



# The role of radiogenomics in breast radiotherapy

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**Contributions:** (I) Conception and design: CH Yip; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Radiotherapy after surgery for breast cancer can induce adverse and undesirable side effects in a small proportion of women, which can affect quality of life. In recent years, it is believed that there is a genetic component to this occurrence, and the term radiogenomics has been established to explore this genetic link to radiosensitivity. A literature review was carried out to determine genetic variants that are associated with post-radiotherapy adverse events in breast cancer patients and review the scoring systems for these adverse effects. A literature search on PubMed was done using a combination of the keywords: “radiation”, “breast cancer”, “genetics”, and “toxicity”. A separate search on PubMed was done for comparing scoring systems, using a combination of keywords: “radiation”, “toxicity”, “scoring”, “comparison”. Sixteen studies on the effect of genetic polymorphism on radiotherapy toxicity were reviewed. *ATM* and *XRCC1* were the most commonly studied gene polymorphisms. Four out of 7 studies on *ATM* polymorphisms and 3 out of 11 studies on *XRCC1* showed a significant effect on radiation toxicity. Five studies reviewed compared scoring systems for late radiotherapy toxicity. RTOG, CTC and LENT-SOMA were the commonly used scoring systems. In 4 studies, LENT-SOMA was better for grading late radiation-induced adverse effects. Different radiation techniques, surgical and host factors can also affect outcomes from radiation therapy, apart from genetic polymorphisms, making it difficult to determine the contribution of each individual factor. Although there appears to be some correlation between genetic polymorphisms and radiosensitivity, it remains inconclusive, as there is no uniform scoring system to grade radiation toxicity. The prospect of an individual’s genetic profile being linked to radiosensitivity can enable a more personalized approach to radiotherapy, with customization of dosage to minimise the risk of developing radiation-induced damage to the breast.

**Keywords:** Breast cancer; radiotherapy; radiation toxicity; radiogenomics

Received: 25 November 2019; Accepted: 29 December 2019; Published: 25 March 2020.

doi: 10.21037/abs.2019.12.01

**View this article at:** <http://dx.doi.org/10.21037/abs.2019.12.01>

## Introduction

Radiotherapy is the mainstay in the treatment of a number of cancers, including breast cancer. It is typically administered as primary treatment or as a part of combination treatment. The process involves the use of ionising radiation targeted at cancer cells with the aim of killing the cells and prevent any further invasion or spread. It has been suggested that radiation therapy may

be warranted in up to 50% of breast cancer patients (1), and is essential for patients who have had breast conserving surgery (BCS). The indications for radiotherapy in post-mastectomy patients include the involvement of four or more axillary lymph nodes, T4 disease, tumour size of more than 5 cm, or positive surgical margins. The traditional method of administering radiation is through external beam radiotherapy (EBRT), which irradiates the whole breast. Radiotherapy has been shown to reduce the 10-year risk

of any recurrence following BCS by roughly 50% and the 15-year risk of death by 15% (2).

In recent years, the advent of accelerated partial breast irradiation (APBI) has emerged, which involves the irradiation of a specific area of the breast during BCS. The rationale behind this technique is the evidence that local recurrence of breast cancer tend to arise from the tissue around the site of the original surgery, hence irradiating the cavity after lumpectomy can reduce local recurrence and will avoid irradiation of healthy breast tissue. One of the methods of APBI is intraoperative radiotherapy (IORT) which delivers a single dose of radiation to the cavity bed after lumpectomy at the time of surgery. The American Society for Radiation Oncology (ASTRO) concluded in a Consensus Statement in 2016 that in properly selected low-risk patients, APBI provides outcomes similar to whole breast irradiation (3). The use of IORT eliminates the need for patients to continuously visit the hospital for sessions of EBRT, which is a positive factor when patients' convenience is considered.

While most patients tolerate radiotherapy without complications, a proportion of patients undergoing radiotherapy will develop an adverse reaction. These adverse reactions are categorised into either early or late effects. Early effects are defined as adverse events that arise during or right after therapy or have not healed after 90 days following therapy. Late effects arise in a span of months to years following the cessation of therapy and are more permanent and chronic in their effect resulting in pain, poor cosmesis, or loss of organ function (4).

In the breast, the skin is most commonly affected due to the high turnover rate of the skin cells. Early effects of radiation on the breast can range from mild erythema to necrosis or ulceration, all of which are considered as acute skin toxicity, whereas late effects include telangiectasia, atrophy or subcutaneous fibrosis. Telangiectasia was seen to have a higher risk of developing when there was prior acute skin toxicity (5). An association between genetic variants and the risk of developing radiotherapy-induced acute skin adverse events have also been reported (6). In addition, there have been several risk factors that have been suggested to increase the risk of developing adverse effects related to radiotherapy post-breast surgery. Women with larger breast size are more likely to develop late effects of radiation possibly due to greater dose variation (7). Other risk factors for radiotherapy toxicity include higher body mass, more advanced disease, hormone receptor negative disease and conventionally fractionated treatment regimens (8).

Given that DNA damage caused by ionising radiation is typically repaired by the DNA repair pathway, it has been suggested that individuals with an inherited variant in the DNA repair pathway may have a reduced ability to repair damage caused by ionising radiation and therefore, may be more susceptible to adverse effects of radiation. Indeed, a number of studies have reported a candidate gene approach to examine the association between variants in known DNA repair genes, such as *XRCC1* and *ATM*, with radiosensitivity (9,10).

Scoring systems for the adverse effects of radiation have been established, for example, the American College of Radiology developed a staging system for radiation-associated acute and late changes, known as the Radiation Therapy Oncology Group (RTOG) Morbidity Scheme, which grades adverse effects on a scale from 0 to 4 (11). The Common Toxicity Criteria (CTC) is a scoring system developed by the National Institutes of Health (NIH) to grade acute toxicity effects (12). Another scoring system that is widely used for late changes is the LENT-SOMA scale (13,14) (*Table 1*). The existence of these different scoring systems leads to the question of which one is better at grading toxicities of radiotherapy, particularly the late effects.

## Objectives

The objective of this literature review is twofold.

Firstly, we plan to determine the strength of the association between genetic variants in DNA repair genes with adverse reactions to radiotherapy, in breast cancer patients.

Secondly, we sought to review and compare the current scoring systems of late radiation-induced changes across different types of cancers, using the RTOG Morbidity Scheme, CTC, and the LENT-SOMA scale as reference. We chose to focus on grading the late adverse effects of radiotherapy as these effects are more permanent and disabling compared to more acute adverse effects.

## Methodology

A literature search on PubMed was done using a combination of the keywords: "radiation", "radiotherapy", "breast cancer", "genetic", "gene", and "toxicity".

A separate search on PubMed was done for comparing scoring systems, using the combination of keywords: "radiation", "toxicity", "scoring", "grading", "comparison".

**Table 1** LENT-SOMA scale

	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Breast edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Fibrosis	Barely palpable, increased density	Definite increased density and firmness	Very marked density, retraction and fixation	
Telangiectasia	<1 cm <sup>2</sup>	1–4 cm <sup>2</sup>	>4 cm <sup>2</sup>	
Arm edema	2–4 cm increase	>4–6 cm increase	>6 cm increase	Useless arm
Ulceration	Epidermal only, <1 cm <sup>2</sup>	Dermal only, >1 cm <sup>2</sup>	Subcutaneous	Bone exposed, necrosis
Atrophy	10–25%	>25–40%	>40–75%	Whole breast
<b>Treatment</b>				
Pain	Occasional, no narcotics	Regular, no narcotics	Regular, narcotics	Surgical intervention
Breast edema			Medical intervention	Surgical intervention/mastectomy
Arm edema		Elastic stocking/elevate arm	Intensive physiotherapy/compression wrapping	Surgical intervention/amputation
Ulceration		Medical intervention	Surgical intervention/wound debridement	Surgical intervention/mastectomy
Atrophy				Surgical management

The latest search was carried out on 30 October 2019.

Results were limited to English only for all searches. All types of articles were included. Titles that appeared relevant to the research topic were selected. Abstract and full text, if available, were reviewed and selected titles were narrowed down from there.

A total of 21 articles were selected for this literature review. Ten were originally found and through cross-referencing and using the ‘Similar Articles’ feature on PubMed, a further 11 articles were sourced.

## Limitations

As radiotherapy side effects are a relatively rare event, most of the studies had a small sample size.

Another limitation is the genetic polymorphisms themselves. The penetrance of the genetic polymorphisms was not defined, although it is believed that the adverse response to radiotherapy can be because of multiple low-penetrance variants.

Whilst each study described the method for assessing the severity of adverse events, this was not standardised across studies, making it difficult to meta-analyse the results. The

end-outcome of the studies were not uniformly defined, ranging from vague descriptions such as ‘late changes’ to specific terms such as ‘fibrosis’.

Another limitation is that the meta-analyses/systematic reviews we analysed might include overlapping studies. Some meta-analyses included other non-breast cancers. The dosage of the radiation used is not clearly stated either, which can lead to different effects.

## Results

### Overview of studies

A total of 17 studies on the effect of genetic polymorphism on radiotherapy toxicity were reviewed (15–31). Seven studies investigated the effect of the *ATM* genetic polymorphism (15–19,27,29). Eleven studies investigated the effect of the *XRCC1* genetic polymorphisms (19–28,30), and 9 studies included other genetic polymorphisms. (18,19,22,24,26–28,30,31) (Table 2).

The most widely researched *ATM* polymorphism is the SNP *rs1801516*. Based on all the studies, 4 of the 7 studies on the *ATM* gene suggested a significant association with adverse effects (15–17,29). Two studies showed an increase

**Table 2** Comparison of studies on genetic polymorphisms and adverse reactions to radiotherapy

Lead author, Ref.	Year	Study type	N	Title	Cancer	Scale	Outcome & results
Andreassen CN (15)	2006	Research	41	ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy	Breast	LENT-SOMA	Fibrosis grade $\geq 3$ ATM ED50 (dose that resulted in a 50% incidence of Grade 3 fibrosis) carriers vs. non-carriers enhancement ratio = 1.13 (1.05–1.22)
Dong L (16)	2015	Meta-analysis	1,588	Ataxia telangiectasia-mutated gene polymorphisms and acute normal tissue injuries in cancer patients after radiation therapy: a systematic review and meta-analysis	Breast & prostate	RTOG/EORTC, CTC	Grade $\geq 2$ acute radiation injury ATM/rs1801516 OR = 1.3 (1.04–1.71)
Zhang Y (17)	2016	Meta-analysis	2,000	Single Nucleotide Polymorphism rs1801516 in Ataxia Telangiectasia-Mutated Gene Predicts Late Fibrosis in Cancer Patients After Radiotherapy	Breast, prostate, head & neck, nasopharynx, meningioma	LENT-SOMA, RTOG/EORTC, STAT	Late fibrosis ATM/rs1801516 OR = 1.78 (1.07–2.94)
Su M (18)	2014	Meta-analysis	4,868	Meta-analysis of associations between ATM Asp1853Asn and TP53 Arg72Pro polymorphisms and adverse effects of cancer radiotherapy	Breast, prostate, lung, head & neck, nasopharynx, cervix	LENT-SOMA, RTOG/EORTC, CTC	Early & late effects ATM Asp1853Asn (rs1801516) GA+AA vs. GG OR = 1.09 (0.86–1.39) TP53 Arg72Pro (rs1042522) GC+CC vs. GG OR = 0.86 (0.70–1.05)
Zschenker O (19)	2010	Retrospective	69	Association of single nucleotide polymorphisms in ATM, GSTP1, SOD2, TGFB1, XPD and XRCC1 with clinical and cellular radiosensitivity	Breast	LENT-SOMA	Fibrosis grade $\geq 2$ ATM GA vs. GG: OR=0.23 (0.02–1.04) GSTP1 AG vs. AA: OR= 0.43 (0.12–1.37) SOD2 CT vs. CC: OR= 0.62 (0.23–1.60) TGFB1 CT vs. CC: OR= 1.70 (0.64–4.52) XPD GT vs. GG: OR= 0.76 (0.26–2.10) XRCC1 GA vs. GG: OR = 1.77 (0.82–3.92)
Xie XX (20)	2012	Meta-analysis	2,199	Predictive Value of Xrcc1 Gene Polymorphisms for Side Effects in Patients undergoing Whole Breast Radiotherapy: a Meta-analysis	Breast	RTOG/EORTC, LENT-SOMA, CTC, NIH	Overall radiation toxicity XRCC1/399Gln GlnGln + GlnArg vs. ArgArg: OR=1.28 (1.00–1.64) XRCC1/280His GlnGln + GlnArg vs. ArgArg: OR=0.67 (0.44–1.02)
Zhou L (21)	2011	Research	NA	Association of XRCC1 variants with acute skin reaction after radiotherapy in breast cancer patients		CTC	Acute skin toxicity Grade $\geq 2$ XRCC1 -77TC&CC: 2.86-fold increase

**Table 2** (Continued)

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Lead author, Ref.	Year	Study type	N	Title	Cancer	Scale	Outcome & results
Chang-Claude J (22)	2009	Retrospective	409	Genetic polymorphisms in DNA repair and damage response genes and late normal tissue complications of radiotherapy for breast cancer	Breast	RTOG/EORTC, LENT-SOMA	Telangiectasia APEX1/148Gln TG+GG vs. TT: OR = 0.90 (0.53–1.54) XRCC1 - 77 T>C TC+CC vs. TT: OR = 1.17 (0.71–1.95) XRCC1/194Trp CT+TT vs. CC: OR = 0.57 (0.24–1.38) XRCC1/280His GA+AA vs. GG: OR = 0.43 (0.17–1.09) XRCC1/399Gln GA+AA vs. GG: OR = 0.96 (0.59–1.57) XRCC2/188His GA+AA vs. GG: OR = 0.84 (0.41–1.74) XRCC3/241Met CT+TT vs. CC: OR = 1.07 (0.65–1.77) NBS1/185Gln GC+CC vs. GG: OR = 1.06 (0.65–1.72) XPD/312Asn GA+AA vs. GG: OR = 1.36 (0.82–2.24) XPD/751Gln AC+CC vs. AA: OR = 1.16 (0.70–1.92) P21/31Arg CA+AA vs. CC: OR = 1.27 (0.60–2.68) TP53/72Pro GC+CC vs. GG: OR = 1.66 (1.02–2.71) TP53 PIN3 A1A2+A2A2 vs. A1A1: OR = 1.95 (1.13–3.37)
Moullan N (23)	2003	Retrospective	566	Polymorphisms in the DNA Repair Gene XRCC1, Breast Cancer Risk, and Response to Radiotherapy	Breast	EORTC	Adverse radiotherapy response XRCC1/194Trp Trp vs. Arg: OR = 1.98 (0.92–4.17) XRCC1/280His His vs. Arg: OR = 0.96 (0.42–2.04) XRCC1/399Gln Gln vs. Arg: OR = 1.30 (0.85–1.99)
Andreassen CN (24)	2003	Retrospective	41	Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes	Breast	LENT-SOMA	Fibrosis Grade 3 ED50 enhancement ratio TGFB1 codon 10 Leu/Leu vs. Pro/Leu: 1.09 (0.97–1.24) TGFB1 codon 25 Arg/Arg vs. Arg/Pro: 1.07 (0.98–1.18) TGFB1 position -509 C/C vs. C/T: 1.06 (0.97–1.16) SOD2 codon 16 Val/Val vs. Val/Ala: 1.15 (1.01–1.30) XRCC3 codon 241 Met/Met vs. Thr/Met: 1.02 (0.80–1.30) XRCC1 codon 399 Gln/Gln vs. Arg/Gln: 1.07 (0.94–1.22) APEX codon 148 Glu/Glu vs. Asp/Glu: 1.18 (0.98–1.40) LENT-SOMA Telangiectasia Grade 2-3 ED50 enhancement ratio TGFB1 codon 10 Leu/Leu vs. Pro/Leu: 1.18 (0.89–1.56) TGFB1 codon 25 Arg/Arg vs. Arg/Pro: 1.04 (0.95–1.15) TGFB1 position -509 C/C vs. C/T: 1.03 (0.95–1.13) SOD2 codon 16 Val/Val vs. Val/Ala: 1.16 (0.95–1.41) XRCC3 codon 241 Met/Met vs. Thr/Met: 1.15 (0.95–1.38) APEX codon 148 Glu/Glu vs. Asp/Glu: 1.11 (0.99–1.25)
Seibold P (25)	2015	Meta-analysis	1,883	XRCC1 Polymorphism Associated With Late Toxicity After Radiation Therapy in Breast Cancer Patients.	Breast	RTOG/EORTC, LENT-SOMA, CTCAE, STAT	Skin toxicity XRCC1/rs2682585: OR = 0.77 (0.61–0.96) Breast fibrosis XRCC1/rs2682585: OR = 0.86 (0.71–1.05)

Table 2 (Continued)

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Lead author, Ref.	Year	Study type	N	Title	Cancer	Scale	Outcome & results
Mangoni M (26)	2011	Prospective	87	Association Between Genetic Polymorphisms in the XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, and MGMT Genes and Radiosensitivity in Breast Cancer Patients	Breast	CTC	Acute skin toxicity Grade $\geq 2$ XRCC1/399Gln A/A+G/A vs. G/G: HR =3.04 (0.58–15.90) XRCC1/Arg 194Trp C/T+T/T vs. C/C: HR =1.81 (0.19–17.08) XPD/Asp312Asn A/A+G/A vs. G/G/T+T/T vs. C/C: HR =0.88 (0.19–4.14) XPD/Lys751Gln A/C+C/C vs. A/A: HR =0.95 (0.21–4.29) GSTM1 null allele deletion vs. wild type: HR =1.24 (0.27–5.65) GSTT1 null allele deletion vs. wild type: HR =0.80 (0.15–4.34) MSH2 gIVS12-6T>C C/T+C/C vs. T/T: HR =10.92 (1.61–73.89) MLH1-Ile219Val G/A+G/G vs. A/A: HR =1.35 (0.09–19.28) MGMT-Leu84Phe C/T+T/T vs. C/C: HR =0.58 (0.10–3.51)
Raabe A (27)	2012	Retrospective	83	Association of single nucleotide polymorphisms in the genes ATM, GSTP1, SOD2, TGFB1, XPD and XRCC1 with risk of severe erythema after breast conserving radiotherapy.	Breast	RTOG	Acute skin toxicity grade $\geq 2$ ATM GA vs. GG: OR =1.18 (0.45–3.25) GSTP1 AG vs. AA: OR =1.01 (0.49–2.09) TGFB1 CT vs. CC: OR =1.26 (0.65–2.50) XPD GT vs. GG: OR =1.85 (0.90–4.00) XRCC1 GA vs. GG: OR =1.02 (0.54–1.93)
Chang-Claude J (28)	2005	Prospective	446	Association between Polymorphisms in the DNA Repair Genes, XRCC1, APE1, and XPD and Acute Side Effects of Radiotherapy in Breast Cancer Patients	Breast	Modified CTC	Acute skin toxicity XRCC1/194Trp CT vs. CC: HR =0.77 (0.35–1.70) XRCC1/280His GA vs. GG: HR =0.51 (0.20–1.31) XRCC1/399Gln GA vs. GG: HR =0.96 (0.58–1.57) APE1/148Glu TG vs. TT: HR =0.88 (0.52–1.49) XPD/312Asn GA vs. GG: HR =0.87 (0.54–1.41) XPD/751Gln AC vs. AA: HR =0.66 (0.40–1.08)
Andreassen CN (29)	2016	Meta-analysis	5,456	Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients	Breast & prostate	Z STAT	Acute injury ATM/rs1801516 (Asp/Asp + Asp/Asn vs. Asn/Asn) OR =1.49 (1.17–1.88) Late injury ATM/rs1801516 (Asp/Asp + Asp/Asn vs. Asn/Asn) OR =1.16 (0.99–1.34)

Table 2 (Continued)

Table 2 (Continued)

Lead author, Ref.	Year	Study type	N	Title	Cancer	Scale	Outcome & results
Terrazzino S (30)	2012	Retrospective	286	Common variants of eNOS and XRCC1 genes may predict acute skin toxicity in breast cancer patients receiving radiotherapy after breast conserving surgery	Breast	RTOG	Acute skin toxicity Grade $\geq 2$ XRCC1 T-77C TT+TC vs. CC: OR =2.240 (1.015-4.941) eNOS G894T TT vs. GT+GG: OR =2.473 (1.220-5.012)
Grossberg (31)	2018	Prospective	287	Association of Transforming Growth Factor $\beta$ Polymorphism C-509T With Radiation-Induced Fibrosis Among Patients With Early-Stage Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial	Breast	LENT-SOMA	Fibrosis grade $\geq 2$ TGFB1 (C-509T) CT+TT vs. CC: OR =4.47 (1.25-15.99)

risk of acute events (16,29), while another 2 studies showed a significant association with late fibrosis (15,17). One study showed a borderline association with late fibrosis (29).

For the *XRCC1* polymorphs, *399Gln*, *280His*, and *194Trp* and *T-77C* were the commonly analysed variants. Out of the 11 studies on the *XRCC1* gene polymorphs, only 3 had a polymorphism that showed significant association with radiosensitivity (20,21,30). In one study (20), *399Gln* was showed a borderline significance with overall radiotoxicity while *280His* did not. In another study (21), *XRCC1 T-77C* mutation was shown to have a 2.86-fold increase in acute skin toxicity. Another study (30) also found that *XRCC1 T-77C* mutation had an increased risk of acute skin toxicity. However, the majority of studies found no significant association of *XRCC1* polymorphisms with radiation toxicity.

A total of 5 studies on the scoring system for radiation toxicity were reviewed (32-36) (Table 3). Three studies compared RTOG with LENT-SOMA (34-36), 1 study compared RTOG with CTC (33), and 1 study compared all three scoring systems (34). In the comparison between RTOG and LENT-SOMA, all related articles concluded that LENT-SOMA is a better scoring system for late radiation toxicities (32,34-36). This could be due to the fact that LENT-SOMA is more comprehensive as it covers a wider range of adverse effects (34) LENT SOMA was noted to more accurately reflect the condition of the patient (36).

On the other hand, the LENT-SOMA scoring has its weaknesses as well. It was noted that the LENT-SOMA scoring is more complex and time-consuming than the RTOG scoring, therefore it would not be ideal in a situation that has time constraints (34,35).

In the single comparison between RTOG and CTC, the conclusion was that RTOG had a higher interobserver agreement, however, there was moderate correlation between the two scales in terms of consistency of findings, suggesting that there was not a tangible difference (33).

## Discussion

### *The genetics behind radiosensitivity*

After analysing the results of the reviewed articles, there appears to be some correlation between genetic polymorphisms and the presence of radiosensitivity. However, there remain inconsistent results, therefore it cannot be said for certain that there is a genetic link between the two. Several other factors can affect the

**Table 3** Comparison of studies on scoring systems for radiation toxicity

Lead author	Year	N	Title	Comparison	Conclusion
Denis F (32)	2003	226	Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems	RTOG vs. LENT-SOMA vs. CTC	LENT-SOMA most accurate Low correlation between 3 scales Need for a common toxicity scale to be used
Chinnachamy AN (33)	2013	55	Evaluation of interobserver and interscale agreement in assessing late bowel toxicity after pelvic radiation in patients with carcinoma of the cervix	RTOG vs. CTC	RTOG has higher interobserver agreement Moderate correlation between 2 scales
Hoeller U (34)	2003	259	Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores	RTOG vs. LENT-SOMA	LENT-SOMA a better grading tool
Anacak Y (35)	2001	116	Late radiation effects to the rectum and bladder in gynecologic cancer patients: the comparison of LENT/SOMA and RTOG/EORTC late-effects scoring systems	RTOG vs. LENT-SOMA	LENT-SOMA a further step on reporting late effects Precision makes up for its complexity
Mao MH (36)	2017	109	Comparing the RTOG/EORTC and LENT-SOMA scoring systems for the evaluation of late skin toxicity after <sup>125</sup> I seed brachytherapy for parotid gland cancer	RTOG vs. LENT-SOMA	LENT-SOMA more accurate in the evaluation of late skin & subcutaneous toxicities

development of radiation-induced tissue damage, as a study pointed out that different breast volumes affected the predisposition towards injury (7).

Due to the lack of a uniform scoring system for radiotherapy side effects, it is important to consider that the results of some studies may have been over- or underestimated. Regarding studies that showed a reduced association of the genetic variant with radiosensitivity, they might be considered as anomalies due to the lack of reproducibility when compared to most of the similar studies that prove otherwise. However, each result cannot be discounted, as they all carry their own weight.

There has been a theory that proposes that the phenotype of increased radiosensitivity is a complicated polygenic trait, where multiple gene polymorphisms are involved in bringing out the effect (10). This has been suggested in 4 of the reviewed articles (19,23,24,26). One article showed no increased risk when computing a risk score for multiple alleles (27). The idea is that on their own, these polymorphisms offer low penetrance, but the more polymorphisms an individual has, the combined penetrance will increase the total risk of developing radiosensitivity.

More research needs to be done regarding this hypothesis, as there are limited studies on this topic.

The traditional approach to identifying these gene SNPs have been candidate gene studies, where only selected genes that have been linked to radiosensitivity were researched. The flaw of this technique is that it is unlikely to find more SNPs that can be linked to radiosensitivity. A more recent method has been Genome-Wide Association Studies (GWAS), in which a wider spectrum of SNPs can be discovered (37,38). However, a large sample size, in the thousands, is required for GWAS to be considered reliable, and it may detect many false positive SNPs. It is important for replication studies to be carried out to distinguish the true positive SNPs.

So far, there is no validated genetic biomarker that can be used to predict susceptibility to radiosensitivity. All the studies done have not been conclusive enough to identify a genetic polymorphism that can be used as an indicator. The replicability of data is a major issue, as a lack of consistency in results are detrimental to the overall validity of the proposed hypothesis. Currently, there's the ongoing REQUITE study that aims to validate genetic biomarkers that can be used in the future to predict radiosensitivity (39).

### *The effect of different radiotherapy techniques on adverse effects*

Over the past two decades, there have been technical advances in adjuvant breast cancer radiation, with the advantage of minimising toxicity to the skin, heart and lungs. Radiation factors such as treatment volume (tangential breast fields only versus three or more fields), whole breast dose as well as the boost to the tumour bed, and dose homogeneity, can affect the cosmetic outcome (40). The shorter “hypofractionated” radiation therapy to the whole breast which takes only 4 weeks has been shown to be equivalent to the longer conventional course of radiotherapy which takes 6 weeks. The shorter course is more convenient for patients and is cheaper (41). Current interest in accelerated partial breast irradiation, where only the area around the tumour is irradiated, has led to the completion of several clinical trials, notable the TARGIT-A randomised controlled trial, which demonstrated that low risk patients with early breast cancer, a single dose of radiotherapy delivered at the time of breast conservation surgery, is equivalent to external beam radiotherapy delivered over several weeks (42). Intensity-modulated radiotherapy (IMRT) and volumetric-arc modulated radiotherapy (VMAT) are new radiation techniques that can improve radiation conformity and homogeneity.

### *The role of surgical factors on adverse outcomes*

Besides radiation technique, surgical factors such as excision of large volumes of tissue, and post-operative wound infection can also lead to poor cosmetic outcomes. Recent advances in oncological techniques in breast conserving surgery with use of local tissue flaps and movement of large volumes of breast tissue has also led to better cosmetic outcomes (43).

### *Scoring systems dilemma*

All the studies used different scoring systems to grade late radiotherapy side effects. Besides a few studies using vague terms to describe tissue injury with no reference to any criteria, the most commonly used scoring systems were the RTOG and LENT-SOMA scale. CTC was only referenced in two studies (32,33).

The consensus is that the LENT-SOMA scale is the most accurate and reliable scoring system. However, it is specific to late toxicities. This result is no surprise, considering

the history of the development of the LENT-SOMA scale in which the original creators of the RTOG scoring system helped its development with the aim of improving reporting and establishing a uniform scoring system for late toxicities (13). The scoring of early radiotherapy toxicities is beyond the scope of this review.

The use of multiple scoring systems to judge toxicity brings about an aura of uncertainty. End-outcomes for studies can be inconsistent and involve different outcomes across the board, making it difficult to make a proper judgment regarding the true effect of SNPs on radiosensitivity. This makes it harder to draw comparisons across multiple studies, especially when performing a review.

## **Conclusions**

Radiogenomics is an upcoming field of research with much potential. The prospect of an individual’s genetic profile being linked to radiosensitivity can enable a more personalized approach to radiotherapy, with customization of dosage to minimise the risk of developing radiation-induced damage to the breast.

However, the genetic links that have been researched and reviewed in this article remain inconclusive. Although there is a general correlation seen between genetic polymorphisms and radiosensitivity post-breast surgery, the research done so far is limited and with small sample sizes. There is still no validated genetic marker that can be used to predict radiosensitivity, although there are studies ongoing. To conclusively establish a genetic component to radiosensitivity, a multi-centre prospective study should be carried out to determine the genetic polymorphisms that affect radiosensitivity. With different radiation techniques, surgical and host factors, it is difficult to determine the contribution of each factor in cosmetic outcomes.

The lack of a uniform scoring system to assess the side effects of radiation is an obstacle in the attempt to accurately determine how genetics affect radiosensitivity. While it is common for different institutions to have their own preference regarding which scoring criteria is adopted, this will make it hard for the analysis and coordination of data when their research comes together.

In conclusion, there is likely a genetic link to radiosensitivity. However, this remains inconclusive as there are no valid markers to predict radiosensitivity. As of right now, radiogenomics is an upcoming field of research. In the future, studies may be able to accurately identify specific

genetic markers. Until then, radiogenomics remains an ocean of vast potential.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob.2019.12.01>). CHY serves as an unpaid editorial board member of *Annals of Breast Surgery* from Oct 2019 to Sep 2021. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/abs.2019.12.01

**Cite this article as:** Song CY, Song CV, Ho GF, Yip CH. The role of radiogenomics in breast radiotherapy. *Ann Breast Surg* 2020;4:7.