Euthanasia and Depression: A Prospective Cohort Study Among Terminally Ill Cancer Patients
Marije L. van der Lee, Johanna G. van der Bom, Nikkie B. Swarte, A. Peter M. Heintz, Alexander de Graeff, and Jan van den Bout

ABSTRACT

Purpose
To study the association between depression and the incidence of explicit requests for euthanasia in terminally ill cancer patients.

Patients and Methods
A prospective cohort study was conducted on 138 consecutive cancer patients with an estimated life expectancy of 3 months or less, in the period between September 1999 and August 2003. At inclusion, participants completed the Hospital Anxiety and Depression Scale. To identify “depressed mood” we used a cutoff score of 20. Kaplan-Meier curves and Cox regression analyses were used to assess the association between depressed mood and the risk of a request for euthanasia.

Results
Of 138 patients, 32 patients had depressed mood at inclusion. Thirty patients (22%) made an explicit request for euthanasia. The risk to request euthanasia for patients with depressed mood was 4.1 times higher than that of patients without depressed mood at inclusion (95% CI, 2.0 to 8.5).

Conclusion
Depression in cancer patients with an estimated life expectancy of less than 3 months is associated with a higher likelihood to request for euthanasia. The question of whether depressed mood can adequately be treated in this terminally ill population, and if so, whether it would lower the incidence of requests for euthanasia needs further investigation.

J Clin Oncol 23:6607-6612. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Euthanasia and physician-assisted suicide are hotly debated issues. Opposition stems partly from the perspective of suicide as a symptom of mental illness and the tendency to extend this view of suicide in the physically healthy onto euthanasia and physician-assisted suicide in the terminally ill.1 Recent studies among terminally ill patients found that a desire for hastened death or an interest in assisted suicide was associated with depression.2-14 It has therefore been suggested that a request for euthanasia may be a symptom of depression and that the depression should be treated before a request for euthanasia is granted.11,15,16 There are two reasons why we felt uncomfortable with this idea. First, the ideas studied previously, such as the patient’s wish to hasten death, cannot be put on par with a well-considered and persistent request for euthanasia in an environment where euthanasia is customary. Second, in our experience, requests for euthanasia are mostly well considered and commonly not associated with depression. Terminally ill cancer patients who request euthanasia often do so from a position of acceptance of their impending death, rather than being driven by an underlying psychiatric disturbance. We
therefore expected that patients requesting euthanasia might be even less depressed. Patients who are aware of their limited life expectancy, and are able to talk about this openly, more often speak about their desire for euthanasia. Accordingly, it was suggested that patients who deny their prognosis or are uncertain about their impending death may be more depressed or anxious.\(^{18,19}\)

So far, only the Netherlands and Belgium have legalized euthanasia. Euthanasia is defined as the intentional termination by a physician of the life of a patient at the patient’s explicit request. In the Netherlands, three nationwide studies on medical practice concerning the end of life were conducted. The most recent study shows the rate of euthanasia to be 7.4% of all cancer-related deaths.\(^{20-22}\) These studies have greatly contributed to the debate about the role of euthanasia in modern healthcare. However, whether depression is associated with a request for euthanasia has not been studied.\(^{20}\)

The aim of this study was to investigate whether depression in terminally ill oncology patients is associated with the occurrence of explicit requests for euthanasia.

### Design and Study Population

A prospective cohort study was conducted between September 1999 and August 2003 on cancer patients with an estimated life expectancy of 3 months or less. The cohort comprised all consecutive cancer patients from the departments of gynecology, medical oncology, lung diseases, and head and neck surgery of the University Medical Center Utrecht (Utrecht, the Netherlands). This hospital is one of the 10 tertiary referral centers for cancer patients in the Netherlands. A patient was eligible for inclusion into the cohort when the attending physician estimated his or her life expectancy to be 3 months or less, and considered the patient able to participate, ie, the patient was aware the cancer was untreatable and the patient was able to answer questions regarding depression. Eligible individuals were informed about the study, but the term euthanasia was not explicitly mentioned. Instead, the term “medical decisions concerning the end of life” was used because in practice the physician does not initiate talking about euthanasia, the patient has to bring the topic up. Once a patient decided to participate, he or she was asked to sign an informed consent form. We chose to study the association between depressed mood and explicit requests for euthanasia and not actual death by euthanasia. The reason for that is that two thirds of all requests for euthanasia are not carried out, and in 31% of these non-granted requests (18% of all requests), depression is a reason why the physician did not grant the request.\(^{23}\) We were interested in the relationship between depression and requests for euthanasia by patients, regardless of the approval of the physician. The study was approved by the Medical Ethics Committee at the University Medical Center Utrecht.

### Baseline and Follow-Up Assessments

At inclusion into the cohort, the participant completed a questionnaire that included a screening instrument for depression, the Hospital Anxiety and Depression Scale (HADS). An advantage of using the HADS is that it does not depend on suicidal thoughts, or on symptoms that can also be caused by physical disease. Others have shown that HADS has a good discriminative ability in a palliative care setting.\(^{24}\) In addition, it has recently been demonstrated that the HADS predicts the development of major depression in terminally ill cancer patients. To diagnose “depressed mood” we used a cutoff score of 20 on the total scale (instead of using two separate scales) of the HADS, as recommended in a palliative setting.\(^{24}\)

After inclusion, the patient’s general practitioner received a letter with information about the study and an appeal was made to the physician to contact the researcher in case of a well-considered persistent request for euthanasia, or if the patient died of natural causes. All physicians from the cooperating departments in the hospital were acquainted with the study and were reminded of their patients’ participation in the study with an entry in the patients’ medical file.

A follow-up measurement was performed when a patient of the cohort explicitly and consistently requested euthanasia, and the euthanasia procedure was started. This implies that the patient’s request was discussed by the medical team and a second opinion from an independent physician was obtained. Among these patients and among a randomly selected sample of the rest of the cohort, the presence of current and life-time depressive episodes was assessed by the Composite International Diagnostic Interview (CIDI-auto).\(^{26-29}\) The Composite International Diagnostic Interview is a structured clinical interview that diagnoses of major depression, based on the criteria of the International Classification of Diseases, Tenth Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classification system. It has excellent psychometric properties.\(^{26,27,28}\)

The moment a case subject was interviewed, then two controls were randomly assigned from the cohort, and contacted for an interview. The physicians were blinded to the findings of both measurements because we did not want to influence standard care. According to The Royal Dutch Medical Association’s guidelines for handling euthanasia requests, a request for euthanasia has to be voluntary, well considered, and consistent, but a psychiatric consultation is not mandatory.\(^{22}\)

The physician or nurse rated the patient’s functional level on the Karnofsky Performance Status Scale (KPS) after the baseline measurement.\(^{30}\) Scores ranged from 0 (indicating that the patient has died) to 100 (no functional limitation in activities of daily living).

To check whether we missed cases of euthanasia, we obtained information about all distributed euthanatics (pancuronium dibromide and thiopental natrium) during the study period from the pharmacy in our hospital.

### Statistical Analyses

Two patients had more than 10% missing responses in the HADS questionnaire; these patients were excluded from the analyses concerning depressed mood. When calculating person years, follow-up ended at death or on April 1, 2004. Relative risks and their 95% CI were estimated by Cox proportional hazards regression without and with adjustment for age and sex. Analyses were performed using SPSS Version 11.5 for Windows package (SPSS Inc, Chicago, IL).

### RESULTS

#### Characteristics and Follow-Up

Between September 1999 and August 2003, 198 patients were asked to participate, 40 patients refused to participate,
and 18 gave consent but were not able to complete the questionnaire (Fig 1). The cohort consisted of predominantly female patients (64%), most of the primary tumor sites were gynecological (35.8%) or urological (16.8%), most of the patients were hospitalized, and 15% of the patients filled out the questionnaire at home and returned it by mail. Antitumor treatment was discontinued at a median period of 2.7 months before inclusion. Eleven patients were still alive when the data were analyzed. Thirty patients (22%) from the cohort made explicit requests for euthanasia. Eight of these patients died before the euthanasia was carried out, the physician did not agree with the euthanasia requests of two patients, and the medical file for one patient from a hospice got lost, so the actual cause of death is unknown for this individual. The remaining nineteen patients died by euthanasia; two in a hospice, seven at home, and 10 in our hospital (Fig 1).

Between September 1999 and August 2003, the pharmacy at the University Medical Center distributed euthanatics to 46 patients: to 12 patients included in the study, to three patients who refused to participate in the study, to seven patients we missed when accruing patients onto the study because the researcher was not informed of the patients’ status (especially in the beginning of the study when not all physicians were well acquainted with the study), and to 24 patients who were not eligible for our study. The main reason patients were ineligible was that they were under treatment by departments not participating in this study (18 patients).

**Euthanasia and Depressed Mood at Inclusion**

At baseline, 32 patients (23%) had depressed mood as assessed by the HADS questionnaire (score, > 20 points). Table 1 lists the characteristics of the patients according to presence or absence of depressed mood at inclusion. Fourteen (44%) of 32 patients with depressed mood at inclusion requested euthanasia during follow-up. Sixteen (15%) of 105 patients without depressed mood at inclusion requested euthanasia during follow-up. The risk of a request for euthanasia by patients with depressed mood was 4.1 (95% CI, 2.0 to 8.5) times higher than that of patients without depressed mood at inclusion (Fig 2). After adjustment for age and sex, the relative risk did not change. In order to assess whether the prevalence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Depressed Mood (n = 32)</th>
<th>Patients Without Depressed Mood (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>18/56</td>
<td>70/67</td>
</tr>
<tr>
<td>Age, years</td>
<td>58/60</td>
<td>35-81</td>
</tr>
<tr>
<td>Range</td>
<td>22-69/67</td>
<td></td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>22/69</td>
<td>24/77</td>
</tr>
<tr>
<td>Children</td>
<td>10/31</td>
<td>15/45</td>
</tr>
<tr>
<td>Religious</td>
<td>27/84</td>
<td></td>
</tr>
<tr>
<td>Tumor site</td>
<td>9/26</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>5/16</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4/13</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2/6</td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td>6/19</td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>7/22</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>5/16</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3/9</td>
<td></td>
</tr>
<tr>
<td>Functional status (Karnofsky performance status)</td>
<td>51/56</td>
<td>30-80/56</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual survival rate after inclusion, days*</td>
<td>34/56</td>
<td>2-328/1-683</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since incurable status at inclusion, months</td>
<td>2.48/2.85</td>
<td>0-28/0-69</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients alive in April 2004 were excluded when calculating median survival.

**Euthanasia and Depression**

![Fig 1. Patient inclusion into cohort. CIDI, Composite International Diagnostic Interview.](www.jco.org)
of depressed mood increased with shorter life expectancy, which could have been an alternative explanation for our findings, we examined the association between depressed mood and survival among those patients dying without euthanasia (thus 19 patients were excluded). There was no association between depressed mood and survival (relative risk, 1.1; 95% CI, 0.7 to 1.8; Fig 3).

Follow-Up Measurement of Depressive Disorder by CIDI

Twelve of the 30 patients with a request for euthanasia had a follow-up assessment for depression (Fig 1). Fourteen times the researcher was not able to contact the patient since she was not aware that euthanasia was about to take place; in eight of these cases the patient died before euthanasia could have been given. It was not feasible to interview two patients; one patient had aphasia, and one was too dazed by morphine. One patient refused to participate in the interview because of the distress he was in, and one patient was too ill to participate.

Forty-two control subjects were selected for a follow-up assessment. Four individuals refused to participate, one could not be reached, and 19 died before the interview could take place (before random selection, those patients known to have died were already excluded), and one patient was too ill to be interviewed (Fig 1). Seventeen control subjects were interviewed. In two cases, it was not feasible to visit the patient, and in these cases the CIDI was done by telephone or with the partner of the patient.

Of the twelve patients that were interviewed after the request for euthanasia was made, the CIDI revealed that two had a major depression (one with mild recurrent episodes, the other with a single severe episode) according to DSM-IV criteria at the time of the interview. In addition, two individuals had major depression within the year before the interview took place. None of the seventeen patients without a request for euthanasia at that moment (controls) were diagnosed with depression at the time of the interview; two of them had depression within the year before the interview took place. Eight subjects in the control group suffered from depression at any previous time in their lives; and four subjects with a euthanasia request suffered from depression at any previous time in their lives.

Discussion

We performed a prospective cohort study among cancer patients with an estimated life expectancy of three months or less. One fifth of these patients with terminal cancer made an explicit request for euthanasia. Patients with depressed mood (as assessed by the HADS) were associated with a four times’ greater risk of requesting euthanasia. Two of twelve patients for whom we assessed current and lifetime episodes of depression after their explicit request for euthanasia had major depression, compared with none of the seventeen control patients, at the time of the interview.

Our study is the first to examine the relationship between depressed mood and incidence of euthanasia requests in terminally ill cancer patients.

In the protocol for the present study, we hypothesized that depressed mood would show an inverse association

Fig 2. Time to request for euthanasia for depressed and not depressed patients. HADS, Hospital Anxiety and Depression Scale.

Fig 3. Survival without euthanasia for depressed and not depressed patients. HADS, Hospital Anxiety and Depression Scale.
with requests for euthanasia. Our clinical impression was that such requests were well-considered decisions, thoroughly discussed with healthcare workers and family. We thought the patients requesting euthanasia were more accepting their impending death and we therefore expected them to be less depressed. To our surprise, we found that a depressed mood was associated with more requests.

Two important questions arise from our findings. The first is whether it is true that depressed mood is related to requests for euthanasia. To answer it some aspects regarding the design of the study need to be discussed. First, we recruited patients from the University Medical Center Utrecht. This hospital is one of the ten tertiary referral centers for cancer patients in the Netherlands, and patients may have been referred to this hospital for complex problems requiring specialized treatment. Therefore, the sample may not be representative of the general population of terminally ill cancer patients. The prevalence of euthanasia requests in our sample (22%) was comparable with the prevalence of euthanasia requests among cancer patients in the nationwide study; the prevalence of patients who died by euthanasia was somewhat higher (13% vs 7%) than in the nationwide study. Second, not all of the departments treating cancer patients participated in this study. This may have resulted in an overrepresentation of patients with gynecologic and urologic tumor sites in the cohort. We are not sure if the association between depressed mood and euthanasia will also be valid for patients from other departments who will probably have different types of cancer, or for patients with diseases other than cancer. Finally, results were based on the questionnaires from 138 patients, leaving out 60 patients who did not want or were not able to participate, most often due to reasons inherent to being terminally ill. As a result, the prevalence of depression in this group may have been lower. There is, however, no reason to believe that this would affect the association between depression and euthanasia.

We would like to emphasize that the Hospital Anxiety and Depression Scale is not a diagnostic tool but a screening instrument for depression. Unfortunately, we did not succeed in assessing depression with the Composite International Diagnostic Interview in a considerable proportion of the patients for a variety of reasons (see Fig 1). Nevertheless, the findings from this subgroup do not contradict the findings based on the HADS interview, which was conducted in all patients.

The second question is what are the consequences of the fact that depressed mood is related to requests for euthanasia? Treatment of major depression in terminally ill patients can be difficult, especially because time is limited. We would urge physicians to be aware of early signs of depression so that appropriate treatment can be initiated. Psychostimulants have shown to be useful to depressed patients with cancer because of their rapid onset of action, and the value of cognitive behavioral treatment in cancer patients has been demonstrated in a prospective randomized trial. The question of whether depressed mood can be adequately treated in this terminally ill population, and if so whether or not it would lower the prevalence of requests for euthanasia, needs further investigation.

The assumption, as discussed in the Introduction, that a request for euthanasia could be considered as a symptom of a psychiatric disorder can be disputed, because by far not all patients who make a request were found to suffer from major depression. The value of a psychiatric consultation as part of the standard procedure for handling euthanasia requests has been studied before. Bannink et al concluded that standard psychiatrist consultation should not be mandatory because the advantages needed to be balanced against the disadvantages and results showed that standard psychiatric evaluation only changed the policy of the primary physician in 9% of cases, though in general, staff appreciated the expertise. Therefore, we would encourage physicians to consult a psychiatrist whenever they have doubts about whether the depressed mood of a patient affects his or her decision-making ability. The disadvantage of mandatory psychiatric evaluation is that it might burden terminally ill patients. Of course, the decision for mandatory psychiatric evaluation ultimately depends on the stand which is taken on this question: Must major depression always be a reason not to grant a request for euthanasia, or only if it affects the patients decision making ability? Because views on assisted suicide for terminally ill patients may also influence the clinical opinions of psychiatrists regarding patient competence, we think the opinions on this topic may differ in countries outside the Netherlands.

Our findings suggest that depressed mood in the last months of life is associated with a higher risk for request for euthanasia. Replication of these findings in a larger sample, and with information on the presence of major depression in all patients, is needed.

**Acknowledgment**

We thank all of the physicians and patients who took part in the study.
Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Employment</th>
<th>Leadership</th>
<th>Consultant</th>
<th>Stock</th>
<th>Honoraria</th>
<th>Research Funds</th>
<th>Testimony</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Lee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Research Institute of Psychology and Health (A)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

REFERENCES