

**Title:** Is improvement in comorbid major depression associated with longer survival in people with cancer? A long-term follow-up of participants in the SMaRT Oncology-2 and 3 trials.

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**Financial support:**

NIHR CLAHRC Oxford, Cancer Research UK and the Chief Scientist Office of the Scottish Government.

**Word count:** currently 3087 (abstract 250)

## **ABSTRACT [250 words]**

### **Objective**

There is evidence that patients with cancer have worse survival if they have comorbid major depression, but uncertainty whether a reduction in depression severity improves survival. We aimed to address this question.

### **Methods**

We did a secondary analysis of data from participants in the SMaRT Oncology-2 and 3 trials of depression treatment in patients with cancer and comorbid major depression (total n= 642). Participants' data were analysed as cohorts, defined by treatment (usual care or *Depression Care for People with Cancer*, an intensive treatment programme, in both trials) and cancer prognosis (good or poor, in SMaRT Oncology-2 and 3 respectively). We measured change in depression severity from randomisation to 12 weeks using Symptom Checklist Depression Scale (SCL-20) scores and assessed survival by linked mortality data. We used Cox regression to estimate the effect of a one-unit decrease in SCL-20 score on survival, controlling for measured confounders.

### **Results**

We found no evidence for an association between improvement in depression and survival in any of the four cohorts, after adjusting for age, sex, primary cancer, baseline cancer severity and baseline depression severity. Pooling the cohorts in a fixed-effects meta-analysis yielded an estimated 7% reduction in the hazard of death per one-unit decrease in SCL-20 score. This finding was not statistically significant; the 95% confidence interval extended from a 26% decrease to an 18% increase in hazard of death.

## **Conclusion**

We found no evidence that reduction in severity of comorbid major depression is associated with longer survival in patients with cancer.

## **KEY WORDS**

Cancer; survival; depression; cohort study

## INTRODUCTION

There is considerable interest in the relationship between psychological factors and survival in patients with cancer. A particularly important psychological factor to consider in relation to cancer is comorbid major depression. Major depression affects approximately 10% of patients with cancer and there is evidence that depressed patients have a worse survival than patients who are not depressed [1-4]. But does a reduction in the severity of this comorbid depression improve patient survival? The answer to this question is important, not only because it has implications for clinical care, but also because it may help us to elucidate whether the relationship between depression and worse survival in patients with cancer is a causal one, or merely an association.

We currently have limited evidence about improvement in depression severity and survival in patients with cancer. We are not aware of any studies directly addressing this question. However, we have found three of potential relevance [5-7]. All three studies merely compared changes in depression symptom scores with survival, in samples of patients not selected for having comorbid major depression; two found some evidence for an association and one did not.

The availability of data on participants in two previously published clinical trials, linked with their long-term survival data, provided us with a unique opportunity to study the relationship between change in severity of depression and survival in patients with cancer and comorbid major depression. In both these trials (SMaRT Oncology-2 in good prognosis cancers and SMaRT Oncology-3 in lung cancer, a poor prognosis cancer), we found that an intensive depression treatment programme (*Depression Care for People with Cancer*, DCPC) was much more effective than usual care in reducing the severity of major depression [8, 9].

In a previously published follow-up analysis of these trials , we also found that participants' treatment allocation (to DCPC or to usual care) in these trials had no significant effect on their survival, despite the large difference in their effectiveness in reducing severity of depression [10].

In this paper, we aimed to address an additional and separate question: Does improvement in depression severity predict subsequent survival in patients with cancer and comorbid major depression?

## METHODS

### Design

We analysed data from participants in two clinical trials (SMaRT oncology-2 and SMaRT oncology-3) that had been subsequently linked with long-term survival data. The trials were two-arm parallel group randomised controlled studies which compared a depression treatment programme called *Depression Care for People with Cancer* (DCPC) with usual care in patients with cancer and comorbid major depression. DCPC is a manualised, multicomponent (with both pharmacological and psychological components), collaborative care treatment that is delivered systematically by a team of cancer nurses and psychiatrists in collaboration with oncologists and primary care physicians [11]. Usual care was provided by the participants' own primary care physician and oncology team. The trials were registered with Current Controlled Trials, numbers ISRCTN40568538 and ISRCTN75905964.

We recruited a total of 642 participants to these two trials from three cancer centres in Scotland, UK and their associated clinics. SMaRT oncology-2 recruited five hundred patients with good prognosis cancers (predicted survival  $\geq 12$  months estimated by their cancer specialist) and comorbid major depression between 12<sup>th</sup> May 2008 and 13<sup>th</sup> May 2011. SMaRT oncology 3 recruited one hundred and forty-two patients with lung cancer (predicted survival  $\geq 3$  months) and comorbid major depression between 5<sup>th</sup> January 2009 and 9<sup>th</sup> September 2011.

In both trials participants were randomly allocated (1:1) to either DCPC or usual care. DCPC was found to be highly effective in reducing depression severity. The trial methods, treatments and findings are described in detail in the relevant publications [8, 9, 12, 13].

Because this analysis sought an association between change in depression severity and survival, rather than an association with treatment given and survival, we analysed the participant data in cohorts. As the association between change in depression severity and survival may differ with type of depression treatment and also with prognosis of the cancer, we created four separate cohorts from the four trial arms (two trials, each with two arms). The cohorts therefore comprised participants with: (a) good prognosis cancer (SMaRT Oncology-2) allocated to usual care (n=247); (b) poor prognosis cancer (SMaRT Oncology-3) allocated to usual care (n=74); (c) good prognosis cancer (SMaRT Oncology-2) allocated to DCPC (n=253); and (d) poor prognosis cancer (SMaRT Oncology-3) allocated to DCPC (n=68).

## **Measures**

### *Change in Depression Severity*

Depression severity was measured in the trials using the self-rated Symptom Checklist Depression Scale (SCL-20). This widely-used scale is derived from the longer SCL-90 scale [14]. There are two versions of the SCL-20; version B was used in the trials [15]. The SCL-20 has 20 items, each of which is rated from 0 to 4. The overall SCL-20 score is an average of the 20 individual item scores and therefore also ranges from 0 to 4. A one unit decrease in the overall score indicates a mean decrease of one level of severity across the 20 symptoms. The scale has been found to have good agreement with other commonly used measures of depression severity, such as the Patient Health Questionnaire-9 and the Hamilton Depression Rating Scale [16][17].



For this analysis, we defined change in depression severity as the change in a participant's SCL-20 score between baseline (trial randomisation) and 12-weeks post-randomisation. We chose this particular time interval to allow sufficient time from baseline for changes in depression to occur, whilst also minimising missing data from early deaths. We standardised changes in depression severity to take into account the actual date of follow-up (for example if a participant's SCL-20 score was actually collected at 13 weeks after randomisation, the change was multiplied by 12/13).

### *Survival*

We obtained mortality data on trial participants (dates and causes of death) from the National Records of Scotland database. We did this by sending a minimal dataset (each participant's trial number, name, date of birth, gender, Community Health Index number, postcode, and date of randomisation) securely to the Information Services Division of NHS Scotland for record linkage. We calculated survival from 12 weeks post-randomisation, censoring follow-up in participants who had left Scotland (at their date of emigration) or at the latest date that data were available (31<sup>st</sup> July, 2015). Our main outcome was death from any cause. We also did a sensitivity analysis restricted to deaths attributed to cancer.

### **Ethical Approval**

The analysis of trial data including participants' survival data was approved by the Scotland A Research Ethics Committee (08/MRE00/23; 08/MRE00/95) and the NHS Scotland Privacy

Advisory Committee. At the time of trial enrolment, participants had given written consent for us to obtain follow-up information from their medical records.

## **Statistical analysis**

We investigated the associations between changes in depression severity and subsequent survival using Cox proportional hazards regression models. We used two separate models to analyse the four cohorts; one for the two cohorts of patients with good prognosis cancers and the other for the two cohorts of patients with poor prognosis cancer. We did this because we considered that survival, and potentially the effects of confounders, may differ with cancer prognosis. Associations were expressed as hazard ratios (HRs) for a one-unit decrease in SCL-20 score.

We adjusted for possible confounders of the association between change in depression severity and survival within cohorts. In order to decide which factors to adjust for, we constructed a causal diagram (see Figure 1) making plausible assumptions about the potential confounders. Those we included were: age, sex, primary cancer, baseline cancer severity (measured using cancer disease status for SMaRT Oncology-2 participants and cancer stage and treatment intent variables for SMaRT-Oncology-3 participants), and baseline depression severity. The diagram highlights a “minimally sufficient” subset of adjustment covariates that we explicitly adjusted for in the Cox models [18, 19].

In each model, we included interactions between treatment allocation and all of the “minimally sufficient” covariates, thereby allowing estimation of cohort-specific effects. If the assumptions made in the causal diagram are correct, the causal model approach is

statistically more efficient than including all confounders in the analysis model, and is equally effective in controlling bias from all the potential confounders.

[Figure 1 here]

For illustration (and as a companion to our formal analysis treating change in depression severity as a continuous variable) we plotted adjusted Kaplan-Meier survival estimates for each of the four cohorts, according to change in depression severity dichotomised at the median change. To make the adjustments, we used the inverse probability weighting method described by Cole and Hernan including the same set of covariates as in the Cox models [20]. We paired each Kaplan-Meier plot with a box-plot displaying the distribution of the changes in depression severity in the cohort and the median change.

We pooled the hazard ratios obtained from the cohorts in stages: first, we combined the two usual care cohorts, then we combined the two DCPC cohorts and finally we combined all four cohorts. We did this after checking at each stage that there was no evidence of heterogeneity in the hazard ratios. We used this approach because we anticipated greater similarity in the effect of depression improvement on survival in the two cohorts which received DCPC (and correspondingly in the two usual care cohorts). This was because the DCPC cohorts had received an intervention that substantially reduced the severity of depression in many of the participants, and thereby offered greater ability to detect an association between change in depression severity and survival. The procedure we used was

first to pool log hazard ratios (for a 1-unit change in SCL-20 scores) for the two usual care cohorts using the inverse variance method in a fixed-effects meta-analysis, and then to do the same for those from the two DCPC cohorts, testing for heterogeneity using a Wald test in each case. We then estimated an overall pooled log hazard ratio combining the results from the (pooled over trials) usual care and DCPC cohorts, again testing for heterogeneity using a Wald test. We repeated the pooled analysis looking at only deaths attributed to cancer.

We performed all Cox regression analyses using Stata v15 (StataCorp, College Station, TX, USA) and the meta-analyses using the package “meta” in R v3.4.1.

## RESULTS

In total 589/642 (92%) of the SMaRT Oncology-2 and 3 trial participants were included in the analysis. The remainder had either died (4% of the SMaRT Oncology-2 sample and 10% of the SMaRT Oncology-3 sample) or had missing depression severity data due to loss to follow-up (an additional 4% of the SMaRT Oncology-2 sample and 11% of the SMaRT Oncology-3 sample) at the 12-week follow-up. All participants included in the analysis had follow up data from 12 weeks post-randomisation (the time-point at which change in depression severity from randomisation was calculated) until their death, or until 31<sup>st</sup> July, 2015 if that was sooner. The median duration of follow up for each cohort was as follows: Good prognosis cancer (SMaRT Oncology-2) and usual depression care 4.9 (IQR: 4.2, 5.5) years; poor prognosis cancer (SMaRT Oncology-3) and usual depression care 1.0 (IQR: 0.44, 2.8) year; good prognosis cancers (SMaRT Oncology-2) and DCPC 4.1 (IQR: 4.8, 5.7) years; poor prognosis cancers (SMaRT Oncology-3) and DCPC 1.9 (IQR: 0.64, 4.2) years.

Table 1 shows the demographic and clinical characteristics of the participants included in the analysis. Their mean age was 57.8 years and 85% were female.

[Table 1 here]

*Change in depression severity*

Table 1 and the boxplots in Figure 2 show that, in each of the four cohorts, the majority of participants reported improvement in depression severity, with the average change being markedly greater, and the standard deviation slightly larger, in the cohorts who had been allocated to DCPC. A small number of participants had a worsening of depression.

[Figure 2 here]

### *Survival*

112 of the participants (37%) in the usual care cohorts and 90 (31%) in the DCPC cohorts died during the follow-up period. The primary causes of death are shown in Table 2. Most of the deaths (174/202; 86%) were attributed to cancer and none to suicide.

[Table 2 here]

### *Association between change in depression severity and survival*

We found no statistically significant associations between the change in depression severity and survival in any of the four cohorts. The HRs shown in Figure 3 estimate the effect of a one-unit decrease in SCL-20 score, from baseline to 12 weeks, on hazard of death, adjusted explicitly for baseline depression severity and baseline cancer severity, and implicitly for primary cancer, age, and sex. The associations between change in depression and survival

are also illustrated in the adjusted Kaplan-Meier survival curves (Figure 2), where the red lines track the 50% of participants with the most depression improvement and blue lines the 50% with the least (including the participants who worsened) in each cohort.

[Figure 3 here]

There was no evidence of heterogeneity in the hazard ratios seen in the two usual care cohorts ( $I^2=0$ ,  $p=0.54$ ) or in the two DCPC cohorts ( $I^2=0$ ,  $p=0.66$ ), we computed pooled estimates for both. There was also no evidence of associations between change in depression severity and survival in either the pooled usual care cohorts ( $p=0.30$ ) or the pooled DCPC cohorts ( $p=0.88$ ), and no evidence for heterogeneity in the hazard ratios ( $p=0.38$ ). We therefore pooled all four cohorts.

The pooled sample yielded an estimated overall 7% reduction in the hazard of death (0.93, 95% C.I. 0.74 to 1.18) per unit decrease in SCL-20 at 12 weeks ( $I^2=0$ ,  $p=0.72$ ). However, as can be seen in Figure 3, the wide confidence interval around this pooled estimate is consistent with both a moderate increase and a moderate decrease in survival. The final pooled estimate was not sensitive to cause of death. We censored deaths that were not primarily caused by cancer and re-ran the analysis, but this had little effect on the result (HR 0.94, 95% CI [0.73, 1.21]).

## DISCUSSION

In this analysis of clinical trial data we found no statistically significant evidence for an association between an improvement in comorbid major depression and longer subsequent survival in people with cancer. Whilst we did observe an estimated seven percent reduction in the hazard of death per unit decrease in SCL-20 depression severity score measured over 12 weeks, when we pooled the four cohorts studied, the 95% confidence interval around this estimate extended from a 26% decrease to an 18% increase, indicating a range of associations from modest benefit to modest harm. Restricting the analysis to deaths attributed to cancer did not substantially alter this finding.

The main strengths of the study were: First, all the participants had oncologist-diagnosed cancer and interview-diagnosed major depression. Furthermore, most participants had changes in the severity of their depression over the 12-week period used in the analysis. Second, the participants were divided into clearly defined cohorts according to both the treatment they had been allocated to and the prognosis of their cancer type as assessed at baseline. Third, the follow-up data on survival of participants were complete.

The study also had limitations: First, the size of the cohorts available offered only limited power to detect potentially small effects of changes in depression severity on survival. Second, the participants were predominantly female and had a variety of cancer types, potentially limiting the generalisability of the findings. Third, we only measured change in depression severity over a 12-week period; although substantial changes in depression severity were observed during this period. Fourth, we only assessed depression status up to 12 weeks and are therefore unable to determine the cumulative exposure to depression that patients had between then and the time of their death. Fifth, we may not have been



able to account for all the potential confounders of the association between depression change and survival, including changes in cancer status and cancer treatment given after assessment at baseline. Finally, although we were able to obtain long-term mortality data, we were not able to follow up all trial participants to the date of their death. Whilst this limitation makes us potentially unable to detect a longer-term effect of changes in depression severity on survival, it seems likely that the effect of a reduction in depression severity would manifest in the study period.

Depression, particularly major depressive disorder, is an established risk factor for mortality in the general population [21]. Depression has also been found to predict worse survival in people suffering from a variety of medical conditions, including myocardial infarction, heart failure, diabetes and stroke, as well as in patients receiving renal dialysis and organ transplant [22-27]. Whilst the presence of depression has been found to predict worse subsequent survival in patients with a variety of cancers, the nature of the association has not been established.

We are not aware of any other studies that have directly addressed the question. However, we have identified three previous studies with relevant findings: First, a cohort study of patients with lung cancer found that patients who had high baseline depressive symptom scores that reduced in severity between baseline and one year (n=156) survived longer than those whose scores did not decrease [5]. Second, a secondary analysis of a trial of group psychotherapy in breast cancer patients (n=125) which had found no effect of treatment on survival, found an association between reduced depressive symptom scores (in the trial arms combined) and better survival [6]. Finally, a trial of early palliative care for patients with non-small cell lung cancer, found that palliative care improved survival, but a

secondary analysis of the trial data did not find an association between survival and changes in depression severity [7]. Importantly, all three of these studies examined only the association of changes in score on depression questionnaires, not on the reduction in severity of diagnosed major depression. If a reduction in the severity of depression improves survival it would seem unlikely that such an effect would be found with small improvements in depression in a general sample of cancer patients but not with substantial reductions in depression in a sample of cancer patients with comorbid major depression.

As far as we are aware, the current study is the first to seek evidence of an association between a change in depression severity and survival in patients with diagnoses of cancer and comorbid major depression. Our previous analysis using data from the same trials found that allocation to intensive depression treatment (DCPC) did not improve survival over usual care [10]. This study answers the related but separate question of whether improvement in depression is associated with longer subsequent survival. Despite a substantial improvement in depression severity in many of the SMaRT Oncology-2 and 3 trial participants, there was no good evidence of an association between this improvement in depression and increased survival, although the confidence intervals around the findings were wide and compatible with both a moderate increase and a moderate decrease in hazard of death. Future studies could be designed to examine potential differential associations with different clusters of depressive symptoms and also possible threshold effects of substantial reductions in depression severity.

## **Conclusion**

Major depression is a common and important problem in patients with cancer that is associated with both reduced quality of life and worse survival. In the SMaRT Oncology-2 and 3 trials of depression treatment, we observed a strong effect of DCPC on depression and quality of life. However whilst comorbid major depression predicts poorer survival in cancer patients, we did not find that improvement in depression severity is associated with longer survival. Despite this finding, the beneficial effect of treatment of depression on quality of life provides sufficient reason to make it an important part of cancer care [28].

## **ACKNOWLEDGEMENTS**

This work was funded by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust (the views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health). SMaRT Oncology-2 and 3 were funded by the charity Cancer Research UK (grant no. C5547/A7375). JW is supported by Sir Michael Sobell House Hospice, Oxford. We also wish to thank Ruth Harman PhD for proof reading the text.

## **DECLARATION OF INTEREST**

None.

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