**Thoughts of self harm and depression as prognostic factors in palliative care patients**

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**Abstract**

**Background**

This study explored whether scores indicating depression on Patient Health Questionnaire 9 and patient reports of thoughts of self harm were prognostic factors for survival in advanced cancer

**Method**

Patients with advanced cancer were recruited into the study from palliative care day units and invited to complete measures for depression which included Patient Health Questionnaire 9, and Edinburgh Depression Scale at recruitment, and at 8, 16 and 24 weeks

**Results**

629 patients were recruited into the study; One hundred and thirty nine patients (22%) died during 6 month follow up and 235 patients (37.4%) died during the study period. The age range of patients recruited was 21-94 years – mean age 66 years and 67% of patients recruited were female. The overall median survival of patients recruited was 37.1 weeks (95% CI   36.0, 39.9 weeks) (range 0 weeks – 116 weeks). The estimated median survival time of patients whose baseline PHQ9>=9 was 36 weeks with 95% confidence interval of (31, 39) and for patients whose baseline PHQ9<9 was 39 weeks (95% CI 37, 45) - baseline PHQ9 alone was predictive of death. The median survival times were 37.9 weeks for patients who did not indicate thoughts of self harm and 34.7 weeks for patients who reported thoughts of self-harm at baseline suggesting that risk of death was 1.4 times higher among patients who reported thoughts of self harm.

**Limitations**

Patients were recruited only from within palliative day care units and assessments were made only by validated tools and not by clinical interviews

**Conclusions**

In this large longitudinal study, moderate to severe depression as measured by pHQ9 and patient reports of thoughts of self harm were associated with earlier mortality. This paper supports the need for supporting patients psychologically at the end of life and specifically in treating depression in this patient group.

**Key words**; Prognosis; Depression; Self Harm; Palliative Care; longitudinal study; cancer; EDS; PHQ-9

**Introduction**

Depression can lead to morbidity and has been reported as an independent predictor for earlier death in patients with cancer (Gripp et al 2007; Pinquart & Duberstein 2010; Lazure et al (2009)Lloyd-Wiliams et al 2009). Thoughts of self harm are not infrequent in patients with advanced cancer (Lloyd-Williams 2002) and are linked to presence of psychological morbidity (Spencer et al 2012), however it is not known whether thoughts of self harm themselves are prognostic factors for earlier mortality. Determining prognosis is complex in patients with advanced metastatic cancer and while studies have reported that patients frequently ask about prognosis (Gilbertson-White et al 2011) - a recent large study (Gilliam et al 2011) found that eleven core variables predicted two week and two month survival. However, this study focussed mainly on physical variables and biochemical profiles and although the Abbreviated Mental Test Score was used (and found to be one of eleven core variables) there were no specific measures of psychological well- being.

A study by Cheung et al (2009) did not find psychological distress to be predictive of time to death in cancer patients and a review carried out by Maltoni et al (2005) did not include depression as a clinical predictors for survival. A longitudinal study by Lui et al (2011) reported that “feeling sad” was a predictive factor for survival in a study of 256 hospitalised patients with advanced cancer where the mean survival was 49 days, but did not report survival benefit. Most of these studies were in hospitalised palliative care patients with a short prognosis where any effective treatment of depression would be difficult due to the deterioration of the patient. In a meta-analysis including all cancer patients (Satin et al 2009) depression was found to predict mortality and effect remained after adjustment for clinical prognosticators, similarly Gao et al (2011) found higher scores on GHQ-12 items predicted shorter survival in palliative care patients. There is marked uncertainty associated with interpretation of depression scores at end of life (Reeve et al 2008) and the suggestion that depression increases at the end of life has not been confirmed in recent studies (Lichtenthal et al 2009; Rabkin et al 2009, Cheung et al 2009). The difficulties are also compounded by uncertainties related to best ways to measure depression in this patientpopulation and the small numbers of patients included in many studies.

We report the results of finding of a large longitudinal study of 629 palliative care patients which was carried out to determine whether depression and thoughts of self harm are predictors for earlier mortality in patients with advanced cancer.

**Patients and Methods**

**Design and Study**

This study was carried out in twenty palliative care day units in North West of England who all accepted referrals for patients with advanced cancer. Patients are referred to palliative care day units ( usually located within a hospice) for symptom control and social support and usually attend for at least one day weekly. Recruitment into the study started on 1st November 2007 and data collection ended on 28th February 2010.

**Patients**

The inclusion criteria were patients with locally advanced or metastatic disease over the age of 18 years and believed by hospice day care staff to have at least 6 months estimated survival in order to be able to complete the follow up for the study. There was no upper age limit for the study. Exclusion criteria were not being able to speak or read English; a non cancer diagnosis and cognitive impairment. All patients were assessed using the Abbreviated Mental Test Score ( AMTS) (Hodkinson 1971) which is a 10 point dichotomous scale with a score of 6 or less indicative of cognitive impairment - a score of 6 or less was an exclusion for participation in the study.

**Procedure**

Eligible consecutive patients attending palliative day care units with a diagnosis of locally advanced or metastatic cancer and who were believed by hospice day care staff to have at least 6 months estimated survival were informed about the study by hospice day care staff and the team of researchers who were based within the hospices. Patients who were interested in the study were invited to complete a reply slip to ask a researcher to contact them. All patients received detailed information and were asked to give written consent prior to participating in the study. At recruitment, patents were given the questionnaires and asked baseline demographic information – this data was collected by face to face interview with member of the research team and the interviews were conducted in the hospice or within the patient’s own home. Patients usually completed follow up questionnaires by post, with a small number opting for researcher contact due to clinical issues e.g patients with poor eyesight etc. Any patient found to be a case of depression on either of the depression measures at any time point were referred onto the day care nurse or member of clinical staff and managed according to each unit’s clinical practice. Full ethical approval for the study was obtained from the Research Ethics committee 07/Q1505/24.

**Questionnaires**

Patients were invited to complete two tools to assess for depression namely PHQ 9 and EDS as a secondary aim of the study was to determine cut off thresholds for severity for Edinburgh Depression scale – the findings of which will be reported at a later date. The Edinburgh Depression scale (EDS) (Cox et al 1987) is a 10 item scale and each item is rated on a 0–3 scale. The EDS has been previously validated in palliative care patients against a structured psychiatric interview and was found to have acceptable validity (Lloyd-Williams et al 2001) with a cut off threshold of 13 indicating presence of depression and is widely used in screening for depression in palliative care. The PHQ9 is a self-report measure and consists of 9 items selected to assess the presence of the DSM-IV criteria for Major Depressive Episode using a 4-point response scale and has validated cut offs for mild, moderate and severe depression (Spitzer et al 1999) and has been validated for use with a cancer population (Thekkumpurath et al 2011).At recruitment, the following independent variables were collected age, sex, marital status, past history of depression, site of primary cancer and metastases, date of diagnosis, current medication including antidepressant medication. This information was collected from the patients and verified from the medical case notes. At 8, 16 and 24 weeks follow-up patients were invited to complete the EDS and PHQ9. Performance status was assessed at baseline using ECOG performance status (Oken et al 1982) which is scored from 0-4 – a score of 0 indicating no dependence and 4 maximum dependence. This was carried out by the researchers who utilized the ECOG criteria for performance status.

**Statistical Analysis**

Data was managed via the MACRO database and this study was supported by the Cancer Trials Unit. Statistical significance was set at p<0.05 and analyses were conducted in the statistical package R version 2.9.2 for Windows. Descriptive statistics were calculated along with confidence intervals. Wilcoxon signed ranks test (non-parametric version of the “paired” t-test) were used to assess whether there was any difference between the baseline and final visit of each patient since scores were not normally distributed. Kaplan-Meier survival function was used to summarise survival between groups. The Cox proportional-hazards regression model was used to determine whether depression or self-harm predicted survival by comparing survival distributions between two groups and to estimate corresponding hazard ratios. Joint modelling of longitudinal depression scores and time to death was used to estimate the relationship between the variation of scores over time on survival .

**Results**

**Recruitment and Attrition**

A total of nine hundred and twenty one patients who met eligibility criteria were given information leaflets by day care staff; 694 patients requested the researcher to contact them and 629 patients participated in the study. The main reasons for non participation were patients not feeling well enough to participate in a 6 month longitudinal study. Ethical approval was not given to collect data on non participants.

Six hundred and twenty nine patients completed baseline measures and their data were included in the final analysis; four hundred and ninety four patients (78.5%) completed 8 week follow-up; four hundred and five (64.3%) completed 16 week follow up and three hundred and forty nine (55.5%) completed 24 week follow-up. The majority of follow-up data was collected by post, with some patients opting for face to face interview. We attribute the excellent follow-up rates to researchers being present within the palliative care day unit which may have served as informal prompts / reminders to patients to complete their follow up questionnaires. One hundred and thirty nine patients (22%) died during 6 month follow up and 235 patients (37.4%) died during the study period. Survival data was collected from hospice databases. The diagnoses of patients included 32% breast cancer, 17% gastrointestinal and 12 % lung cancer and most cancer diagnoses were included in the sample recruited. At recruitment the ECOG performance status of patients were recorded as 5% ECOG 0; 42% ECOG 1; 28% ECOG 2; 21% ECOG 3; 4% ECOG of 4. The age range of patients recruited was 21-94 years – mean age 66 years; 67% of patients recruited were female and three hundred and twenty three patients (51%) married. The majority (97%) regarded their ethnicity as white British and the median time since initial cancer diagnosis was 3 years . The overall median survival of patients recruited into the study was 37.1 weeks (95% CI   36.0, 39.9 weeks ).

The PHQ9 has validated cut offs for mild (5-9) moderate (9-14) severe (15+) for cases of depression and 33% scored 9 or more on the PHQ9 scale at baseline with 11% scoring 15 or more indicating severe depression. The EDS has a validated cut off of 13 for cases of depression, 17% scored 13 or more on the EDS at baseline.

(Table 1 about here)

**Can PHQ9 or EDS predict death once adjusted for other confounding effects?**

Kaplan- Meier estimates for survival were calculated for patients whose baseline PHQ 9 score were greater than or equal to 9 and for patients whose EDS scores were greater than or equal to 13.

**EDS**

 Kaplan-Meier estimates for survival were calculated for EDS. Estimated median survival time of patients whose baseline EDS >=13 was 39 weeks (95% CI 36, 40) and for patients whose baseline EDS <13 was 37 weeks (95% CI 32, NA), the upper limit of 95% CI is not defined due to lack of data.Unadjusted and adjusted analysis estimated the hazard ratio 0.82 (95% CI 0.56, 1.21) (p-value 0.3180) and 1.01 (95% CI 0.67, 1.53) (p-value 0.9662) respectively which suggested that risk of death for patient with EDS>=13 and EDS<13 at baseline was not significantly different.

**PHQ 9**

The estimated median survival time of patients whose baseline PHQ9>=9 ( indicating moderate or severe depression) was 36 weeks with 95% confidence interval of (31, 39) and that for patients whose baseline PHQ9<9 was 39 weeks (95% CI 37, 45) which suggests that half of patients who had a score on PHQ9 of less than 9 at baseline survived 3 weeks more than those with a PHQ9 of greater than 9. A Cox proportional hazards model was fitted to determine the association between baseline PHQ9 and the time to death. An unadjusted analysis estimated the hazard ratio 1.33 (95% CI 1.02, 1.74), (p-value 0.0330) showed risk of death to be 1.3 times higher among patients with PHQ9>=9 at baseline. The adjusted analysis estimates an increased hazard ratio of death, 1.38 (95% CI 1.04, 1.82), (p-value 0.0235).

(Figure 1 about here)

**Thoughts of Self Harm in Advanced Cancer**

Thoughts of self harm was defined by scoring 1 or above on either item 10 of EDS scale or item 9 of PHQ 9 at baseline. Data was available for 625 patients and 74 patients (12%) scored positively for thoughts of self harm at baseline. There were no significant differences in terms of age, gender or domestic status for those reporting thoughts of self harm as compared to study population. The Kaplan Meier estimate of survival is shown in Figure 2; 29 of the 74 patients died – none of these deaths were due to reported suicide. The median survival times were 37.9 weeks for patients who did not indicate thoughts of self harm and 34.7 weeks for patients who reported thoughts of self-harm at baseline. Cox proportional hazards model was fitted with self-harm (yes, no) as covariate to find out whether self harm could predict death. An unadjusted analysis estimated the hazard ratio to be 1.40 (95% CI 0.95, 2.08) and p-value 0.0918 suggests a non-significant effect at 5% level, However, in this case, lower limit of the 95% CI (0.95) is just below 1.00 implies a borderline significance, and hence we conclude the risk of death was 1.4 times higher (marginal significance) among patients who reported thoughts of self harm. The adjusted analysis estimates an increased hazard ratio of death, 1.48 (95% CI 0.96, 2.26), (p-value 0.0747), a borderline significance effect.

( Table 2 and Figure 2 about here)

**Discussion**

This large longitudinal study revealed that depression and thoughts of self harm were not unusual in patients with advanced cancer. The overall median survival of patients recruited was 37.1 weeks (95% CI   36.0, 39.9 weeks) - patients who were not depressed as measured by PHQ9 had a survival benefit compared to patients who were depressed. We found that half the patients who had a PHQ9 score of less than 9 at baseline survived 3 weeks more than those with a PHQ9 of greater than 9 – to our knowledge this is the first study to report such a finding. Scoring above 13 on EDS did not appear to influence survival – the EDS is widely used as a screening tool but does not have severity thresholds of the PHQ9 - scoring above 13 on EDS merely indicates a patient may be depressed and requires further assessment. We used a threshold of 9 or greater on PHQ9 which is indicative of moderate depression to severe depression and we therefore suggest that it is moderate and severe depression that influences survival and not minor depression.

The median survival times for patients who did not indicate thoughts of self harm were 37.9 weeks for patients and 34.7 weeks for patients who reported thoughts of self-harm at entry into the study. At recruitment 12% of patients reported thoughts of self harm and during follow up 22% of patients reported thoughts of self harm at some time point during the study. Thoughts of self harm were present at baseline in seventy four of the six hundred and twenty five patients (12%) which is higher than reported in other studies of cancer patients (Walker et al 2008; Walker et al 2010;Spencer et al 2012). During follow up, 22% of patients reported thoughts of self harm at some time point. In the vast majority of cases, the presence of thoughts of self harm had not been previously known to the clinical teams. In a retrospective study of suicidal ideation ( Akechi et al 2010), performance status was linked to suicidal ideation in males but not in females, but that was not found in our study. High rates of psychological distress and depression have previously been reported as risk factors for thoughts of self harm in cancer patients (Breitbart et al 2000). A limitation of our study was that we were relying on self report measures for thoughts of self harm from questionnaires and did not interview the patients therefore specific information regarding aetiology of thoughts of self harm was not possible to determine

This study suggests that moderate to severe depression is associated with shortened survival in patients with advanced cancer. The important question is whether effective treatment of depression in palliative care patients can influence survival? Previous studies have found that antidepressants are often started very late in life with insufficient time for clinical benefit (Lloyd-Williams et al 1999). A large trial in patients with cancer found that identification and treatment of depression impacted on survival, however these were predominantly patients with early cancer rather than patients with advanced metastatic disease (Gallo et al 2007) and we are unaware of a comparable treatment study in patients with advanced cancer.

**Limitations of the Study**

To our knowledge this is the first study to report impact of depression and thoughts of self harm on survival in patients with advanced cancer. The study’s main limitation is that recruitment was within palliative day care settings and it is not known how representative these patients are of the general populations of patients with advanced metastatic disease and whether reasons for referral to day care which include physical and psychological morbidity infers that our sample were skewed in terms of higher psychological morbidity and mortality. We did not collect data as to whether patients in our study were receiving specific psychosocial support ( in addition to holistic support which is offered to all patients within palliative day care), however previous authors have reported on general lack of co-ordinated psychosocial care for patients with advanced cancer (Rodin et al 2009) and this lack of referral to specialised psychosocial care is more common for older patients ( Ellis et al 2009) who make up the majority of patients in our study). Additionally we did not carry out psychiatric interviews, but utilised

previously validated tools including the PHQ9 which has validated cut off thresholds for severity of depression.

**Conclusions**

This large longitudinal study suggests that depression and thoughts of self harm are not unusual within advanced cancer patients attending palliative day care services and appear to be independent predictors for reduced survival in this patient group. This study reinforces the need for appropriate and timely assessment of depression for patients with advanced cancer and also for further research as to what may be most effective collaborative methods of supporting patients psychologically at the end of life and in specifically treating depression in this patient group.

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**Declarations of Interest**

None are declared