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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