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Review

A systematic review and meta-analysis of clinician-reported versus patient-reported outcomes of radiation dermatitis

Emily Lam, Caitlin Yee, Gina Wong, Marko Popovic, Leah Drost, Kucy Pon, Danny Vesprini, Henry Lam, Saleh Aljabri, Hany Soliman, Carlo DeAngelis, Edward Chow*

Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Radiation dermatitis is a common adverse effect of radiotherapy (RT) in breast cancer patients. Although radiation dermatitis is reported by either the clinician or the patient, previous studies have shown disagreement between clinician-reported outcomes (CROs) and patient-reported outcomes (PROs). This review evaluated the extent of discordance between CROs and PROs for radiation dermatitis. Studies reporting both clinician and patient-reported outcomes for external beam RT were eligible. Nine studies met the inclusion criteria for the systematic review, while 8 of these studies were eligible for inclusion in a meta-analysis of acute and late skin toxicities. We found an overall agreement between CROs and PROs of acute skin colour change, fibrosis and/or retraction, and moist desquamation ($p > 0.005$). Reporting of late breast pain, breast edema, skin colour change, telangiectasia, fibrosis and/or retraction and induration/fibrosis alone ($p > 0.005$) were also in agreement between clinicians and patients. Our meta-analysis revealed a greater reporting of acute breast pain by patients (RR = 0.89, 95% CI 0.87–0.92, $p < 0.001$), greater reporting of acute breast edema by physicians (RR = 1.80, 95% CI 1.65–1.97, $p < 0.001$) and a greater reporting of late breast shrinkage by patients (RR = 0.61, 95% CI 0.44–0.86, $p = 0.005$). However, our review was limited by the discrepancies between PRO and CRO measurement tools as well as the absence of standard time points for evaluation of radiation dermatitis. Given potential discrepancies between CROs and PROs, both measures should be reported in future studies. Ultimately, we advocate for the development of a single tool to assess symptoms from both perspectives.

Contents

* Corresponding author. Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada.
E-mail address: edward.chow@sunnybrook.ca (E. Chow).

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1. Introduction

Breast cancer patients receiving radiotherapy (RT) commonly experience acute skin reactions, which affect approximately 90% of treated patients [1]. Although the onset of acute radiation dermatitis (RD) occurs within 1–4 weeks of RT exposure [2], there may also be late effects in the treated area, such as telangiectasia and fibrosis [3]. Notably, fibrosis may increase up to 2 years post-RT before stabilizing [4].

Traditionally, clinician-reported outcomes (CROs) are used to assess skin toxicity [5]. However, there has been recent interest in incorporating patient-reported outcomes (PROs), as these have been shown to enhance symptom management [6]. PROs have been used in cancer research for decades to describe subjective outcomes such as quality of life (QoL) [7]. Although both are often reported individually across studies, the reporting of RD-related CROs and PROs together are uncommon. This is partly because standardized measurement tools used by clinicians and patients tend to measure different outcomes, limiting direct comparisons between CROs and PROs.

For CROs, the most frequently used validated measurement tool for assessing skin toxicity is the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [8]. The majority of PRO measurement tools in the oncology setting are designed to measure QoL [9] and very few have been validated specifically for RD. Previous studies comparing PROs and CROs of other primary cancers have reported disagreement in symptom reporting between patients and clinicians [10–12]. A more comprehensive understanding of studies reporting CROs and PROs related to RT skin reactions in breast cancer patients is needed to assess the validity of current symptom reporting methods and identify areas for improvement.

The purpose of this systematic review and meta-analysis was to evaluate the level of agreement between CROs and PROs in capturing acute and late skin toxicities for breast cancer patients receiving external beam RT.

2. Material and methods

2.1. Search strategy

Ovid MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases were searched (1946–January 2019) using combinations of the following subject headings and free text keywords: 'breast cancer', 'breast neoplasm', 'breast tumour', 'radiotherapy', 'radiation', 'irradiation', 'radiation injuries', 'radiation dermatitis', 'radiodermatitis', 'dermatitis', 'patient' or 'physician' or 'doctor' or 'oncologist' (Appendix A).

2.2. Study selection

Studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Two authors (EL, GW) independently screened the search results for eligibility first by titles and abstracts, then by full text. Discrepancies in inclusion were discussed and resolved with consultation of a third party.

Studies published before January 2019 in the English language reporting both CROs and PROs for acute or late RD in breast cancer patients were eligible. Only studies evaluating skin toxicity due to external beam RT were included. Studies were excluded if endpoints evaluated by CROs did not correspond to those evaluated by PROs. Review articles, case reports, case series and studies of patients with cancer other than breast cancer were excluded. Studies were included in the quantitative analysis if one or more other studies reported the same symptom at a similar time point. The heterogeneity of study time points and skin toxicity assessment tools were limitations to our meta-analysis; however, we sought to compare outcomes measured at similar time points to provide an overview of the literature on this topic.

2.3. Data collection and analysis

The publication year, sample size, time point of toxicity and severity of reactions were recorded. Acute skin toxicity outcomes were defined as those reported within 3 months of RT completion. Outcomes measured more than 3 months after completion of RT were classified as late toxicity. Data extraction was completed by one author (EL) and verified by another author (CY).

2.4. Statistical analysis

Statistical analysis was performed using Review Manager (RevMan 5.3) for Cochrane IMS. For all included categorical variables, the Mantel-Haenszel method was applied alongside a random effect analysis model to generate risk ratios (RR) and 95% confidence intervals (CI). Heterogeneity across studies was tested using the I^2 statistic; $I^2<0.25$ was considered low heterogeneity, $I^2 = 0.25–0.50$ was considered moderate heterogeneity, and $I^2>0.50$ was considered high heterogeneity. A p value of less than 0.05 was considered statistically significant in the test for overall effect and heterogeneity.

3. Results

3.1. Search results

The initial search identified 1099 studies, and 374 duplicates were removed. From the title and abstract screening, 240 records were excluded, with an additional 476 excluded after full-text screening. Altogether, nine studies met the inclusion criteria and were included in the systematic review (Fig. 1). One of these studies [7] was excluded from the meta-analysis because the CROs and PROs for individual symptoms were not reported separately.

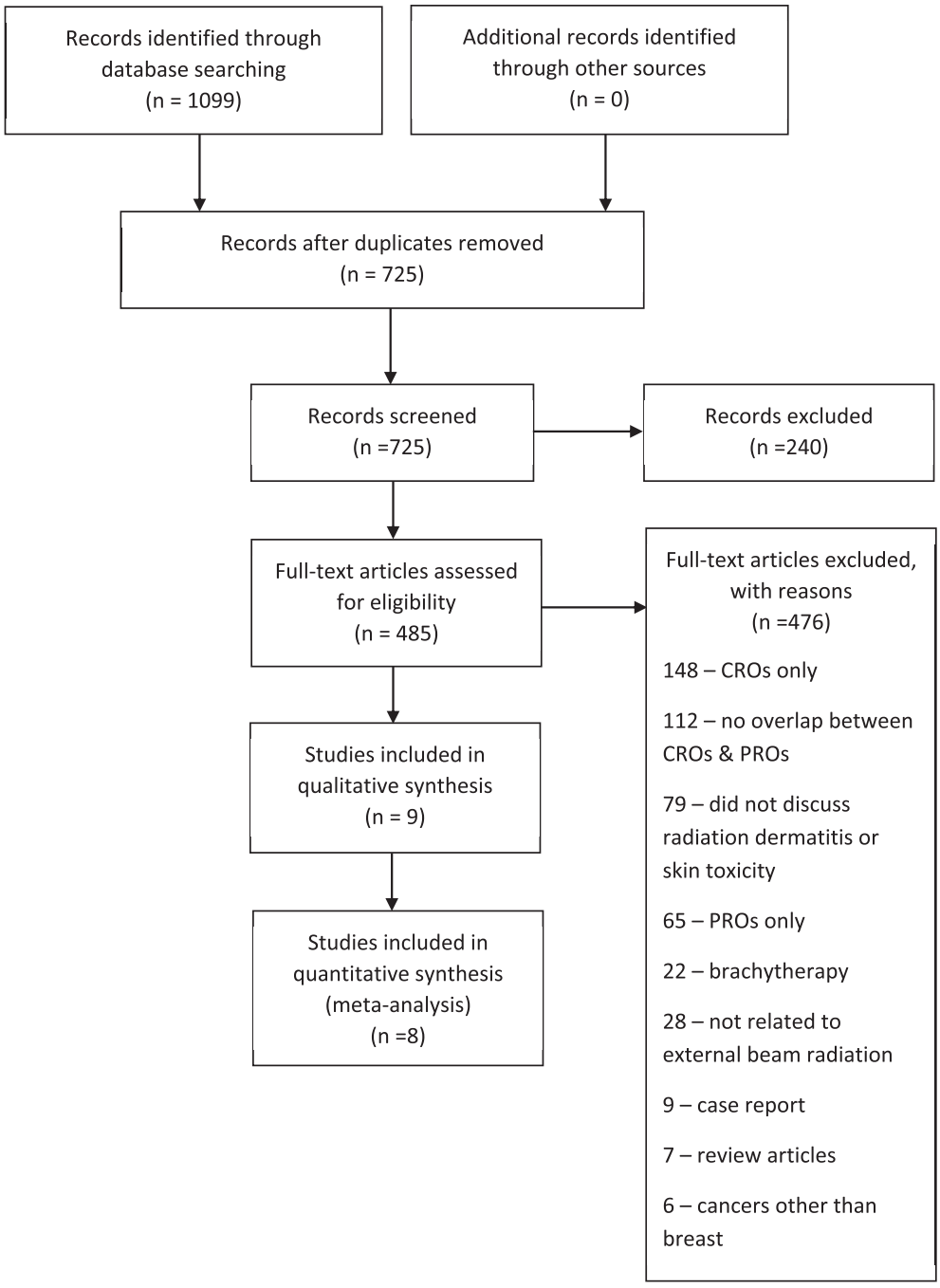


Fig. 1. PRISMA flow diagram.

However, this study was included in the qualitative portion of the systematic review because the correlation between assessment tools was reported for individual symptoms. A single data set had been presented in two publications [14,15]; only one [15] was included in the present review.

3.2. Patient and treatment characteristics

Patient and treatment characteristics are summarized in Table 1. The median sample size was 1029 (range, 20–4451). Of the nine studies, five [15–19] reported the tumour histology, eight [5,7,15,17–21] reported on surgery type and five [5,15–17,20] reported treatment with systemic therapies. All patients received external beam RT. Treatment modalities included accelerated partial breast irradiation (APBI) [18,19], partial breast irradiation (PBI) [15,16] and whole breast irradiation (WBI) [15,17,21]. The most commonly prescribed radiation dose was 40 Gray (Gy) in either 10 or 15 fractions [15,18,19,21]. Supine treatment positioning was only specified in two studies [14,16]. Additionally, only two studies [14,17] reported whether an additional dose of radiotherapy (i.e. boost) was administered to the tumour bed.

Treatment approaches used for the management of RD in most of the studies were not specified, except for Neben-Wittich et al.'s [7] randomized controlled trial comparing mometasone cream to placebo. Reporting of acute and late skin toxicity across studies is summarized in Tables 2 and 3, respectively.

Table 1
Patient and treatment characteristics.

Reference	Sample Size	Age in years (range)	Tumour Type		Tumour Stage			Surgery Type		Chemotherapy	Endocrine Therapy	Radiation Technique	Radiation Dose (Gy)	Fractions	Position	Boost, %
			Invasive carcinoma	DCIS	1	2	3	MX	BCS							
Kozak et al. [16]	20	62[a] (46–75)	20	NA	NS	NS	NS	NS	NS	1	16	PBI	32[c]	8	supine	NS
Jagsi et al. [17]	2309	61.2[a]	1814	495	NS	NS	NS	NA	2309	700	1580	WBI[d]	50.4[a]	NS	NS	84.7
Coles et al. [15]	1343	62[a] (57–67)	1141	NA	NS	NS	NS	NA	1343	62	1212	WBI/PBI	40[c]	15	NS	NS
Sayan et al.[a] [18]	40	73[b] (65–88)	36	NA	20	16	4	NA	42	NS	NS	APBI	40[c]	10	NS	NS
Brouwers et al. [20]	1029	54[a]	NS	NS	NS	NS	NS	28	213	118	106	NS	NS	NS	NS	NS
Azoury et al. [19]	30	64.5[b] (53–79)	28	2	NS	NS	NS	NA	30	NS	NS	APBI	40[c]	10	NS	NS
Mukesh et al. [21]	1145	NS	NS	NS	223	527	240	NA	1145	NS	NS	WBI	40[c]	15	NS	NS
Neben-Wittich et al. [7]	176	58[b] (27–89)	NS	NS	NS	NS	NS	29	140	NS	NS	NS	50[d]	1.75	NS	NS
														−2.12		
Haviland et al. [5]	4451	57[a] (23–86)	4078	NS	1073	2166	1138	513	3938	1284	3760	WBI	50, 41.6, 39	25, 13	supine	51.3

*Abbreviations. BCS = breast conserving surgery; MX = mastectomy; NA = not applicable; APBI = Accelerated partial breast irradiation; NS = not specified; PBI=Partial breast irradiation; WBI=Whole breast irradiation.
[a] Mean.
[b] median.
[c] Prescribed dose.
[d] minimum prescription dose of 50Gy.

3.3. Clinician-reported outcomes

CROs were documented by physicians in all studies except two [20,21], where the CRO was documented by a physician and a trained breast research radiographer or a physician and trial physician assistant. Digital photographs were taken in four studies [5,15,19,21] at various time-points post-RT.

The skin assessment tools used by clinicians included four-point Likert scales (n = 4) [5,15,16,21] where responses were graded as none/mild/moderate/severe or none/a little/quite a bit/very much, the CTCAE (n = 3) [7,17,20], Harvard Breast Cosmesis Scale (HBCS; n = 1) [19], Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC; n = 1) and. These are summarized in Appendix B.

Three studies [16,17,19] reported acute toxicity outcomes, while seven [5,15,16,18–21] reported late skin toxicity outcomes.

3.4. Patient-reported outcomes

PROs were measured using the same tool as the CROs in seven studies [5,15,16,18–21]. Whereas CROs were generally measured using a single tool, PROs were measured using a combination of questionnaires in two studies [7,17]. These included a modified Brief Pain Inventory [22] aimed specifically at assessing breast pain, an 8-item modified Skindex questionnaire, and the Skin Toxicity Assessment Tool (STAT). The Skindex-16 uses an analog scale from 0 (best) to 6 (worst) to measure RD and emotional and functional symptoms related to the skin [23], and the STAT measures acute RD using 3 main components: patient and treatment parameters, objective grading, and PROs on a scale from 0 (best) to 5 (worst) [24]. These tools are summarized in Appendix C.

3.5. Concordance between grading of skin toxicity

Neben-Wittich et al. [7] reported the overall correlation between CROs and PROs rather than individual toxicities. These results could not be included in our quantitative analysis due to an absence of comparative points, this study provided insight into the correlation between skin toxicity grading tools. Both PRO measurement tools had a mild to moderate overall correlation with each other (r = 0.07–0.69), but neither correlated significantly with the CRO tool (CTCAE). Notably, there was a strong correlation between the CRO and PRO items for pruritus and itching, respectively (r = 0.74).

Haviland et al. [5] reported the percent agreement between CROs and PROs at 2 and 5 years, including breast shrinkage (53.4% and 47.4%, respectively), breast induration (47.0% and 49.9%, respectively), breast edema (78.1% and 86.4%, respectively), telangiectasia (55.7% and 62.2%, respectively) and overall changes in breast appearance assessed by photographic comparison (37.9% and 38.4%, respectively).

A comprehensive list of findings from the meta-analysis can be found in Appendix D, and results of the qualitative analysis are summarized in Appendix E.

3.6. Acute Skin Toxicity

Three studies reported acute breast pain [16,17,19]. The pooled analysis of clinician-assessed acute breast pain against patients' self-assessed acute breast pain (Fig. 2) demonstrated that patients reported significantly more acute breast pain than clinicians (RR = 0.89, 95% CI 0.87–0.92, $p < 0.001$, $I^2 = 0$).

Two studies reported acute breast edema [16,17]. A pooled analysis of these two studies showed that physicians reported significantly more acute breast edema than patients (RR = 1.80, 95%

Table 2
Acute skin toxicities.

Reference	Toxicity Time Point	Toxicity Level	Skin Assessment Tool	CRO or PRO	Sample Size	Breast Pain (n = 1739)	Breast Edema (n = 1097)	Skin Colour Change (n = 26)	Fibrosis/ Retraction (n = 4)	Moist desquamation (n = 535)
Kozak et al. [16]	3–4 weeks	Mild/ Mod/Sev	NS	CRO	19	9	6	17	4	4
				PRO	20	11	5	16	10	9
Jagsi et al. [17]	0–7 days	Grade 1-3	CTCAE	CRO	2309	1727	1091	NS	NS	531
				PRO	1723	1441	451	286	NS	349
Azoury et al. [19]	1 month	Mod/Sev	HBCS	CRO	30	3	NS	9	0	NS
				PRO	30	7	NS	7	8	NS

*Abbreviations. CRO = clinician-reported outcome; PRO = patient-reported outcome; CTCAE = Common Terminology Criteria for Adverse Events; HBCS = Harvard Breast Cosmesis Scale; NS = not specified.

Table 3
Late skin toxicities.

Reference	Time Point	Toxicity Level	Skin Assessment Tool	CRO or PRO	Sample Size	Breast pain	Breast Edema	Skin Colour Change	Fibrosis/ Retraction	Induration/ Fibrosis Alone	Breast Shrinkage	Telangiectasia
Kozak et al. [16]	6 months	Mod/Sev	NS	CRO	18	4	0	13	4	NS	NS	NS
				PRO	17	5	0	11	5	NS	NS	NS
Coles et al. [15]	5 years	Mod	CTCAE	CRO	1343	NS	4	NS	NS	45	74	NS
				PRO	1723	NS	2	NS	NS	42	122	NS
Sayan et al. [18]	4.5 years	Mild/Mod	RTOG/EORTC	CRO	37	NS	11	NS	NS	NS	NS	7
				PRO	39	NS	3	NS	NS	NS	NS	5
Brouwers et al. [20]	10 years	Any/Mod/ Sev	CTCAE	CRO	243 (211[a])	120	20	NS	NS	44	NS	NS
				PRO	332 (283[a])	137	98	NS	NS	85	NS	NS
Azoury et al. [19]	2 years	Mod/Sev	HBCS	CRO	25	6	NS	4	3	NS	NS	NS
				PRO	25	8	NS	2	6	NS	NS	NS
Mukesh et al. [21]	5 years	Mild/ Mod/Sev	NS	CRO	576	NS	105	NS	NS	393	229	97
				PRO	576	NS	55	NS	NS	273	261	175
Haviland et al. [5]	5 years	Mild/ Mod/Sev	NS	CRO	1260	NS	79	NS	NS	351	446	128
				PRO	1260	NS	124	NS	NS	597	735	527

*Abbreviations. CRO = clinician-reported outcome; PRO = patient-reported outcome; CTCAE = Common Terminology Criteria for Adverse Events; HBCS = Harvard Breast Cosmesis Scale; Mod = moderate; NS = not specified; RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer; Sev = severe.
[a] Induration/fibrosis alone sample size.

CI 1.65–1.97, $p < 0.001$, $I^2 = 0$) (Fig. 2).

There was no significant difference between PROs and CROs in their reporting of acute skin colour changes (Fig. 2) [16,19], fibrosis and retraction (Fig. 2) [16,19], or moist desquamation (Fig. 2) [15,21].

3.7. Late skin toxicity

Pooled analyses of late breast pain (Fig. 3) [16,19,20], breast edema (Fig. 3) [5,15,16,18,20,21], skin colour changes (Fig. 3) [16,19], telangiectasia (Fig. 3) [5,18,21], fibrosis and retraction (Fig. 3) [16,19], and induration or fibrosis alone (Fig. 3) [5,15,20,21] showed no significant differences between CROs and PROs.

There was a significant difference between CROs and PROs for late breast shrinkage [5,15,21] (RR = 0.61, 95% CI 0.44–0.86, $p = 0.005$, $I^2 = 94\%$), with patients reporting chronic breast shrinkage more often than physicians (Fig. 3). No studies specified whether breast shrinkage was considered to be the same as retraction; therefore, the results were analyzed separately.

3.8. Heterogeneity

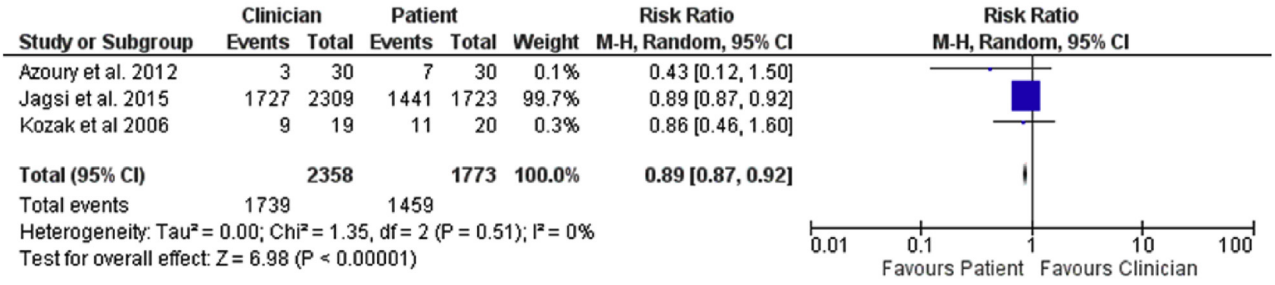
Of all twelve analyzed toxicity outcomes, six parameters contained suitable levels of heterogeneity. The analyses of acute breast pain, acute skin colour change, acute breast edema, late breast pain, late skin colour change and late breast fibrosis/retraction had low heterogeneity (I^2<0.25) with an I^2 statistic of 0. The remaining six analyses had high heterogeneity (I^2 >0.50) with I^2 values ranging from 0.52% to 0.98%.

4. Discussion

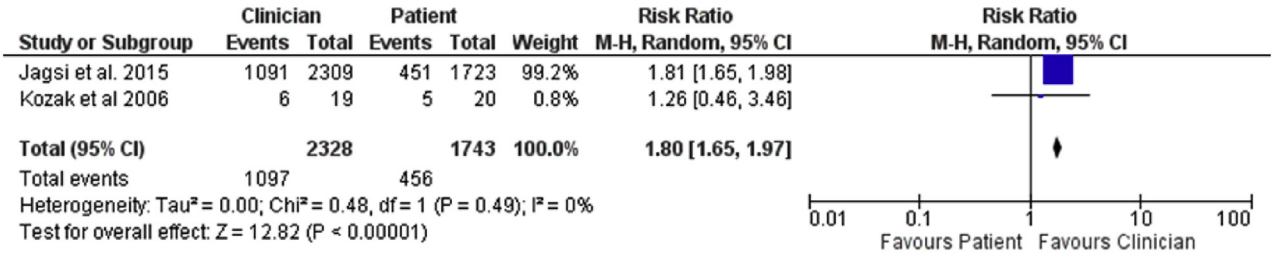
To our knowledge, this is the first meta-analysis comparing CROs and PROs for RD in breast cancer. The findings of this systematic review and meta-analysis suggest that CROs and PROs of RD are largely in agreement. Acute breast pain, acute breast edema and late breast shrinkage were the only measures that were significantly different between CROs and PROs. Of note the symptoms that were similar between CROs and PROs remain of great importance due to its impact on QoL and patient care.

There was considerable variation in the skin assessment tools employed for measuring RD. Of the nine studies examined, two did not report which tools were used to assess the skin [18,21]. Most notably, there lacked a single assessment tool which evaluated skin reactions from both the patients' and physicians' perspectives. One of the restrictions to implementing a single tool into clinical practice is that although oncologists may be familiar with CTCAE gradings, the terminology from the patients' perspective must be adjusted and simplified [25]. Furthermore, patients and clinicians may differ in whether changes to the treated breast are evaluated based on the treated breast at baseline or the untreated breast following therapy [5]. There may be value in implementing a weighted tool for outcomes based on the degree of possible bias from not being able to observe skin toxicities.

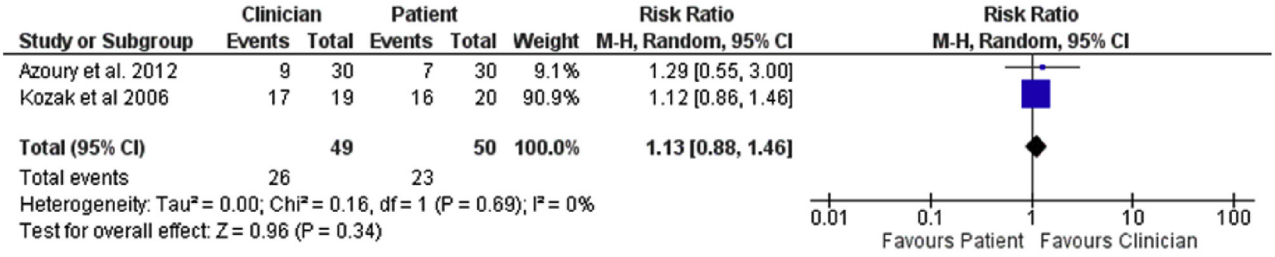
B.1. Acute Breast Pain



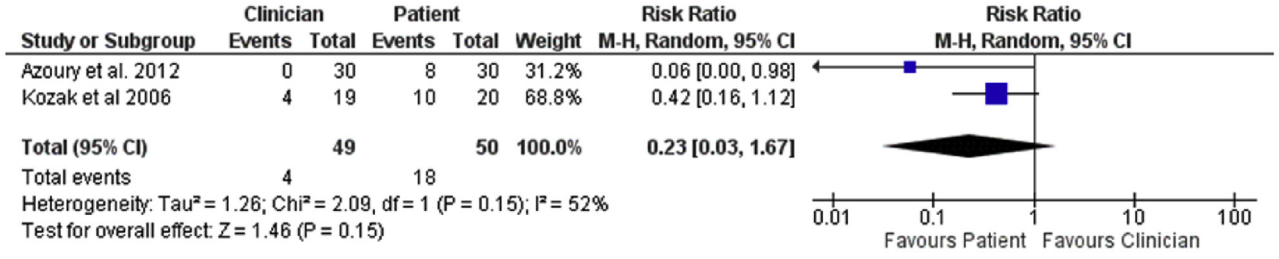
B.2. Acute Breast Edema



B.3. Acute Skin Colour Change



B.4. Acute Fibrosis/Retraction



B.5. Acute Moist Desquamation

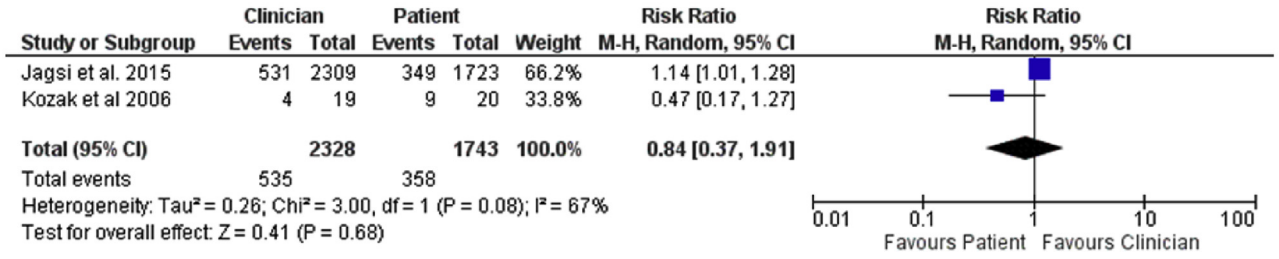
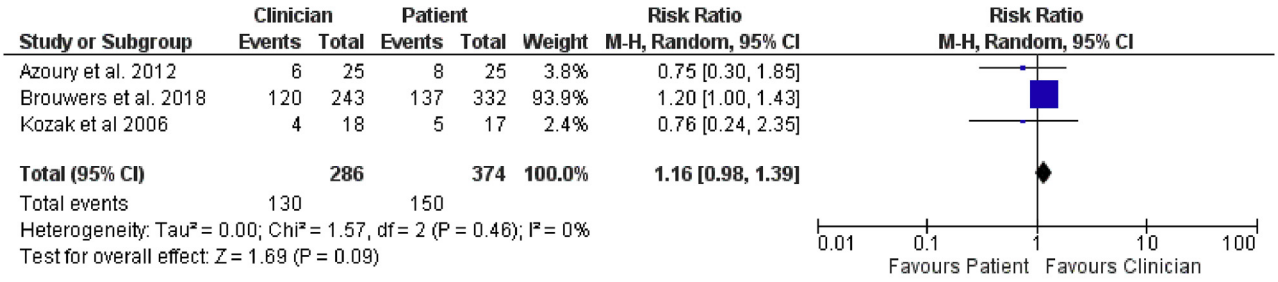
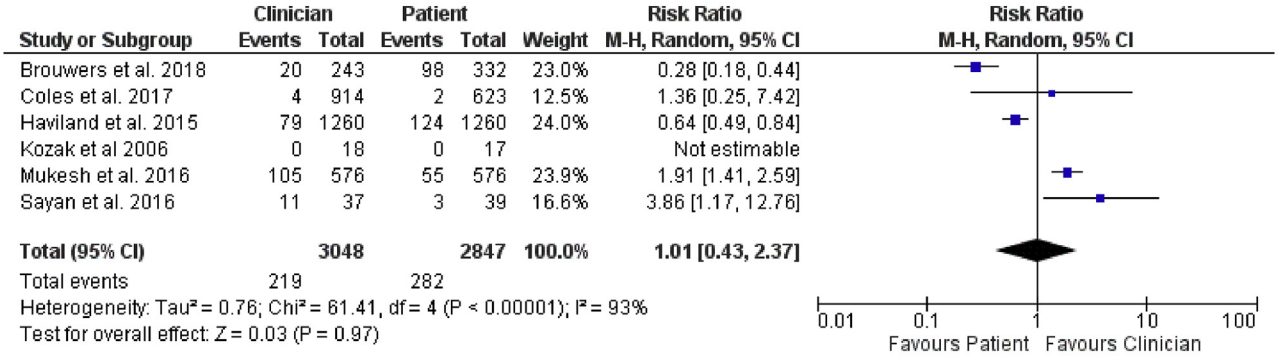


Fig. 2. Acute skin toxicity.

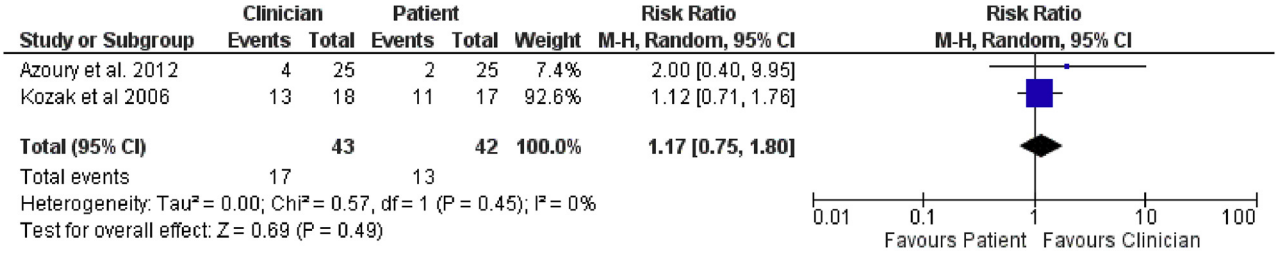
C.1. Late Breast Pain



C.2. Late Breast Edema



C.3. Late Skin Colour Change



C.4. Late Telangiectasia

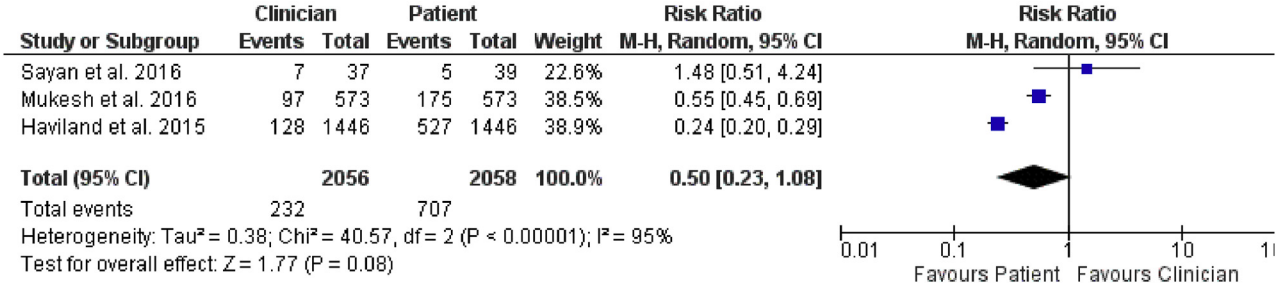
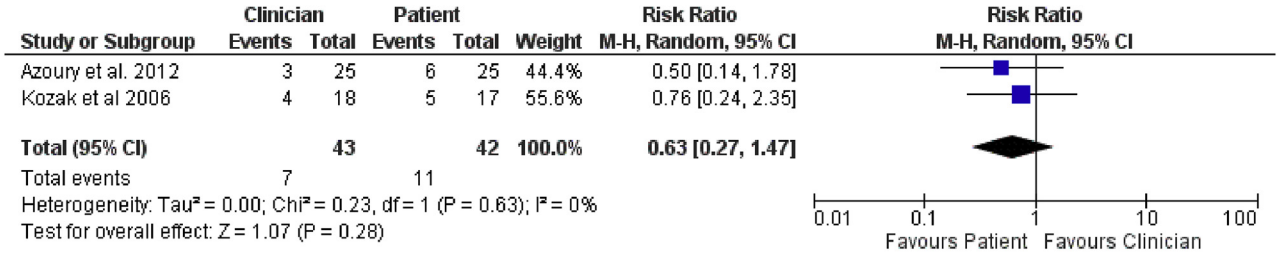


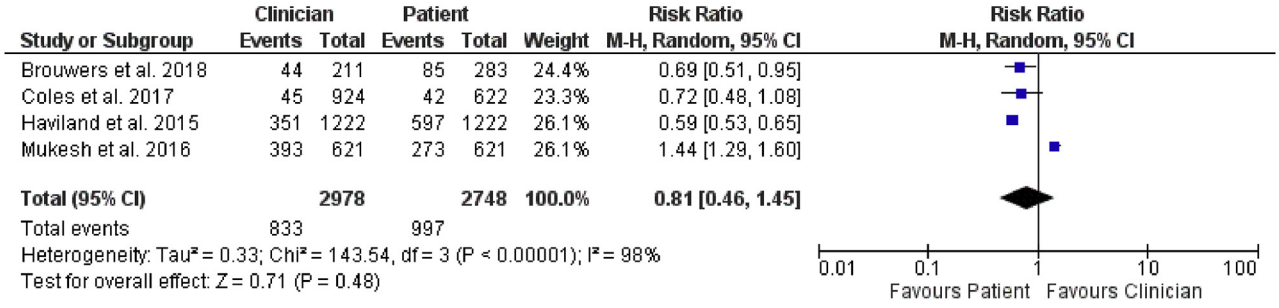
Fig. 3. Late skin toxicity.

The finding that clinicians reported significantly more acute breast edema was heavily weighted on the results from Jagsi et al. [17]. This study had a much larger sample size than the study by Kozak et al. [16], which found no significant difference between patients and physicians in reporting acute breast edema. Notably, there was a discrepancy between edema prompts given to physicians and patients in the study by Jagsi et al.: physicians assessed the maximum toxic effect of 'lymphedema of breast' using the

C.5. Late Fibrosis/Retraction



C.6. Late Induration/Fibrosis Alone



C.7. Late Breast Shrinkage

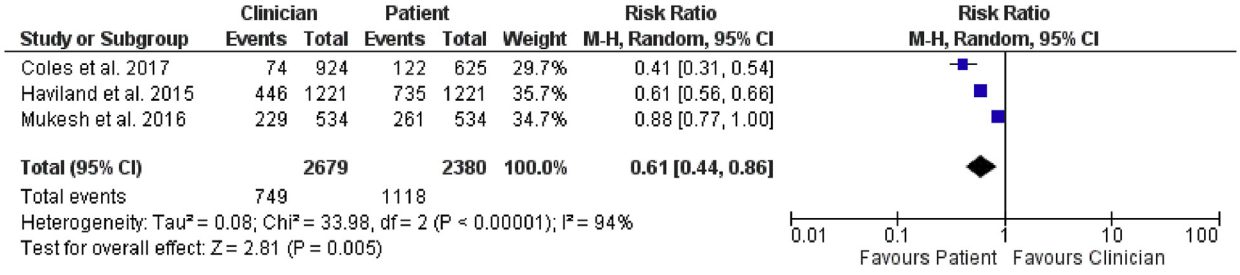


Fig. 3. (*continued*).

CTCAE grading scale from 0 to 2, whereas patients were asked if they were experiencing 'swelling of your breast' using a binary scale (yes or no). Kozak et al. used the same grading scale for physicians and patients. Kozak et al. used external beam proton therapy whereas Jagsi et al. used conventional RT; however, comparisons between proton therapy and conventional RT showed minimal differences in reducing RD in breast cancer patients [26].

The higher rates of physician-reported acute edema could be related to the observability and seriousness of the symptoms [27]. Edema may be more evident to physicians upon physical examination than to patients. Additionally, physicians may be more aware of the serious complications associated with unmonitored edema [28] which may influence increased reporting.

Overall, we found no significant difference between CROs and PROs of late breast edema, although Sayan et al. [18] found that physicians reported significantly more chronic breast edema than patients. This study was the only study in the present review where all patients were ≥65 years old. Limited evidence-based treatment guidelines for elderly breast cancer patients [29] might lead physicians to rely more heavily on clinical judgement, leading to higher reporting of these symptoms. Late skin toxicity outcomes such as this one may also have been confounded by the presence of other treatment or patient-related factors, which could explain the non-significant differences seen between many CROs and PROs. Haviland et al. [5] reported 86.4% agreement and Bhattacharya et al. [14] reported 90.6% agreement between clinicians and patients for breast edema at 5 years which supports the findings of our analysis.

Our meta-analysis demonstrated a significantly greater proportion of patients reporting chronic breast shrinkage than physicians. This is supported by the three studies which showed low agreement between PROs and CROs (47.4% [5] and 47.7% [14]) for breast shrinkage at 5 years. In all three studies, patients reported late breast shrinkage more frequently than clinicians. This could be due to greater self-awareness from patients regarding gross breast volume over time. A cross-sectional study examining body image in long-term breast cancer survivors reported that women who experienced loss or disfigurement of their breasts were more sensitive to their body image [30]. This increased sensitivity may help explain why patients report these changes more often than their physicians which should be taken into consideration due to its impact on QoL. A previous analysis of symptom reporting noted that when physicians reported an absence of symptoms, patients were still experiencing mild symptoms [31]. Although mild patient-reported symptoms may be associated with relatively minor issues, physicians may discontinue treatment before symptoms have completely resolved which can impact QoL [31]. Therefore, accurate

acknowledgement of even mild symptoms has the potential to impact future RD treatment.

Overall, breast fibrosis and retraction were reported significantly more often by patients than clinicians [19]. However, patients did not associate this change with a poorer cosmetic outcome [16,19,20]. Only Mukesh et al. [21] found that clinicians over-reported fibrosis and/or retraction and late toxicities; the authors attributed the difference to adaptations of patients to their health situations. The high overall cosmetic satisfaction reported by patients in this study is consistent with reports in the literature that patients receiving WBI following breast conserving surgery reported good or excellent cosmetic outcomes [32]. Another possible explanation for this difference in this study is that physicians compared the treated breast to baseline photographs, whereas patients made observations based on a comparison of the treated to the contralateral breast [21].

Pain is one of the most commonly reported and notable radiation side effects experienced by patients [33]. Interest in improving the clinical management of pain has led to an increase in studies addressing the prevalence of cancer pain in recent decades [33]. Our pooled analyses of acute pain showed significantly greater reporting by patients ($p < 0.001$) [17,19]. Common reasons for underreporting pain include patients' reluctance to report pain, reluctance of physicians to prescribe analgesics, and insufficient education in pain management for health care providers [34]. The American Pain Society Recommendations [35] for cancer pain management highlight the importance of assessing both clinical practice patterns and patient outcomes in order to better comprehend the source of pain reporting discrepancies and implement changes into clinical practice. Notably, the importance of differentiating between iatrogenic pain and cancer pain may further our understanding of pain management for patients undergoing radiotherapy for breast cancer.

Our results could impact the provision of care received by breast cancer patients by identifying symptoms that are often under-reported by clinicians. Clinicians may more accurately and quickly address patient needs with a more comprehensive understanding of barriers to symptom reporting. Additional education may also be beneficial for patients as it provides the necessary tools to recognize and differentiate expected and abnormal symptoms.

4.1. Study limitations

The limitations of the review included the limited number of studies comparing patient- and clinician-reported skin toxicity outcomes, the absence of standardized measurement tools that allowed for direct comparison between the health care provider and patient, and the varied endpoints for data collection among different studies. The concordance between clinician and patient outcomes was a secondary objective in most of these studies; therefore, some studies might have collected skin toxicity data from clinicians and patients without specifying overall toxicity gradings or individual symptoms that would have allowed for more meaningful comparisons. Furthermore, the absence of information regarding treatment technique and use of breast boost [7,15,16,18–21] limited the comparison between hypofractionation compared to standard fractionation with regards to skin toxicity severity, which has been shown to be greater in patients receiving hypofractionation [3].

The various assessment tools used in the different studies also limited the comparisons made in the meta-analyses. Some studies failed to disclose which assessment scale was used. Furthermore, the ambiguous terminology and difficulties in translating medical terms to more patient-friendly language used in some studies presented the opportunity for inaccuracy when matching outcomes reported by patients and clinicians. For example, Mukesh et al. [21] used the item 'telangiectasia', however the corresponding PRO was 'change in skin appearance'. Although the scales used by Jagsi et al. were different between clinicians and patients, relatively equal comparisons were made because any pain reported (mild or moderate or severe) by clinicians allowed for similar comparisons to patients reporting the presence of pain (yes). Additionally, differences in approaches to prevention and management of RD could therefore have contributed to the heterogeneity in study design and may have affected the PROs and CROs across studies. This review highlighted the lack of standardized reporting tools for RD, both from the perspective of patients and clinicians.

Lastly, our analysis was limited by the time points at which data was collected. The commonly used time points for acute reactions were between 3 weeks and 3 months. Furthermore, late skin toxicities were reported between 6 months and 10 years after radiotherapy. The lack of standard time reporting measures made comparisons between the symptoms more varied, leading to a high degree of statistical heterogeneity. For reactions such as hyperpigmentation, the amount of time elapsed might impact the degree and severity of the observed reaction. Management of RD by patients' treating physicians may have also impacted the reporting rate of late skin toxicities. Despite the wide range of time points between studies, there was no difference for follow-up time between PROs and CROs within individual studies.

5. Conclusion

CROs and PROs of breast RD generally demonstrated strong concordance, although clinicians reported significantly more acute edema, significantly less acute breast pain, and significantly less chronic breast shrinkage than patients. In recent years, the combined application of CROs and PROs has become more prevalent in clinical trials. Discrepancies between clinician and patient reporting of skin toxicities in individual studies highlight an important issue with respect to the accuracy of symptom reporting and subsequent management provided to patients. Future studies should take into consideration the importance of reporting standardized items between physicians and patients. The development of a single tool that accurately and precisely measures RD from both the clinician and patient perspective could greatly improve data collection in future studies and benefit physician comprehension of patients' perceived RD, thereby improving patient care.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.09.009.

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