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Quality of life of elderly patients with solid tumours receiving adjuvant cancer therapy: a systematic review

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Abstract

Objectives

The measurement of quality of life (QoL) in elderly cancer population is increasingly being recognized as an important part of clinical decision-making and the evaluation of treatment outcome. This systematic review aimed to examine the literature on QoL among elderly cancer patients receiving adjuvant therapy.

Methods

A systematic search was conducted of studies published from inception to December 2016 through major databases. Eligible studies included patients aged ≥65 years old and had solid tumours treated with adjuvant chemotherapy and/or radiotherapy, and QoL was reported as an outcome of the study.

Results

Eighteen studies of moderate-to-high methodological quality evaluating 1,779 patients were identified. Of these 1,779 patients, 1,639 completed the baseline QoL questionnaire and with at least one QoL measurement during and/or following adjuvant therapy were included for data synthesis. Meta-analyses on elderly breast cancer patients treated with standard chemotherapy regimen revealed statistically significant declination of QoL as measured by EORTC QLQ-C30 during (mean difference 8.15, 95% CI 1.65 to 14.65, 721 participants) and at the completion of chemotherapy (mean difference 9.31, 95% CI 1.56 to 17.07, 720 participants). For the studies that did not permit meta-analysis, narrative analysis indicated stable or improved QoL over the course of adjuvant therapy and at follow-up evaluations. Elderly patients with glioblastoma had a significant declination of QoL as measured by EORTC QLQ-C30 at completion of radiotherapy (mean difference 5.70, 95% CI 2.47 to 8.93,

142 participants). Narrative analysis on QoL in elderly patients with colon, prostate, lung, or cervical cancer revealed a uniformly stable or improved QoL over the course of adjuvant therapy and at follow-up evaluations across the studies.

Conclusions

This review suggests that adjuvant chemotherapy and radiotherapy have no longitudinal detrimental impact on QoL in elderly cancer population. Larger studies in different elderly cancer settings are warranted to validate the results.

Strengths and limitations of this study

- This study involved in synthesis of the evidence of global or overall quality of life (QoL) during and following adjuvant chemotherapy and/or radiotherapy in comparison with the baseline in elderly cancer population.
- The studies included in this systematic review were of moderate-to-high quality as assessed by Mols et al's quality rating criteria.
- Due to heterogeneity and lack of availability of data, meta-analysis was not performed in all of the included studies.

Keywords

Elderly cancer patients, quality of life, chemotherapy, radiotherapy, solid tumours, oncology

Introduction

Many countries in the world have an increasing incidence of cancer among older people. This can be attributed to the remarkable growth of the elderly demographic and the common pathophysiology of cancer and aging.[1-2] The demands for and importance of broadening clinical trials to include older adults along with incorporating geriatric-specific endpoints,[3] and integrating geriatric assessment to address the needs of individuals are growing.[4] Although quality of life (QoL) is not formally part of the geriatric assessment, the measurement of QoL in the elderly cancer population is increasingly being recognized as an important patient-reported outcome to complement the clinician's evaluation of disease progression, and the determination of the clinical benefit and burden of cancer treatment, along with toxicity, survival and mortality rates. QoL is also considered as a useful outcome measure to enhance patient-clinician communication and patient compliance in elderly patients with breast cancer during cancer treatment.[5] In a short literature review, Wedding et al (2007) indicated that elderly cancer patients tend to perceive their QoL as more important than gain in survival when compared to younger patients.[6] Nevertheless, our understanding of the impact of cancer treatment on QoL in elderly patients is still very limited at present. Clinically, the decisions regarding cancer therapy and clinical management of elderly cancer patients may be complicated by their vulnerability to chemo-toxicity and the pathological changes of aging together with different considerations of treatment benefit and harm margins, functional decline, tolerability and QoL issues. Extermann et al (2015) revealed an association of QoL impact with dose modification of chemotherapy in older patients in a univariate analysis.[7] The literature indicated that elderly cancer patients are less likely than their younger counterparts to be treated with a full course of adjuvant chemotherapy and radiotherapy.[8] Consideration should be given to approaches that could prolong life expectancy but not at the expense of QoL and physical and psychological functioning. For

cancers with an extremely poor prognosis, such as glioblastoma, extension of survival is less clinically meaningful if the patient has a decline in QoL.[9] It has also been suggested that QoL should be the main endpoint to support clinical decision-making if different cancer treatments have been shown to be equally effective in terms of survival.[10] To our knowledge, a systematic review of the impact of adjuvant therapy on QoL in elderly cancer patients has not yet been published. This systematic review therefore aimed to examine the available evidence in the literature on global or overall QoL and other domains pertaining to QoL during and following adjuvant therapy in elderly cancer patients, and, where possible, to pool data for meta-analysis. The review question was "Does global or overall QoL during and following adjuvant chemotherapy and/or radiotherapy decline or improve in comparison with the baseline in elderly patients with solid tumours?"

Methods

Literature search and study selection

A systematic electronic search of peer-reviewed English-language articles published in CINAHL, CENTRAL, PubMed, PsycINFO, and Web of Science from inception to December 2016 was conducted. A pilot search on CINAHL to identify relevant keywords contained in the title, abstract, and subject descriptors was performed. Three broad categories of concepts were searched: "elderly", "cancer" and "quality of life". The search terms included: (older* OR elder* OR geriatric OR gerontology* OR senior OR aged) AND (oncology OR cancer* OR neoplasm*) AND (quality of life OR QOL). The reference lists of included articles were also examined to identify additional eligible articles.

Clinical trials or observational studies including elderly patients (aged 65 years old or above) with solid tumour who were receiving adjuvant chemotherapy and/or radiotherapy and

prospectively collecting QoL data were eligible. We required that baseline and at least one global or overall QoL data during and/or following adjuvant chemotherapy and/or radiotherapy were collected in the studies so as to allow for comparison before and after adjuvant therapy. Studies that covered heterogeneous age groups were included where subgroup analysis was provided for those aged 65 years old or above. Studies were excluded if they involved patients with haematological malignancy, distant metastatic cancer or recurrent cancer without separate analysis and report of solid tumour or non-metastatic/regional metastatic cancer, and if they evaluated surgical or procedure-related treatment. Studies presented in abstract form, case reports, qualitative studies, and literature review articles were also excluded. Two review authors (LEYT and TDRL) independently performed searching and eligibility assessments. Discrepancies and disagreements in study selection were resolved by consensus.

Data extraction and quality assessment

Review authors (LEYT and TDRL) also independently reviewed and extracted the data from each included study, and the first author (CKKF) performed double-checking. Publication information, sample characteristics, functional status and co-morbidities at baseline (if specified), type of cancer, type of adjuvant chemotherapy and/or radiotherapy, therapy-related adverse effects (if specified), and QoL measurements and results were extracted. Functional status and co-morbidities at baseline, and therapy-related adverse effects (if specified) were also extracted due to concern that they might co-vary with cancer therapy to alter the change of QoL.

The potential bias and quality of the included studies were assessed by the same review authors independently using criteria for assessing the methodological quality of studies of

QoL.[11-12] These criteria include 14 items assessing the methodological aspects of QoL studies; sampling (two items), selection of QoL measurement (one item), data collection process (two items), response rate (two items), group comparison (one item), clarity of reporting (five items), and determination of prognostic factors (one item). For each item, a score of 1 or 0 was made; 1 was assigned for an item meeting the criteria, while 0 was assigned if an item neither met the criteria nor described sufficiently. The possible score ranged from 0 – 14, with ≥10, 7 – 9, and ≤6 indicating high, moderate, and low quality, respectively.

Any persistent discrepancies and disagreements that arose during study selection, data extraction, and quality assessment were reviewed by the first author (CKKF).

Data synthesis

The mean difference in QoL score from baseline to follow-up measurement during and/or following adjuvant chemotherapy and/or radiotherapy with a 95% confidence interval for each study was computed and pooled for meta-analysis using RevMan5.3 software if sufficient information was available (e.g., mean, standard deviation, and sample size of the study). Given that the included studies was heterogeneous in cancer populations, the mean difference of individual studies based on cancer site and adjuvant therapy was pooled for meta-analyses when QoL was measured with the same scale. Heterogeneity between studies was assessed using the Chi^2 test and I^2 statistic. Fixed effects model was used when I^2 value ≤50%, while Random effects model was used when I^2 value >50%. Where meta-analysis was deemed impossible, we summarized the results in a narrative format.

Results

Search results and study characteristics

The initial search identified 56,935 articles, of which 440 were considered potentially relevant after checking for duplicates, title and abstract screening. Of 440 articles for full-text assessment, 18 met the eligibility criteria for inclusion into the review and analysis (Figure 1).[13-30] In most cases, articles were excluded due to the absence of QoL assessment during cancer treatment, age-stratified analysis, and separate reports of QoL for patients receiving adjuvant therapy and for patients with non-metastatic cancer.

The scores of the methodological quality evaluation of the included studies are shown in Table 1. The mean quality score was 9.8 ± 1.2 (range 7 – 12); ten studies attained scores ≥10 (high quality)[13,14,17,20,21,22,24,27,29,30] and eight scored 7 – 9 (moderate quality).[15,16,18,19,23,25,26,28] Items where neither met the criteria nor described sufficiently were sampling (44.4%), clarity of reporting (77.8%), and determination of prognostic factors (100%).

INSERT TABLE 1 HERE

Eleven studies were published between 2000 to 2009, and seven in 2010 to 2015. With respect to country of origin, ten were from Europe, four from the USA, two from South Korea, one from Canada, and one was multi-countries. As for study design, 13 studies were prospective observational studies assessing QoL in patients receiving adjuvant chemotherapy,[14,16,17,19,21,27,28,30] radiotherapy,[13,29] or concomitant chemotherapy and radiotherapy.[23-25] Four were RCTs;[15,18,20,22] of which two compared different chemotherapy regimens on QoL, one study compared chemotherapy and hormonal therapy against hormonal alone on QoL, and another one compared radiotherapy and supportive care with

supportive care alone on QoL. One was validation study which involved QoL evaluation for patients undergoing radiotherapy with or without hormonal therapy.[26]

Sample size was reported by 17 of the 18 studies.[13-28,30] Caffo 2003 did not separately report the number of patients by aged ≥65 years.[29] The sample size of each study varied from 11 to 368.[13-28,30] In all, these 17 studies included 1,779 patients.[13-28,30] Of these 1,779 patients, 1639 completed the baseline QoL questionnaire. The baseline completion rate was 69.5 – 100% across studies. Where reported, the age range of the patients was 65 – 92 years across studies, and the mean age range was 67 – 83 years.[13,14,16,17,19,21-25,28-30] Eleven studies included patients aged ≥80 years.[13,17,19,21,22,24,25,27-30] As for cancer diagnosis, eight studies included patients with breast cancer,[13-20] four studies were glioblastoma,[21-24] and two studies were colon cancer.[27-28] Mixed,[25] prostate,[26] cervical,[29] and lung cancer[30] each were included in one study.

The most frequently used QoL instrument was European Organization for Research and Treatment of Cancer general questionnaire (EORTC QLQ-C30) (14 studies).[13,14,18-24,26-30] Perceived Adjustment to Chronic Illness Scale (PACIS),[15] Breast Cancer Chemotherapy Questionnaire (BCQ),[16] Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B),[17] and M.D. Anderson Symptom Inventory[25] each were used in one study. Nine studies also used a disease-specific QoL instrument together with EORTC QLQ-C30 for breast,[13,14,18-20] brain,[21,22,24] and lung[30] cancer populations.

The follow-up QoL evaluation reported at various intervals during adjuvant therapy and at post-treatment period. Ten studies reported at least one QoL evaluation during adjuvant therapy,[14-16,18-22,28,29] while five evaluated QoL immediately after completion of adjuvant

therapy.[17-19,25,26] Length of QoL evaluation following adjuvant therapy ranged from one month post-treatment to 24 months after the 1st day of adjuvant therapy. Ten studies followed patients for ≤6 months after the completion of adjuvant therapy.[13,14,16,17,19,22,26-28,30] Two studies had QoL evaluation of 24 months after the 1st day of chemotherapy.[15,18]

Geriatric domains of functional status and/or co-morbidities at the baseline were examined and reported in 13 studies.[13-15,17,18,20-24,26,28,30] As shown in Table 2, two studies reported the mean of the Karnofsky Performance Scale (KPS) as ≥90,[13,26] while three reported the median of the KPS as ≥70 at the baseline.[22-24] KPS <70 was used as a cut-off for recruitment criterion in one study.[21] Co-morbid conditions were reported in seven studies;[13,14,17,18,20,28,30] five of these involved patients with limiting co-morbidity or with ≥3 co-morbidities.[13,14,18,28,30] Twelve studies measured cancer therapy-related toxicity during adjuvant therapy,[13,15-18,20-23,28-30] and nine of these used NCI CTCAE.[13,17,18,20,21,22,23,28,30] For haematological toxicity, two studies reported <10% grade 3 – 4 toxicity,[15,28] and four reported ≥25% during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[7,21,23,30] For non-haematological toxicity, a study reported <10% grade 3 – 4 toxicity,[15] and three reported ≥25% during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[17,23,28]

INSERT TABLE 2 HERE

QoL of elderly patients with breast cancer

EORTC QLQ-C30

Three studies measured global or overall QoL using EORTC QLQ-C30 at baseline, in the midst of chemotherapy, at immediately completion of chemotherapy, and at 4 – 12 months

after completion of chemotherapy in elderly patients with breast cancer.[14,18,19] Patients in these studies were treated with the standard chemotherapy regimen for breast cancer, including anthracycline-based, cyclophosphamide/ methotrexate/ flurouracil (CMF) or flurouracil/ epirubicin/ cyclophosphamide (FEC) regimen. In the study of Kornblith et al,[18] about half of the patients received capecitabine. The mean difference in global or overall QoL score from baseline to follow-up measurements of these three studies could be included in the meta-analysis.[14,18,19] Since the study by Kornblith et al[18] involved comparison of standard chemotherapy and capecitabine, separate QoL scores were used in meta-analysis. As showed in Figures 2a and b, the pooled mean difference in global or overall QoL score from baseline to the midst of chemotherapy was 8.15 (95% CI 1.65 to 14.65, 721 participants, I^2 = 78%) and from baseline to immediately completion of chemotherapy was 9.31 (95% CI 1.56 to 17.07, 720 participants, I^2 = 84%), indicating there were significant reductions of global or overall QoL in the midst and at immediately completion of chemotherapy. Major contributor to the high level of heterogeneity (I^2 of 78% and 84%) could be the study of Kornblith et al,[18] which showed small mean difference in the midst and at the completion of capecitabine in compared with those studies involved standard chemotherapy regimen for breast cancer. Nevertheless, the sensitivity analysis by repeating the meta-analysis with the exclusion of Kornblith et al's capecitabine group[18] showed similar results about the declination of QoL during and at the completion of chemotherapy. On the other hand, the pooled mean difference in global or overall QoL score from baseline to 4 – 12 months after completion of chemotherapy was -1.33 (95% CI -4.10 to 1.44, 694 participants, I^2 = 20%), indicating no significant change in QoL at 4 – 12 months after chemotherapy (Figure 2c). Chemotherapy-induced toxicity was not reported in Browall et al and Watters et al's studies.[14,19] Kornblith et al revealed a significantly fewer adverse effects in patients treated with capecitabine than standard regimen during and at the completion of chemotherapy.[18]

INSERT FIGURES 2A-C HERE

Browall et al and Watters et al also reported domain scores and were included in the meta-analysis. [14,19] The pooled mean differences in role and social functioning scores of the EORTC QLQ-C30 from baseline to at completion of chemotherapy were statistically significant, with mean differences of 18.63 (95% CI 9.54 to 27.72, 105 participants, $I^2 = 0\%$) and 12.37 (95% CI 4.20 to 20.55, 105 participants, $I^2 = 0\%$), respectively, indicating there were significant reductions of role and social well-being at the completion of chemotherapy (Figures 3a-b). No significant reductions in role and social functioning scores in the midst and at 4 – 12 months after completion of chemotherapy was found. Only the emotion domain was showed improvement from baseline through follow-up evaluations, with a statistically significantly higher score in the midst of chemotherapy in comparison with the baseline (mean difference -8.79, 95% CI -15.71 to -1.88, 108 participants, $I^2 = 19\%$) (Figure 3c). The domains of physical and cognitive functioning revealed no significant differences from baseline through follow-up evaluations.

INSERT FIGURES 3A-C HERE

The study of Perrone et al used the EORTC QLQ-C30 but provided insufficient data for inclusion in meta-analysis, thus the results of this study is described narratively.[20] On global and domain scores, Perrone et al found no differences from baseline through follow-up measurements of patients treated with CMF or docetaxel.[20] It is of note that 79% and 47% of patients suffered from >grade 2 haematological and non-haematological toxicities, respectively.[20] Arraras et al measured QoL using the EORTC QLQ-C30 in elderly breast

cancer patients treated with radiotherapy.[13] Although this study at baseline started off with a lower level of QoL (score of 59.5), the global or overall QoL scores continually increased significantly from baseline through immediately and 6 weeks after completion of radiotherapy. Severe radiotherapy-induced toxicity did not report in this study.[13]

Other QoL measures

The study of Dees et al measured QoL using the BCQ and found a non-significant declination of global or overall QoL score from baseline to last dose of chemotherapy.[16] Patients in this study was treated with doxorubicin/ cyclophosphamide (AC) regimen, and clinically significant age-related trends in toxicity was not reported.[16] The study of Hurria et al found no significant difference in global or overall as well as physical, social, and emotional well-being from baseline through immediately and 6 months after completion of chemotherapy.[17] Patients in this study were treated with the anthracycline-based, taxane-based, or CMF regimen. It is of note that 27% and 31% of patients suffered from grade 3 – 4 haematological and non-haematological toxicities, respectively.[17] Only the study of Crivellari et al measured QoL using the PACIS and found a statistically significantly improvement in global or overall QoL score from baseline to 18 months of follow-up of chemotherapy.[15] It is of note that patients in this study were treated with CMF regimen and had a low QoL score of 59 at baseline. Less than 10% of patients manifested grade 3 toxicity.[15]

QoL of elderly patients with glioblastoma

The EORTC QLQ-C30 was used in three studies for elderly patients with glioblastoma treated with radiotherapy[22] or concomitant radiotherapy and chemotherapy.[23,24] Because Minniti et al did not report standard deviations,[24] only the studies of Keime-Gulbert et al and Minniti et al were included in the meta-analysis.[22,23] As shown in Figure 4, the pooled mean

difference in global or overall QoL score from baseline to completion of radiotherapy of 5.70 was statistically significant (95% CI 2.47 to 8.93, 142 participants, $I^2 = 83\%$), indicating there was significantly lower global or overall QoL at completion of radiotherapy.[22,23] Keime-Gulbert et al and Minniti et al also reported statistically significantly lower scores in physical, cognitive and social domains, and physical, role and social domains, respectively, during and after radiotherapy in compared with baseline scores.[22,23] Of note, in the study of Minniti et al,[23] patients at baseline started off with a lower level of QoL (score of 58.3), and 28% of them developed grade 3 – 4 haematological toxicity during chemotherapy. Conversely, severe radiotherapy-induced adverse effects was not reported in Keime-Gulbert et al's study.[22] The result of the study of Minniti et al is described narratively.[24] On global or overall and social and cognitive domain scores, Minniti et al found statistically significant improvements from baseline to six months from the start of radiotherapy.[24]

INSERT FIGURE 4 HERE

Gallego et al measured QoL using the EORTC QLQ-C30 in elderly patients with glioblastoma treated with temozolomide, and reported statistically significantly improvements in global or overall QoL and physical, role, cognitive and social domains scores over time.[21] Of note, 25% of patients manifested grade 3 – 4 haematological toxicity in Gallego et al's study.[21]

QoL of elderly patients with colon cancer

Two studies measured global or overall QoL using EORTC QLQ-C30 at baseline, in the midst of chemotherapy, and after chemotherapy in elderly patients with colon cancer.[27,28] However, they provided insufficient data for meta-analysis, thus the results of this study is

described narratively. In the study of Bouvier et al,[27] patients were treated with flurouracil/ oxaliplatin/ capecitabine regimen. This study showed a trend for an increase of global or overall QoL score over time, however, no information about the p-value. The study of Chang et al found no significant worsening of global or overall and functional QoL during capecitabine.[28]

QoL of elderly patients with prostate cancer

The study of Arraras et al measured QoL using the EORTC QLQ-C30.[26] There was no difference in global or overall QoL score from baseline to the last dose of radiotherapy, while a statistically significantly higher QoL score was reported between the last dose and 6 weeks after radiotherapy.[26]

QoL of elderly patients with lung cancer

A study measured overall or global QoL using EORTC QLQ-C30 at baseline and one month after completion of cisplatin plus vinorelbine or carboplatin plus paclitaxel in elderly patients with resectable non-small cell lung carcinoma.[30] In this study, the QoL score of 52 at baseline was low. No significant deterioration of overall or global QoL between baseline and after completion of chemotherapy was found. Severe haematological toxicity was manifested by 39% of patients.[30]

QoL of elderly patients with other cancers

The study of Mohile et al involved different types of cancer, and the QoL was measured before and after radiotherapy using the M.D. Anderson Symptom Inventory.[25] In this study, the score of 2.07 on the scale of 10 at baseline was low. A higher global or overall QoL score

at the completion of radiotherapy in comparison with the baseline was reported, however, no information about the p-value.[25]

Discussion

In the context of cancer, although QoL by its nature is a patient's overall appraisal of the impact associated with the cancer and its treatment, it is a patient-centred, relevant and key clinical parameter to assist and support clinicians in setting goals and mapping avenues for effective cancer treatment regimens beyond extending survival. Although the 18 studies included in this systematic review were somewhat heterogeneous in reporting parameters of QoL and characteristics of study population to permit data pooling for meta-analysis, our results provide some insights that will contribute to a better understanding of the impact of adjuvant chemotherapy and/or radiotherapy on QoL in elderly patients 65 years of age and older. Our current review suggests that elderly cancer patients can tolerate adjuvant therapy without compromising their QoL in the long term. For some elderly patients with breast cancer or glioblastoma, the negative change of global or overall QoL was transient. The role and social domains of QoL was mostly compromised for elderly breast cancer patients at the completion of chemotherapy. Narrative analysis on the impact of adjuvant therapy on global or overall QoL in elderly patients with colon, prostate, lung, or cervical cancer revealed a uniformly stable or improved global or overall QoL over the course of adjuvant therapy and at follow-up evaluations across the studies. However, data pooling and precise estimation could not be achieved because of small numbers of articles reporting QoL in these elderly cancer populations. In general, adjuvant chemotherapy and radiotherapy have no longitudinal detrimental impact on global or overall QoL and other QoL domains in the elderly cancer population. Our results corroborate the findings of a previous thematic review of the literature regarding the impact of local and systematic treatments on QoL in early-stage breast cancer in the elderly which indicated that the negative effects on QoL were often transient, occurring during treatment but resolving upon treatment completion.[5] It was expected that adverse effects, altered functional status, and co-morbidities could co-vary with the impact of cancer

therapy on QoL. Nevertheless, it was difficult to discern whether the short period of QoL impairment, and stable and improved QoL over the course of adjuvant therapy and post-treatment was due to less treatment toxicities, less morbid conditions, or to other reasons. The fact that elderly patients' QoL was maintained or elevated over the course of treatment, despite haematological toxicity across studies,[17,20,21,30] suggests that stable and improved QoL is unlikely to be attributable to less treatment toxicity. Alternatively, it may be that elderly cancer patients undergoing adjuvant therapy experience adverse effects but are able to tolerate them with limited impact on QoL. This may also be due to the tendency of certain elderly patients to complain less and endure higher morbidity associated with adverse effects.[5] Stone et al examined the association between global well-being and age profile in 340,847 people, and showed that people over the age of 50 years have increased global well-being and positive emotion even in the face of a decline in physical health.[31] Another possible explanation for stable and improved QoL could be the response shift phenomenon, where the patients shift in how they appreciate their QoL over time as a result of change in their internal standards of measurement, values, or definition of QoL.[32,33] Nevertheless, for those studies reporting stable global or overall QoL (i.e. no difference in means) across time, their sample size was small and might be of insufficient power to detect differences between baseline and follow-up evaluations. [16,17,27,28,30] It could also be the case that the samples of the included studies may be subject to selection bias pertaining to underrepresentation of less healthy older patients and those with limited expectation of treatment benefit in their individual studies.[3]

Conclusion

The current review suggests that for some elderly patients with breast cancer or glioblastoma, the negative change in QoL was short-term during adjuvant therapy. Adjuvant chemotherapy and radiotherapy had no longitudinal detrimental impact on global or overall QoL and other

QoL domains in the elderly cancer population. Older age should therefore not be the reason to deprive patients of adjuvant chemotherapy and radiotherapy, which they may be able to tolerate.[18] Efforts should be made to optimise the use of effective cancer treatment in elderly patients. Nevertheless, our review results should be viewed with caution, due to heterogeneity in measurement of QoL and lack of availability of data which limit pooling of data for meta-analysis and impact the robustness of evidence synthesis. An attempt was made to contact the study authors for data but without success. In addition, small number of articles with respect to colon, prostate, lung, and cervical cancer makes it impossible for meta-analysis and affects the interpretation of the review results. Larger studies of elderly patients in different cancer settings are warranted to validate the present review results, and to further build the evidence and advance the current knowledge base. These studies should include and stratify elderly patients by functional status, co-morbid conditions, geriatric syndromes, and prognosis, in order to be more representative of the real world population and improve the research validity. Future studies should also include a detailed profile of the cytotoxic effects of chemotherapy and radiotherapy so as to allow the full exploration of the direct and indirect effects of adjuvant therapy on QoL.

Contributors

CKKF, KR contributed to the conception or design of the work, and analysis and interpretation of data. CKKF is responsible for drafting the manuscript. KR critically reviewed and revised the manuscript for important intellectual content. LEYT and TDRL contributed to the acquisition of data and critical revision of the manuscript for important intellectual content. CKKF, LEYT, TDRL, KR provided final approval of the version to be published.

Competing interests

The authors declare that they have no competing interests.

Data sharing statement

No additional data are available

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Figure 1: PRISMA flow diagram for study selection process

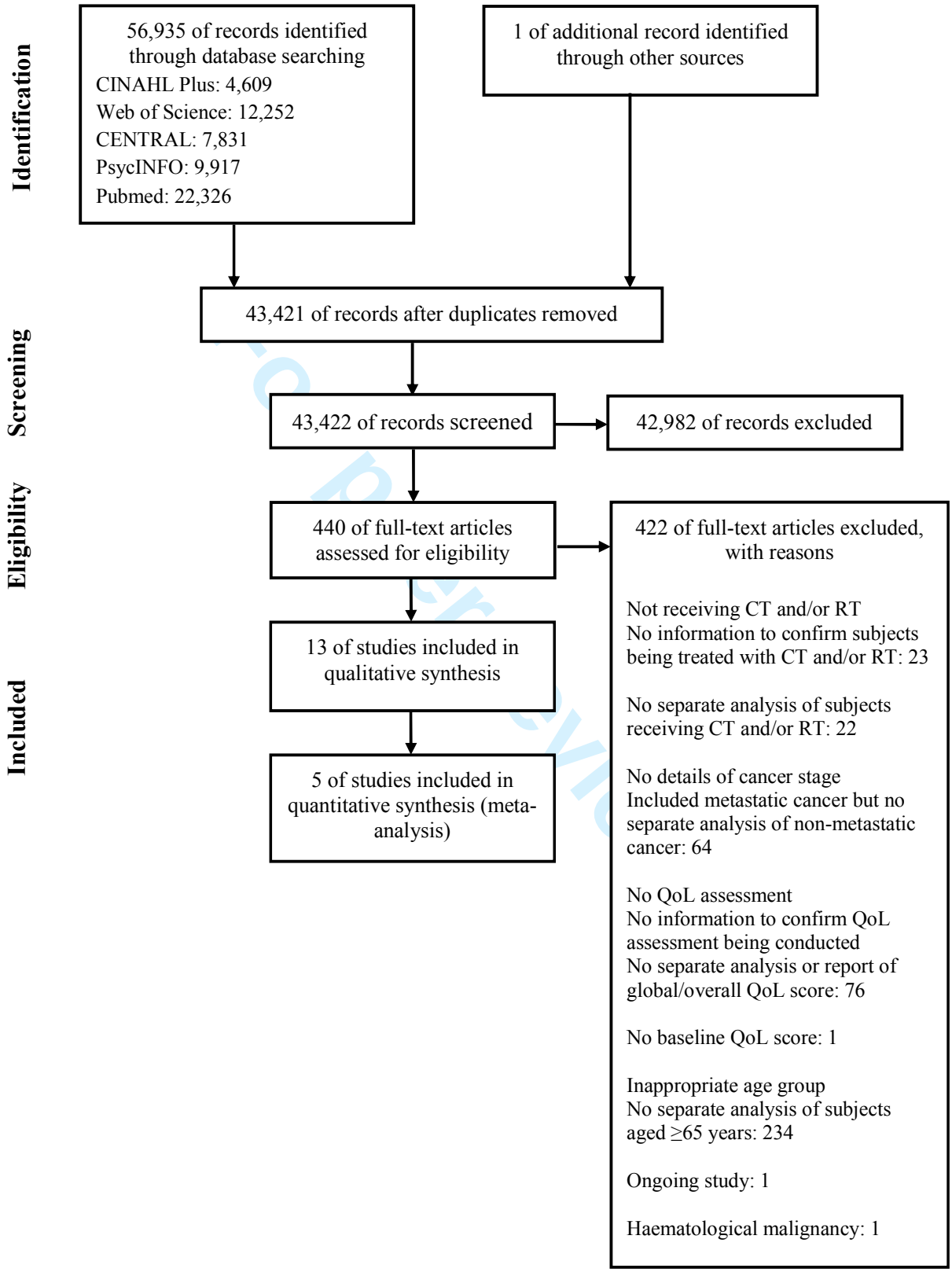

Figure 2a: The pooled MD in global QoL as measured by EORTC QLQ-C30 from baseline to the midst of CT of elderly patients with breast cancer

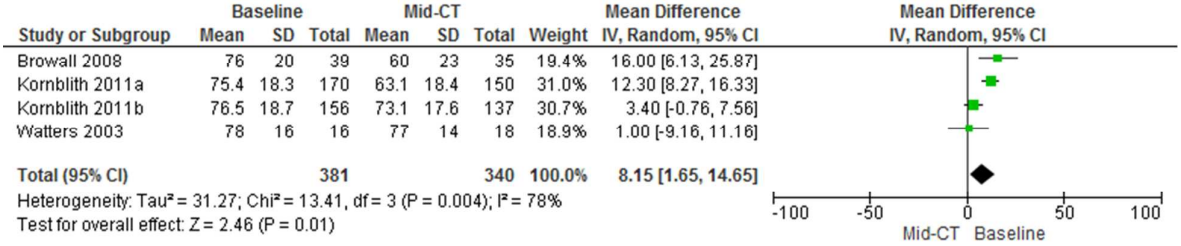

Figure 2b: The pooled MD in global QoL as measured by EORTC QLQ-C30 from baseline to immediately completion of CT of elderly patients with breast cancer

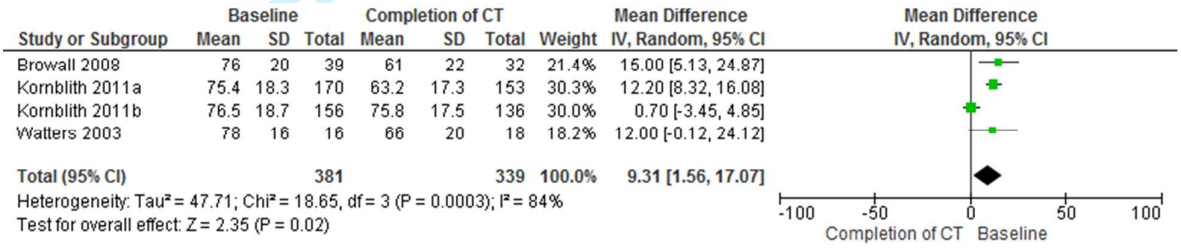

Figure 2c: The pooled MD in global QoL as measured by EORTC QLQ-C30 from baseline to 4-12 months after completion of CT of elderly patients with breast cancer

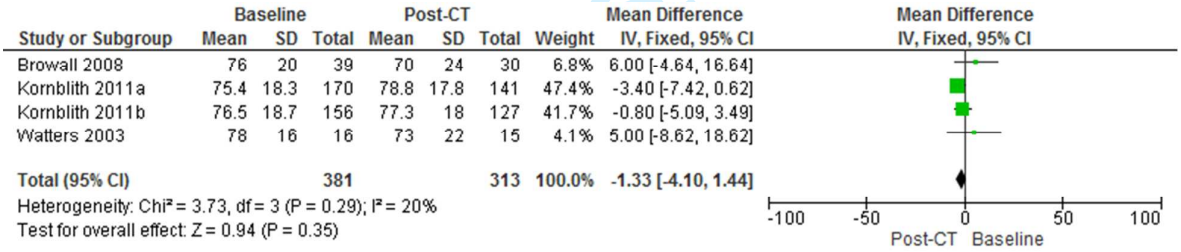

Figure 3a: The pooled MD in role function domain of QoL as measured by EORTC QLQ-C30 from baseline to immediately completion of CT of elderly patients with breast cancer

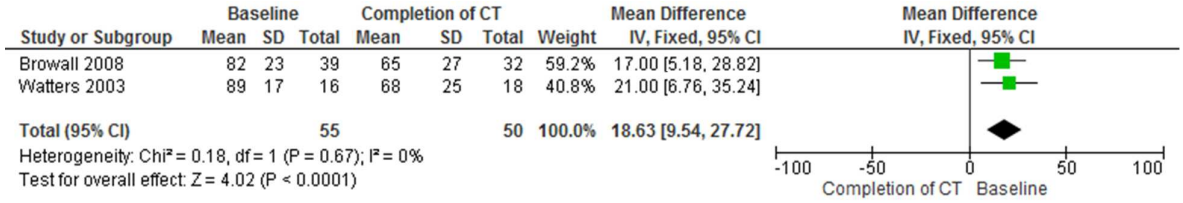

Figure 3b: The pooled MD in social domain of QoL as measured by EORTC QLQ-C30 from baseline to immediately completion of CT of elderly patients with breast cancer

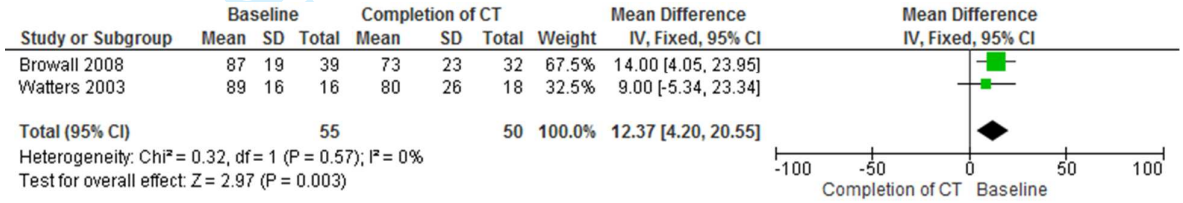

Figure 3c: The pooled MD in emotion domain of QoL as measured by EORTC QLQ-C30 from baseline to the midst of CT of elderly patients with breast cancer

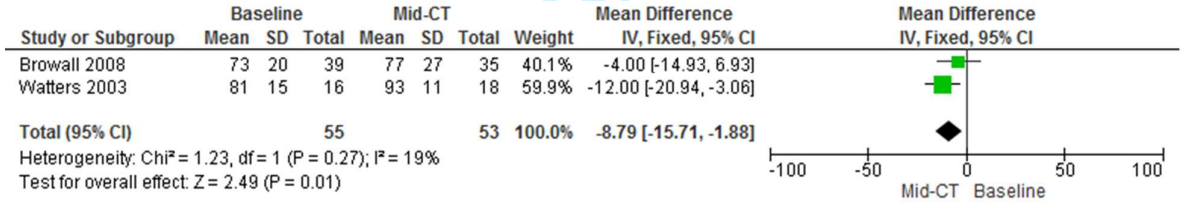

Figure 4: The pooled MD in global QoL as measured by EORTC QLQ-C30 from baseline to immediately completion of RT of elderly patients with glioblastoma

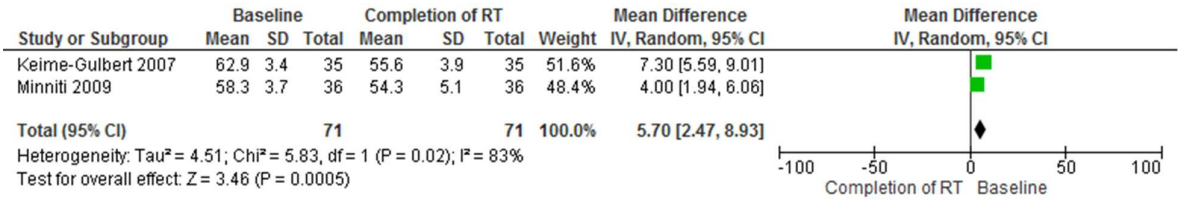

Table 1. Characteristics of the 18 studies reporting on QoL in elderly patients treated with adjuvant chemotherapy and/or radiotherapy

Study / Country	Methodological quality	Type of study	Age (years) Mean ± SD	Sample size	No. of subjects completed baseline QoL measurement (%)	Gender (% female)	Type of cancer	CT/RT	QoL instrument (score range)	QoL measurement time-point
13.Arraras et al (2008), Spain	10, H	Prospective longitudinal observational	72.3 ± 5.7 (range 65-87)	48	48 (100)	100	Breast (Stages 1-III)	RT: Local Locoregional Regional *(no details on dosage)*	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^	• 1st day of RT • Last day of RT • 6 weeks after RT
14. Browall et al (2008), Sweden	11, H	Prospective longitudinal observational	No information on mean age (range 65-77)	39	39 (100)	100	Breast (Stages I-IIIa)	FEC: Flurouracil 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2 for 6 cycles or CMF: Cyclophosphamide 100mg/m^2, methothrexate 40 mg/m^2, flurouracil 600 mg/m^2 for 6 cycles	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^	• Baseline • 1 week after 1st, 2nd, 3rd and last cycle of CT • 4 months post-CT
15. Crivellari et al (2000), Multi-countries	9, M	RCT (longitudinal)	No information on mean age (age ≥65 years)	76	58 (76.3)	100	Breast (Grades I-III)	Tamoxifen for 5 years or Tamoxifen plus 3 early courses of CMF (cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2)	PACIS (0-100)^	• Baseline • 2 months after 1st day of adjuvant therapy then every 3 months until 24 months
16.Dees et al (2000), USA	9, M	Prospective longitudinal observational	71.4 (range 65-79)	17	17 (100)	100	Breast (Early stage)	AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 for 4 cycles	BCQ (0-10)^	• Day 1 of each cycle • 2 months after completing CT • 6 months after completing CT

17.Hurria et al (2006), USA	12, H	Prospective longitudinal observational	68 (range 65-84)	49	49 (100)	100	Breast (Stages I-III)	CMF: Cyclophosphamide 600 mg/m^2, methrotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 for 8 cycles or AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 for 4 cycles or ACT: AC followed by paclitaxel 175 mg/m^2 for 4 cycles or AC followed by paclitaxel 175 mg/m^2 for 12 cycles or ACT-H: ACT followed by trastuzumab 2 mg/kg for 52 weeks *(CT regimen was at the discretion of the treating physician)*	FACT-B (0-148)^	• Prior to CT • Upon completion of CT • 6 months after CT
18. Kornblith et al (2011), USA	9, M	RCT (longitudinal) *(QoL is a sub-study)*	Standard CT (CMF or AC) group 72 ± 4.6 Capecitabine group72 ± 5.0	350	326 (93.1)	100	Breast Stages I-III	Standard CT CMF: Cyclophosphamide 100mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 for 6 cycles or AC: Adriamycin 60 mg/m^2,	#EORTC QLQ-C30 (0-100)^ #EORTC BR23 (0-100)^	• Baseline • Mid-CT (about day 77 for CMF, day 29 for AC, day 63 for capecitabine) • Post-CT (6 to 7 months for CMF, 4 to 5 months for AC and capecitabine) • 12 months post-baseline • 18 months post-

								cyclophosphamide 600 mg/m^2 for 4 cycles or Capecitabine 2000 mg/m^2; dose increased to 2500 mg/m^2 if no toxic effect after 1st cycle for 6 cycles		baseline • 24 months post-baseline
19.Watters et al (2003), Canada	9, M	Prospective longitudinal observational	70±5 (range 65 to 80)	20	16 (80)	100	Breast Stages 1-III	Anthracycline-based adjuvant CT Fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 for 6 cycles	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^ SF-36 (0-100)^	• Prior to CT • Before the 3rd cycle • Completion of CT • 6 months post-CT
20.Perrone et al (2015), Italy	11, H	RCT (longitudinal)	CMF: Median 71 (range 65-79) Docetaxel: Median 71 (range 65-79)	299	252 (84.3)	100	Breast Stages 1-III	Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 on days 1 & 8 every 4 weeks for 4 or 6 cycles or Docetaxel 35 mg/m^2 on days 1, 8 & 15 every 4 weeks for 4 or 6 cycles	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BR23 (0-100)^	• Baseline • End of 1st CT cycle • End of 2nd CT cycle • End of 3rd CT cycle
21.Gallego et al (2011), France	10, M	Prospective longitudinal (non-randomized phase II trial)	Median 77 (range 70-87)	70	59 (84.3)	60	Glioblastoma	Temozolomide (150-200 mg/m^2 for 5 days every 4 weeks for 12 cycles / until disease progression) (*adjusted based on toxicity)*	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Baseline • At least every month
22.Keime-Guibert et al (2007), France	10, M	RCT (longitudinal)	Supportive care + RT group Median 75 (range 70-84)	39	35 (89.7)	37	Glioblastoma	Supportive care (corticosteroids & anticonvulsant agents, physical and psychological support, management by a	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Baseline • Day 30 • Day 60 • Day 90 • Day 135

								palliative care team) & RT (1.8 Gy given 5 days per week, total dose of 50 Gy)		
23.Minniti et al (2009), Italy	9, M	Prospective longitudinal observational	Median 73 (range 70-79)	43	36 (83.7)	51.2	Glioblastoma	Focal hypofractionated RT (total dose of 30 Gy) followed by adjuvant temozolomide up to 12 cycles; 150 mg/m^2 for 1st cycle and adjusted based on toxicity for subsequent cycles	*EORTC QLQ-C30 (0-100)^	• Before RT • After RT • 2nd, 4th & 6th cycles of temozolomide
24.Minniti et al (2013), Italy	10, H	Prospective longitudinal observational	Median 73 (range 70-81)	65	65 (100)	49.2	Glioblastoma	Focal hypofractionated RT (total dose of 40 Gy) plus concomitant temozolomide 75mg/m^2 given 7 days/week followed by adjuvant temozolomide for 12 cycles; 150 mg/m^2 for 1st cycle and 200 mg/m^2 from 2nd cycle	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Before RT • 3-4 weeks after RT • Before CT • Every 8 weeks during treatment until disease progression
25.Mohile et al (2011), USA	7, M	Prospective observational (before/after)	Median 74.1 (range 65-92) (≥65)	368	368 (100)	58.4	Breast Genitourinary Lung Brain and peripheral nervous system Alimentary Haematologic Head and Neck Soft tissue sarcoma: Bone and cartilaginous Skin Gynecologic Melanoma	RT Median total dose of 57.6 Gy (range 30-161)	M.D. Anderson Symptom Inventory (with one rating of overall QOL on an 11-point horizontal scale) ^	• Before RT • After RT
26.Arraras et al (2008), Spain	8, M	Prospective longitudinal (validation)	70.9 ± 5.2	137	137 (100)	0	Prostate (Localized)	Lower risk: RT alone (total dose of 72 Gy) Intermediate risk:	EORTC QLQ-C30 (0-100)^	• 1st day of RT • Last day of RT • 6 weeks after RT

								Neoadjuvant and concomitant combination of an anti-androgen and an LHRH analogue (6 months) + RT (total dose of 76 Gy) High risk: Neoadjuvant and concomitant combination of an anti-androgen and an LHRH analogue (6 months) + RT (total dose of 76 Gy) + adjuvant LHRH analogue		
27.Bouvier et al (2008), France	11,H	Prospective longitudinal observational	No information on mean age (range 75 – 85+)	11 (only 11 patients with stage III colon cancer treated with adjuvant CT and their QoL scores are reported)	11 (100)	NR	Colon	Flurouracil or Oxaliplatin plus flurouracil or Capecitabine *(no details on dosage)*)	EORTC QLQ-C30 (0-100)^	• Baseline • 3 months after diagnosis • 6 months after diagnosis *(CT was given within 6 months after surgery)* • 12 months after diagnosis
28.Chang et al (2012), South Korea	9, H	Prospective longitudinal observational	Median 74.5 (range 70-90)	82	57 (69.5)	64	Colon Stages II-III	Capecitabine (oral, 750-1250 mg/m^2 for 8 cycles) (dose level was based a/c toxicity effects)	EORTC QLQ-C30 (0-100)^	• Baseline • 3 months during CT • 9 months during CT • 3-6 months after completion
29.Caffo et al (2003), Italy	10, H	Prospective longitudinal observational	Median 62.5 (range 46-81)	25 (no information on the breakdown of sample size by age group)	-	100	Cervical endometrium	Post-operative pelvic RT (median total dose of 50.4 Gy)	Authors' developed diary card (0-4)^ EORTC QLQ-C30 (0-100)^	Diary card: • At the start of RT • Daily during RT period (reported as mean weekly scores) EORTC QLQ-C30: • Before RT

										• After RT
30.Park et al (2013), South Korea	11,H	Prospective longitudinal observational	Median 69 (range 65-82)	66	66 (100)	9.1	Non-small-cell lung carcinoma (completely resected stage Ib, II or IIIa)	NP: Cisplatin 80mg/m^2, vinorelbine 25mg/m^2 for 4 cycles or PC: Carboplatin, paclitaxel 175mg/m^2 for 4 cycles	EORTC QLQ-C30 (0-100)^ EORTC QLQ-LC13 (0-100)^	• Before 1st dose of CT at each cycle • 1 month after 4th cycle

^Higher score indicating better quality of life; # Quality of life is the primary endpoint if indicated; * Quality of life is the secondary endpoint if indicated; H is high methodological quality; M is moderate methodological quality

Abbreviations:
BCQ, Breast Cancer Chemotherapy Questionnaire; CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30 general questionnaire; EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer specific module for breast cancer; EORTC QLQ-BN20, European Organization for Research and Treatment of Cancer specific module for brain cancer; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer for lung-specific questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast cancer; NR, not reported; QoL, quality of life; PACIS, Perceived adjustment to chronic illness scale; RCT, randomized controlled trial; RT, radiotherapy

Table 2. Baseline characteristics and the main findings of QoL in the 18 studies

Study	Comprehensive Geriatric Assessment domains	Functional status at baseline *(Functional status during adjuvant therapy if reported)*	Co-morbid condition at baseline	Measurement of CT/RT related toxicity/adverse effect	Toxicity/Adverse effect	Global or overall QoL at baseline	Global or overall QoL's findings *(Other QoL domains/subscales if reported)*
13.Arraras et al 2008	KPS Co-morbidity Daily activities	KPS mean 94.9 *During therapy: KPS decreased from baseline to last dose of RT (mean difference 4.7 [0-100] but returned to baseline 6 weeks after RT)*	Limiting co-morbidity 62.5%	Selected items from NCI CTCAE	At last day of RT: Levels 2-3 skin toxicity 8.4% Level 2 dysphagia 4.2% Level 2 fatigue 4.2% Level 2 pain 2.1%	59.5 (0 – 100)	• Global or overall QoL improved significantly from baseline to final evaluation *Subscales* • Significant worsening in physical and role functioning, and fatigue, pain, and breast symptoms in last day of RT but improved at 6 weeks after RT (final evaluation)
14. Browall et al 2008	Co-morbidity	NR	1 or 2 co-morbidity 61% ≥3 co-morbidities 3%	NR	NR	76 (0 – 100)	• Global health status decreased significantly from baseline to mid-treatment and last dose of CT. The decrease in global health status had not fully recovered to baseline level at 4 months post-CT *Subscales* • Physical (mean difference 15*), role (mean difference 17*), social (mean difference 14*) and cognitive (mean difference 5*) functioning decreased significantly from baseline to last dose of CT • The decrease in physical and role functioning had not fully recovered to baseline levels at 4 months post-CT • No significant change in future perspective, emotional and sexual functioning over time
15. Crivellari et al 2000	ECOG	ECOG ≤2 for subjects to be eligible	NR	Modified WHO toxicity criteria	Grade 3 haematological toxicity 9.2% Other grade 3 toxicity 6.6%	59 (0 – 100)	• Global or overall QoL improved progressively across study points, and from baseline to final evaluation
16.Dees et al 2000	NR	NR	NR	Myelosuppression Cardiotoxicity	Neutropaenic complications and alteration in cardiac function were not	7.65 (0 – 10)	• Global or overall QoL decreased from baseline to last dose of CT but not significant

					significantly age related, no clinically significant age related trends in toxicity		
17.Hurria et al 2006	CCI ADL IADL MMSE GDS BMI	NR	CCI mean 3	NCI CTCAE	Grade 3 or 4 haematological toxicity 27% Grade 3 or 4 non-haematological toxicity 31%	116 (0 – 148)	• No significant longitudinal change in total QoL across all time points *Subscales* • No significant longitudinal change in physical, social, emotional and functional well-being across all time points
18.Kornblith et al 2011	ECOG OARS (Co-morbidity) HADS BOMC Neurobehavioral Functioning & Activities of Living Scale Social Support Survey	ECOG 0-2 for subjects to be eligible Grades 0-1, 96% Grade 2, 4%	0 co-morbidity 4.9% 1 co-morbidity 11.4% 2-3 co-morbidities 21.1% 4-10 co-morbidities 16.3%	NCI CTCAE Systemic adverse effects subscale of EORTC BR23	Patients treated with capecitabine has significantly fewer adverse effects during and at the completion of CT	75.4 (0 – 100) (standard CT) 76.5 (0 – 100) (capecitabine)	• Patients treated with capecitabine had significantly better global QoL than standard CT group. This difference had resolved by 12 months with no further difference at 24 months *Subscales* • Patients treated with capecitabine had significantly better role and social functioning, less fatigue, less nausea and vomiting, less constipation, and better appetite, and less psychological distress than standard CT group at mid-treatment and at treatment completion. These differences had resolved by 12 months with no further difference at 24 months
19.Watters et al 2003	NR	NR	NR	NR	NR	78 (0-100)	• Global or overall QoL decreased significantly from baseline to completion of but improved at 6 months post-CT *Subscales* • Role (mean difference 21*) and social (mean difference 9) functioning decreased significantly from baseline to completion of CT but improved at 6 months post-CT
20.Perrone et al 2015	ECOG CCI ADL IADL	ECOG Grade 0, 83% Grade 1, 17%	No comorbidity 60% 1 comorbidity 31% ≥2 comorbidities 8%	NCI CTCAE	Severe (grade >2) haematological toxicity was suffered by 70% of patients with CMF and 9% with docetaxel, while	NR	Global or overall QoL decreased from baseline to mid-treatment but not significant

					severe non-haematological toxicity was reported in 19% patients with CMF and 28% with docetaxel		
21.Gallego et al 2011	KPS (<70 *as eligibility criteria*) MMSE	Baseline: KPS <70 for subjects to be eligible *During therapy: 33% improved their KPS by ≥10, before disease progression*	NR	NCI CTCAE	Grade 3 or 4 haematological toxicity 25%	NR	• Global or overall QoL improved significantly over time *Subscales* • Physical, role, cognitive and social functioning scores improved significantly over time • For QLQ-BN20, scores on motor dysfunction, drowsiness, and bladder control improved over time before disease progression
22.Keime-Guibert et al 2007	KPS *(≥70 as eligibility criteria)* MMSE	Baseline KPS ≥70 for subjects to be eligible *During therapy: KPS declined over time*	NR	NCI CTCAE	No severe adverse effects related to RT	62.9 (0 – 100) (supportive care + RT)	• Global or overall QoL decreased significantly from baseline to immediately completion of RT *Subscales* • During and after treatment, scores were significantly worse over time on physical, cognitive and social functioning, and fatigue and motor dysfunction
23.Minniti et al 2009	KPS *(≥60 as eligibility criteria)* Co-morbidity	Baseline: KPS ≥60 for subjects to be eligible KPS median 70 *KPS did not change significantly during the study period*	NR	NCI CTCAE	Grades 2-3 confusion and/or somnolence during or after RT 16% Grade 3-4 haematological during CT 28% Moderate-severe fatigue 35%, nausea 10%, constipation 22%, skin rash 9%	58.3 (0-100)	• During treatment, score of global health status did not change significantly *Subscales* • During treatment, scores of functioning subscale, nausea and vomiting, and insomnia did not change significantly • Fatigue and constipation scales worsened slightly from baseline through treatment • Scores of physical, role and social functioning, and fatigue deteriorated significantly between baseline and the 2nd follow up
24.Minniti et al	KPS	KPS ≥60 for subjects to	NR	NR	NR	61.5 (0-100)	• Global health improved significantly over time

2013	MMSE	be eligible KPS median 70					*Subscales* • Social (mean difference 10.4*) and cognitive (mean difference 9.5*) functioning improved significantly from baseline to 6 months from the start of RT • Fatigue (mean difference 5.6*) worsened significantly from baseline to 4 months from the start of RT
25.Mohile et al 2011	No	NR	NR	NR	NR	2.07 (0-10)	• There was an increase of QoL score after RT, however, no information about the p-value • Prevalence of symptoms interfered with QoL increased insignificantly from 49.1% to 58.8% pre and post-RT • Severity of symptoms interfered with QoL increased insignificantly from 2.07 to 2.37 pre and post-RT *Subscales* • The prevalence of memory difficulties and sleep disturbance, and the severity of fatigue and distress significantly increased over the course of RT
26.Arraras et al 2008	KPS	KPS mean 96.1	NR	NR	NR	66.8 (0 – 100)	• No change in global or overall QoL score from baseline to last dose of RT but significantly improved between last dose and 6 weeks after RT
27.Bouvier et al 2008	NR	NR	NR	NR	NR	60	• Graph shows the mean scores of global health increased over time (but no information about the p-value)
28.Chang et al 2012	ECOG PS CACI	ECOG Grade 0, 4.9% Grade 1, 63.4% Grade 2, 31.7%	CACI ≤7, 75.6% ≥8, 24.4%	NCI CTCAE	Grade 3 or 4 haematological toxicity <1% Grade 3 hand-foot syndrome 25.6%	NR	• No significant worsening of global or overall QoL during CT *Subscales* • No significant worsening of functional QoL during CT • A slight and insignificant deterioration in social and cognitive functioning at 3 months during CT but recovered over time

							• No symptoms were significantly exacerbated during therapy
29.Caffo et al 2003	NR	NR	NR	Diarrhoea	The mean no. of daily stools progressively increased during the treatment	2.11 (0 – 4)	• QoL score improved progressively across study points, and from baseline to final evaluation
30.Park et al 2013	ECOG Co-morbidity	ECOG 0-1 for subjects to be eligible	0 co-morbidity 71.2% Any comorbid conditions 28.8%	NCI CTCAE	Grade 3 neutropaenia 39.4%, anaemia 4.5%, thrombocytopaenia 1.5%	52 (0-100)	• Global or overall QoL did not significantly deteriorate over time

* Significant difference ($p < 0.05$)

Abbreviations:
ADLs, Activities of Daily Living; BMI, Body Mass Index; BOMC, Blessed Orientation-Memory-Concentration test; CACI, Charlson-Age Comorbidity Index; CCI, Charlson Comorbidity Index; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GDS, Geriatric Depression Scale; IADLs, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; KPS, Karnofsky Performance Status Scale; NCI CTC, National Cancer Institute Common Toxicity Criteria; NR, not reported; OARS, Older American Resources and Services Questionnaire; RT, radiotherapy

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	√
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	√
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	√
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	√
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	√
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	√
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	√
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	√
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	√
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	√
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	√
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	√
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	√

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	√
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	√
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	√
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	√
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	√
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	√
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	√
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	√
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	√
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	√
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	√
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	√
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review

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Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review

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Abstract

Objectives

The measurement of quality of life (QoL) in elderly cancer population is increasingly being recognized as an important element of clinical decision-making and the evaluation of treatment outcome. This systematic review aimed to summarise the evidence of global or overall QoL during and after adjuvant therapy in elderly cancer patients.

Methods

A systematic search was conducted of studies published from inception to December 2016 through major databases. Eligible studies included RCTs and non-RCTs in which QoL was measured in elderly patients (65 years of age or above) with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy. Because of the heterogeneity and the insufficient data, the results were synthesised narratively.

Results

We included 4 RCTs and 14 non-RCTs on 1,633 participants who completed the baseline QoL questionnaire. In all four RCTs, the risk of bias was low or unclear for most items but high for detection. Of the 14 non-RCTs, 5 studies were judged to have a low or moderate risk of bias for all domains, and the other 9 studies had a serious risk of bias in at least one domain. The bias was observed mainly in the confounding and in the selection of participants for the study. For most elderly patients with breast cancer, the non-significant negative change in the QoL was transient. A significant increase in the QoL during the course of temozolomide in elderly patients with glioblastoma but a decreasing trend in QoL after radiotherapy was shown. This review also shows a uniform trend of stable or improved QoL

during adjuvant therapy and at follow-up evaluations across the studies with prostate, colon or cervical cancer population.

Conclusions

This review suggests that adjuvant chemotherapy and radiotherapy may not have detrimental effects on QoL in most elderly patients with solid tumours.

Strengths and limitations of this study

- A systematic search of the published literature in major databases from their inception to December 2016 was conducted.
- The risk of bias and the methodological aspects of quality of life reporting in the included studies were assessed.
- The search of grey literature, unpublished studies, ongoing clinical trials, and theses and dissertations were not conducted.
- The studies included in this review are mainly non-randomized controlled trials.
- The meta-analysis was not conducted to pool the data and the GRADE approach was not used to assess the quality of evidence of the included studies.

Keywords

Elderly cancer patients, adjuvant therapy, quality of life, chemotherapy, radiotherapy, oncology

Introduction

In many countries, the incidence of cancer among older people is increasing. This increase can be attributed to the remarkable growth of the elderly demographic and the common pathophysiology of cancer and aging.[1-2] As a result, the demands for and the importance of broadening clinical trials to include older adults, incorporating geriatric-specific endpoints,[3] and integrating geriatric assessment to address the needs of individuals are also increasing.[4] Although quality of life (QoL) is not formally a part of the geriatric assessment, the measurement of QoL in the elderly cancer population is increasingly being recognized as an important patient-reported outcome to complement both the clinician's evaluation of disease progression and the determination of the clinical benefit and burden of cancer treatment, along with toxicity, survival and mortality rates. QoL is also considered a useful outcome measure to enhance patient–clinician communication and patient compliance in elderly patients with breast cancer during cancer treatment.[5] In a short literature review, Wedding et al. (2007) reported that elderly cancer patients tend to perceive their QoL as more important than gains in survival when compared to younger patients.[6] Nevertheless, our understanding of the effect of cancer treatment on the QoL of elderly patients remains very limited. Clinically, the decisions regarding cancer therapy and the clinical management of elderly cancer patients may be complicated by their vulnerability to chemo-toxicity and the pathological changes of aging together with different considerations of the treatment benefit and harm margins, functional decline, tolerability and QoL issues. A univariate analysis by Extermann et al. (2015) revealed an association of the QoL effect with dose modification of chemotherapy in older patients.[7] The literature states that elderly cancer patients are less likely than their younger counterparts to be treated with a full course of adjuvant chemotherapy and radiotherapy.[8] Consideration should be given to approaches that can prolong life expectancy, but not at the expense of QoL and physical and psychological

functioning. For cancers with an extremely poor prognosis, such as glioblastoma, the extension of survival is less clinically meaningful if the patient has a decline in QoL.[9] Researchers have also suggested that QoL be used as the main endpoint to support clinical decision-making if different cancer treatments are equally effective in terms of survival.[10] To the best of our knowledge, a systematic review of the effects of adjuvant therapy on the QoL of elderly cancer patients has not yet been published. Therefore, we undertook a systematic review of the literature to summarise the evidence of global or overall QoL and other QoL domains during and after adjuvant therapy in elderly patients with stage I to III solid tumours. The population, intervention, comparison, outcome, study design, commonly known as PICOS, considered the question 'Does the global or overall QoL during and after adjuvant chemotherapy and/or radiotherapy decline, maintain or improve from baseline in elderly patients with solid tumours in randomized controlled trials (RCTs) or non-RCTs?' In this review, QoL refers to the health-related QoL of elderly patients, considering the corresponding global, physical, psychological and social domains as affected by the adjuvant therapy.

Methods

Literature search strategy

A systematic electronic search of peer-reviewed English-language articles published in CINAHL plus (1937–2016), CENTRAL (1993–2016), PubMed (1996–2016), PsycINFO (1967–2016) and Web of Science (1900–2016) from the inception of these databases to December 2016 was conducted. The date last searched was in March 2017. Searches were limited to human studies published in English. A pilot search on CINAHL was performed to identify the relevant keywords contained in the title, abstract and subject descriptors. Three broad categories of concepts were searched: 'elderly', 'cancer' and 'quality of life'. The

search terms included (older* OR elder* OR geriatric OR gerontology* OR senior OR aged) AND (oncology OR cancer* OR neoplasm*) AND (quality of life OR QOL). The full electronic search strategy is presented in Appendix A. The reference lists of the included articles were also examined to identify additional eligible articles.

Study selection

Inclusion criteria

We included RCTs and non-RCTs in which QoL was measured in elderly patients (65 years of age or above) with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy. Non-RCTs include quantitative studies such as observational, before-and-after and longitudinal studies, in which the allocation of intervention (analogy of treatment) occurs during the course of the usual treatment decisions.[11] We required that the baseline and at least one global or overall QoL data element during and/or after adjuvant chemotherapy and/or radiotherapy be collected and reported in the studies so as to allow an in-context comparison of before and after adjuvant therapy. Studies that covered heterogeneous age groups were included if a subgroup analysis was performed and reported for those aged 65 years of age or above.

Exclusion criteria

Studies were excluded if they involved patients with haematological malignancies, distant metastatic cancer or recurrent cancer without a separate analysis and report of solid tumours or non-metastatic/regional metastatic cancer. We also excluded case reports, qualitative studies, literature reviews, studies that evaluated surgical or procedure-related treatment and presented in abstract form.

Process for selecting studies

We screened articles obtained from keyword searching for duplicates electronically with End-Note and then manually. After duplicate removal, we assessed the remaining articles for eligibility based on titles and abstracts. We included studies in full-text screening if they were RCTs or non-RCTs, included elderly patients with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy, and reported QoL. We retrieved full-text articles if we considered the studies relevant and if there was insufficient information to determine eligibility. We then examined each full-text article against the inclusion and exclusion criteria of the review.

Data extraction

We extracted data related to publication information, sample characteristics, type of cancer, type of adjuvant chemotherapy and/or radiotherapy, supportive care, QoL measurements and results, drop-outs and authors' conclusions. Functional status and co-morbidities at baseline and therapy-related adverse effects (where reported) were also extracted because of concern that they might co-vary or confound with those of adjuvant therapy to alter the change of QoL.

Assessment of methodological quality of studies on QoL

The methodological quality of the included studies on QoL was assessed using a checklist of predefined criteria for studies on QoL.[12-13] The checklist was originally developed to assess the internal and external validity of prognostic studies[14] and was modified to assess the methodological aspects of QoL reporting in later studies.[12-13] The checklist covers the following 14 items: sampling (two items), selection of QoL measurement (one item), data collection process (two items), response rate (two items), group comparison (one item),

clarity of reporting (five items), and determination of prognostic factors (one item), all of which are important in QoL studies. For each item, a score of 1 or 0 was given; 1 was assigned to an item meeting the criteria, while 0 was assigned if an item neither met the criteria nor described the related parameter sufficiently. The possible score ranged from 0 to 14, with scores of 10 or above, 7 to 9 and 6 or less indicating high, moderate, and low quality, respectively.[12]

Assessment of risk of bias

The risk of bias (RoB) of the included studies was evaluated using the Cochrane Risk of Bias tool and Risk of Bias tool in Non-Randomised Studies of Interventions (ROBINS-I) for RCTs and non-RCTs, respectively.[11,15] Both tools are domain-based evaluations of RoB with respect to the internal validity of studies. The Cochrane RoB tool covers the domains of selection, performance, detection, attrition and reporting bias, and other source of bias. A judgement of 'yes' indicates a low risk of bias; 'no', a high risk of bias; and 'unclear' either an unclear or unknown risk of bias.[15] The ROBINS-I tool covers seven domains: bias due to confounding; bias in selection of participants into the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result. The risk of bias judgments within each domain are categorized as 'low risk' if the study is comparable to a well-performed RCT, 'moderate risk' if the study is sound but cannot be considered comparable to a well-performed RCT, 'serious risk' for the study has some considerable problems, 'critical risk' for the study is too problematic, and 'no information'. The judgments within each domain contribute to the overall risk of bias.[11]

In this review, two reviewers (LEYT and TDRL) independently performed literature search, eligibility assessments and study selection. The data extraction, methodological quality assessment and the RoB evaluation were conducted by CKKF and LEYT. Discrepancies and disagreements were discussed and resolved by consensus.

Data synthesis

Because of the variations in study design, cancer populations and QoL scales, and the insufficient data among the included studies, a meta-analysis was deemed impossible, and the results were synthesised narratively taking into account of the RoB of individual studies. In addition, we report a change in QoL scores from baseline to the middle of and to the completion of adjuvant therapy, and to the post-treatment follow-up period of individual studies where data were available. We defined '0' as no change; '↑' denotes better QoL than baseline and '↓' represents worse QoL than baseline. The effect size (ES) was also calculated for individual studies for which sufficient information was available: 0.2 to <0.5 was considered small, 0.5 to <0.8 moderate and ≥0.8 large.

Results

Search results

The initial search identified 56,935 articles, of which 440 were considered potentially relevant after checking for duplicates and title and abstract screening. After full-test assessment of the 440 articles, 18 met the eligibility criteria for inclusion in the review and analysis (Figure 1).[16-33] In most cases, the articles were excluded because of the lack of QoL assessment during adjuvant therapy, a separate report of participants 65 years of age or above and/or a separate report of the QoL for participants who were underoing adjuvant therapy or suffering from non-metastatic cancer.

Description of studies

Eleven studies were published between 2000 and 2009, and seven between 2010 and 2015. With respect to the country of origin, 10 were from Europe, four from the United States, two from South Korea and one from Canada; the other was a multi-country study. As for study design, 13 studies were non-RCTs (before-and-after or longitudinal studies) that assessed the QoL of patients who were undergoing adjuvant chemotherapy,[17,19,20,22,24,30,31,33] radiotherapy[16,32] or concomitant chemotherapy and radiotherapy.[26-28] Four were RCTs[18,21,23,25]; two of these compared the effects of different chemotherapy regimens on QoL, one study compared the effects of chemotherapy and hormonal therapy against those of hormonal alone on QoL, and the other compared the effects of radiotherapy and supportive care with those of supportive care alone on QoL. One was a validation study that involved a QoL evaluation of participants who were undergoing radiotherapy with or without hormonal therapy[29] (Table 1).

Table 1. Characteristics of the included studies

Study / Country	Type of study	Age (years) Mean ± SD	Sample size (≥65 years cohort)	No. of participants completed baseline QoL measurement (%)	Gender (% female)	Type of cancer	CT/RT	Measurement of CGA domains	Measurement of CT/RT related toxicity/adverse effect	QoL scale (score range)	QoL measurement time-point
Arraras et al (2008a)[16], Spain	Descriptive longitudinal	72.3 ± 5.7 (range 65-87)	48	48 (100)	100	Breast (Stage 1-III)	RT: Local Locoregional Regional *(no details on dosage)*	KPS Co-morbidity Daily activities	Selected items from NCI CTCAE	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^	• 1st day of RT • Last day of RT • 6 weeks after RT
Browall et al (2008)[17], Sweden	Descriptive longitudinal	No information on mean age (range 65-77)	39	39 (100)	100	Breast (Stage I-IIIa)	FEC: Flurouracil 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2 for 6 cycles or CMF: Cyclophosphamide 100mg/m^2, methothrexate 40 mg/m^2, flurouracil 600 mg/m^2 for 6 cycles *(30 women also had the CT combined with RT; a 5-week RT course starting 3-4 weeks after CT)*	Co-morbidity	NR	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^	• Baseline • 1 week after 1st, 2nd, 3rd and last cycle of CT • 4 months post-CT
Crivellari et al (2000)[18], Multi-countries	RCT (longitudinal) *(elderly women was a subset of the original study)*	No information on mean age (age ≥65 years)	76	58 (76.3)	100	Breast (Grade I-III)	Tamoxifen for 5 years or Tamoxifen plus 3 early courses of CMF (cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, 5-	ECOG Co-morbidity	Modified WHO toxicity criteria	PACIS (0-100)^	• Baseline • 2 months after 1st day of adjuvant therapy then every 3 months until 24 months

							fluorouracil 600 mg/m^2 every 28 days for 4 cycles)				
Dees et al (2000)[19], USA	Descriptive longitudinal	71.4 (range 65-79)	17	11 (64.7)	100	Breast (Early stage)	AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 for 4 cycles	NR	Myelosuppression Cardiotoxicity	BCQ (0-10)^	• Day 1 of each cycle • 2 months after completing CT • 6 months after completing CT
Hurria et al (2006)[20], USA	Descriptive longitudinal	68 (range 65-84)	49	49 (100)	100	Breast (Stage I-III)	CMF: Cyclophosphamide 600 mg/m^2, methrotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 every 3 weeks for 8 cycles or AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles or ACT: AC followed by paclitaxel 175 mg/m^2 every 2 or 3 weeks for 4 cycles or AC followed by paclitaxel 175 mg/m^2 weekly for 12 cycles or ACT-H: ACT followed by trastuzumab 2 mg/kg weekly for 52 weeks	CCI ADL IADL MMSE GDS BMI	NCI CTCAE	FACT-B (0-148)^	• Prior to CT • Upon completion of CT • 6 months after CT

							(CT regimen was at the discretion of the treating physician)				
Kornblith et al (2011)[21], USA	RCT (longitudinal) *(QoL was a sub-study)*	Standard CT (CMF or AC) group 72 ± 4.6 Capecitabine group72 ± 5.0	350	326 (93.1)	100	Breast (Stage I-III)	Standard CT CMF: Cyclophosphamide 100mg/m^2 from days 1 to 14, methotrexate 40 mg/m^2 & 5-fluorouracil 600 mg/m^2 on days 1 & 8 for 6 cycles or AC: Adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2 on day 1 for 4 cycles or Test cytotoxic drug Capecitabine 2000 mg/m^2 for 14 days; dose increased to 2500 mg/m^2 if no toxic effect after 1st cycle for 6 cycles	ECOG OARS (Co-morbidity) HADS BOMC Neurobehavioral Functioning & Activities of Living Scale Social Support Survey	NCI CTCAE Systemic adverse effects subscale of EORTC BR23	*EORTC QLQ-C30 (0-100)^ *EORTC BR23 (0-100)^	• Baseline • Mid-CT (about day 77 for CMF, day 29 for AC, day 63 for capecitabine) • Post-CT (6 to 7 months for CMF, 4 to 5 months for AC and capecitabine) • 12 months post-baseline • 18 months post-baseline • 24 months post-baseline
Watters et al (2003)[22], Canada	Descriptive longitudinal	70±5 (range 65 to 80)	20	16 (80)	100	Breast (Stage 1-III)	Anthracycline-based adjuvant CT Fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 at 21 days interval for 6 cycles	KPS	NR	EORTC QLQ-C30 (0-100)^ EORTC QLQ-BR23 (0-100)^ SF-36 (0-100)^	• Prior to CT • Before the 3rd cycle • Completion of CT • 6 months post-CT
Perrone et al (2015)[23], Italy	RCT (longitudinal)	CMF: Median 71 (range 65-79) Docetaxel: Median 71	299	252 (84.3)	100	Breast (Stage 1-III)	CMF: Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 on days 1 & 8 every 4 weeks for 4 or 6	ECOG CCI ADL IADL	NCI CTCAE	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BR23 (0-100)^	• Baseline • End of 1st CT cycle • End of 2nd CT cycle • End of 3rd

		(range 65-79)					cycles or Docetaxel 35 mg/m^2 on days 1, 8 & 15 every 4 weeks for 4 or 6 cycles				CT cycle
Gallego et al (2011)[24], France	Descriptive longitudinal (phase II trial)	Median 77 (range 70-87)	70	59 (84.3)	60	Glioblastoma	Temozolomide (150-200 mg/m^2 for 5 days every 4 weeks for 12 cycles / until disease progression) (*adjusted based on toxicity)*	KPS (<70 *as eligibility criteria*) MMSE	NCI CTCAE	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Baseline At least every month (restricted to the period of temozolomide period due to poor-prognosis)
Keime-Guibert et al (2007)[25], France	RCT (longitudinal)	Supportive care + RT group Median 75 (range 70-84)	39	35 (89.7)	37	Glioblastoma	Supportive care (corticosteroids & anticonvulsant agents, physical and psychological support, management by a palliative care team) & RT (1.8 Gy given 5 days per week, total dose of 50 Gy)	KPS *(≥70 as eligibility criteria)* MMSE	NCI CTCAE	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Baseline • Day 30 • Day 60 • Day 90 • Day 135
Minniti et al (2009)[26], Italy	Descriptive longitudinal	Median 73 (range 70-79)	43	36 (83.7)	51.2	Glioblastoma	Focal hypofractionated RT (total dose of 30 Gy in 6 fractions over 2 weeks) followed by adjuvant temozolomide 5 days every 28 days up to 12 cycles; 150 mg/m^2 for 1st cycle and adjusted based on toxicity for subsequent cycles	KPS *(≥60 as eligibility criteria)* Co-morbidity	NCI CTCAE	*EORTC QLQ-C30 (0-100)^	• Before RT • After RT • 2nd, 4th & 6th cycles of temozolomide
Minniti et al (2013)[27], Italy	Descriptive longitudinal (phase II trial)	Median 73 (range 70-81)	71	65 (91.5)	49.2	Glioblastoma	Focal hypofractionated RT (total dose of 40 Gy in 15 fractions) plus concomitant temozolomide 75mg/m^2	KPS MMSE	NR	*EORTC QLQ-C30 (0-100)^ *EORTC QLQ-BN20 (0-100)^	• Before RT • 4 weeks after RT (before the start of

							given 7 days/week followed by adjuvant temozolomide 5 days every 28 days for 12 cycles (adjuvant was started 4 weeks after the completion of RT); 150 mg/m^2 for 1st cycle and 200 mg/m^2 from 2nd cycle onwards				adjuvant temozolomide) • Every 8 weeks during treatment until disease progression
Mohile et al (2011)[28], USA	Descriptive before/after	Median 74.1 (range 65-92)	368	368 (100)	58.4	Breast (17.1%) Genitourinary (30.4%) Lung (15.8%) Brain and peripheral nervous system (6.5%) Alimentary (10.1%) Haematologic (4.9%) Head and Neck (6.3%) Soft tissue sarcoma (1.6%) Bone and cartilaginous (1.4%) Skin (3.3%) Gynecologic (0.8%) Melanoma (0.3%)	RT Median total dose of 57.6 Gy (range 30-161)	NR	NR	M.D. Anderson Symptom Inventory^ (with an item rating of overall QOL on an 11-point horizontal scale) ^	• Before RT • During the last week of RT
Arraras et al (2008b)[29], Spain	Descriptive longitudinal (validation)	70.9 ± 5.2	137	137 (100)	0	Prostate (Localized)	Lower risk: RT alone (total dose of 72 Gy) Intermediate risk: Neoadjuvant and concomitant combination of an anti-androgen and an LHRH	KPS	NR	EORTC QLQ-C30 (0-100)^	• 1st day of RT • Last day of RT • 6 weeks after RT

							analogue (6 months) + RT (total dose of 76 Gy) High risk: Neoadjuvant and concomitant combination of an anti-androgen and an LHRH analogue (6 months) + RT (total dose of 76 Gy) + adjuvant LHRH analogue				
Bouvier et al (2008)[30], France	Descriptive longitudinal survey	No information on mean age (range 75 – 85+)	11 (only 11 patients with stage III colon cancer treated with adjuvant CT and their QoL scores were reported)	11 (100)	NR	Colon	Flurouracil or Oxaliplatin plus flurouracil or Capecitabine *(no details on dosage)*)	NR	NR	EORTC QLQ-C30 (0-100)^	• At the time of diagnosis • 3 months after diagnosis • 6 months after diagnosis *(CT was given within 6 months after surgery)* • 12 months after diagnosis
Chang et al (2012)[31], South Korea	Descriptive longitudinal	Median 74.5 (range 70-90)	82	57 (69.5)	64	Colon (Stage II-III)	Capecitabine (oral, 750-1250 mg/m^2 , twice daily on days 1-14 every 3 weeks for 8 cycles) *(dose level was determined a/c toxicity effects during the first and preceding cycles)*	ECOG PS *(0-2 as eligibility criteria)* CACI	NCI CTCAE *(adequate hematologic, hepatic, and renal function status as eligibility criteria)*	EORTC QLQ-C30 (0-100)^	• Baseline • 3 months during CT • 6 months during CT • 3-6 months after completion of CT
Caffo et al (2003)[32], Italy	Descriptive longitudinal	Median 62.5 (range 46-81)	25 (no information on the breakdow	-	100	Cervical endometrium	Post-operative external pelvic RT (median total dose of 50.4 Gy, range 45-66.6 Gy, at a dose of 1.8-2.0 Gy 5	NR	Diarrhoea	Diary card (1-4)^(adapted from previous cancer setting)	Diary card: • At the start of RT • Daily during RT period

			n of sample size by age group)				times/week)			EORTC QLQ-C30 (0-100)^	(reported as mean weekly scores) EORTC QLQ-C30: • Before RT • After RT
Park et al (2013)[33], South Korea	Descriptive longitudinal	Median 69 (range 65-82)	66	66 (100)	9.1	Non-small-cell lung carcinoma (completely resected stage Ib, II or IIIa)	NP: Cisplatin 80mg/m^2 on day 1, vinorelbine 25mg/m^2 on days 1 and 8 at 3-week interval for 4 cycles (n=30, 45.5%) or PC: Carboplatin, paclitaxel 175mg/m^2 on day 1 at 3-week interval for 4 cycles (n=36, 54.5%) *(at the physician's discretion)*	ECOG Co-morbidity	NCI CTCAE	EORTC QLQ-C30 (0-100)^ EORTC QLQ-LC13 (0-100)^	• Before 1st dose of CT at each cycle • 1 month after 4th cycle

^Higher score indicating better quality of life; * Quality of life is the secondary endpoint if indicated

Abbreviations:
BCQ, Breast Cancer Chemotherapy Questionnaire; CGA, Comprehensive Geriatric Assessment; CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30 general questionnaire; EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer specific module for breast cancer; EORTC QLQ-BN20, European Organization for Research and Treatment of Cancer specific module for brain cancer; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer for lung-specific questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast cancer; NR, not reported; QoL, quality of life; PACIS, Perceived adjustment to chronic illness scale; RCT, randomized controlled trial; RT, radiotherapy

The sample size of participants 65 years of age or older was reported by 17 of the 18 studies[16-31,33]; Caffo et al. (2003) did not separately report the number of participants 65 years of age and older.[32] The sample size ranged from 11 to 368.[16-31,33] In all, these 17 studies included 1,753 participants.[16-31,33] Of these 1,753 participants, 1633 completed the baseline QoL questionnaire. Furthermore, the baseline completion rates ranged from 64.7 to 100%. Where reported, the age range of the participants was 65 to 92 years.[16,17,19,20,22,24-28,31-33] Eleven studies included participants 80 years of age and older.[16,20,22,24,25,27,28,30-33] As for the cancer diagnosis, eight studies included participants with breast cancer,[16-23] four studies focused on glioblastoma[24-27] and two studies considered participants were colon cancer.[30-31] We included one study each on mixed,[28] prostate,[29] cervical[32] and lung cancer[33] participants.

The most frequently used QoL instrument was the European Organization for Research and Treatment of Cancer general questionnaire (EORTC QLQ-C30; 13 studies).[16,17,21-29,30,31,33] Nine studies also used a disease-specific QoL instrument along with the EORTC QLQ-C30 for breast,[16,17,21-23] brain[24,25,27] and lung[33] cancer populations. The follow-up QoL evaluation was conducted at various intervals during adjuvant therapy and the post-treatment period. Ten studies reported at least one QoL evaluation during adjuvant therapy,[17-19,21-25,31,32] and five evaluated QoL immediately after the completion of adjuvant therapy.[20-22,28,29] The timing of the QoL evaluation after adjuvant therapy ranged from 1 month after treatment to 24 months after the first day of adjuvant therapy. Ten studies followed participants for 6 months or less after the completion of adjuvant therapy.[16,17,19,20,22,25,29-31,33] Two studies included a QoL evaluation of 24 months after the first day of chemotherapy.[18,21]

The geriatric domains of functional status and/or co-morbidities at baseline were examined and reported in 14 studies.[16-18,20,21-27,29,31,33] As shown in Table 2, two studies reported the

mean of the Karnofsky Performance Scale (KPS) as 90 or above,[16,29] whereas three reported the median of the KPS as 70 or above at baseline.[25-27] A KPS score of less than 70 was used as a cut-off for the recruitment criterion in one study.[24] Co-morbid conditions were reported in eight studies[16,17,20,21,23,26,31,33]; six of these involved participants with a limiting co-morbidity or with 3 or more co-morbidities.[16,17,21,23,31,33] Twelve studies measured cancer therapy-related toxicity during adjuvant therapy,[16,18-21,23-26,31-33] and nine of these used National Cancer Institute's Common Terminology Criteria for Adverse Events.[16,20,21,23-26,31,33] With respect to haematological toxicity, two studies reported grade 3 or 4 toxicity in fewer than 10% of participants,[18,31] and five reported such toxicity in 25% or higher during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[20,23,24,26,33] With respect to non-haematological toxicity, a study reported grade 3 or 4 toxicity in fewer than 10% of participants,[18] and four reported such toxicity in 25% or higher during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[20,23,26,31] (Table 2)

Table 2. Summary of the main findings of QoL

Study	Functional status at baseline *(Functional status during adjuvant therapy if reported)*	Co-morbid condition at baseline	Toxicity/Adverse effect	Supportive care where reported	Global or overall QoL scores (scale range)	Global or overall QoL scores Adjuvant chemotherapy and/or radiotherapy Baseline Mean ± SD No. of participants	In the middle	At the time of completion	Follow-up period	Findings of global or overall QoL *(Other QoL domains/subscales if reported)*	Authors' conclusions
Arraras 2008a	KPS mean 94.9 *During therapy: KPS decreased from baseline to last dose of RT (mean difference 4.7 [0-100] but returned to baseline 6 weeks after RT)*	Limiting co-morbidity 62.5%	At last day of RT: Levels 2-3 skin toxicity 8.4% Level 2 dysphagia 4.2% Level 2 fatigue 4.2% Level 2 pain 2.1%	NR	Global HQoL (0 – 100) 59.5 ±12 n=48			56.4 ± 11.2 n=48	66.5 ±14.8 (6 weeks after RT) n=46	• †Global QoL improved significantly from baseline to final evaluation *Subscales* • †Significant worsening in physical and role functioning, and fatigue, pain, and breast symptoms in last day of RT but improved at 6 weeks after RT (final evaluation)	• QoL data indicates RT was well tolerated by elderly women with localized breast cancer
Browall 2008	NR	1 or 2 co-morbidity 61% ≥3 co-morbidities 3%	NR	NR	Global HQoL (0 – 100) 76 ± 20 n=39		60 ± 23 n=35	61 ± 22 n=32	70 ± 24 (4 months after CT & about 7 wks after RT) n=30	• †Global QoL decreased significantly from baseline to mid-treatment and last dose of CT. The decrease in global health status had not fully recovered to baseline level at 4 months post-CT *Subscales* • †Physical, role, social and cognitive functioning decreased significantly from baseline to last dose of CT • The decrease in physical and role functioning had not fully recovered to baseline levels at 4	• There was a significant decrease in global QoL, body image, physical & role functioning during and after CT, but the decrease was independent of age

									months post-CT • No significant change in future perspective, emotional and sexual functioning over time	
Crivellari 2000	ECOG ≤2 for participants to be eligible	No specific data reported for those 58 participants who completed baseline QoL measurement	Grade 3 haematological toxicity 9.2% Other grade 3 toxicity 6.6%	NR	Perceived adjustment to chronic illness QoL (0 – 100) Median 59 n=58 (CMF plus tamoxifen)	Median 68 n=55		Median 82 (18 months after 1st day of CT) n=55	• QoL improved progressively across study points (within CMF plus tamoxifen group)	• Adding CMF to tamoxifen provided little survival benefits for the older patients, and patients continued to report more effort to cope (low QoL) in the tamoxifen plus CMF group compared with the tamoxifen alone group across time • CMF tolerability and effectiveness were reduced for elderly patients with breast cancer
Dees 2000	NR	NR	Neutropaenic complications and alteration in cardiac function were not significantly age related, no clinically significant age related trends in toxicity		Overall QoL (0 – 10) 7.65 ± 0.88 n=11		6.63 ± 1.48 n=7	*(authors mentioned to collect data at 2 and 6 months after completing CT, but they did not report the results/data)*	• Overall QoL decreased from baseline to last dose of CT but not significant	• There was no evidence of decline QoL in older breast cancer patients treated with adjuvant AC compared with younger ones
Hurria 2006	NR	CCI mean 3	Grade 3 or 4 haematological toxicity 27% Grade 3 or 4 non-haematological toxicity 31%	NR	Overall HQoL (0 – 148) 116 (no information on SD) n=49		116 (no information on SD) n=49	119 (no information on SD) (6 months post CT) n=48	• No significant longitudinal change in overall QoL across all time points *Subscales* • No significant longitudinal change in	• Despite about half of patients experiencing grade 3 or 4 toxicity, from the perspective of QoL and functional outcomes, women

									physical, social, emotional and functional well-being across all time points	tolerated adjuvant CT with no decline in QoL, functional status (patients maintained their baseline ability to perform ADLs & IADLs), comorbid or psychological status
Kornblith 2011	ECOG 0-2 for participants to be eligible Grade 0-1, 96% Grade 2, 4%	0 co-morbidity 4.9% 1 co-morbidity 11.4% 2-3 co-morbidities 21.1% 4-10 co-morbidities 16.3%	Participants treated with capecitabine has significantly fewer adverse effects during and at the completion of CT	NR	Global QoL (0 – 100) 75.4 ± 18.3 n=170 (standard CT) 76.5 ± 18.7 n=156 (capecitabine)	63.1 ± 18.4 n=150 (standard CT) 73.1 ± 17.6 n=137 (capecitabine)	63.2 ± 17.3 n=153 (standard CT) 75.8 ± 17.5 n=136 (capecitabine)	78.8 ± 17.8 n=141 (standard CT) (12 months post-CT) 77.4 ± 17.6 n=137 (standard CT) (18 months post-CT) 77.2 ± 17.6 n=137 (standard CT) (24 months post-CT) 77.3 ± 18.0 n=127 (capecitabine) (12 months post-CT) 78.2 ± 17.1 n=114 (capecitabine) (18 months post-CT) 76.5 ± 17.7 n=109	• Global QoL decreased across all time points within group but no information of p-value • *(Participants treated with capecitabine had significantly better global QoL, role and social functioning, less fatigue, less nausea and vomiting, less constipation, and better appetite, and less psychological distress than standard CT group. This difference had resolved by 12 months with no further difference at 24 months)*	• As reported in the original study, standard CT was associated with a significant improvement in relapse-free survival and overall survival compared with capecitabine • The short period of poorer Qol with standard CT is a modest price to pay for a chance at improved survival

								(capecitabine) (24 months post-CT)		
Watters 2003	Baseline KPS - NR *During therapy: KPS declined during and by the completion of CT, but did not differ from baseline at follow-up*	NR	NR	NR	Global QoL (0 – 100) 78 ± 16 n=20	77 ± 14 n=20	66 ± 20 n=20	73 ± 22 (6 months post-CT) n=20	• †Global QoL decreased significantly from baseline to the time of completion of CT but improved at 6 months post-CT *Subscales* • †Role and social functioning decreased significantly from baseline to the time of completion of CT but improved at 6 months post-CT	• Selected older women tolerated anthracycline-based adjuvant CT for breast cancer well
Perrone 2015	ECOG Grade 0, 83% Grade 1, 17%	No comorbidity 60% 1 comorbidity 31% ≥2 comorbidities 8%	Severe (grade >2) haematological toxicity was suffered by 70% of participants with CMF and 9% with docetaxel, while severe non-haematological toxicity was reported in 19% participants with CMF and 28% with docetaxel	G-CSF & erythropoiet in were used according to standard guidelines. G-CSF was also recommended for prophylaxis when grade ≥2 neutropenia occurred	No information on mean or median n=252	No information on mean or median			• Global QoL decreased from baseline to mid-treatment in both standard CMF and docetaxel groups but not significant • *(A statistically significant worsening with docetaxel was found for systemic therapy side-effects, future perspective, nausea & vomiting, diarrhea, appetite loss, upset by hair loss & body image domains)*	• There was no significant interaction of treatment arms & geriatric scales measuring patients' ability or comorbidities • Docetaxel is not superior to standard CMF in survival. Docetaxel worsens several QoL subscales and causes more non-haematological toxicity
Gallego 2011	Baseline: KPS <70 for participants to be eligible *During therapy: 33% improved their KPS by*	NR	Grade 3 or 4 haematological toxicity 25% Most adverse events were mild or moderate	NR	No information on mean or median n=59	1.4 points increase per month n=35			• †Global QoL improved significantly over time *Subscales* • †Physical, role, cognitive and social functioning scores improved significantly over time	• Temozolomide was generally well tolerated • Temozolomide appears to increase survival, and is associated with a

	≥10, before disease progression		According to MMSE, Patient's cognitive function improved over time					• For QLQ-BN20, scores on motor dysfunction, drowsiness, and bladder control improved over time before disease progression	significant improvement of QoL and functional status before tumor progression
Keime-Guibert 2007	Baseline KPS ≥70 for participants to be eligible *During therapy: KPS declined over time*	NR	No severe adverse effects related to RT	Corticosteroids and anticonvulsant agents, physical and psychological support, management by a palliative care team	Global QoL (0 – 100) 62.9 ± 3.4 n=35 (supportive care + RT)		55.6 ± 3.9 n=NR 58.8 ± 4.5 (~3 months post-RT) n=26	• Global QoL did not deteriorate significantly over time (supportive care + RT) *Subscales* • †During and after treatment, scores were significantly worse over time on physical, cognitive and social functioning, and fatigue and motor dysfunction	• Supportive care + RT was superior to supportive alone in survival benefit. Global assessment of deterioration of QoL over time did not differ significantly between supportive care + RT group and supportive care group alone • RT results in a modest improvement in survival without reducing QoL
Minniti 2009	Baseline: KPS ≥60 for participants to be eligible KPS median 70 *KPS did not change significantly during the study period*	Diabetes 19% out of 43 Hypertension 33% out of 43 Cardiovascular disease 16% out of 43	Grade 2-3 confusion and/or somnolence during or after RT 14% out of 43 Grade 3-4 haematological during CT 28% out of 43 (which led to the early discontinuation of CT in half of participants) Moderate-severe fatigue 35% out of 43, nausea 10%	Anticonvulsionants and dexamethasone	Global QoL (0 – 100) 58.3 ± 3.7 n=36		54.3 ± 5.1 (completion of RT) n=36 57.9 ± 6.8 (mid-CT; RT followed by CT) n=36	• Score of global health status did not change significantly *Subscales* • During treatment, scores of functioning subscale, nausea and vomiting, and insomnia did not change significantly • Fatigue and constipation scales worsened slightly from baseline through treatment • †Scores of physical, role and social functioning,	• Temozolomide is well tolerated. • The association of hypofractionated RT and temozolomide had no negative effect on QoL • A short course of RT followed by temozolomide may provide survival benefit while maintaining QoL

			out of 43, constipation 22% out of 43, skin rash 9% out of 43						and fatigue deteriorated significantly between baseline and the 2nd follow up	
Minniti 2013	KPS ≥60 for participants to be eligible KPS median 70	NR	NR	NR	Global QoL (0 – 100) 61.5 ± 20.8 n=65	60.0 (no information on SD) (1 month after RT and concomitant temozolomide) n=53 72.0 (no information on SD) (6 month from the start of RT) n=27			• †Global QoL improved significantly between baseline and 6-month from the start of RT (in the midst of adjuvant temozolomide) *Subscales* • †Social and cognitive functioning improved significantly between baseline and 6-month from the start of RT p • †Fatigue worsened significantly between baseline and 4-month follow up	• A short course of RT in combination with temozolomide was associated with survival benefit (median survival and 1-year survival rates of 12.4 months and 58%, respectively) without a negative effect on QoL
Mohile 2011	NR	NR	NR	NR	Overall QoL (0 – 10) 2.07 (no information on SD) n=368		2.37 (no information on SD) n=368		• There was an increase of QoL score after RT, however, no information about the *p* value • Prevalence and severity of symptoms interfered with QoL increased insignificantly from pre- to post-RT *Subscales* • †The prevalence of memory difficulties and sleep disturbance, and the severity of fatigue and distress significantly increased over the course of RT	• Symptoms interfered with QoL after RT • There were no differences in the change in total symptom burden and interference with QoL between older and younger patients during RT
Arraras 2008b	KPS mean 96.1	NR	NR	NR	Global QoL (0 – 100) 66.8 ± 17.9		66.7 ± 20.9 n=132	71.3 ± 18.6 (1.5 months after completion	• No change in global QoL score from baseline to last dose of RT but significantly improved	• There was a tendency to a worsening of QoL at the end of the

					n=137			of RT) n=126	from last dose to 1.5 months after RT *Subscales* • †There was a significant worsening of physical, cognitive and social functioning from baseline to last dose of RT, but physical functioning improved significantly from last dose to 1.5 months after RT	treatment, with a recovery in most scales in the follow-up measurement that could be due to RT low toxicity level
Bouvier 2008	NR	NR	NR	NR	Global QoL (0 – 100) 60 (no information of SD) n=11	No information on mean or median	No information on mean or median		• Graph shows the mean scores of global QoL increased over time, but no information about the *p* value *Subscales* • †The overall mean score for physical functioning was significantly higher for participants treated with CT than untreated patients regardless of follow-up period. Emotional functioning were found to significantly increase between at diagnosis and 6 months after diagnosis	• Global QoL for patients with stage III colon cancer treated with adjuvant CT did not vary significantly from that of patients who did not receive CT across time
Chang 2012	ECOG Grade 0, 4.9% Grade 1, 63.4% Grade 2, 31.7% *(data for the original sample of 82)*	CACI ≤7, 75.6% ≥8, 24.4% *(data for the original sample of 82)*	Grade 3 or 4 haematological toxicity <1% Grade 3 hand-foot syndrome 25.6% *(data for the original sample of 82)*	NR	Global QoL (0 – 100) 59 (no information of SD) n=57	No information on mean or median n=55		No information on mean or median (3-6 months after completion of CT) n=48	• No significant worsening of global QoL during CT *Subscales* • No significant worsening of functional QoL during CT • A slight and insignificant deterioration in social and cognitive functioning at 3 months during CT but recovered over time	• By using a tailored-dose escalation strategy, unnecessary dose reduction could be avoided without an increment of toxic effects in patients receiving capecitabine. The toxicity profiles were favorable.

									• No symptoms were significantly exacerbated during therapy	Compromised QoL after surgery was not worsened by adjuvant capecitabine and improved after the completion of CT
Caffo 2003	NR	NR	The mean no. of daily stools progressively increased during the treatment	Participants experiencing grade 3-4 diarrhea were given loperamide with adequate water and saline support. If loperamide was ineffective, treatment with octreotide was planned	Overall QoL (Daily card) (1 – 4) *(No data reported for EORTC)* 2.11 ± 0.75 n was not reported	2.46 ± 0.67 n was not reported	2.55 ± 1.05 n was not reported		• Global QoL score improved progressively across study points, and from baseline to final evaluation (during RT), but no information about the *p* value	• The authors' conclusion is not related to QoL
Park 2013	ECOG 0-1 for participants to be eligible	0 co-morbidity 71.2% Any comorbid conditions 28.8%	Grade 3 neutropaenia 39.4%, anaemia 4.5%, thrombocytopaenia 1.5%	NR	Global QoL (0 – 100) 53 (no information of SD) n=66	No information on mean or median (after 2nd cycle of CT) n=63	No information on mean or median (after 4th cycle of CT) n=60		• Global QoL did not significantly deteriorate over time	• Postoperative CT did not substantially reduce QoL in elderly NSCLC patients

† Significant difference reported by the study authors ($p < 0.05$)

ADLs, Activities of Daily Living; BMI, Body Mass Index; BOMC, Blessed Orientation-Memory-Concentration test; CACI, Charlson-Age Comorbidity Index; CCI, Charlson Comorbidity Index; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GDS, Geriatric Depression Scale; IADLs, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; KPS, Karnofsky Performance Status Scale; NCI CTC, National Cancer Institute Common Toxicity Criteria; NR, not reported; OARS, Older American Resources and Services Questionnaire; RT, radiotherapy

Methodological quality

Thirteen studies attained scores of 10 or higher (high quality),[16-27,33] three scored 7 to 9 (moderate quality),[28,30,31] and two scored 6 or lower (low quality).[29,32] The main methodological drawbacks were the lack of determination of prognostic factors for QoL (100%), and the lack of data on time since diagnosis or treatment (77.8%) and characteristics of non-responders (77.8%). (Table 3)

Table 3. Results of the methodological quality assessment

	Sampling		Selection of QoL instrument	Data collection process		Response rate		Group comparison		Clarity of reporting				Determination of prognostic factor QoL	
Studies	**B**	**O**	**I**	**C**	**M**	**G**	**H**	**E**	**A**	**D**	**F**	**J**	**K**	**L**	**Quality score**
Arraras 2008a	1	1	1	1	1	1	0	1	1	1	0	1	1	0	11
Browall 2008	1	1	1	1	1	1	1	1	1	1	0	1	1	0	12
Crivellari 2000	1	1	0 (PACIS)	1	1	1	0	1	1	1	0	1	1	0	10
Dees 2000	1	1	1	1	1	1	0	1	1	1	0	0	1	0	10
Hurria 2006	1	1	1	1	1	1	0	1	1	1	1	1	1	0	12
Kornblith 2011	1	1	1	1	1	1	0	1	1	1	0	0	1	0	10
Watters 2003	1	1	1	1	1	1	0	1	1	1	0	1	1	0	11
Sirrone 2015	1	1	1	1	1	1	1	1	1	1	0	1	0	0	11
Gallego 2011	1	1	1	1	1	1	0	1	1	1	1	1	0	0	11
Keime-Guibert 2007	1	1	1	0	1	1	0	1	1	1	1	1	1	0	11
Minniti 2009	1	1	1	1	1	1	0	1	1	1	1	1	1	0	12
Minniti 2013	1	1	1	1	1	1	1	1	1	1	0	1	1	0	12
Mohile 2011	1	1	0 (MD Anderson Symptom Inventory)	1	0	1	0	1	1	1	0	0	1	0	8
Arraras 2008b	0	1	1	0	0	1	0	1	0	0	0	1	1	0	6
Bouvier 2008	0 (only age and cancer diagnosis were reported)	1	1	1	0	0 (only among 30 respondents undergoing curative surgical resection for stage III cancer with 11 received adjuvant CT was reported)	1	1	1	0 (no information on dosage)	0	1 (only graphical information was reported)	1 (only graphical information was reported)	0	8
Chang 2012	1	1	1	1	0	1	0	1	1	1	0	1	0	0	9
Caffo 2003	0	0	0 (both diary care and EORTC-QLQ C30 were used but only diary data was reported)	1	1	1	0	1	0	1	0	0	1	0	6
Park 2013	1	1	1	1	1	1	0	1	1	1	0	1 (only	1 (only	0	11

graphical information was reported)	graphical information was reported)

A= Socio-demographic and medical data is described (e.g. age, race, employment status, educational status, tumour stage at diagnosis etc.); B= Inclusion and/or exclusion criteria are formulated; C= The process of data collection is described (e.g., interview or self-report etc.); D= The type of cancer treatment is described; E= The results are compared between two groups or more (e.g., healthy population, groups with different cancer treatment or age, comparison with time at diagnosis etc.); F= Mean or median and range or standard deviation of time since diagnosis or treatment is given; G= Participation and response rates for patient groups have to be described and have to be more than 75%; H= Information is presented about patient/ disease characteristics of responders and non-responders or if there is no selective response; I= A standardized or valid quality of life questionnaire is used; J= Results are not only described for quality of life but also for the physical, psychological and social domain; K= Mean, median, standard deviations or percentages are reported for the most important outcome measures (HQoL); L= An attempt is made to find a set of determinants with the highest prognostic value (HQoL); M= Patient signed an informed consent form before study participation; N=No; O= The degree of selection of the patient sample is described

Risk of bias

RCTs

In all four RCTs, the risk of bias was low or unclear for most items but high for detection because of the subjective and self-reporting nature of the QoL assessment. One RCT did not blind the participants and staff and thus was judged to have a high risk of performance bias.[18] The remaining three RCTs did not report information on blinding of participants and personnel to allow for a judgement of the performance bias.[21,23,25] We judged three RCTs to have an unclear risk of attrition bias because of the lack of explicit information on lost to follow-up and missing data.[18,21,25] (Figure 2)

INSERT FIGURE 2 HERE

Non-RCTs

Of the 14 non-RCTs, five studies were judged to have a low or moderate risk of bias for all domains,[16,20,26,31.33] and the other nine studies had a serious risk of bias in at least one domain.[17,19,22,24,28-30,32] The bias were observed mainly in the confounding, in the selection of participants for the study and in the measurement of outcomes. Although most of the studies measured some confounding variables (e.g., functional performance status or co-morbidity) at baseline, no stratification in the study design or adjustment in the data analysis was made to control their effects.[16,17,20, 22-24,27,29,31,33] Four non-RCTs did not measure functional performance status or co-morbidities at baseline.[19,28,30,32] The bias in the selection of participants was either moderate or serious in all the non-RCTs.[16,17,19,20,22-24,27-33] Only fit and functional elderly patients seemed to have been enrolled in these studies, and hence, the study cohorts might not be representative of the real world population. Like the RCTs, all 14 non-RCTs had a moderate-to-serious risk of bias in the measurement outcomes because of the

subjective and self-reporting nature of the QoL assessment. The bias in the selection of reported results was unclear in all the non-RCTs because of unavailability of study protocols.[16,17,19,20,22-24,27-33] (Table 4)

Table 4. Risk of bias summary for Non-RCTs (ROBINS-I)

	Pre-intervention		At intervention	Post-intervention				
Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Arraras 2008a	M	M	M	M	M	M	unclear	Low or moderate risk if bias for all domains
Browall 2008	M	M	M	S	M	M	unclear	Serious risk of bias in at least one domain
Dees 2000	S	S	L	M	M	M	unclear	Serious risk of bias in at least one domain
Hurria 2006	M	M	L	M	L	M	unclear	Low or moderate risk if bias for all domains
Watters 2003	S	M	L	M	L	M	unclear	Serious risk of bias in at least one domain
Gallego 2011	M	M	L	M	S	S	unclear	Serious risk of bias in at least one domain
Minniti 2009	M	M	L	M	L	M	unclear	Low or moderate risk if bias for all domains
Minniti 2013	M	M	L	M	S	M	unclear	Serious risk of bias in at least one domain
Mohile 2011	S	M	M	unclear	L	M	unclear	Serious risk of bias in at least one domain
Arraras 2008b	M	S	unclear	unclear	M	M	unclear	Serious risk of bias in at least one domain
Bouvier 2008	S	M	unclear	unclear	L	M	unclear	Serious risk of bias in at least one domain
Chang 2012	M	M	L	M	M	M	unclear	Low or moderate risk if bias for all domains
Caffo 2003	S	S	L	unclear	M	M	unclear	Serious risk of bias in at least one domain
Park 2013	M	M	M	M	M	M	unclear	Low or moderate risk if bias for all domains

L=low risk; M=moderate risk; S=serious risk; C=critical risk

QoL outcomes

Breast cancer

EORTC QLQ-C30

Three studies reported the global QoL scores at baseline, during chemotherapy, at the time of completion of chemotherapy and 4 to 12 months after the completion of chemotherapy.[17,21,22] The participants in these studies were treated with the standard chemotherapy regimen for breast cancer, including an anthracycline-based, cyclophosphamide/ methotrexate/ flurouracil (CMF) or flurouracil/ epirubicin/ cyclophosphamide regimen. In Kornblith et al. (2011),[21] approximately half of the participants received capecitabine. Browall et al. (2008) reported statistically significantly lower global QoL scores during (ES, 0.74) and immediately after the completion of chemotherapy (ES, 0.71) than at baseline and a non-significant decline in the global QoL score 4 months after chemotherapy.[17] Watters et al. (2003) also revealed a statistically significantly lower global QoL score immediately after the completion of chemotherapy (ES, 0.66) than at baseline and a non-significant decline in the global QoL scores during and 6 months after chemotherapy.[22] Browall et al. (2008) and Watters et al. (2003) also reported the domain scores, wherein statistically significantly lower scores in the role and social functioning domains were found immediately after the completion of chemotherapy than at baseline. No significant reductions in role and social well-being were reported during or 4 to 6 months after the completion of chemotherapy.[17,22] Emotion was the only domain that showed an improvement from baseline to the follow-up evaluations, with a statistically significant higher score during chemotherapy. The domains of physical and cognitive functioning revealed no statistically significant differences across time.[17,22] In Kornblith et al. (2011), both standard chemotherapy and capecitabine groups showed a decline in the global QoL during and immediately after the completion of chemotherapy,

whereas an increase in the global QoL was reported from baseline to 12 months after the completion of chemotherapy.[21] (Tables 2 and 5)

Table 5. Matrix of baseline and change of QoL scores, attrition rate, methodological quality score, and RoB

Type of cancer Studies	QoL scale	Baseline	From baseline to the middle of adjuvant CT/or RT	From baseline to the time of completion of adjuvant CT/or RT	From baseline to post adjuvant CT/or RT follow-up period	Attrition (last follow-up) where reported (%)	Methodological quality	Overall risk of bias judgment for non-RCTs
Breast								
RCTs								
Kornblith 2011	EORTC	Standard CT 75.4	↓ (no information on *p* value)	↓ (no information on *p* value)	↑ (no information on *p* value)	17	10	(refer to RoB summary)
		Capecitabine 76.5	↓ (no information on *p* value)	↓ (no information on *p* value)	↑ (no information on *p* value)	18.6		
Perrone 2015	EORTC	Standard CT (mean or median was not reported)	↓ (narrative; mean or median was not reported			No information	11	(refer to RoB summary)
		Docetaxel (mean or median was not reported)	↓ (narrative; mean or median was not reported					
Crivellari 2000	PACIS	Median 59	↑ (no information on *p* value)		↑ (no information on *p* value)	5.2	10	(refer to RoB summary)
Non-RCTs								
Arraras 2008	EORTC	59.5		↓	↑† ES 0.52	4.2	11	low or moderate
Browall 2008	EORTC	76	↓† ES 0.74	↓† ES 0.71	↓ (an improving trend)	23.1	12	serious
Dees 2000	BCQ	7.65 on the scale of 0-10		↓		36.4	10	serious
Hurria 2006	FACT-B	116 on the scale of 0-148		0	↑	2	12	low or moderate
Watters 2003	EORTC	78	↓	↓† ES 0.66	↓ (an improving trend)	0	11	serious
Glioblastoma								
RCT								
Keime-Guibert 2007	EORTC	62.9		↓	↓ (an improving trend)	25.7	11	(refer to RoB summary)
Non-RCTs								
Gallego 2011	EORTC	Mean or median was not reported	↑†			40.7	11	serious

			(narrative; mean or median was not reported)					
Minniti 2009	EORTC	58.3		↓		0	12	low or moderate
Minniti 2013	EORTC	61.5	↑†			58.5	12	serious
Mixed								
Mohile 2011	MD Anderson SI	2.07 on the scale of 0-10		↑ (no information on *p* value)		0	8	serious
Prostate								
Arraras 2008	EORTC	66.8		0	↑† ES=0.25	8	6	serious
Colon cancer								
Bouvier 2008	EORTC	60	↑ (graphical data; mean or median was not reported)	↑ (graphical data; mean or median was not reported)		No information	8	serious
Chang 2012	EORTC	59	↓ (narrative; mean or median was not reported)		↑ (narrative; mean or median was not reported)	15.8	9	low or moderate
Cervical								
Caffo 2003	Diary card	2.11 on the scale of 1-4	↑	↑		No information	6	serious
Lung								
Park 2013	EORTC	53	↓ (narrative; mean or median was not reported)	↓ (narrative; mean or median was not reported)		9.1	11	low or moderate

'0' represents no change; '↑' denotes better QoL than baseline; '↓' represents worse QoL than baseline; †$p < 0.05$
ES=Effect size which was calculated for significant result and where mean, SD and sample size were available of the respective article
QoL scale is on the scale of 0-100 unless specified otherwise

Perrone et al. (2015) examined the global and domain QoL scores of participants treated with CMF or docetaxel at baseline and during chemotherapy. This study reported a decline in the QoL scores over time; however, no information about the *p* value was provided.[23] Note that 79% and 47% of the participants suffered from grade 2 or higher haematological and non-haematological toxicities, respectively.[23] Arraras et al. (2008a) measured the QoL of elderly participants treated with radiotherapy at baseline, at the completion of radiotherapy and 6 weeks after the completion of radiotherapy.[16] Although this study started with a lower QoL (score of 59.5) at baseline, the global QoL score increased significantly from baseline to 6 weeks after the completion of radiotherapy.[16]

Other QoL measures

Dees et al. (2000) measured QoL using the Breast Cancer Chemotherapy Questionnaire (BCQ) and found a non-significant decline in the overall QoL score from baseline to the last dose of doxorubicin/cyclophosphamide.[19] Hurria et al. (2006) revealed no significant differences in overall or in physical, social and emotional well-being as measured by Functional Assessment of Cancer Therapy-Breast (FACT-B) from baseline to immediately after and 6 months after completion of an anthracycline-based, taxane-based, or CMF regimen.[20] Note that 27% and 31% of the participants in this study suffered from grade 3 or 4 haematological and non-haematological toxicities, respectively.[20] Crivellari et al. (2000) reported increased global QoL scores as measured by Perceived Adjustment to Chronic Illness Scale (PACIS), during and 18 months after the completion of the CMF regimen.[18] Note that the participants in this study had a low QoL score of 59 at baseline. Fewer than 10% of the participants manifested grade 3 toxicity.[18]

Glioblastoma

All four studies were conducted on in participants with glioblastoma treated with temozolomide[24] or focal hypofractionated radiotherapy[25] or combined radiotherapy and temozolomide.[26,27] These studies assessed QoL using the EORTC QLQ-C30. Gallego et al. (2011) reported statistically significant improvements in the global and the physical, role, cognitive and social domains scores during the course of temozolomide.[24] Note that 25% of the participants manifested grade 3 to 4 haematological toxicity in this study.[21] Minniti et al. (2013) also showed statistically significant improvements in the global score and the social and cognitive domain scores from baseline to 6 months from the start of radiotherapy (which was during the course of temozolomide).[27] Both Keime-Gulbert et al. (2007) and Minniti et al. (2009) reported a decline in the global QoL at the completion of focal hypofractionated radiotherapy.[25,26] With respect to the domain scores, these two studies reported statistically significantly lower scores for the physical, cognitive and social domains, and the physical, role, and social domains, respectively, during and after radiotherapy than at baseline [25,26] The participants in both studies were treated with corticosteroids and anticonvulsants as supportive care. Note that in Minniti et al. (2009), the participants began with a lower QoL (score of 58.3) at baseline and that 14% of these participants developed grade 2 or 3 confusion and/or somnolence during or after radiotherapy.[26]

Colon cancer

Two studies measured QoL with the EORTC QLQ-C30 at baseline and during and after chemotherapy in participants with colon cancer.[27,28] In Bouvier et al. (2008), the participants were treated with flurouracil/oxaliplatin/capecitabine regimen.[30] This study reported an increase in the global QoL scores over time; however, no information about the *p* value was

provided. Chang et al. (2012) found no significant worsening of the global and functional QoL during capecitabine treatment.[31]

Prostate cancer

Arraras et al. (2008b) measured QoL by using the EORTC QLQ-C30 in participants treated with radiotherapy for prostate cancer.[29] No difference in the global QoL score was observed from baseline to the last dose of radiotherapy, whereas a statistically significantly higher QoL score was reported at 6 weeks after radiotherapy (ES, 0.25).[29]

Lung cancer

Park et al. (2013) measured QoL using the EORTC QLQ-C30 at baseline and 1month after the completion of therapy with cisplatin plus vinorelbine or carboplatin plus paclitaxel in participants with resectable non-small cell lung carcinoma.[33] In this study, the QoL score of 53 at baseline was low. No significant deterioration of the global QoL between baseline and the follow-up evaluation was observed. Severe haematological toxicity was manifested in 39% of the participants.[33]

Other cancers

Mohile et al. (2011) studied different types of cancer, and QoL was measured before and after radiotherapy using the M.D. Anderson Symptom Inventory.[25] In this study, the overall QoL score of 2.07 on the scale of 10 at baseline was low. A higher overall QoL score was shown at the completion of radiotherapy; however, no information about the *p* value was provided.[28]

Discussion

In the context of cancer, QoL by its nature is a patient's overall appraisal of the effect of cancer and its treatment. It is a patient-centred, relevant and key clinical parameter that can assist and support clinicians in setting goals and mapping avenues for effective and tolerable cancer treatment regimens beyond extending patient survival. Although the 18 studies included in this systematic review had somewhat heterogeneous study designs, cancer populations, and measurement scales and reporting parameters of QoL to permit data pooling for meta-analysis and precise estimation, our results provide some insights that will contribute to a better understanding of the effects of adjuvant chemotherapy and/or radiotherapy on the QoL of elderly patients 65 years of age or above. Our current review suggests that QoL during and after adjuvant chemotherapy and/or radiotherapy is maintained or improves in most of patients with solid tumours.

For elderly patients with breast cancer, the non-significant negative change in the global or overall QoL was transient (during and immediately after chemotherapy or radiotherapy), as measured by the EORTC QLO-C30, FACT-B and BCQ. No lasting adverse effect on QoL was observed after completion of the adjuvant treatment (overall low or moderate to serious RoB).[16,19,20,21,23] Browall et al. (2008) and Watters et al. (2003) revealed an initial statistically significant declines (moderate ES), followed by progressive improvement in global QoL scores from baseline to 4 to 6 months after chemotherapy (overall serious RoB). The role and social domains of QoL was mostly impaired immediately after the completion of chemotherapy.[17,22]

Another finding of this review is the significant increase in the global QoL during the course of temozolomide treatment in elderly patients with glioblastoma (overall low or moderate to

serious RoB)[24,27] but a decreasing trend in QoL immediately after the completion of radiotherapy and 3 months after radiotherapy.[25,26] Note that the studies by Gallego et. (2011) and Minniti et al. (2013) had substantial amounts of missing data (>40%), mainly because of the rapid progression of the disease in the glioblastoma population. However, the approach of complete case evaluation used in the final QoL analysis could have led to a systematic bias in the estimation of the true effect of adjuvant therapy on QoL towards high QoL scores. Therefore, some caution should be taken in the interpretation of the significant QoL improvement during the course of adjuvant therapy of elderly patients with glioblastoma. Nevertheless, attrition bias is always an issue in clinical trials involving QoL assessments and longitudinal follow-ups.

Adjuvant chemotherapy or radiotherapy also does not seem to compromise the QoL of elderly patients with prostate, colon or cervical cancer. This review shows a uniform trend of stable or improved global or overall QoL over the course of adjuvant therapy and at follow-up evaluations across the studies with prostate, colon or cervical cancer population (overall serious RoB).[28,29,30,32] A decreasing trend in global or overall QoL during and immediately after the completion of cisplatin or carboplatin treatment in elderly patients with lung cancer was reported in one study (overall low to moderate RoB).[33]

We expected altered functional status, co-morbidities, adverse effects, haematological status, and liver and renal functional status to co-vary with the effect of adjuvant therapy on QoL, and hence, to be plausible confounding factors in the geriatric and adjuvant settings. However, as is the case in non-RCT settings, adjuvant therapy was allocated during the course of usual treatment decisions. The non-RCTs included in this review might suffer from the methodological drawbacks of uncontrolled confounding at baseline and even during the

follow-up. Because no attempt was made to control confounding with a stratified design and analysis, caution is warranted in the interpretation of the results. Nevertheless, we found it difficult to discern whether the short period of QoL impairment and the stable or improved QoL over the course of adjuvant therapy and after treatment were due to the relatively low treatment toxicities, the relatively few morbid conditions or to other reasons. The fact that, where reported, the QoL of elderly patients was maintained or improved over the course of treatment, despite the haematological toxicity across studies,[20,23,24,33] suggests that stable or improved QoL is unlikely to be attributable to relatively low treatment toxicity. Alternatively, elderly cancer patients who undergo adjuvant therapy may experience adverse effects but can tolerate them with a limited effect on their QoL. This finding may also be attributed to the tendency of certain elderly patients to complain less and endure the relatively high morbidity associated with adverse effects.[5] Elderly patients may also have a positive perception of the adjuvant therapy and may adjust better to the treatment. Stone et al. examined the association between global well-being and the age profile of 340,847 people and showed that people over 50 years of age have increased global well-being and positive emotion even in the face of a decline in the physical health.[34] Another possible explanation for the stable or improved QoL could be the response shift phenomenon, in which patients experience a shift in how they appreciate their QoL over time as a result of the changes in their internal standards of measurement, values or definition of QoL.[35,36] A future qualitative study is needed to explore in detail elderly cancer patients' QoL perception and experiences in adjuvant settings and their adjustment to the treatment. Nevertheless, for studies that reported a stable global or overall QoL (i.e. no difference in the means) across time, a small sample size and attrition bias might limit the statistical power to detect differences between the baseline and the follow-up evaluations.[19,21,23,25,31] Furthermore, the samples of the included studies appear highly functional at baseline,[16-23,25-33] so these studies may be subject to a selection bias

pertaining to under-representation of less healthy older patients and those with limited expectation of treatment benefits.[3]

Conclusion

This review suggests that a negative change in QoL was short-lived during adjuvant chemotherapy for some elderly patients with breast cancer. Adjuvant chemotherapy and radiotherapy may not have detrimental effects on global or overall QoL and other QoL domains in most elderly patients with solid tumours. These findings could be translated to help future elderly patients better understand the impact of adjuvant therapy on their QoL, and hence make treatment decisions. Nevertheless, our review results should be viewed with caution because of RoB within and across the included studies. In addition, heterogeneity in study design and measurement of QoL, and lack of availability of data limit the pooling of data for meta-analysis and affect the robustness of the evidence synthesis. An attempt was made to contact the study authors for data, but without success. There is also a possibility of incompleteness of evidence because of unclear bias of the selection of reported result and the search of this review did not include grey literature, unpublished studies, ongoing clinical trials, and theses and dissertations. Larger and well-designed studies of elderly patients in different cancer settings are warranted to further build the evidence and validate these review results. These studies should include and stratify elderly patients by functional status, co-morbid conditions, geriatric syndromes and prognosis to be more representative of the real-world population and improve the research validity. Future studies should also include a detailed profile of the cytotoxic effects of chemotherapy and radiotherapy to allow a full exploration of the direct and indirect effects of adjuvant therapy on QoL. In future systematic review, if sufficient data are available, meta-regression should also be conducted to examine the association and interaction between the confounding factors and the QoL.

Contributors

CKKF, KR contributed to the conception or design of the work, and analysis and interpretation of data. CKKF is responsible for drafting the manuscript. KR critically reviewed and revised the manuscript for important intellectual content. LEYT contributed to the acquisition of data and critical revision of the manuscript for intellectual content. CKKF, LEYT, KR provided final approval of the version to be published.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

No additional data are available

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Review protocol registration

Nil

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Figure 1. Study flow diagram

Figure 2. Risk of bias summary for RCTs

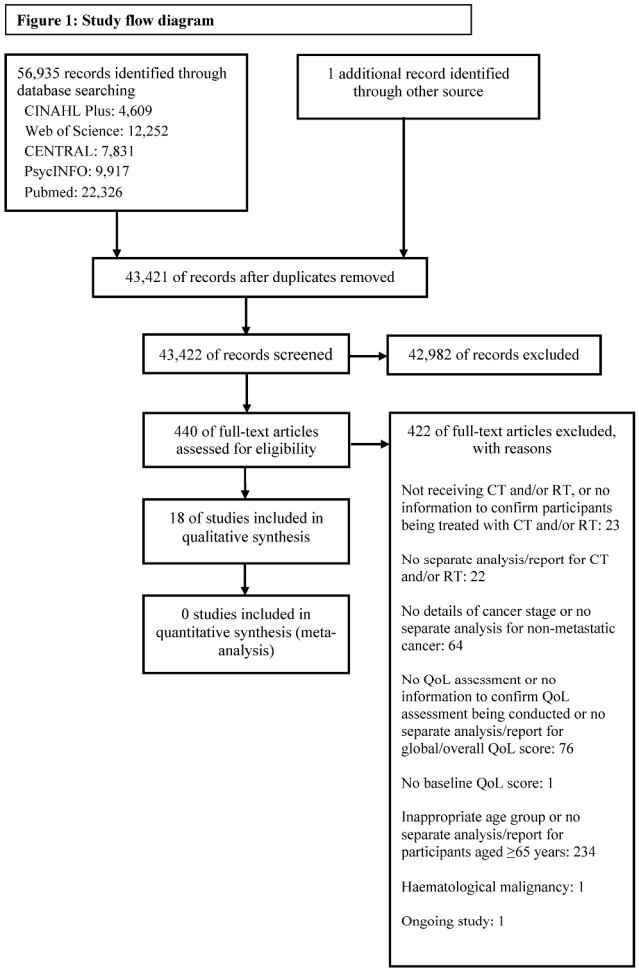

Figure 1. Study flow diagram

297x420mm (300 x 300 DPI)

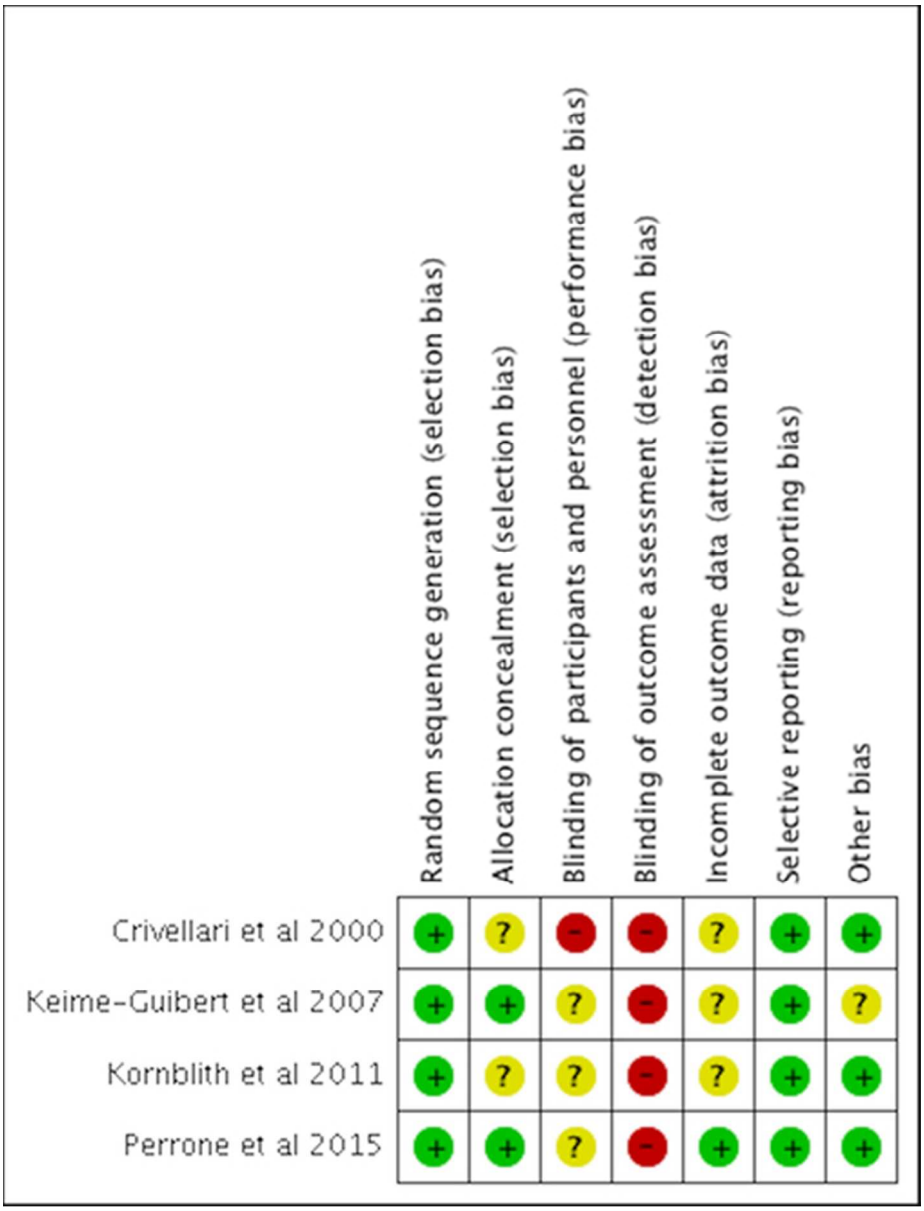

Figure 2. Risk of bias summary for RCTs

42x55mm (300 x 300 DPI)

Appendix A

Electronic search strategy for PsycINFO

1. older*.af. OR elder*.af. OR geriatric.af. OR gerontolog*.af. OR senior.af. OR aged.af.
2. oncology.af. OR cancer*.af. OR neoplasm*.af.
3. “quality of life” .af. OR “QOL” .af.
4. #1 AND #2 AND #3

Limits: English Language, Human

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	31-32
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No additional analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, 17,18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	31-32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33 Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No meta-analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	31-32
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No additional analysis
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	41-42
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	42, 44
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	45

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review

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Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review

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Abstract

Objectives

The measurement of quality of life (QoL) in elderly cancer population is increasingly being recognized as an important element of clinical decision-making and the evaluation of treatment outcome. This systematic review aimed to summarise the evidence of QoL during and after adjuvant therapy in elderly cancer patients.

Methods

A systematic search was conducted of studies published in CINAHL plus, CENTRAL, PubMed, PsycINFO and Web of Science from the inception of these databases to December 2016. Eligible studies included RCTs and non-RCTs in which QoL was measured in elderly patients (65 years of age or above) with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy. Because of the heterogeneity and the insufficient data among the included studies, the results were synthesised narratively.

Results

We included 4 RCTs and 14 non-RCTs on 1,785 participants. In all four RCTs, the risk of bias was low or unclear for most items but high for detection. Of the 14 non-RCTs, 5 studies were judged to have a low or moderate risk of bias for all domains, and the other 9 studies had a serious risk of bias in at least one domain. The bias was observed mainly in the confounding and in the selection of participants for the study. For most elderly patients with breast cancer, the non-significant negative change in the QoL was transient. A significant increase in the QoL during the course of temozolomide in elderly patients with glioblastoma but a decreasing trend in QoL after radiotherapy was shown. This review also shows a

uniform trend of stable or improved QoL during adjuvant therapy and at follow-up evaluations across the studies with prostate, colon or cervical cancer population.

Conclusions

This review suggests that adjuvant chemotherapy and radiotherapy may not have detrimental effects on QoL in most elderly patients with solid tumours.

Strengths and limitations of this study

- A systematic search of the published literature in major databases from their inception to December 2016 was conducted.
- The risk of bias and the methodological aspects of quality of life reporting in the included studies were assessed.
- The search of grey literature, unpublished studies, ongoing clinical trials, and theses and dissertations were not conducted.
- The studies included in this review are mainly non-randomized controlled trials.
- The meta-analysis was not conducted to pool the data and the GRADE approach was not used to assess the quality of evidence of the included studies.

Keywords

Elderly cancer patients, adjuvant therapy, quality of life, chemotherapy, radiotherapy, oncology

Introduction

In many countries, the incidence of cancer among older people is increasing. This increase can be attributed to the remarkable growth of the elderly demographic and the common pathophysiology of cancer and aging.[1-2] As a result, the demands for and the importance of broadening clinical trials to include older adults, incorporating geriatric-specific endpoints,[3] and integrating geriatric assessment to address the needs of individuals are also increasing.[4] Although quality of life (QoL) is not formally a part of the geriatric assessment, the measurement of QoL in the elderly cancer population is increasingly being recognised as an important patient-reported outcome to complement the clinician's evaluation of disease progression and the determination of the clinical benefit and the burden of cancer treatment, along with toxicity, survival and mortality rates. QoL is also considered a useful outcome measure to enhance patient–clinician communication and patient compliance in elderly patients with breast cancer during cancer treatment.[5] In a short literature review, Wedding et al. (2007) reported that elderly cancer patients tend to perceive their QoL as more important than gains in survival when compared to younger patients.[6] Nevertheless, our understanding of the effect of cancer treatment on the QoL of elderly patients remains very limited. Clinically, the decisions regarding cancer therapy and the clinical management of elderly cancer patients may be complicated by their vulnerability to chemo-toxicity and the pathological changes of aging together with different considerations of the treatment benefit and harm margins, functional decline, tolerability and QoL issues. A univariate analysis by Extermann et al. (2015) revealed an association of the QoL effect with dose modification of chemotherapy in older patients.[7] The literature states that elderly cancer patients are less likely than their younger counterparts to be treated with a full course of adjuvant chemotherapy and radiotherapy.[8] Consideration should be given to approaches that can prolong life expectancy, but not at the expense of QoL and physical and psychological

functioning. For cancers with an extremely poor prognosis, such as glioblastoma, the extension of survival is less clinically meaningful if the patient has a decline in QoL.[9] Researchers have also suggested that QoL be used as the main endpoint to support clinical decision-making if different cancer treatments are equally effective in terms of survival.[10] To the best of our knowledge, a systematic review of the effects of adjuvant therapy on the QoL of elderly cancer patients has not yet been published. Therefore, we undertook a systematic review of the literature to summarise the evidence of global or overall QoL and other domains pertaining to QoL during and after adjuvant therapy in elderly patients with stage I to III solid tumours. The population, intervention, comparison, outcome, study design, commonly known as PICOS, considered the question 'Does the global or overall QoL during and after adjuvant chemotherapy and/or radiotherapy decline, maintain or improve from baseline in elderly patients with solid tumours in randomised controlled trials (RCTs) or non-RCTs?' In this review, QoL refers to the health-related QoL of elderly patients, considering the corresponding global, physical, cognitive, psychological and social domains as affected by the adjuvant therapy.

Methods

The methodology of this systematic review included a pre-specified literature search strategy, inclusion and exclusion criteria, process for selecting studies, assessment of methodological quality of studies and data synthesis. The review protocol was unregistered to an international register. The conduct and reporting of this systematic review were in accordance with the planned review methods except for the addition of assessment of risk of bias (RoB) of the included studies using the Cochrane Risk of Bias tool for RCTs and Risk of Bias tool in Non-Randomised Studies of Interventions (ROBINS-I).

Literature search strategy

A systematic electronic search of peer-reviewed English-language articles published in CINAHL plus (1937–2016), CENTRAL (1993–2016), PubMed (1996–2016), PsycINFO (1967–2016) and Web of Science (1900–2016) from the inception of these databases to December 2016 was conducted. The date last searched was in March 2017. Searches were limited to human studies published in English. A pilot search on CINAHL was performed to identify the relevant keywords contained in the title, abstract and subject descriptors. Three broad categories of concepts were searched: 'elderly', 'cancer' and 'quality of life'. The search terms included (older* OR elder* OR geriatric OR gerontology* OR senior OR aged) AND (oncology OR cancer* OR neoplasm*) AND (quality of life OR QOL). The full electronic search strategy is presented in Appendix A. The reference lists of the included articles were also examined to identify additional eligible articles.

Study selection

Inclusion criteria

We included RCTs and non-RCTs in which QoL was measured in elderly patients (65 years of age or above) with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy. Non-RCTs include quantitative studies such as observational, before-and-after and longitudinal studies, in which the allocation of intervention (analogy of treatment) occurs during the course of the usual treatment decisions.[11] We required that the baseline and at least one global or overall QoL data element during and/or after adjuvant chemotherapy and/or radiotherapy be collected and reported in the studies so as to allow an in-context comparison of before and after adjuvant therapy. Studies that covered heterogeneous age groups were included if a subgroup analysis was performed and reported for those aged 65 years of age or above.

Exclusion criteria

Studies were excluded if they involved patients with haematological malignancies, distant metastatic cancer or recurrent cancer without a separate analysis and report of solid tumours or non-metastatic/regional metastatic cancer. We also excluded case reports, qualitative studies, literature reviews, studies that evaluated surgical or procedure-related treatment and presented in abstract form.

Process for selecting studies

We screened articles obtained from keyword searching for duplicates electronically with End-Note and then manually. After duplicate removal, we assessed the remaining articles for eligibility based on titles and abstracts. We included studies in full-text screening if they were RCTs or non-RCTs, included elderly patients with stage I to III solid tumours who were undergoing adjuvant chemotherapy and/or radiotherapy, and reported QoL. We retrieved full-text articles if we considered the studies relevant and if there was insufficient information to determine eligibility. We then examined each full-text article against the inclusion and exclusion criteria of the review.

Data extraction

We extracted data related to publication information, sample characteristics, type of cancer, type of adjuvant chemotherapy and/or radiotherapy, supportive care, QoL measurements and results, drop-outs and authors' conclusions. Functional status and co-morbidities at baseline and therapy-related adverse effects (where reported) were also extracted because of concern that they might co-vary or confound with those of adjuvant therapy to alter the change of QoL.

Assessment of methodological quality of studies on QoL

The methodological quality of the included studies on QoL was assessed using a checklist of predefined criteria for studies on QoL.[12-13] The checklist was originally developed to assess the internal and external validity of prognostic studies[14] and was modified to assess the methodological aspects of QoL reporting in later studies.[12-13] The checklist covers the following 14 items: sampling (two items), selection of QoL measurement (one item), data collection process (two items), response rate (two items), group comparison (one item), clarity of reporting (five items), and determination of prognostic factors (one item), all of which are important in QoL studies. For each item, a score of 1 or 0 was given; 1 was assigned to an item meeting the methodological criteria, while 0 was assigned if an item neither met the criteria nor described the related parameter sufficiently. The possible score ranged from 0 to 14, with scores of 10 or above, 7 to 9 and 6 or less indicating high, moderate, and low quality, respectively.[12]

Assessment of risk of bias

The risk of bias (RoB) of the included studies was evaluated using the Cochrane Risk of Bias tool and the Risk of Bias tool in Non-Randomised Studies of Interventions (ROBINS-I) for RCTs and non-RCTs, respectively.[11,15] Both tools are domain-based evaluations of RoB with respect to the internal validity of studies. The Cochrane RoB tool covers the domains of selection, performance, detection, attrition and reporting bias, and other sources of bias. A judgement of 'yes' indicates a low risk of bias; 'no', a high risk of bias; and 'unclear', either an unclear or unknown risk of bias.[15] The ROBINS-I tool covers seven domains: bias due to confounding; bias in selection of participants into the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported results. The risk of

bias judgments within each domain are categorized as 'low risk' if the study is comparable to a well-performed RCT, 'moderate risk' if the study is sound but cannot be considered comparable to a well-performed RCT, 'serious risk' if the study has some considerable problems, 'critical risk' if the study is too problematic, and 'no information'. The judgments within each domain contribute to the overall risk of bias.[11]

In this review, two reviewers (LEYT and TDRL) independently performed the literature search, eligibility assessments and study selection. The data extraction, methodological quality assessment and the RoB evaluation were conducted by CKKF and LEYT. Discrepancies and disagreements were discussed and resolved by consensus.

Data synthesis

Because of the variations in study design, cancer populations and QoL scales and the insufficient data among the included studies, a meta-analysis was deemed impossible, and the results were synthesised narratively taking into account of the RoB of individual studies. In addition, we report a change in QoL scores from baseline to the middle of and to the completion of adjuvant therapy, and to the post-treatment follow-up period of individual studies where data were available. We defined '0' as no change, '↑' denotes better QoL than baseline and '↓' represents worse QoL than baseline. The effect size (ES) was also calculated for individual studies for which sufficient information was available: 0.2 to <0.5 was considered small, 0.5 to <0.8 moderate and ≥0.8 large.

Results

Search results

The initial search identified 56,935 articles, of which 440 were considered potentially relevant after checking for duplicates and title and abstract screening. After full-text assessment of the 440 articles, 18 met the eligibility criteria for inclusion in the review and analysis (Figure 1).[16-33] In most cases, the articles were excluded mainly because of the lack of QoL assessment during adjuvant therapy, a separate report of participants 65 years of age or above and/or a separate report of the QoL of participants who were underoing adjuvant therapy or suffering from non-metastatic cancer.

Description of studies

Eleven studies were published between 2000 and 2009, and seven between 2010 and 2015. With respect to the country of origin, 10 were from Europe, four from the United States, two from South Korea and one from Canada; the other was a multi-country study. As for the study design, 13 studies were non-RCTs (before-and-after or longitudinal studies) that assessed the QoL of patients who were undergoing adjuvant chemotherapy,[17,19,20,22,24,30,31,33] radiotherapy[16,32] or concomitant chemotherapy and radiotherapy.[26-28] Four were RCTs[18,21,23,25]; two of these compared the effects of different chemotherapy regimens on QoL, one study compared the effects of chemotherapy and hormonal therapy against those of hormonal therapy alone on QoL, and the other compared the effects of radiotherapy and supportive care with those of supportive care alone on QoL. One was a validation study that involved a QoL evaluation of participants who were undergoing radiotherapy with or without hormonal therapy[29] (Table 1).

Table 1. Characteristics of the included studies

Study / Country	Type of study	Age (years) Mean ± SD	Sample size (≥65 years cohort)	No. of participants completed baseline QoL measurement (%)	Gender (% female)	Type of cancer	CT/RT	Measurement of CGA domains	Measurement of CT/RT related toxicity/adverse effect	QoL scale (domains/subscales and score ranges)	QoL measurement time-point
Arraras et al (2008a)[16], Spain	Descriptive longitudinal	72.3 ± 5.7 (range 65-87)	48	48 (100)	100	Breast (Stage 1-III)	RT: Local Locoregional Regional *(no details on dosage)*	KPS Co-morbidity Daily activities	Selected items from NCI CTCAE	EORTC QLQ-C30[34] *(30 items – global QoL; physical, role, cognitive, emotion and social functioning scales; fatigue, nausea/vomiting and pain symptom scales; 5 single-item assessing additional symptoms and 1 single-item assessing perceived financial impact; all scales and single –item measure scores are transformed to a scale of 0 to 100, a higher score for the QoL / a functional scale indicates a better level of QoL / functioning and a higher score on a symptom scale / item represents a worse level of symptom)* EORTC QLQ-BR23[35] *(23 items – symptoms and side effects related to different treatment modalities, body image, sexuality,*	• 1st day of RT • Last day of RT • 6 weeks after RT

										and future perspective specific to breast cancer; all items and scale scores are transformed to a 0–100 scale, a higher score for the a functional scale indicates a better level of functioning and a higher score on a symptom scale / item represents a worse level of symptom)	
Browall et al (2008)[17], Sweden	Descriptive longitudinal	No information on mean age (range 65-77)	39	39 (100)	100	Breast (Stage I-IIIa)	FEC: Flurouracil 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2 for 6 cycles or CMF: Cyclophosphamide 100mg/m^2, methothrexate 40 mg/m^2, flurouracil 600 mg/m^2 for 6 cycles *(30 women also had the CT combined with RT; a 5-week RT course starting 3-4 weeks after CT)*	Co-morbidity	NR	EORTC QLQ-C30 EORTC QLQ-BR23	• Baseline • 1 week after 1st, 2nd, 3rd and last cycle of CT • 4 months post-CT
Crivellari et al (2000)[18], Multi-countries	RCT (longitudinal) *(elderly women was a subset of the original study)*	No information on mean age (age ≥65 years)	76	58 (76.3)	100	Breast (Grade I-III)	Tamoxifen for 5 years or Tamoxifen plus 3 early courses of CMF (cyclophosphamide 100	ECOG Co-morbidity	Modified WHO toxicity criteria	PACIS[36] *(a single-item measure – assessing the amount of effort it costs to cope with illness which influences*	• Baseline • 2 months after 1st day of adjuvant therapy then every 3 months until 24 months

							mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 every 28 days for 4 cycles)			*subjective well-being and QoL; score range 0-100^)*	
Dees et al (2000)[19], USA	Descriptive longitudinal	71.4 (range 65-79)	17	11 (64.7)	100	Breast (Early stage)	AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 for 4 cycles	NR	Myelosuppression Cardiotoxicity	BCQ[37] *(30 items – overall QoL; consequences of alopecia, positive well-being, physical symptoms, inconvenience associated with treatment, fatigue, emotional dysfunction and nausea subscales; score range 0-10^)*	• Day 1 of each cycle • 2 months after completing CT • 6 months after completing CT
Hurria et al (2006)[20], USA	Descriptive longitudinal	68 (range 65-84)	49	49 (100)	100	Breast (Stage I-III)	CMF: Cyclophosphamide 600 mg/m^2, methrotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 every 3 weeks for 8 cycles or AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles or ACT: AC followed by paclitaxel 175 mg/m^2 every 2 or 3 weeks for 4 cycles or AC followed by paclitaxel 175 mg/m^2 weekly for 12 cycles or	CCI ADL IADL MMSE GDS BMI	NCI CTCAE	FACT-B[38] *(44 items covering FACT-General plus the Breast Cancer Subscale – overall QoL (total FACT-B score including all the subscales, score range 0-144^); breast well-being (score range 0-36^), emotional well-being (score range 0-24^), functional well-being (score range 0-28^), physical well-being (score range 0-28^) and social well-being subscales (score range 0-28^)*	• Prior to CT • Upon completion of CT • 6 months after CT

							ACT-H: ACT followed by trastuzumab 2 mg/kg weekly for 52 weeks *(CT regimen was at the discretion of the treating physician)*				
Kornblith et al (2011)[21], USA	RCT (longitudinal) *(QoL was a sub-study)*	Standard CT (CMF or AC) group 72 ± 4.6 Capecitabine group72 ± 5.0	350	326 (93.1)	100	Breast (Stage I-III)	Standard CT CMF: Cyclophosphamide 100mg/m^2 from days 1 to 14, methotrexate 40 mg/m^2 & 5-fluorouracil 600 mg/m^2 on days 1 & 8 for 6 cycles or AC: Adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2 on day 1 for 4 cycles or Test cytotoxic drug Capecitabine 2000 mg/m^2 for 14 days; dose increased to 2500 mg/m^2 if no toxic effect after 1st cycle for 6 cycles	ECOG OARS (Co-morbidity) HADS BOMC Neurobehavioral Functioning & Activities of Living Scale Social Support Survey	NCI CTCAE Systemic adverse effects subscale of EORTC BR23	*EORTC QLQ-C30 *EORTC BR23	• Baseline • Mid-CT (about day 77 for CMF, day 29 for AC, day 63 for capecitabine) • Post-CT (6 to 7 months for CMF, 4 to 5 months for AC and capecitabine) • 12 months post-baseline • 18 months post-baseline • 24 months post-baseline
Watters et al (2003)[22], Canada	Descriptive longitudinal	70±5 (range 65 to 80)	20	16 (80)	100	Breast (Stage 1-III)	Anthracycline-based adjuvant CT Fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 at 21 days interval for 6 cycles	KPS	NR	EORTC QLQ-C30 EORTC QLQ-BR23 SF-36[39] *(36 items – physical functioning, role limitations because of physical health*	• Prior to CT • Before the 3rd cycle • Completion of CT • 6 months post-CT

									problems, bodily pain, social functioning, general mental health, role limitations because of emotional health problems, vitality and general health perceptions domains; all domain scores are transformed to a scale of 0 to 100^; these domain scores then combined to calculate the physical & mental component scores; score range 0-100^)	
Perrone et al (2015)[23], Italy	RCT (longitudinal)	CMF: Median 71 (range 65-79) Docetaxel: Median 71 (range 65-79)	299	252 (84.3)	100	Breast (Stage 1-III)	CMF: Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 on days 1 & 8 every 4 weeks for 4 or 6 cycles or Docetaxel 35 mg/m^2 on days 1, 8 & 15 every 4 weeks for 4 or 6 cycles	ECOG CCI ADL IADL	NCI CTCAE	*EORTC QLQ-C30 *EORTC QLQ-BR23	• Baseline • End of 1st CT cycle • End of 2nd CT cycle • End of 3rd CT cycle
Gallego et al (2011)[24], France	Descriptive longitudinal (phase II trial)	Median 77 (range 70-87)	70	59 (84.3)	60	Glioblastoma	Temozolomide (150-200 mg/m^2 for 5 days every 4 weeks for 12 cycles / until disease progression) (*adjusted based on toxicity)*	KPS (<70 *as eligibility criteria*) MMSE	NCI CTCAE	*EORTC QLQ-C30 *EORTC QLQ-BN20[40] *(20 items – functional deficits, symptoms, toxic effects of treatment, and uncertainty about the future; all items and scale scores*	• Baseline At least every month (restricted to the period of temozolomide period due to poor-prognosis)

										are transformed to a 0–100 scale, with higher scores of functioning indicating greater functioning and higher scores on symptoms reflecting worse symptoms)	
Keime-Guibert et al (2007)[25], France	RCT (longitudinal)	Supportive care + RT group Median 75 (range 70-84)	39	35 (89.7)	37	Glioblastoma	Supportive care (corticosteroids & anticonvulsant agents, physical and psychological support, management by a palliative care team) & RT (1.8 Gy given 5 days per week, total dose of 50 Gy)	KPS *(≥70 as eligibility criteria)* MMSE	NCI CTCAE	*EORTC QLQ-C30 *EORTC QLQ-BN20	• Baseline • Day 30 • Day 60 • Day 90 • Day 135
Minniti et al (2009)[26], Italy	Descriptive longitudinal	Median 73 (range 70-79)	43	36 (83.7)	51.2	Glioblastoma	Focal hypofractionated RT (total dose of 30 Gy in 6 fractions over 2 weeks) followed by adjuvant temozolomide 5 days every 28 days up to 12 cycles; 150 mg/m^2 for 1st cycle and adjusted based on toxicity for subsequent cycles	KPS *(≥60 as eligibility criteria)* Co-morbidity	NCI CTCAE	*EORTC QLQ-C30	• Before RT • After RT • 2nd, 4th & 6th cycles of temozolomide
Minniti et al (2013)[27], Italy	Descriptive longitudinal (phase II trial)	Median 73 (range 70-81)	71	65 (91.5)	49.2	Glioblastoma	Focal hypofractionated RT (total dose of 40 Gy in 15 fractions) plus concomitant temozolomide 75mg/m^2 given 7 days/week followed by adjuvant temozolomide 5 days every 28 days for 12 cycles (adjuvant was started 4 weeks after the completion of RT); 150 mg/m^2 for 1st cycle and	KPS MMSE	NR	*EORTC QLQ-C30 *EORTC QLQ-BN20	• Before RT • 4 weeks after RT (before the start of adjuvant temozolomide) • Every 8 weeks during treatment until disease

							200 mg/m^2 from 2nd cycle onwards				progression
Mohile et al (2011)[28], USA	Descriptive before/after	Median 74.1 (range 65-92)	368	368 (100)	58.4	Breast (17.1%) Genitourinary (30.4%) Lung (15.8%) Brain and peripheral nervous system (6.5%) Alimentary (10.1%) Haematologic (4.9%) Head and Neck (6.3%) Soft tissue sarcoma (1.6%) Bone and cartilaginous (1.4%) Skin (3.3%) Gynecologic (0.8%) Melanoma (0.3%)	RT Median total dose of 57.6 Gy (range 30-161)	NR	NR	Symptom Inventory (*10 items adapted from the core set of symptom items and 5 items adapted from symptom interference items of the M.D. Anderson Symptom Inventory[41] – symptoms and side effects related to cancer and its treatment, and interference of symptoms; and an additional item of interference with overall QoL; score range 0-10, with higher scores indicating worse symptoms / worse interference with QoL)*	• Before RT • During the last week of RT
Arraras et al (2008b)[29], Spain	Descriptive longitudinal (validation)	70.9 ± 5.2	137	137 (100)	0	Prostate (Localized)	Lower risk: RT alone (total dose of 72 Gy) Intermediate risk: Neoadjuvant and concomitant combination of an anti-androgen and an LHRH analogue (6 months) + RT (total dose of 76 Gy) High risk: Neoadjuvant and concomitant	KPS	NR	EORTC QLQ-C30	• 1st day of RT • Last day of RT • 6 weeks after RT

							combination of an anti-androgen and an LHRH analogue (6 months) + RT (total dose of 76 Gy) + adjuvant LHRH analogue				
Bouvier et al (2008)[30], France	Descriptive longitudinal survey	No information on mean age (range 75 – 85+)	11 (only 11 patients with stage III colon cancer treated with adjuvant CT and their QoL scores were reported)	11 (100)	NR	Colon	Flurouracil or Oxaliplatin plus flurouracil or Capecitabine *(no details on dosage)*)	NR	NR	EORTC QLQ-C30	• At the time of diagnosis • 3 months after diagnosis • 6 months after diagnosis *(CT was given within 6 months after surgery)* • 12 months after diagnosis
Chang et al (2012)[31], South Korea	Descriptive longitudinal	Median 74.5 (range 70-90)	82	57 (69.5)	64	Colon (Stage II-III)	Capecitabine (oral, 750-1250 mg/m^2 , twice daily on days 1-14 every 3 weeks for 8 cycles) *(dose level was determined a/c toxicity effects during the first and preceding cycles)*	ECOG PS *(0-2 as eligibility criteria)* CACI	NCI CTCAE *(adequate hematologic, hepatic, and renal function status as eligibility criteria)*	EORTC QLQ-C30	• Baseline • 3 months during CT • 6 months during CT • 3-6 months after completion of CT
Caffo et al (2003)[32], Italy	Descriptive longitudinal	Median 62.5 (range 46-81)	25 (no information on the breakdown of sample size by age group)	-	100	Cervical endometrium	Post-operative external pelvic RT (median total dose of 50.4 Gy, range 45-66.6 Gy, at a dose of 1.8-2.0 Gy 5 times/week)	NR	Diarrhoea	Diary card[42] *(12 items – global QoL, physical side effects observed during external pelvic RT, daily activities, and psychological well-being; score range 1-4 , with higher scores of QoL, psychological well-*	Diary card: • At the start of RT • Daily during RT period (reported as mean weekly scores) EORTC QLQ-C30:

										being and daily activities indicating better condition and higher scores on symptoms reflecting intense symptoms) EORTC QLQ-C30	• Before RT • After RT
Park et al (2013)[33], South Korea	Descriptive longitudinal	Median 69 (range 65-82)	66	66 (100)	9.1	Non-small-cell lung carcinoma (completely resected stage Ib, II or IIIa)	NP: Cisplatin 80mg/m^2 on day 1, vinorelbine 25mg/m^2 on days 1 and 8 at 3-week interval for 4 cycles (n=30, 45.5%) or PC: Carboplatin, paclitaxel 175mg/m^2 on day 1 at 3-week interval for 4 cycles (n=36, 54.5%) *(at the physician's discretion)*	ECOG Co-morbidity	NCI CTCAE	EORTC QLQ-C30 EORTC QLQ-LC13[43] *(13 items – lung cancer related symptoms, treatment-related adverse effects and the use of pain medication; all items and scale scores are transformed to a 0–100 scale, with higher scores of functioning indicating greater functioning and higher scores on symptoms reflecting worse symptoms)*	• Before 1st dose of CT at each cycle • 1 month after 4th cycle

^Higher scores indicating better quality of life unless specified otherwise; * Quality of life is the secondary endpoint if indicated

Abbreviations:
BCQ, Breast Cancer Chemotherapy Questionnaire; CGA, Comprehensive Geriatric Assessment; CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30 general questionnaire; EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer specific module for breast cancer; EORTC QLQ-BN20, European Organization for Research and Treatment of Cancer specific module for brain cancer; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer for lung-specific questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast cancer; NR, not reported; QoL, quality of life; PACIS, Perceived adjustment to chronic illness scale; RCT, randomized controlled trial; RT, radiotherapy; SF-36, 36-item short-form survey

The sample size of participants 65 years of age or older was reported by 17 of the 18 studies[16-31,33]; Caffo et al. (2003) did not separately report the number of participants 65 years of age and older.[32] The sample sizes ranged from 11 to 368 per study.[16-31,33] In all, these 17 studies included 1,785 participants; 764 participants from RCTs and 1021 participants from non-RCTs. [16-31,33] Of these 1,785 participants, 1,633 completed the baseline QoL questionnaire; 671 participants from RCTs and 962 participants from non-RCTs. Furthermore, the baseline completion rates ranged from 64.7% to 100%. Where reported, the age range of the participants was 65 to 92 years.[16,17,19,20,22,24-28,31-33] Eleven studies included participants 80 years of age and older.[16,20,22,24,25,27,28,30-33] As for the cancer diagnosis, eight studies included participants with breast cancer,[16-23] four studies focused on glioblastoma participants[24-27] and two studies considered participants with colon cancer.[30-31] We included one study each on mixed,[28] prostate,[29] cervical[32] and lung cancer[33] participants.

The most frequently used QoL instrument was the European Organization for Research and Treatment of Cancer general questionnaire (EORTC QLQ-C30; 13 studies).[16,17,21-29,30,31,33] Nine studies also used a disease-specific QoL instrument along with the EORTC QLQ-C30 for breast,[16,17,21-23] brain[24,25,27] and lung[33] cancer populations. The follow-up QoL evaluation was conducted at various intervals during adjuvant therapy and the post-treatment period. Ten studies reported at least one QoL evaluation during adjuvant therapy,[17-19,21-25,31,32] and five evaluated QoL immediately after the completion of adjuvant therapy.[20-22,28,29] The timing of the QoL evaluation after adjuvant therapy ranged from 1 month after treatment to 24 months after the first day of adjuvant therapy. Ten studies followed participants for 6 months or less after the completion of adjuvant therapy.[16,17,19,20,22,25,29-31,33] Two studies included a QoL evaluation of 24 months after the first day of chemotherapy.[18,21]

The geriatric domains of functional status and/or co-morbidities at baseline were examined and reported in 14 studies.[16-18,20,21-27,29,31,33] As shown in Table 2, two studies reported the mean score of the Karnofsky Performance Scale (KPS) as 90 or above,[16,29] whereas three reported the median score of the KPS as 70 or above at baseline.[25-27] A KPS score of less than 70 was used as a cut-off for the recruitment criterion in one study.[24] Co-morbid conditions were reported in eight studies[16,17,20,21,23,26,31,33]; six of these involved participants with a limiting co-morbidity or with three or more co-morbidities.[16,17,21,23,31,33] Twelve studies measured cancer therapy-related toxicity during adjuvant therapy,[16,18-21,23-26,31-33] and nine of these used National Cancer Institute's Common Terminology Criteria for Adverse Events.[16,20,21,23-26,31,33] With respect to haematological toxicity, two studies reported grade 3 or 4 toxicity in fewer than 10% of participants,[18,31] and five reported such toxicity in 25% or higher during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[20,23,24,26,33] With respect to non-haematological toxicity, a study reported grade 3 or 4 toxicity in fewer than 10% of participants,[18] and four reported such toxicity in 25% or higher during adjuvant chemotherapy or concomitant radiotherapy and chemotherapy.[20,23,26,31] (Table 2)

Table 2. Summary of the main findings of QoL

Study	Functional status at baseline *(Functional status during adjuvant therapy if reported)*	Co-morbid condition at baseline	Toxicity/Adverse effect	Supportive care where reported	Global or overall QoL scores (scale range)	Global or overall QoL scores Adjuvant chemotherapy and/or radiotherapy Baseline Mean ± SD No. of participants	In the middle	At the time of completion	Follow-up period	Findings of global or overall QoL *(Other QoL domains/subscales if reported)*	Authors' conclusions
Arraras 2008a	KPS mean 94.9 *During therapy: KPS decreased from baseline to last dose of RT (mean difference 4.7 [0-100] but returned to baseline 6 weeks after RT)*	Limiting co-morbidity 62.5%	At last day of RT: Levels 2-3 skin toxicity 8.4% Level 2 dysphagia 4.2% Level 2 fatigue 4.2% Level 2 pain 2.1%	NR	Global HQoL (0 – 100) 59.5 ±12 n=48			56.4 ± 11.2 n=48	66.5 ±14.8 (6 weeks after RT) n=46	• †Global QoL improved significantly from baseline to final evaluation *Subscales* • †Significant worsening in physical and role functioning, and fatigue, pain, and breast symptoms in last day of RT but improved at 6 weeks after RT (final evaluation)	• QoL data indicates RT was well tolerated by elderly women with localized breast cancer
Browall 2008	NR	1 or 2 co-morbidity 61% ≥3 co-morbidities 3%	NR	NR	Global HQoL (0 – 100) 76 ± 20 n=39		60 ± 23 n=35	61 ± 22 n=32	70 ± 24 (4 months after CT & about 7 wks after RT) n=30	• †Global QoL decreased significantly from baseline to mid-treatment and last dose of CT. The decrease in global health status had not fully recovered to baseline level at 4 months post-CT *Subscales* • †Physical, role, social and cognitive functioning decreased significantly from baseline to last dose of CT • The decrease in physical and role functioning had not fully recovered to baseline levels at 4	• There was a significant decrease in global QoL, body image, physical & role functioning during and after CT, but the decrease was independent of age

									months post-CT • No significant change in future perspective, emotional and sexual functioning over time	
Crivellari 2000	ECOG ≤2 for participants to be eligible	No specific data reported for those 58 participants who completed baseline QoL measurement	Grade 3 haematological toxicity 9.2% Other grade 3 toxicity 6.6%	NR	Perceived adjustment to chronic illness QoL (0 – 100) Median 59 n=58 (CMF plus tamoxifen)	Median 68 n=55		Median 82 (18 months after 1st day of CT) n=55	• QoL improved progressively across study points (within CMF plus tamoxifen group)	• Adding CMF to tamoxifen provided little survival benefits for the older patients, and patients continued to report more effort to cope (low QoL) in the tamoxifen plus CMF group compared with the tamoxifen alone group across time • CMF tolerability and effectiveness were reduced for elderly patients with breast cancer
Dees 2000	NR	NR	Neutropaenic complications and alteration in cardiac function were not significantly age related, no clinically significant age related trends in toxicity		Overall QoL (0 – 10) 7.65 ± 0.88 n=11		6.63 ± 1.48 n=7	*(authors mentioned to collect data at 2 and 6 months after completing CT, but they did not report the results/data)*	• Overall QoL decreased from baseline to last dose of CT but not significant	• There was no evidence of decline QoL in older breast cancer patients treated with adjuvant AC compared with younger ones
Hurria 2006	NR	CCI mean 3	Grade 3 or 4 haematological toxicity 27% Grade 3 or 4 non-haematological toxicity 31%	NR	Overall HQoL (0 – 148) 116 (no information on SD) n=49		116 (no information on SD) n=49	119 (no information on SD) (6 months post CT) n=48	• No significant longitudinal change in overall QoL across all time points *Subscales* • No significant longitudinal change in	• Despite about half of patients experiencing grade 3 or 4 toxicity, from the perspective of QoL and functional outcomes, women

									physical, social, emotional and functional well-being across all time points	tolerated adjuvant CT with no decline in QoL, functional status (patients maintained their baseline ability to perform ADLs & IADLs), comorbid or psychological status
Kornblith 2011	ECOG 0-2 for participants to be eligible Grade 0-1, 96% Grade 2, 4%	0 co-morbidity 4.9% 1 co-morbidity 11.4% 2-3 co-morbidities 21.1% 4-10 co-morbidities 16.3%	Participants treated with capecitabine has significantly fewer adverse effects during and at the completion of CT	NR	Global QoL (0 – 100) 75.4 ± 18.3 n=170 (standard CT) 76.5 ± 18.7 n=156 (capecitabine)	63.1 ± 18.4 n=150 (standard CT) 73.1 ± 17.6 n=137 (capecitabine)	63.2 ± 17.3 n=153 (standard CT) 75.8 ± 17.5 n=136 (capecitabine)	78.8 ± 17.8 n=141 (standard CT) (12 months post-CT) 77.4 ± 17.6 n=137 (standard CT) (18 months post-CT) 77.2 ± 17.6 n=137 (standard CT) (24 months post-CT) 77.3 ± 18.0 n=127 (capecitabine) (12 months post-CT) 78.2 ± 17.1 n=114 (capecitabine) (18 months post-CT) 76.5 ± 17.7 n=109	• Global QoL decreased across all time points within group but no information of p-value • *(Participants treated with capecitabine had significantly better global QoL, role and social functioning, less fatigue, less nausea and vomiting, less constipation, and better appetite, and less psychological distress than standard CT group. This difference had resolved by 12 months with no further difference at 24 months)*	• As reported in the original study, standard CT was associated with a significant improvement in relapse-free survival and overall survival compared with capecitabine • The short period of poorer Qol with standard CT is a modest price to pay for a chance at improved survival

								(capecitabine) (24 months post-CT)		
Watters 2003	Baseline KPS - NR *During therapy: KPS declined during and by the completion of CT, but did not differ from baseline at follow-up*	NR	NR	NR	Global QoL (0 – 100) 78 ± 16 n=20	77 ± 14 n=20	66 ± 20 n=20	73 ± 22 (6 months post-CT) n=20	• †Global QoL decreased significantly from baseline to the time of completion of CT but improved at 6 months post-CT *Subscales* • †Role and social functioning decreased significantly from baseline to the time of completion of CT but improved at 6 months post-CT	• Selected older women tolerated anthracycline-based adjuvant CT for breast cancer well
Perrone 2015	ECOG Grade 0, 83% Grade 1, 17%	No comorbidity 60% 1 comorbidity 31% ≥2 comorbidities 8%	Severe (grade >2) haematological toxicity was suffered by 70% of participants with CMF and 9% with docetaxel, while severe non-haematological toxicity was reported in 19% participants with CMF and 28% with docetaxel	G-CSF & erythropoiet in were used according to standard guidelines. G-CSF was also recommended for prophylaxis when grade ≥2 neutropenia occurred	No information on mean or median n=252	No information on mean or median			• Global QoL decreased from baseline to mid-treatment in both standard CMF and docetaxel groups but between group difference was not significant. No information on within group difference. *Subscales* • Physical, role, social and cognitive functioning decreased from baseline to mid-treatment in both standard CMF and docetaxel groups but between group differences were not significant. No information on within group difference. • *(A statistically significant worsening with docetaxel was found for systemic therapy side-effects, future perspective, nausea*	• There was no significant interaction of treatment arms & geriatric scales measuring patients' ability or comorbidities • Docetaxel is not superior to standard CMF in survival. Docetaxel worsens several QoL subscales and causes more non-haematological toxicity

									& vomiting, diarrhea, appetite loss, upset by hair loss & body image domains)	
Gallego 2011	Baseline: KPS <70 for participants to be eligible *During therapy: 33% improved their KPS by ≥10, before disease progression*	NR	Grade 3 or 4 haematological toxicity 25% Most adverse events were mild or moderate According to MMSE, Patient's cognitive function improved over time	NR	No information on mean or median n=59	1.4 points increase per month n=35			• †Global QoL improved significantly over time *Subscales* • †Physical, role, cognitive and social functioning scores improved significantly over time • For QLQ-BN20, scores on motor dysfunction, drowsiness, and bladder control improved over time before disease progression	• Temozolomide was generally well tolerated • Temozolomide appears to increase survival, and is associated with a significant improvement of QoL and functional status before tumor progression
Keime-Guibert 2007	Baseline KPS ≥70 for participants to be eligible *During therapy: KPS declined over time*	NR	No severe adverse effects related to RT	Corticosteroids and anticonvulsant agents, physical and psychological support, management by a palliative care team	Global QoL (0 – 100) 62.9 ± 3.4 n=35 (supportive care + RT)		55.6 ± 3.9 n=NR	58.8 ± 4.5 (~3 months post-RT) n=26	• Global QoL did not deteriorate significantly over time (supportive care + RT) *Subscales* • †During and after treatment, scores were significantly worse over time on physical, cognitive and social functioning, and fatigue and motor dysfunction	• Supportive care + RT was superior to supportive alone in survival benefit. Global assessment of deterioration of QoL over time did not differ significantly between supportive care + RT group and supportive care group alone • RT results in a modest improvement in survival without reducing QoL
Minniti 2009	Baseline: KPS ≥60 for participants to be eligible	Diabetes 19% out of 43 Hypertension 33% out of 43	Grade 2-3 confusion and/or somnolence during or after RT	Anticonvulsionants and dexamethasone	Global QoL (0 – 100) 58.3 ± 3.7		54.3 ± 5.1 (completion of RT) n=36		• Score of global health status did not change significantly	• Temozolomide is well tolerated. • The association of

	KPS median 70 *KPS did not change significantly during the study period*	Cardiovascular disease 16% out of 43	14% out of 43 Grade 3-4 haematological during CT 28% out of 43 (which led to the early discontinuation of CT in half of participants) Moderate-severe fatigue 35% out of 43, nausea 10% out of 43, constipation 22% out of 43, skin rash 9% out of 43		n=36		57.9 ± 6.8 (mid-CT; RT followed by CT) n=36		*Subscales* • During treatment, scores of functioning subscale, nausea and vomiting, and insomnia did not change significantly • Fatigue and constipation scales worsened slightly from baseline through treatment • †Scores of physical, role and social functioning, and fatigue deteriorated significantly between baseline and the 2nd follow up	hypofractionated RT and temozolomide had no negative effect on QoL • A short course of RT followed by temozolomide may provide survival benefit while maintaining QoL
Minniti 2013	KPS ≥60 for participants to be eligible KPS median 70	NR	NR	NR	Global QoL (0 – 100) 61.5 ± 20.8 n=65	60.0 (no information on SD) (1 month after RT and concomitant temozolomide) n=53 72.0 (no information on SD) (6 month from the start of RT) n=27			• †Global QoL improved significantly between baseline and 6-month from the start of RT (in the midst of adjuvant temozolomide) *Subscales* • †Social and cognitive functioning improved significantly between baseline and 6-month from the start of RT p • †Fatigue worsened significantly between baseline and 4-month follow up	• A short course of RT in combination with temozolomide was associated with survival benefit (median survival and 1-year survival rates of 12.4 months and 58%, respectively) without a negative effect on QoL
Mohile 2011	NR	NR	NR	NR	Overall QoL (0 – 10) 2.07 (no information on SD) n=368		2.37 (no information on SD) n=368		• There was an increase of interference with QoL score after RT, however, no information about the *p* value *Subscales* • †The prevalence of memory difficulties and sleep disturbance, and the	• There were no differences in the change in interference with QoL between older and younger patients during RT

									severity of fatigue and distress significantly increased over the course of RT	
Arraras 2008b	KPS mean 96.1	NR	NR	NR	Global QoL (0 – 100) 66.8 ± 17.9 n=137		66.7 ± 20.9 n=132	71.3 ± 18.6 (1.5 months after completion of RT) n=126	• No change in global QoL score from baseline to last dose of RT but significantly improved from last dose to 1.5 months after RT *Subscales* • †There was a significant worsening of physical, cognitive and social functioning from baseline to last dose of RT, but physical functioning improved significantly from last dose to 1.5 months after RT	• There was a tendency to a worsening of QoL at the end of the treatment, with a recovery in most scales in the follow-up measurement that could be due to RT low toxicity level
Bouvier 2008	NR	NR	NR	NR	Global QoL (0 – 100) 60 (no information of SD) n=11	No information on mean or median	No information on mean or median		• Graph shows the mean scores of global QoL increased over time, but no information about the *p* value *Subscales* • †The overall mean score for physical functioning was significantly higher for participants treated with CT than untreated patients regardless of follow-up period. Emotional functioning were found to significantly increase between at diagnosis and 6 months after diagnosis	• Global QoL for patients with stage III colon cancer treated with adjuvant CT did not vary significantly from that of patients who did not receive CT across time
Chang 2012	ECOG Grade 0, 4.9% Grade 1, 63.4% Grade 2, 31.7%	CACI ≤7, 75.6% ≥8, 24.4% *(data for the*	Grade 3 or 4 haematological toxicity <1% Grade 3 hand-foot	NR	Global QoL (0 – 100) 59 (no	No information on mean or median		No information on mean or median	• No significant worsening of global QoL during CT *Subscales*	• By using a tailored-dose escalation strategy, unnecessary dose

	(data for the original sample of 82)	*original sample of 82)*	syndrome 25.6% *(data for the original sample of 82)*		information of SD) n=57	n=55		(3-6 months after completion of CT) n=48	• No significant worsening of functional QoL during CT • A slight and insignificant deterioration in social and cognitive functioning at 3 months during CT but recovered over time • No symptoms were significantly exacerbated during therapy	reduction could be avoided without an increment of toxic effects in patients receiving capecitabine. The toxicity profiles were favorable. Compromised QoL after surgery was not worsened by adjuvant capecitabine and improved after the completion of CT
Caffo 2003	NR	NR	The mean no. of daily stools progressively increased during the treatment	Participants experiencing grade 3-4 diarrhea were given loperamide with adequate water and saline support. If loperamide was ineffective, treatment with octreotide was planned	Overall QoL (Daily card) (1 – 4) *(No data reported for EORTC)* 2.11 ± 0.75 n was not reported	2.46 ± 0.67 n was not reported	2.55 ± 1.05 n was not reported		• Global QoL score improved progressively across study points, and from baseline to final evaluation (during RT), but no information about the *p* value	• The authors' conclusion is not related to QoL
Park 2013	ECOG 0-1 for participants to be eligible	0 co-morbidity 71.2% Any comorbid conditions 28.8%	Grade 3 neutropaenia 39.4%, anaemia 4.5%, thrombocytopaenia 1.5%	NR	Global QoL (0 – 100) 53 (no information of SD) n=66	No information on mean or median (after 2nd cycle of CT) n=63	No information on mean or median (after 4th cycle of CT) n=60		• Global QoL did not significantly deteriorate over time	• Postoperative CT did not substantially reduce QoL in elderly NSCLC patients

† Significant difference reported by the study authors ($p < 0.05$)

Abbreviations:

ADLs, Activities of Daily Living; BMI, Body Mass Index; BOMC, Blessed Orientation-Memory-Concentration test; CACI, Charlson-Age Comorbidity Index; CCI, Charlson Comorbidity Index; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GDS, Geriatric Depression Scale; IADLs, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; KPS, Karnofsky Performance Status Scale; NCI CTC, National Cancer Institute Common Toxicity Criteria; NR, not reported; OARS, Older American Resources and Services Questionnaire; RT, radiotherapy

Methodological quality

Thirteen studies attained scores of 10 or higher (high quality),[16-27,33] three scored 7 to 9 (moderate quality),[28,30,31] and two scored 6 or lower (low quality).[29,32] The main methodological drawbacks of the included studies were the lack of determination of the prognostic factors for QoL (100%) and the lack of data on the time since diagnosis or treatment (77.8%) and the characteristics of non-responders (77.8%). (Table 3)

Table 3. Results of the methodological quality assessment

	Sampling		Selection of QoL instrument	Data collection process		Response rate		Group comparison		Clarity of reporting				Determination of prognostic factor QoL	
Studies	**B**	**O**	**I**	**C**	**M**	**G**	**H**	**E**	**A**	**D**	**F**	**J**	**K**	**L**	**Quality score**
Arraras 2008a	1	1	1	1	1	1	0	1	1	1	0	1	1	0	11
Browall 2008	1	1	1	1	1	1	1	1	1	1	0	1	1	0	12
Crivellari 2000	1	1	0 (PACIS)	1	1	1	0	1	1	1	0	1	1	0	10
Lees 2000	1	1	1	1	1	1	0	1	1	1	0	0	1	0	10
Murria 2006	1	1	1	1	1	1	0	1	1	1	1	1	1	0	12
Kornblith 2011	1	1	1	1	1	1	0	1	1	1	0	0	1	0	10
Watters 2003	1	1	1	1	1	1	0	1	1	1	0	1	1	0	11
Sirrone 2015	1	1	1	1	1	1	1	1	1	1	0	1	0	0	11
Gallego 2011	1	1	1	1	1	1	0	1	1	1	1	1	0	0	11
Keime-Guibert 2007	1	1	1	0	1	1	0	1	1	1	1	1	1	0	11
Minniti 2009	1	1	1	1	1	1	0	1	1	1	1	1	1	0	12
Minniti 2013	1	1	1	1	1	1	1	1	1	1	0	1	1	0	12
Mohile 2011	1	1	0 (MD Anderson Symptom Inventory)	1	0	1	0	1	1	1	0	0	1	0	8
Arraras 2008b	0	1	1	0	0	1	0	1	0	0	0	1	1	0	6
Bouvier 2008	0 (only age and cancer diagnosis were reported)	1	1	1	0	0 (only among 30 respondents undergoing curative surgical resection for stage III cancer with 11 received adjuvant CT was reported)	1	1	1	0 (no information on dosage)	0	1 (only graphical information was reported)	1 (only graphical information was reported)	0	8
Zhang 2012	1	1	1	1	0	1	0	1	1	1	0	1	0	0	9
Caffo 2003	0	0	0 (both diary care and EORTC-QLQ C30 were used but only diary data was reported)	1	1	1	0	1	0	1	0	0	1	0	6
Park 2013	1	1	1	1	1	1	0	1	1	1	0	1 (only	1 (only	0	11

graphical information was reported)	graphical information was reported)

A= Socio-demographic and medical data is described (e.g. age, race, employment status, educational status, tumour stage at diagnosis etc.); B= Inclusion and/or exclusion criteria are formulated; C= The process of data collection is described (e.g., interview or self-report etc.); D= The type of cancer treatment is described; E= The results are compared between two groups or more (e.g., healthy population, groups with different cancer treatment or age, comparison with time at diagnosis etc.); F= Mean or median and range or standard deviation of time since diagnosis or treatment is given; G= Participation and response rates for patient groups have to be described and have to be more than 75%; H= Information is presented about patient/ disease characteristics of responders and non-responders or if there is no selective response; I= A standardized or valid quality of life questionnaire is used; J= Results are not only described for quality of life but also for the physical, psychological and social domain; K= Mean, median, standard deviations or percentages are reported for the most important outcome measures (HQoL); L= An attempt is made to find a set of determinants with the highest prognostic value (HQoL); M= Patient signed an informed consent form before study participation; N=No; O= The degree of selection of the patient sample is described

Risk of bias

RCTs

In all four RCTs, the risk of bias was low or unclear for most items but high for detection because of the subjective and self-reporting nature of the QoL assessment. One RCT did not blind the participants and staff and thus was judged to have a high risk of performance bias.[18] The remaining three RCTs did not report information on the blinding of participants and personnel to allow for a judgement of the performance bias.[21,23,25] We judged three RCTs to have an unclear risk of attrition bias because of the lack of explicit information on patients' lost to follow-up and missing data.[18,21,25] (Figure 2)

INSERT FIGURE 2 HERE

Non-RCTs

Of the 14 non-RCTs, five studies were judged to have a low or moderate risk of bias for all domains,[16,20,26,31.33] and the other nine studies had a serious risk of bias in at least one domain.[17,19,22,24,28-30,32] The bias were observed mainly in the confounding, in the selection of participants for the study and in the measurement of outcomes. Although most of the studies measured some confounding factors (e.g., functional performance status or co-morbidity) at baseline, no stratification in the study design or adjustment in the data analysis was made to control their effects.[16,17,20, 22-24,27,29,31,33] Four non-RCTs did not measure functional performance status or co-morbidities at baseline.[19,28,30,32] The bias in the selection of participants was either moderate or serious in all the non-RCTs.[16,17,19,20,22-24,27-33] Only fit and functional elderly patients seemed to have been enrolled in these studies, and hence, the study cohorts might not be representative of the real world population. Like the RCTs, all 14 non-RCTs had a moderate-to-serious risk of bias in the measurement outcomes because of the

subjective and self-reporting nature of the QoL assessment. The bias in the selection of reported results was unclear in all the non-RCTs because of unavailability of study protocols.[16,17,19,20,22-24,27-33] (Table 4)

Table 4. Risk of bias summary for Non-RCTs (ROBINS-I)

	Pre-intervention		At intervention	Post-intervention				
Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Arraras 2008a	M	M	M	M	M	M	unclear	Low or moderate risk if bias for all domains
Browall 2008	M	M	M	S	M	M	unclear	Serious risk of bias in at least one domain
Dees 2000	S	S	L	M	M	M	unclear	Serious risk of bias in at least one domain
Hurria 2006	M	M	L	M	L	M	unclear	Low or moderate risk if bias for all domains
Watters 2003	S	M	L	M	L	M	unclear	Serious risk of bias in at least one domain
Gallego 2011	M	M	L	M	S	S	unclear	Serious risk of bias in at least one domain
Minniti 2009	M	M	L	M	L	M	unclear	Low or moderate risk if bias for all domains
Minniti 2013	M	M	L	M	S	M	unclear	Serious risk of bias in at least one domain
Mohile 2011	S	M	M	unclear	L	M	unclear	Serious risk of bias in at least one domain
Arraras 2008b	M	S	unclear	unclear	M	M	unclear	Serious risk of bias in at least one domain
Bouvier 2008	S	M	unclear	unclear	L	M	unclear	Serious risk of bias in at least one domain
Chang 2012	M	M	L	M	M	M	unclear	Low or moderate risk if bias for all domains
Caffo 2003	S	S	L	unclear	M	M	unclear	Serious risk of bias in at least one domain
Park 2013	M	M	M	M	M	M	unclear	Low or moderate risk if bias for all domains

L=low risk; M=moderate risk; S=serious risk; C=critical risk

QoL outcomes

Breast cancer

EORTC QLQ-C30

Three studies reported the global QoL scores at baseline, during chemotherapy, at the time of completion of chemotherapy and 4 to 12 months after the completion of chemotherapy.[17,21,22] The participants in these studies were treated with the standard chemotherapy regimen for breast cancer, including an anthracycline-based, cyclophosphamide/ methotrexate/ fluorouracil (CMF) or fluorouracil/ epirubicin/ cyclophosphamide regimen. In Kornblith et al. (2011),[21] approximately half of the participants received capecitabine. Browall et al. (2008) reported statistically significantly lower global QoL scores during (ES, 0.74) and immediately after the completion (ES, 0.71) of chemotherapy than at baseline and a non-significant decline in the global QoL score 4 months after chemotherapy.[17] Watters et al. (2003) also revealed a statistically significantly lower global QoL score immediately after the completion of chemotherapy (ES, 0.66) than at baseline and a non-significant decline in the global QoL scores during and 6 months after chemotherapy.[22] Browall et al. (2008) and Watters et al. (2003) also reported the domain scores, wherein statistically significantly lower scores in the role and social functioning domains were found immediately after the completion of chemotherapy than at baseline. No significant reductions in role and social well-being were reported during or 4 to 6 months after the completion of chemotherapy.[17,22] Emotion was the only domain that showed an improvement from baseline to the follow-up evaluations, with a statistically significantly higher score during chemotherapy. The domains of physical and cognitive functioning revealed no statistically significant differences across time.[17,22] In Kornblith et al. (2011), both standard chemotherapy and capecitabine groups showed a decline in the global QoL during and immediately after the completion of

chemotherapy, whereas an increase in the global QoL was reported from baseline to 12 months after the completion of chemotherapy.[21] (Tables 2 and 5)

Table 5. Matrix of baseline and change of QoL scores, attrition rate, methodological quality score, and RoB

Type of cancer Studies	QoL scale	Baseline	From baseline to the middle of adjuvant CT/or RT	From baseline to the time of completion of adjuvant CT/or RT	From baseline to post adjuvant CT/or RT follow-up period	Attrition (last follow-up) where reported (%)	Methodological quality	Overall risk of bias judgment for non-RCTs
Breast								
RCTs								
Kornblith 2011	EORTC	Standard CT 75.4	↓ (no information on *p* value)	↓ (no information on *p* value)	↑ (no information on *p* value)	17	10	(refer to RoB summary)
		Capecitabine 76.5	↓ (no information on *p* value)	↓ (no information on *p* value)	↑ (no information on *p* value)	18.6		
Perrone 2015	EORTC	Standard CT (mean or median was not reported)	↓ (narrative/graph; mean or median was not reported			No information	11	(refer to RoB summary)
		Docetaxel (mean or median was not reported)	↓ (narrative/graph; mean or median was not reported					
Crivellari 2000	PACIS	Median 59	↑ (no information on *p* value)		↑ (no information on *p* value)	5.2	10	(refer to RoB summary)
Non-RCTs								
Arraras 2008	EORTC	59.5		↓	↑† ES 0.52	4.2	11	low or moderate
Browall 2008	EORTC	76	↓† ES 0.74	↓† ES 0.71	↓ (an improving trend)	23.1	12	serious
Dees 2000	BCQ	7.65 on the scale of 0-10		↓		36.4	10	serious
Hurria 2006	FACT-B	116 on the scale of 0-148		0	↑	2	12	low or moderate
Watters 2003	EORTC	78	↓	↓† ES 0.66	↓ (an improving trend)	0	11	serious
Glioblastoma								
RCT								
Keime-Guibert 2007	EORTC	62.9		↓	↓ (an improving trend)	25.7	11	(refer to RoB summary)
Non-RCTs								
Gallego 2011	EORTC	Mean or median was not reported	↑†			40.7	11	serious

			(narrative; mean or median was not reported)					
Minniti 2009	EORTC	58.3		↓		0	12	low or moderate
Minniti 2013	EORTC	61.5	↑†			58.5	12	serious
Mixed								
Mohile 2011	MD Anderson SI	2.07 on the scale of 0-10		↑ (no information on *p* value)		0	8	serious
Prostate								
Arraras 2008	EORTC	66.8		0	↑† ES=0.25	8	6	serious
Colon cancer								
Bouvier 2008	EORTC	60	↑ (graphical data; mean or median was not reported)	↑ (graphical data; mean or median was not reported)		No information	8	serious
Chang 2012	EORTC	59	↓ (narrative; mean or median was not reported)		↑ (narrative; mean or median was not reported)	15.8	9	low or moderate
Cervical								
Caffo 2003	Diary card	2.11 on the scale of 1-4	↑	↑		No information	6	serious
Lung								
Park 2013	EORTC	53	↓ (narrative; mean or median was not reported)	↓ (narrative; mean or median was not reported)		9.1	11	low or moderate

'0' represents no change; '↑' denotes better QoL than baseline; '↓' represents worse QoL than baseline; †$p < 0.05$
ES=Effect size which was calculated for significant result and where mean, SD and sample size were available of the respective article
QoL scale is on the scale of 0-100 unless specified otherwise

Perrone et al. (2015) examined the global QoL and functioning domain scores of participants treated with standard CMF or docetaxel at baseline and during chemotherapy. The graphs of this study showed a decline in the global QoL and the physical, role, social and cognitive functioning domains scores over time in both CMF and docetaxel groups; with the mean score changes were greater than 10 (out of the score range of 100) from baseline to the completion of the third chemotherapy cycle. However, no information about the *p* value for within group difference was provided.[23] Note that 79% and 47% of the participants suffered from grade 2 or higher haematological and non-haematological toxicities, respectively.[23] Arraras et al. (2008a) measured the QoL of elderly participants treated with radiotherapy at baseline, at the completion of radiotherapy and 6 weeks after the completion of radiotherapy.[16] Although this study started with a lower QoL (score of 59.5) at baseline, the global QoL score increased significantly from baseline to 6 weeks after the completion of radiotherapy.[16]

Other QoL measures

Dees et al. (2000) measured QoL using the Breast Cancer Chemotherapy Questionnaire (BCQ) and found a non-significant decline in the overall QoL score from baseline to the last dose of doxorubicin/ cyclophosphamide.[19] Hurria et al. (2006) revealed no significant differences in overall or in physical, social and emotional well-being as measured by Functional Assessment of Cancer Therapy-Breast (FACT-B) from baseline to immediately after and 6 months after completion of an anthracycline-based, taxane-based, or CMF regimen.[20] Note that 27% and 31% of the participants of this study suffered from grade 3 or 4 haematological and non-haematological toxicity, respectively.[20] Crivellari et al. (2000) reported increased global QoL scores as measured by the Perceived Adjustment to Chronic Illness Scale (PACIS), during and 18 months after the completion of the CMF regimen.[18]

Note that the participants of this study had a low QoL score of 59 at baseline. Fewer than 10% of the participants manifested grade 3 toxicity.[18]

Glioblastoma

All four studies were conducted on participants with glioblastoma treated with temozolomide[24] or focal hypofractionated radiotherapy[25] or combined radiotherapy and temozolomide.[26,27] These studies assessed QoL using the EORTC QLQ-C30. Gallego et al. (2011) reported statistically significant improvements in the global score and the physical, role, cognitive and social domain scores during the course of temozolomide.[24] Note that 25% of the participants manifested grade 3 to 4 haematological toxicity in this study.[21] Minniti et al. (2013) also showed statistically significant improvements in the global score and the social and cognitive domain scores from baseline to 6 months from the start of radiotherapy (which was during the course of temozolomide).[27] Both Keime-Gulbert et al. (2007) and Minniti et al. (2009) reported a decline in the global QoL at the completion of focal hypofractionated radiotherapy.[25,26] With respect to the domain scores, these two studies reported statistically significantly lower scores for the physical, cognitive and social domains, and the physical, role, and social domains, respectively, during and after radiotherapy than at baseline [25,26] The participants in both studies were treated with corticosteroids and anticonvulsants as supportive care. Note that in Minniti et al. (2009), the participants began with a lower QoL (score of 58.3) at baseline and that 14% of these participants developed grade 2 or 3 confusion and/or somnolence during or after radiotherapy.[26]

Colon cancer

Two studies measured the global QoL with the EORTC QLQ-C30 at baseline and during and after chemotherapy in participants with colon cancer.[30,31] In Bouvier et al. (2008), the

participants were treated with a fluorouracil/ oxaliplatin/ capecitabine regimen.[30] This study reported an increase in the global QoL scores over time; however, no information about the *p* value was provided. Chang et al. (2012) found no significant worsening of the global and functional QoL during capecitabine treatment.[31]

Prostate cancer

Arraras et al. (2008b) measured QoL by using the EORTC QLQ-C30 in participants treated with radiotherapy for prostate cancer.[29] No difference in the global QoL score was observed from baseline to the last dose of radiotherapy, whereas a statistically significantly higher QoL score was reported at 6 weeks after radiotherapy (ES, 0.25).[29]

Lung cancer

Park et al. (2013) measured the global QoL using the EORTC QLQ-C30 at baseline and 1month after the completion of therapy with cisplatin plus vinorelbine or carboplatin plus paclitaxel in participants with resectable non-small cell lung carcinoma.[33] In this study, the QoL score of 53 at baseline was low. No significant deterioration of the global QoL between baseline and the follow-up evaluation was observed. Severe haematological toxicity was manifested in 39% of the participants.[33]

Other cancers

Mohile et al. (2011) studied different types of cancer, and QoL was measured before and after radiotherapy using an item of interference with overall QoL together with the modified M.D. Anderson Symptom Inventory.[25] In this study, the overall QoL score of 2.07 on the scale of 10 at baseline was low. A slightly higher overall QoL score was shown at the

completion of radiotherapy (score of 2.37); however, no information about the *p* value was reported.[28]

Discussion

In the context of cancer, QoL by its nature is a patient's overall appraisal of the effect of cancer and its treatment. It is a patient-centred, relevant and key clinical parameter that can assist and support clinicians in setting goals and mapping avenues for effective and tolerable cancer treatment regimens beyond extending patient survival. Although the 18 studies included in this systematic review had somewhat heterogeneous study designs, cancer populations, and measurement scales and reporting parameters of QoL to permit data pooling for a meta-analysis and precise estimation, our results provide some insights that will contribute to a better understanding of the effects of adjuvant chemotherapy and/or radiotherapy on the QoL of elderly patients 65 years of age or above. Our review suggests that QoL during and after adjuvant chemotherapy and/or radiotherapy is maintained or improved in most patients with solid tumours.

For elderly patients with breast cancer, the non-significant negative change in the global or overall QoL was transient (during and immediately after chemotherapy or radiotherapy), as measured by the EORTC QLO-C30, FACT-B and BCQ. No lasting adverse effect on QoL was observed after completion of the adjuvant treatment (overall low or moderate to serious RoB).[16,19,20,21,23] Browall et al. (2008) and Watters et al. (2003) revealed an initial statistically significant decline (moderate ES), followed by progressive improvement in global QoL scores from baseline to 4 to 6 months after chemotherapy (overall serious RoB). The role and social domains of QoL was mostly impaired immediately after the completion of chemotherapy.[17,22]

Another finding of this review is the significant increase in the global QoL during the course of temozolomide treatment in elderly patients with glioblastoma (overall low or moderate to serious RoB)[24,27] but a decreasing trend in QoL immediately after the completion of radiotherapy and 3 months after radiotherapy.[25,26] Note that the studies by Gallego et. (2011) and Minniti et al. (2013) had substantial amounts of missing data (>40%), mainly because of the rapid progression of the disease in the glioblastoma population. However, the approach of complete case evaluation used in the final QoL analysis could have led to a systematic bias in the estimation of the true effect of adjuvant therapy on QoL towards high QoL scores. Therefore, some caution should be taken in the interpretation of the significant QoL improvement during the course of adjuvant therapy of elderly patients with glioblastoma. Nevertheless, attrition bias is always an issue in clinical trials involving QoL assessments and longitudinal follow-ups.

Adjuvant chemotherapy or radiotherapy also does not seem to compromise the QoL of elderly patients with prostate, colon or cervical cancer. This review shows a uniform trend of stable or improved global or overall QoL over the course of adjuvant therapy and at follow-up evaluations across the studies with prostate, colon or cervical cancer population (overall serious RoB).[28,29,30,32] A decreasing trend in global or overall QoL during and immediately after the completion of cisplatin or carboplatin treatment in elderly patients with lung cancer was reported in one study (overall low to moderate RoB).[33]

We expected altered functional status, co-morbidities, adverse effects, haematological status, and liver and renal functional status to co-vary with the effect of adjuvant therapy on QoL and hence, to be plausible confounding factors in the geriatric and adjuvant settings. However, as is the case in non-RCT settings, adjuvant therapy was allocated during the course of usual

treatment decisions. The non-RCTs included in this review might suffer from the methodological drawbacks of uncontrolled confounding factors at baseline and even during the follow-up. Because no attempt was made to control confounding factors with a stratified design and analysis, caution is warranted in the interpretation of the results. Nevertheless, we found it difficult to discern whether the short period of QoL impairment and the stable or improved QoL over the course of adjuvant therapy and after treatment were due to the relatively low treatment toxicities, the relatively few morbid conditions or other reasons. The fact that, where reported, the QoL of elderly patients was maintained or improved over the course of treatment, despite the haematological toxicity across studies,[20,23,24,33] suggests that stable or improved QoL is unlikely to be attributable to relatively low treatment toxicity. Alternatively, elderly cancer patients who undergo adjuvant therapy may experience adverse effects but can tolerate them with a limited effect on their QoL. This finding may also be attributed to the tendency of certain elderly patients to complain less and endure the relatively high morbidity associated with adverse effects.[5] Elderly patients may also have a positive perception of the adjuvant therapy and may adjust better to the treatment. Stone et al. examined the association between global well-being and the age profile of 340,847 people and showed that people over 50 years of age have increased global well-being and positive emotions even in the face of a decline in the physical health.[44] Another possible explanation for the stable or improved QoL could be the response shift phenomenon, in which patients experience a shift in how they appreciate their QoL over time as a result of the changes in their internal standards of measurement, values or definition of QoL.[45,46] A future qualitative study is needed to explore in detail elderly cancer patients' QoL perception and experiences in adjuvant settings and their adjustment to the treatment. Nevertheless, for studies that reported a stable global or overall QoL (i.e. no difference in the means) across time, a small sample size and attrition bias might limit the statistical power to detect the differences

between the baseline and the follow-up evaluations.[19,21,23,25,31] It could also be argued that another possible bias was the poor sensitivity of the generic QoL measures to tap dimensions of health status that are particularly salient to elderly cancer patients during adjuvant therapy. While we cannot rule out the possible bias, in future clinical trials and observational studies attempts should be made to use geriatric oncology-specific QoL measures such as EORTC-QLQ-ELD14 to validate the review results.[47] Furthermore, the samples of the included studies appear highly functional at baseline,[16-23,25-33] so these studies may be subject to a selection bias pertaining to under-representation of less healthy older patients and those with limited expectations of treatment benefits.[3]

Conclusions

This review suggests that a negative change in QoL was short-lived during adjuvant chemotherapy for some elderly patients with breast cancer. Adjuvant chemotherapy and radiotherapy may not have detrimental effects on global or overall QoL and other QoL domains in most elderly patients with solid tumours. These findings could be translated to help future elderly patients better understand the impact of adjuvant therapy on their QoL, and hence make better treatment decisions. Nevertheless, our review results should be viewed with caution because of RoB within and across the included studies. In addition, heterogeneity in study design and measurement of QoL, and lack of availability of data limit the pooling of data for meta-analysis and affect the robustness of the evidence synthesis. An attempt was made to contact the study authors for data, but without success. There is also a possibility of incompleteness of evidence because of unclear bias of the selection of reported result and the search of this review did not include grey literature, unpublished studies, ongoing clinical trials, and theses and dissertations. Larger and well-designed studies of elderly patients in different cancer settings are warranted to validate these review results and

to further build evidence to advance the current knowledge base. These studies should include and stratify elderly patients by functional status, co-morbid conditions, geriatric syndromes and prognosis to be more representative of the real-world population and improve the research validity. Future studies should also include a detailed profile of the cytotoxic effects of chemotherapy and radiotherapy to allow a full exploration of the direct and indirect effects of adjuvant therapy on QoL. In future systematic reviews, if sufficient data is available, meta-regression should also be conducted to examine the association and interaction between the confounding factors and the QoL.

Contributors

CKKF, KR contributed to the conception or design of the work, and analysis and interpretation of data. CKKF is responsible for drafting the manuscript. KR critically reviewed and revised the manuscript for important intellectual content. LEYT contributed to the acquisition of data and critical revision of the manuscript for intellectual content. CKKF, LEYT, KR provided final approval of the version to be published.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

No additional data are available

Source of funding

Nil

Review protocol registration

Nil

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Figure 1. Study flow diagram
Figure 2. Risk of bias summary for RCTs

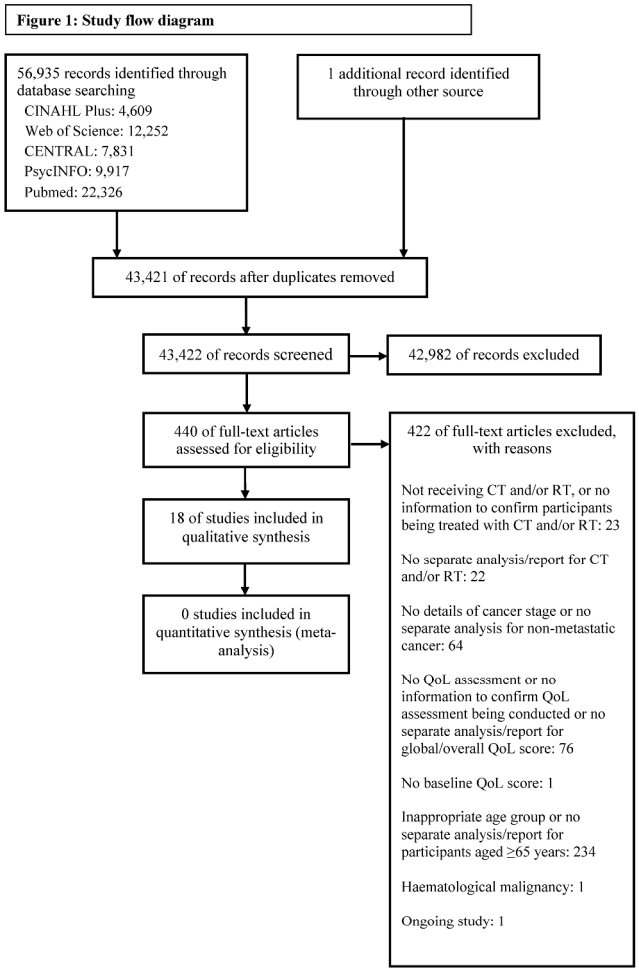

Figure 1. Study flow diagram

297x420mm (300 x 300 DPI)

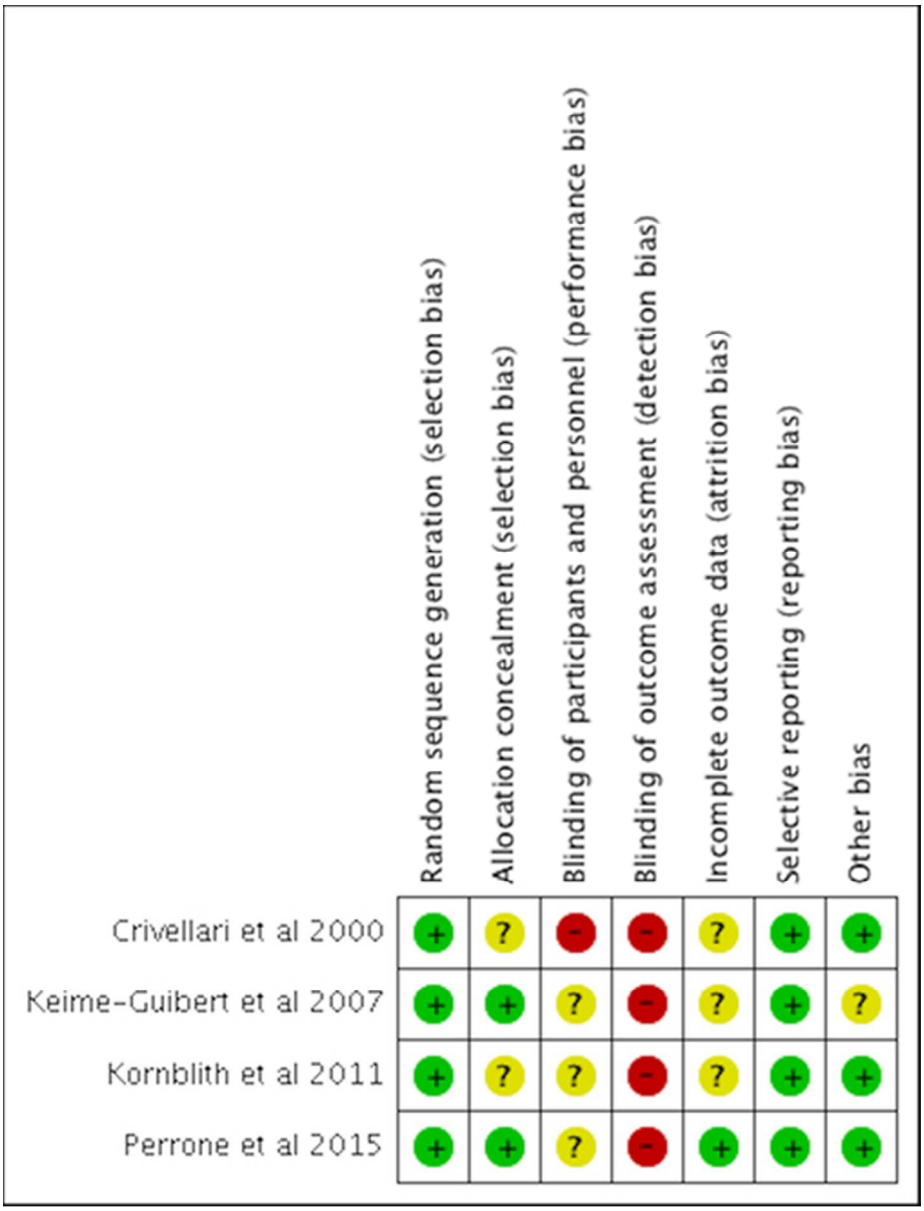

Figure 2. Risk of bias summary for RCTs

42x55mm (300 x 300 DPI)

Appendix A

Electronic search strategy for PsycINFO

1. older*.af. OR elder*.af. OR geriatric.af. OR gerontolog*.af. OR senior.af. OR aged.af.
2. oncology.af. OR cancer*.af. OR neoplasm*.af.
3. “quality of life” .af. OR “QOL” .af.
4. #1 AND #2 AND #3

Limits: English Language, Human

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	31-32
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No additional analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, 17,18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	31-32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33 Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No meta-analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	31-32
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No additional analysis
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	41-42
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	42, 44
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	45

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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