The Relationship between Cancer Patient's Fear of Recurrence and Radiotherapy: A Systematic Review and Meta-Analysis

Yuan Yang[1]·Josie Cameron[2]·Gerry Humphris[1, 2] *

1. School of Medicine, University of St Andrews, St Andrews, UK
2. Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK

Correspondence to: School of Medicine, Medical and Biological Sciences Building, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9TF, UK.
Email: gmh4@st-andrews.ac.uk. Tel: +44 01334463565
Fax: +44 01334467470

Acknowledgement

We thank Dr. Derek Lowe, Naseem Ghazali and Simon N. Rogers for providing additional data on the study that was included in the meta-analysis. The authors are also grateful to the Breast Cancer Now for supporting this research (grant reference number 6873).

Abstract

Objective: This review aims to provide an overview of the current knowledge available on the nature and extent of the relationship between external-beam radiotherapy (RT) and fear of cancer recurrence (FoR).

Methods: PubMED, Medline and Embase databases were searched to identify relevant studies. Systematic review procedures were followed including a quality assessment. Meta-analysis of suitable studies was conducted.

Results: Twenty-five eligible studies were included in the systematic review and fifteen of them were included in further meta-analysis. Meta-analysis of the available data confirmed a weak relationship between RT and FoR (15 studies, 9567 patients, overall r = 0.053, 95%, CI: 0.021-0.085, P=0.001). Subgroup analysis based on cancer site (breast cancer versus other

types of cancer) revealed that the correlation between RT and FoR was statistically significant in 'other cancer' group (P<0.001) but was nonsignificant in 'breast cancer' group (P=0.538).

Conclusions: While meta-analysis reports a statistically significant association between cancer patient's FoR and the receipt of RT, these results should be interpreted with caution due to significant variability between studies. Further longitudinal studies should be conducted to address the trajectory of FoR over RT in greater detail. Standardized validated FoR measurement would assist this investigation.

Keywords: radiotherapy; fear of recurrence; cancer; oncology; meta-analysis

Background

Radiotherapy is a treatment frequently used for cancer patients involving the use of high-energy radiation [1]. Almost a half to two-thirds of cancer patients will have radiotherapy as part of their treatment plan (adjuvant treatment), and almost 75% of patients who received radiotherapy are treated to cure the cancer, rather than to relieve symptoms such as pain [2]. Radiotherapy is delivered in two ways – external to the body by a machine (external-beam radiation treatment, RT) or within the body by judicious siting of radioactive material (brachytherapy, BT). According to the latest data, about 88 percent of patients received RT while the remaining 12 percent of patients received BT [1, 2].

The fear of recurrence (FoR) is common among cancer patients and survivors [3]. FoR is considered to persist long after the termination of treatment and into the chronic stage of survivorship [3]. FoR is reported by 33% to 96% of cancer patients [4-7] and may predict poorer quality of life outcomes up to six years after diagnosis [8]. Cancer patients who suffer from high FoR report negative behaviour change (e.g. avoidance behaviour and excessive personal checking behaviours) [9], increased health service use [10], inability to plan for the future [11] and significant psychological distress, such as depression, anxiety and post-traumatic stress symptoms [4, 12-14].

In recently published studies, a variety of factors were found to be associated with patients' FoR level [3]. Demographic characteristics such as, female gender, young age, and a higher level of education have been reported to be related with higher FoR. In addition, studies have

shown that white women are more likely to have higher worry levels than African Americans [15-21]. Various treatment characteristics, such as having received a mastectomy or chemotherapy, and having more physical symptoms have been identified as strong predictors of FoR. However, these findings are not always consistent [16, 17, 21-23]. For example, Mellen *et al*. [24] and Leake *et al*. [22] reported that treatment type (chemotherapy, surgery or radiotherapy) was not related to patient's FoR. Llewellyn *et al*. [8] reported that FoR had no association with any socio-demographic or treatment factors.

To date, although studies have reported that cancer patients may suffer from different psychological problems such as anxiety, depression as well as psychological distress, in the course of RT [25, 26], there have been few studies investigating, specifically, the relationship between patient's FoR and RT. A previous systematic review by Simard *et al*. [3] reported a weak to moderate association between treatment type (surgery/chemotherapy/radiotherapy) and FoR. However, the result is not entirely convincing as it combines RT and BT. They are different treatment applications, as previously highlighted, and are likely to be perceived by patients with a variety of psychological representations. Therefore, our research team decided to focus deliberately on a specific study of RT and its possible association with FoR and exclude BT. The reasons to focus, solely on RT, as opposed to, or in combination with BT, is that RT is the most frequent medium of treatment using ionizing radiation which involves specific units including resource intensive physical and capital environments in the design of clinics and specialist units, while BT is more novel, delivered on a smaller scale and with less public awareness of the procedure. There may be value to the health provider team to learn of patient reaction to their treatment and enable additional avenues of intervention to assist patients through the experience of a common treatment delivery in cancer care.

The aim of this study is to conduct a systematic overview and meta-analysis of FoR-RT-related quantitative studies to test the association between cancer patient's FoR and the receipt of RT. By systematically summarising current knowledge, an indication of the influence of RT on FoR may be provided.

Method

Literature search

The study was conducted in accordance with the PRISMA guidelines for a systematic review and meta-analysis [27]. The Ovid MEDLINE, PubMed and Ovid EMBASE (1974 to May, 2016) databases were utilised. The key search terms were: cancer/carcinoma/neoplasm, fear/worry/concern, recurrence/progression/return, and radiation/radiotherapy/radiation therapy. Searching was performed using the OR and AND functions. The detailed search strategy is outlined in Supplementary Table 1. The reference lists of identified review articles as well as all included studies were also screened manually for any additional relevant studies. No restrictions were placed on publication date.

Inclusion and exclusion criteria

To be included in the review, references had to (a) be published in a peer-reviewed journal; (b) be written in English; (c) include adult patients; (d) include patients who had been treated with RT (with/without other treatment type) (e) be quantitative studies and report FoR results. Studies using similar, but not accurate key words, such as 'fear of dying', 'fear of the worst happening' or 'chemoradiotherapy' were excluded. Additionally, studies were excluded if they were case studies, commentaries, reviews, conference abstracts, dissertations, as well as qualitative studies. Studies were screened for eligibility and codetermined by two reviewers (YY and GH).

Data extraction and quality assessment

The search identified potential eligible records. After removing duplicate studies, titles and abstracts of search results were reviewed and unsuitable studies were excluded. Then full papers were obtained and examined, and articles that fulfilled the inclusion criteria for the review were included. For each study, the following information was gathered: first author's name, year of publication, study design and basic demographic information, such as country where the study was conducted, age, and sample size. In addition, cancer type, measure of FoR and main findings were noted.

The quality of each included study was assessed using QualSyst criteria (Standard Quality Assessment Criteria for quantitative studies [28], see Supplementary Table 2). Items were scored on the specific criteria (Yes=2, Partial=1, No=0). A summary score was calculated for each paper and defined as strong (score of >0.80), good (0.70-0.80), adequate (0.50-0.70), or

limited (<0.50). Any paper of limited quality was excluded. In case of disagreement about a paper, reviewers (YY and GH) repeated their assessment of the study and in discussion reached consensus.

Statistical Analysis

On completion of the systematic review, a quantitative meta-analytic approach was applied. The programme Comprehensive Meta-analysis was employed [29]. The effect size was calculated by applying routines to derive a correlation (r) with accompanying 95% confidence intervals (CI). The effect size was calculated by r but not Hedges' g because several of the included articles [20, 30, 31] had very large sample sizes. The corresponding authors of articles with incomplete data were contacted by email to obtain the required data unavailable in the published article. Studies for which the corresponding authors could not be reached were subsequently excluded from the meta-analysis.

Statistical heterogeneity among the articles was reported by the Q statistic, a P-value less than 0.10 or an I-squared value greater than 50% was considered as substantial heterogeneity [29]. If substantial heterogeneity was observed, the correlation will be calculated according to the random-effects model, otherwise, the results would be calculated based on the fixed-effects model. The selection of the computational model was based on the understanding of the underlying distribution. Under the fixed-effect model we assumed that the true effect size was the same in all studies, while in the random-effect meta-analysis, we expected the effect size to be similar but not identical across studies. True effect sizes were assumed to be normally distributed under this model [29].

A subgroup analysis based on the cancer site was performed (breast cancer versus other types of cancer). The percentage of breast cancer patients treated with RT has increased substantially during the past two decades [32]. According to the best available evidence, RT would be recommended in 83% (95% confidence interval, 82-85%) of patients with breast cancer [33]. In the articles included in the meta-analysis, over half of the patients were diagnosed as having breast cancer (5680 out of 9567 patients, 59%). Therefore, the subgroups breast vs. other cancers were chosen pragmatically, to investigate the potential value of cancer type on the relationship between RT and FoR. In addition, Rosenthal's 'fail safe N' procedure was adopted to estimate the number of negative studies that would be required to overturn the total aggregated result. Funnel plot and Egger's regression intercept test were also performed in this review in order to assess publication bias.

Results

Characteristics of included studies

The search process is shown in Supplementary Figure 1. The literature search of three databases identified 751 references. Duplicates were excluded revealing 356 titles. Examination of abstracts for appropriateness left 55 articles. After retrieving full texts and further assessment, 25 studies were included in the systematic review. All of them were evaluated using the QualSyst criteria, and none of them had the score of limited quality (see Table 1). However, 10 studies were excluded from further meta-analysis (one prevalence rate study [34], two longitudinal studies [35, 36], one strong outlier in funnel plot [37], and six did not report specific statistic values [16, 22, 24, 38-40]). Therefore, 15 articles were finally included in the meta-analysis.

The publication dates of the studies included ranged from 1981 to 2016. One article was published in the 1980s, eleven in the 2000s, and the remaining studies were published since 2010. Thirteen studies were conducted in North America, nine in Europe, and one each in Australia, Korea and China. The cumulative sample size including all studies was 11,129 (ranged from 30 to 2671), and the mean age of cancer patients participating in all studies ranged from 44 to 72 years, with 6 studies not reporting a median or mean age. Regarding the FoR instruments, standardized assessment measures were lacking and self-reported questionnaires were frequently used (as opposed to standardised interview). The number of scale items ranged from 1 to 42 and only ten studies reported the validity/reliability of the measurement. Main characteristics and findings of the included publications are presented in Table 2.

Systematic review

Twenty-five studies were included in the systematic review, one article [34] studied the prevalence rate of FoR after RT in mainland China, two longitudinal studies [35, 36] measured patient's FoR level over/after RT, and the remaining twenty two studies [11, 16, 19, 20, 22, 24, 30, 31, 37-50] evaluated the impact of RT on patient's FoR. Conflicting evidence was found among these 22 studies. Seven articles [19, 20, 40, 44, 46, 49, 50] suggested that RT was associated with higher FoR. One [30] suggested that patients who had received RT **were** less likely to experience moderate/high FoR (OR 0.72, CI 0.55-0.94), while the remaining fourteen studies reported that RT and FoR were not systematically associated [16, 22, 24, 31, 37-39, 41-43, 45, 47, 48, 51].

Meta-analysis

The meta-analysis statistics derived from the 15 articles consisted of the following: P-value (nine articles [11, 20, 42, 43, 45-47, 49, 50]), correlation coefficients (three articles [19, 41, 44]), odds ratios (two article [30, 31]) as well as means and SDs (one article, [48]). Heterogeneity test showed that the Q-value of this review was 29.46, the P-value was less than 0.1, and the I-squared value was greater than 50% (P-value=0.009; I-squared=52.482), therefore, a random-effect model was used. By using random-effect weights, the summary estimate of the correlation was 0.053 with a 95% confidence interval (CI) of 0.021 to 0.085. The Z-value was 3.275, and the P-value was 0.001 (two tailed).

Subgroup analysis showed that cancer type was linked to the degree of association, namely, the 'other cancer' group showed a statistically significant correlation between RT and FoR (P<0.001) while the 'breast cancer' group showed a nonsignificant result (P=0.538, see Figure.1). The correlation value of 'other cancer group' (r=0.089) is significantly higher than 'breast cancer group' (r=0.014, P=0.001). Additionally, the fail-safe-N-value, which calculates the number of missing studies that would bring the P-value to less than the alpha of 1.96 was found to equal 64. In the examination of the funnel plot, 15 studies were noticeably distributed symmetrically about the mean effect size (see Supplementary Figure 2). Egger's regression intercept test showed no statistically significant P-value (intercept=0.448, SE=0.61, T=0.74, and P=0.48), therefore, we assume that no apparent publication bias was found in this review.

Discussion

This is the first systematic review and meta-analysis that explores the association between RT and FoR. Overall meta-analysis indicated that patient's FoR level was statistically significantly associated with the receipt of RT, though the correlation is weak. This result should be interpreted with great caution because even though a positive association is shown, it is questionable if this relationship is clinically significant. A careful inspection of the various studies within this review may signal an understanding of why this relationship, although positive, is not strong.

The collective of breast cancer studies showed a nonsignificant relationship between RT and FoR. One possible reason for this is that Koch's study reported 2671 patients with a negative correlation between RT and FoR. This large-sample study dominated the overall breast

cancer group sample size and had therefore a strong influence on the overall subgroup result. In addition, among all the articles, this was the only study that reported RT as a protective factor for cancer patients. Removal of this study resulted in a significant positive association consistent with subgroup result for the other cancer sites.

According to the systematic review, seven studies demonstrated the positive association of RT receipt with greater FoR. The side effects and symptom burden caused by RT may contribute to this result. Significant side effects are common with RT and contribute to the symptom burden. Previous research revealed that RT-induced side effects are usually chronic, progressive, and can be sustained for many years after the end of treatment [52]. Strong evidence was found for an association between residual physical symptoms and elevated FoR [24]. Therefore, it is reasonable to conceive that RT-related symptoms, such as tiredness and skin reaction, might be viewed by patients as a constant reminder of their cancer or be misinterpreted as an indicator of cancer recurrence, which leads to higher FoR score. Also, some patients may believe that the effect of RT may be a risk factor for new malignancies. The results point to the need for patient education about common RT side effects, both before and after RT, to provide patients with sufficient knowledge that they wish to receive. The aim of this additional attention to patient RT health literacy is to diminish FoR development.

Another reason may be patients' doubts about the efficacy of RT. Due to the more conservative nature of RT, patients may feel less confident and hold concern that the tumour/cancer still exists inside their body, thus, patients are more likely to report higher FoR. One study [53] has found out that conservative treatment such as endoscopic therapy for oesophageal cancer was associated with higher FoR, which may relate to patients' doubts about whether the cancer has been fully removed. A further reason for radiotherapy being interpreted by the patient as linked to FoR may be that they believe they have a more serious form of cancer which requires more intensive treatment. Some patients may regard the extra treatment as a useful and important protection against further disease. However a proportion may well regard the additional mode of treatment with a sinister interpretation such as the disease is difficult to treat and is persistent, even in small traces.

There are, inevitably, limitations in this review that require consideration. These include the overall study sample's homogeneity (mostly white, old cancer patients), which precludes generalizations to more diverse populations or younger people with cancer, especially Asian.

A lack of longitudinal studies over the course of RT is another limitation of this review. Many studies are cross-sectional with follow-up assessment. Further studies should focus attention on the development of FoR and how RT makes an influence on it. Moreover, the lack of standardized validated questionnaires is also an important fact which cannot be ignored. FoR was measured using a range of scales among the included articles, and the number of items varied widely. The publication dates of the studies included also varied significantly (ranged from 1981 to 2016). RT techniques have improved considerately in the past 15 years, therefore, patients may report different experience/side effects to RT. Last but not least, this review only involved a small number of studies, only 15 articles were included in meta-analysis. No attempt was made to search for non-English publications or unpublished articles. Hence, we suggest that our research findings must be interpreted with caution.

Interventions in cancer patients may be warranted to alleviate their FoR and other psychological distress during RT. Such interventions could include the offer of counselling and psychotherapy providing adequate treatment-relevant information, and facilitating the support network from both health professionals and families. Cancer survivors who have high levels of FoR should be carefully identified and invited into appropriate psychological programs to assist them and help address overall negative effects on health-related quality of life.

Conclusions

Though meta-analysis showed a statistically significant association between cancer patient's fear of recurrence and the receipt of external-beam radiation treatment, the relationship might not be clinically significant. Further longitudinal studies should be conducted to address the trajectory of FoR over RT in a more detailed way, and standardized validated FoR measurement should be developed and used.

Compliance with Ethical Standards

Funding: This review was funded by Breast Cancer Now (grant number 6873).

Conflict of Interest: Gerry Humphris has received grant support from Breast Cancer Now. Yuan Yang and Josie Cameron declare that they have no conflict of interest.

Ethics: Ethics not required. This article does not contain any studies with human participants or animals performed by any of the authors.

Reference

1. NHS. Radiotherapy. 2015 [cited 2016 May 23]. Available from: http://www.nhs.uk/Conditions/radiotherapy/Pages/Introduction.aspx.
2. U.S PCaDit. About Radiation Therapy. 2010 [cited 2016 May 23]. Available from: http://www.rtanswers.org/statistics/aboutradiationtherapy/.
3. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, Ozakinci G. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *Journal of cancer survivorship : research and practice* 2013; **7**: 300-322.
4. Simard S, Savard J, Ivers H. Fear of cancer recurrence: specific profiles and nature of intrusive thoughts. *Journal of cancer survivorship : research and practice* 2010; **4**: 361-371.
5. Katz ML, Reiter PL, Corbin S, de Moor JS, Paskett ED, Shapiro CL. Are rural Ohio Appalachia cancer survivors needs different than urban cancer survivors? *Journal of cancer survivorship : research and practice* 2010; **4**: 140-148.
6. Harris K, Chow E, Zhang L, Velikova G, Bezjak A, Wu J, Barton M, Sezer O, Eek R, Shafiq J, Yee A, Clemons M, Brundage M, Hoskin P, van der Linden Y, Johnson CD, Bottomley A, Group EQoL. Patients' and health care professionals' evaluation of health-related quality of life issues in bone metastases. *European journal of cancer* 2009; **45**: 2510-2518.
7. Cappiello M, Cunningham RS, Knobf MT, Erdos D. Breast cancer survivors: information and support after treatment. *Clinical nursing research* 2007; **16**: 278-293; discussion 294-301.
8. Llewellyn CD, Weinman J, McGurk M, Humphris G. Can we predict which head and neck cancer survivors develop fears of recurrence? *Journal of psychosomatic research* 2008; **65**: 525-532.
9. Lasry JC, Margolese RG. Fear of recurrence, breast-conserving surgery, and the trade-off hypothesis. *Cancer* 1992; **69**: 2111-2115.
10. Lebel S, Tomei C, Feldstain A, Beattie S, McCallum M. Does fear of cancer recurrence predict cancer survivors' health care use? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2013; **21**: 901-906.
11. Hart SL, Latini DM, Cowan JE, Carroll PR, Ca PI. Fear of recurrence, treatment satisfaction, and quality of life after radical prostatectomy for prostate cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2008; **16**: 161-169.
12. Lebel S, Rosberger Z, Edgar L, Devins GM. Emotional distress impacts fear of the future among breast cancer survivors not the reverse. *Journal of cancer survivorship : research and practice* 2009; **3**: 117-127.
13. Black EK, White CA. Fear of recurrence, sense of coherence and posttraumatic stress disorder in haematological cancer survivors. *Psycho-oncology* 2005; **14**: 510-515.
14. Avis NE, Smith KW, McGraw S, Smith RG, Petronis VM, Carver CS. Assessing quality of life in adult cancer survivors (QLACS). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2005; **14**: 1007-1023.
15. Vickberg SM. The Concerns About Recurrence Scale (CARS): a systematic measure of women's fears about the possibility of breast cancer recurrence. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2003; **25**: 16-24.
16. Stanton AL, Danoff-Burg S, Huggins ME. The first year after breast cancer diagnosis: hope and coping strategies as predictors of adjustment. *Psycho-oncology* 2002; **11**: 93-102.
17. Lee-Jones C, Humphris G, Dixon R, Hatcher MB. Fear of cancer recurrence--a literature review and proposed cognitive formulation to explain exacerbation of recurrence fears. *Psycho-oncology* 1997; **6**: 95-105.
18. Gill KM, Mishel M, Belyea M, Germino B, Germino LS, Porter L, LaNey IC, Stewart J. Triggers of uncertainty about recurrence and long-term treatment side effects in older African American and Caucasian breast cancer survivors. *Oncology nursing forum* 2004; **31**: 633-639.

19. Deimling GT, Bowman KF, Sterns S, Wagner LJ, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psycho-oncology* 2006; **15**: 306-320.
20. Janz NK, Hawley ST, Mujahid MS, Griggs JJ, Alderman A, Hamilton AS, Graff JJ, Jagsi R, Katz SJ. Correlates of worry about recurrence in a multiethnic population-based sample of women with breast cancer. *Cancer* 2011; **117**: 1827-1836.
21. Phillips KM, McGinty HL, Gonzalez BD, Jim HS, Small BJ, Minton S, Andrykowski MA, Jacobsen PB. Factors associated with breast cancer worry 3 years after completion of adjuvant treatment. *Psycho-oncology* 2013; **22**: 936-939.
22. Leake RL, Gurrin LC, Hammond IG. Quality of life in patients attending a low-risk gynaecological oncology follow-up clinic. *Psycho-oncology* 2001; **10**: 428-435.
23. van den Beuken-van Everdingen MH, Peters ML, de Rijke JM, Schouten HC, van Kleef M, Patijn J. Concerns of former breast cancer patients about disease recurrence: a validation and prevalence study. *Psycho-oncology* 2008; **17**: 1137-1145.
24. Mellon S, Kershaw TS, Northouse LL, Freeman-Gibb L. A family-based model to predict fear of recurrence for cancer survivors and their caregivers. *Psycho-oncology* 2007; **16**: 214-223.
25. Stiegelis HE, Ranchor AV, Sanderman R. Psychological functioning in cancer patients treated with radiotherapy. *Patient education and counseling* 2004; **52**: 131-141.
26. Dunn LB, Aouizerat BE, Cooper BA, Dodd M, Lee K, West C, Paul SM, Wara W, Swift P, Miaskowski C. Trajectories of anxiety in oncology patients and family caregivers during and after radiation therapy. *European journal of oncology nursing : the official journal of European Oncology Nursing Society* 2012; **16**: 1-9.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj* 2009; **339**: b2535.
28. Kmet LML, R. C.; Cook, L. S. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. [cited 2016 May 23]. Available from: http://www.biomedcentral.com/content/supplementary/1471-2393-14-52-s2.pdf.
29. Borenstein M, Hedges, L.V., Higgins, J.P.T., Rothstein, H. R. Introduction to Meta-Analysis. United Kingdom: Wiley; 2009.
30. Koch L, Bertram H, Eberle A, Holleczek B, Schmid-Hopfner S, Waldmann A, Zeissig SR, Brenner H, Arndt V. Fear of recurrence in long-term breast cancer survivors-still an issue. Results on prevalence, determinants, and the association with quality of life and depression from the cancer survivorship--a multi-regional population-based study. *Psycho-oncology* 2014; **23**: 547-554.
31. Skaali T, Fossa SD, Bremnes R, Dahl O, Haaland CF, Hauge ER, Klepp O, Oldenburg J, Wist E, Dahl AA. Fear of recurrence in long-term testicular cancer survivors. *Psycho-oncology* 2009; **18**: 580-588.
32. Vicini FA, Sharpe M, Kestin L, Martinez A, Mitchell CK, Wallace MF, Matter R, Wong J. Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. *International journal of radiation oncology, biology, physics* 2002; **54**: 1336-1344.
33. Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for breast carcinoma: a review of the evidence. *Cancer* 2003; **98**: 1977-1986.
34. Hong JS, Tian J, Han QF, Ni QY. Quality of life of nasopharyngeal cancer survivors in China. *Current oncology* 2015; **22**: e142-147.
35. Mehta SS, Lubeck D, Pasta DJ, Litwin MS. Fear of cancer recurrence in patients undergoing definitive treatment for prostate cancer: results from CaPSURE. *The Journal of urology* 2003; **170**: 1931-1933.
36. Perrucci E, Lancellotta V, Bini V, Falcinelli L, Farneti A, Margaritelli M, Capezzali G, Palumbo I, Aristei C. Quality of life and cosmesis after breast cancer: whole breast radiotherapy vs partial breast high-dose-rate brachytherapy. *Tumori* 2015; **101**: 161-167.

37. Wiley JF, Laird K, Beran T, McCannel TA, Stanton AL. Quality of life and cancer-related needs in patients with choroidal melanoma. *The British journal of ophthalmology* 2013; **97**: 1471-1474.
38. Northouse LL. Mastectomy patients and the fear of cancer recurrence. *Cancer nursing* 1981; **4**: 213-220.
39. Rabin C, Leventhal H, Goodin S. Conceptualization of disease timeline predicts posttreatment distress in breast cancer patients. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2004; **23**: 407-412.
40. Hong YM, Hu JC, Paciorek AT, Knight SJ, Carroll PR. Impact of radical prostatectomy positive surgical margins on fear of cancer recurrence: results from CaPSURE. *Urologic oncology* 2010; **28**: 268-273.
41. Humphris GM, Rogers S, McNally D, Lee-Jones C, Brown J, Vaughan D. Fear of recurrence and possible cases of anxiety and depression in orofacial cancer patients. *International journal of oral and maxillofacial surgery* 2003; **32**: 486-491.
42. Liu Y, Perez M, Schootman M, Aft RL, Gillanders WE, Jeffe DB. Correlates of fear of cancer recurrence in women with ductal carcinoma in situ and early invasive breast cancer. *Breast cancer research and treatment* 2011; **130**: 165-173.
43. Rogers SN, Scott B, Lowe D, Ozakinci G, Humphris GM. Fear of recurrence following head and neck cancer in the outpatient clinic. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies* 2010; **267**: 1943-1949.
44. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2009; **17**: 241-251.
45. Sung TY, Shin YW, Nam KH, Chang HS, Rhee Y, Park CS, Chung WY. Psychological impact of thyroid surgery on patients with well-differentiated papillary thyroid cancer. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011; **20**: 1411-1417.
46. Tewari A, Chagpar AB. Worry about breast cancer recurrence: a population-based analysis. *The American surgeon* 2014; **80**: 640-645.
47. Bergman J, Gore JL, Saigal CS, Kwan L, Litwin MS. Partnership and outcomes in men with prostate cancer. *Cancer* 2009; 115: 4688-4694.
48. Ghazali N, Cadwallader E, Lowe D, Humphris G, Ozakinci G, Rogers SN. Fear of recurrence among head and neck cancer survivors: longitudinal trends. *Psycho-oncology* 2013; **22**: 807-813.
49. Rogers SN, Cross B, Talwar C, Lowe D, Humphris G. A single-item screening question for fear of recurrence in head and neck cancer. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies* 2015.
50. van de Wal M, van Oort I, Schouten J, Thewes B, Gielissen M, Prins J. Fear of cancer recurrence in prostate cancer survivors. *Acta oncologica* 2016: 1-7.
51. Hartl K, Janni W, Kastner R, Sommer H, Strobl B, Rack B, Stauber M. Impact of medical and demographic factors on long-term quality of life and body image of breast cancer patients. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2003; 14: 1064-1071.
52. Fang FM, Chiu HC, Kuo WR, Wang CJ, Leung SW, Chen HC, Sun LM, Hsu HC. Health-related quality of life for nasopharyngeal carcinoma patients with cancer-free survival after treatment. *International journal of radiation oncology, biology, physics* 2002; **53**: 959-968.
53. Humphris GM, Rogers SN. The association of cigarette smoking and anxiety, depression and fears of recurrence in patients following treatment of oral and oropharyngeal malignancy. *European journal of cancer care* 2004; **13**: 328-335.

Table 1. Quality assessment of included studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5-7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Quality
	Question Describe	Study Design	Method of subject	Subject characteristics	Intervention /blinding	Outcome /measure	Sample size	Analytic methods	Estimate of variance	Confounding control	Result Report	Conclusion	
Simard	2	2	2	2	N/A	2	2	2	2	1	2	2	Strong
Janz	2	2	2	2	N/A	2	2	2	1	1	2	2	Strong
Hong	2	2	2	1	N/A	2	2	2	2	2	1	2	Strong
Tewari	2	2	2	1	N/A	1	2	2	1	2	2	2	Strong
Van de Wal	2	2	2	2	N/A	2	2	2	1	1	2	2	Strong
Deimling	2	2	2	2	N/A	2	2	2	1	2	2	2	Strong
Liu	2	2	2	2	N/A	2	2	2	1	0	2	2	Strong
Mellon	2	2	2	2	N/A	2	2	2	2	2	1	2	Strong
Sung	2	2	2	2	N/A	2	2	2	2	0	2	2	Strong
Stanton	2	2	2	1	N/A	2	1	2	1	2	1	2	Strong
Hong	2	2	2	1	N/A	2	2	1	2	0	2	2	Strong
Skaali	2	2	2	2	N/A	1	2	2	2	0	2	2	Strong
Bergman	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Rogers[2]	2	2	2	2	N/A	2	2	2	1	0	2	2	Strong
Koch	2	2	2	2	N/A	2	2	2	2	0	2	2	Strong
Rogers[1]	2	2	2	2	N/A	2	2	1	0	0	2	2	Good
Perrucci	2	2	2	1	N/A	2	2	2	0	0	2	2	Good
Wiley	2	2	2	2	N/A	2	1	2	1	0	1	2	Good
Ghazali	2	2	2	1	N/A	2	2	2	1	0	1	2	Good
Rabin	2	2	1	1	N/A	2	1	2	2	1	1	2	Good
Mehta	2	2	2	2	N/A	2	2	1	1	0	1	2	Good
Hartl	2	2	2	1	N/A	2	2	2	0	0	2	2	Good
Humphris	2	2	2	1	N/A	1	1	2	1	1	1	2	Good
Leake	2	2	2	2	N/A	1	2	1	0	0	1	2	Adequate
Northouse	2	2	1	2	N/A	2	0	1	0	0	1	2	Adequate

Quality assessment of included studies. [1]: Rogers (2010); [2]: Rogers (2015).

Table 2. Characteristics of the 25 included studies.

First Author Year, Country	Study Design	Cancer Type	Sample size analysed	Age at survey Mean (SD)	FoR instruments	Reliability	Main findings
Simard, 2009, Canada	Cross-sectional	Breast prostate lung colorectal	N=600	Breast 59.0 (0.6) Prostate 69.1 (0.5) lung 62.0 (1.5) colorectal 61.6 (1.3)	Fear of Cancer Recurrence Inventory (FCRI) 42-item	Cronbach's alpha=0.95, test-retest r=0.89	A significantly higher FCR was found in cancer patients who had RT (P=0.005)
Janz, 2011, USA	Cross-sectional	Breast	N=1837	56.8 (11.4)	Worry about recurrence scale (3-item, rage 1-5)	Cronbach's alpha=0.88	RT was associated with higher FoR (P<0.001)
Hong, 2010, USA	Longitudinal+ %	Prostate	N=584	unknown	Kornblith Scale (CaPSURE Questionnaire)	unknown	Patients who received radiation and/or hormonal therapy experienced greater FoR (OR 2.78, 95%, CI 1.21-6.39)
Rabin, 2004, USA	Longitudinal+ %	Breast	N=69	48.4 (9.3) Range: 30-73	Study-designed FOR Scale	Cronbach's alpha=0.84, test-retest r=0.50	RT (received vs. did not receive) was unrelated with FoR
Tewari, 2014, USA	Cross-sectional	Breast	N=392	unknown	face-to-face interview (single question)	unknown	Having had RT was correlated with increased worry about recurrence (P=0.04)
Deimling, 2006, USA	Cross-sectional	Breast Colorectal Prostate	N=321	72.3 (7.5)	Cancer-related heath worries scale (4-item)	Cronbach's alpha=0.84	Having had RT was significantly related to worry of recurrence but was not a significant predictor (r=0.13, P<0.05)
Mehta, 2003, USA	Longitudinal*	Prostate	N=53	71.6	Fear of Recurrence Scale (5-item)	unknown	FoR was more severe before RT, improved after RT but didn't change substantially in the 2 years thereafter
Hartl, 2003, Germany	Cross-sectional	Breast	N=274	60.0 (11.6)	QLQ-C30-V2.0 questionnaire	unknown	RT had no significant impact on patient's FoR (P=0.75)
Liu,	Longitudinal+	Breast	N=506	58 (10)	First four items from the	Cronbach's	RT was unrelated to cancer patient's FoR

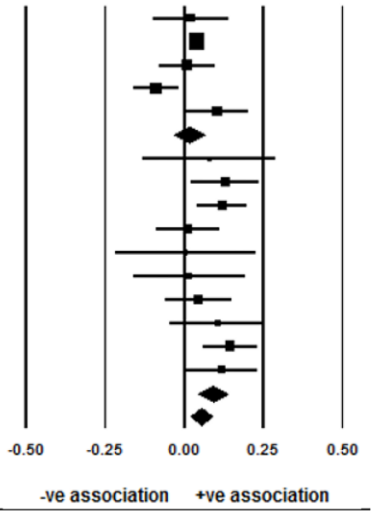
2011, USA					Concern About Recurrence Scale (CARS)	alpha=0.87	(P=0.87)
Humphris, 2003, UK	Cross-sectional	Orofacial	N=87	58.3 (11.3)	Single item from the Worry of Cancer Scale	unknown	RT was unrelated to cancer patient's FoR (r=-0.08)
Northouse, 1981, USA	Cross-sectional[%]	Breast	N=30	Range: 34-74	Fear of Recurrence Questionnaire (22-item)	72% of the items having correlations above 0.6	RT was not significantly related to cancer patient's FoR
Mellon, 2007, USA	Cross-sectional[%]	Breast Colon Uterine Prostate	N=123	65 (6.2) Range: 52-75	Fear of Recurrence Questionnaire (22-item)	Reliability coefficients=0.92	RT was not related to cancer survivors or family caregivers' FoR
Leake, 2001, Australia	Cross-sectional[%]	Gynaecological malignancies	N=202	unknown	A single FoR question	unknown	RT was not related to cancer patient's FoR
Rogers, 2010, UK	Cross-sectional	Head and Neck	N=123	unknown	7-item Fear of Recurrence questionnaire	unknown	There was no relationship between RT and cancer patient's FoR (P=0.86)
Sung, 2011, Korea	Cross-sectional	Thyroid	N=357	43.9 (11.3)	Fear of Progression questionnaire (FoP-Q)	unknown	Use of postoperative radiation treatment had no significant effect on cancer patient's FoP (P=0.414)
Stanton, 2002, USA	Longitudinal[+%]	Breast	N=70	52.63 (11.94) Range: 30-80	6-item from 22-item fear of recurrence Questionnaire	unknown	RT was not significantly related to cancer patient's FoR
Hong, 2015, China	Cross-sectional	Nasopharynx	N=216	47.81 (10.75)	QLQ-C30-V3.0 questionnaire	unknown	FoR was a frequent RT-induced psychological distress in China (Prevalence rate: 18.52%)
Perrucci, 2015, Italy	Longitudinal*	Breast	N=117	unknown	3-item FoR Scale	unknown	FoR was unchanged at a median of 20 and 80 months after partial (P=0.483) or whole breast irradiation (P=0.417)

Skaali, 2009, Norway	Cross-sectional	Testicular	N=1336	44.8 (10.1)	Single question of FoR	unknown	RT was not associated with cancer patient's FoR (P=0.85)
Wiley, 2013, USA	Cross-sectional^	Choroidal melanoma	N=98	63.71 (range-24-88)	The concern of recurrence scale	Cronbach's alpha=0.68	No difference in concern of recurrence between RT/BT group and enucleation group (Fisher's Z=1.280)
Bergman, 2009, USA	Longitudinal+	Prostate	N=78	63 (8)	The memorial anxiety scale (5-item)	unknown	RT was not associated with FoR (P=0.97) and it did not predict change in FoR from baseline to 12 months (P=0.24)
Rogers, 2015, UK	Cross-sectional	Head and Neck	N=513	65 (range 58-72)	Single Item FoR	unknown	There was significant association between having had RT with higher FoR (P=0.001)
Koch, 2013, Germany	Cross-sectional	Breast	N=2671	65	FoP-Q-SF	Cronbach's alpha=0.89	Patient having undergone RT was less likely to experience moderate/high FoR (OR=0.72 (0.55-0.94))
Ghazali, 2013, UK	Longitudinal+	Head and Neck	N=189	62 (12) Range 24-87	7-item FoR Questionnaire	unknown	RT (received vs. did not receive) was not associated with FoR level (M(SD):19.20±9.40 vs. 17.2 ±8.10)
Van de Wal , 2016, Netherlands	Cross-sectional	Prostate	N=283	70 (range 54-89)	Cancer Worry Scale	Cronbach's alpha=0.88	RT is associated with higher FCR (t=-2.033; P=0.043)

Abbreviations: RT: extern-beam radiation treatment; FoR/FCR: Fear of cancer recurrence. FoP: fear or cancer progression; Tx: treatment;
+ Longitudinal design but not over the radiation treatment phase
** Longitudinal design over/after the radiation treatment phase*
% Articles excluded from the meta-analysis - no specific statistical value
^ Article excluded from the meta-analysis - Strong outlier in funnel plot

Fig 1. Meta-analysis of the relationship between RT and FoR

Group by Breast vs Other	Author	Statistics for each study					Correlation and 95% CI
		Correlation	Lower limit	Upper limit	Z-value	P-value	
Breast	Hartl	0.019	-0.099	0.138	0.318	0.750	
Breast	Janz	0.038	0.016	0.061	3.293	0.001	
Breast	Liu	0.007	-0.080	0.094	0.164	0.870	
Breast	Koch	-0.090	-0.163	-0.017	-2.409	0.016	
Breast	Tewari	0.104	0.005	0.201	2.054	0.040	
Breast		0.014	-0.031	0.080	0.616	0.538	
Other	Humphris	0.080	-0.133	0.286	0.735	0.462	
Other	Deimling	0.130	0.021	0.236	2.331	0.020	
Other	Simard	0.120	0.040	0.198	2.946	0.003	
Other	Skaaki	0.011	-0.090	0.112	0.209	0.834	
Other	Bergman	0.004	-0.218	0.227	0.037	0.970	
Other	Rogers 2010	0.016	-0.161	0.193	0.176	0.860	
Other	Sung	0.043	-0.061	0.147	0.816	0.414	
Other	Ghazali	0.105	-0.046	0.251	1.368	0.171	
Other	Rogers 2015	0.145	0.059	0.229	3.295	0.001	
Other	Van de Wal	0.119	0.003	0.232	2.006	0.045	
Other		0.089	0.045	0.133	3.959	0.000	
Overall		0.053	0.021	0.085	3.275	0.001	



Random effects meta-analysis of the correlation between RT and FoR, and subgroup analysis by cancer site. The size of the squares indicates the weight of the study. The diamond indicates the summary correlation. Abbreviation: CI: confidence interval.