SUMMARY
Many patients with cancer in the end-stage of their disease prefer to die at home. The percentage of patients with cancer dying at home varies between 13%-60% for various countries and states. In the Netherlands annually some 43,000 patients (2010) die as a consequence of cancer, of whom approximately 45% (19,000 patients) die at home. Cancer is polysymptomatic and patients may suffer as a consequence of their disease. The suffering may be a direct consequence of the symptoms of the disease, but may also result from consequences of the disease for various domains of life (e.g. social functioning, or work). Additionally suffering may be present unrelated to the disease. Physicians provide (palliative) interventions to relieve suffering. Sometimes the interventions do not take away the suffering and suffering even may become unbearable. Some of the suffering patients request euthanasia. A societal debate in the Netherlands resulted in legislation of euthanasia and physician-assisted suicide (EAS) in 2002, with unbearable suffering as one of the compulsory criteria to permit EAS. In 2010 4050 patients (2.9% of all annual deaths in the Netherlands) died as a consequence of EAS (in 96.5% euthanasia). EAS in 2010 in 88% of all cases was performed in primary care (3550 patients) and cancer was the diagnosis in 79% of the patients in whom EAS was performed. Of end-of-life cancer patients cared for in primary care around one in seven died as a consequence of EAS (2010). In medicine unbearable suffering has only scarcely been investigated through patient directed research. In palliative care research intensity of symptoms in cancer patients frequently is investigated. However, the intensity in which a certain symptom is present is another quality than the measure of suffering caused by that symptom. Such may be observed in clinical practice, where one person with a certain symptom (e.g. shortness of breath) may be suffering as a consequence of that symptom, while another person does not.

This thesis reports on a prospective study into the nature of unbearable suffering, the relationship between unbearable suffering and requests for euthanasia, and the relationship between depression and requests for euthanasia, in patients with an estimated life expectancy of less than half a year in the primary care setting in the Netherlands. To perform this study it was necessary to develop an instrument to measure unbearable suffering. An anticipated hurdle to be taken was recruitment of patients and physicians. Serious recruitment problems have been reported in studies directed at end-
of-life cancer patients. Additional potential negative recruitment factors were
the low per practice prevalence of eligible patients, failing partnership between
researchers and clinicians, the geographically dispersed situation of practices
and patients in their residencies, and the sensitive subject of the investigation.

The following research questions were investigated:
1. How can a measuring instrument to measure unbearable suffering be
developed? (Chapter 2)
2. How is a population of end-of-life cancer patients recruited in a primary
care study into unbearable suffering and what are characteristics of such
a population? (Chapter 3)
3. What is the prevalence of symptoms which result in unbearable suffering
in end-of-life cancer patients cared for in primary care? (Chapter 4)
4. What are differences in unbearable suffering between end-of-life cancer
patients who suffer unbearably overall and end-of-life cancer patients
who do not suffer unbearably overall in primary care? (Chapters 4 and 5)
5. What is the relationship between intensity and unbearable suffering
for symptoms in end-of-life cancer patients cared for in primary care?
(Chapter 5)
6. How do unbearable symptoms evolve over time in end-of-life cancer
patients cared for in primary care? (Chapter 5)
7. What is the prevalence of depression in end-of-life cancer patients with
and without an explicit request for EAS in primary care? (Chapter 6)
8. What is the prevalence of unbearable suffering in end-of-life cancer
patients with and without an explicit request for EAS in primary care?
(Chapter 7)
9. Which sources provide the capacity to bear the suffering? (Chapter 4)
10. Does previous experience with suffering in ill persons influence present
suffering? What is such an influence? (Chapter 4)
11. Are there positive experiences related to the current illness? What are
these experiences? (Chapter 4)

The questions 3-8 were the main research questions.
(The division of the answers to the research questions over the various chapters
was influenced by publication processes; consequently logic in the order of
presentation may be missing)
The State-of-Suffering V (SOS-V) was developed for quantitative and qualitative measuring of unbearable suffering. Depression and depressive feelings were assessed with standardized measuring instruments. A cohort of cancer patients with an expected survival of less than half a year was recruited and was followed up with interviews administered every two months. The study protocol was approved by the medical ethics committee at the VUmc.

Chapter 1 is the introduction in which the relationship between suffering and medicine is discussed. It is questioned what actually is unbearable suffering and it is discussed that quality-of-life is not a valid measure for suffering. Further are discussed the development and practice of EAS in the Netherlands and elsewhere, the possible role of depression in requesting EAS, and palliative care in the home setting.

In Chapter 2 we report on the development and psychometric properties of the measurement instrument for unbearable suffering, the State-of-Suffering V (SOS-V). Unbearable suffering was defined as a subjective experience that is so serious and uncontrollable that it overwhelms one's bearing capacity. Unbearable suffering was considered to be a relative entity, which may be more or less present. Cancer is polysymptomatic, which indicates systematic assessment of symptoms in case of a comprehensive study design.

The SOS-V is a structured, quantitative instrument for comprehensive assessment of unbearable suffering related to symptoms, with additional open ended questions for qualitative investigation of the experience of unbearable suffering. "Symptoms" refers to physical, psychological, social and existential aspects of suffering. Based upon a literature study a framework of domains in which suffering may occur was selected, and symptoms described to be relevant for end-of-life cancer patients were attributed to the domains. The SOS-V systematically addresses 69 symptoms in a framework of five domains: (I) medical symptoms; (II) loss of function; (III) personal aspects; (IV) environment and; (V) nature and prognosis of disease. Patients may add symptoms which they consider to be missing. The SOS-V was administered 153 times. The interview time generally was some 20-40 minutes. Cronbach's alpha's of the subscales were in majority above 0.7. The sum scores of (sub) scales correlated strongly to overall measures on suffering. The SOS-V was found to be an instrument with psychometric properties which make possible to quantitative and qualitative investigate unbearable suffering.
In Chapter 3 the recruitment process of end-of-life cancer patients in general practice for a study into unbearable suffering is reported. The study was conducted in Utrecht, a city with about 235,000 people and 105 general practitioners (GPs). To implement partnership between researchers and clinicians in the recruitment design direct colleagues of the primary investigator (a GP) working in the same area were recruited into the study. The GPs requested eligible patients to participate. Eligible for the study were cancer patients expected to die within half a year, who were expected to live at home (most of the time) until death with the GP as the primary responsible physician. Complete case identification was part of the study design. The baseline interview was administered within a week when patients consented to participate. Follow-up interviews were every two months, or sooner based upon information by GPs that the condition of a patient rapidly deteriorated. All interviews were at the patients' residence. After death of a patient the GPs was asked whether the patient had explicitly requested euthanasia. A study coordinator was appointed to organize the recruitment process, which included identifying and follow-up of all eligible patients in the care of GPs during the study period. The interviewers were a physiotherapist (the study coordinator) and a GP (CR), both trained in interview techniques.

Forty-four GPs participated in the study. The inclusion period lasted from May 2003 until May 2006, and follow-up continued until May 2007. In the inclusion period 258 eligible patients were identified. In 110 patients the GP did not ask for study participation, the main reason being not wanting to burden patients in whom unexpectedly rapid physical deterioration had occurred. Out of 148 patients who were asked to participate 72 patients refused and 76 patients consented. Of the participating patients six stopped participation after one or more interviews, and six patients were alive at the end of the study. Sixty-four patients in the interview study were followed up until death; the mean age was 70 years (range 38-86 years), and the division of sexes was even. The mean monthly recruitment over the whole inclusion period was two patients. The number of patients recruited per GP varied between zero and eight; 36% of the GP's contributed no patient at all to the interview study. In the interviewed population 27% (17 patients) of the 64 patients followed up until death explicitly requested for euthanasia. In the population of patients which was not interviewed 23 patients out of 174 patients followed up until death explicitly requested for euthanasia.
In Chapter 4 the prevalences of symptoms which resulted in unbearable suffering in 64 patients followed up to death are reported. The final SOS-V interview per patient was analyzed. In four patients the SOS-V was abandoned and consequently missing; the general condition had deteriorated too much to administer the interview. A mean of 18 symptoms which resulted in unbearable suffering was present in patients with serious overall unbearable suffering. Overall, half of the symptoms which resulted in unbearable suffering involved the domain of traditional medical symptoms, with most frequent unbearable symptoms weakness, general discomfort, tiredness, pain, loss of appetite and not sleeping well (25%-57%). The other half of the symptoms which resulted in unbearable suffering involved the domains of function, personhood, environment, and nature and prognosis of disease, with most frequent unbearable symptoms impairment of activities, feeling dependant, needing help with housekeeping, not being able to do important things, trouble accepting the situation, being bedridden and loss of control (27%-55%). Overall unbearable suffering occurred in 28% of the interview population. The combination of love and support was the most frequent source (67%) providing strength to bear suffering.

Chapter 5 reports on the relationship per symptom between intensity and unbearable suffering. Longitudinal analysis of prevalences of unbearable symptoms was performed. A schedule was made of categories of suffering considered important in end-of-life cancer patients according to literature, after which the qualitative descriptions of unbearable suffering were analyzed and categorized according to the schedule. The outcomes of the categorization were compared for the patients who suffered unbearably overall and the patients who did not suffer unbearably overall. The final SOS-V was analyzed for the 60 patients in whom the interview was administered at least one time (on average 30 days before death); for the longitudinal study the pre-final and final interviews were analyzed in the 33 patients with at least two SOS-V interviews. In the patients which were interviewed at least one time the symptom which most frequently resulted in unbearable suffering was weakness (57%). Pain resulted in unbearable suffering in 25%. Pain, loss of control over one's life and fear of future suffering frequently resulted in unbearable suffering (89%-92%) when symptom intensity was high. Loss of control over one's life, vomiting and not being able to do important things frequently resulted in unbearable suffering.
(52%-80%) when symptom intensity was low. Unbearable suffering caused by weakness significantly increased between pre-final interview (on average 123 days before death) and final interview. Categorical analysis of the qualitative descriptions demonstrated that unbearable suffering as a consequence of physical suffering, loss of meaning, loss of autonomy, experiencing to be a burden, fear of future suffering and worrying more frequently occurred in patients who suffered unbearably overall.

In Chapter 6 the relationship between depression and explicit requests for EAS is reported. Depression was assessed with the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (only in the baseline interview); depressiveness was assessed and followed up with the Hospital Anxiety and Depression Scale (HADS) and a single-item depression question (taken from the Edmonton Symptom Assessment System) (ESAS). Of the 64 patients in the interview study 27% (n=17) explicitly requested euthanasia. In the interview study major depression was assessed in one patient according to the SCAN algorithm. According to the depression subscale of the HADS, 47% of the patients who explicitly requested euthanasia versus 28% of the patients without an euthanasia request suffered from depressed mood at inclusion; the difference was not significant. Corresponding figures for the last interview before death were 40% versus 41%. It was concluded that major depression was not a major discriminative factor for explicit requests for euthanasia in end-of-life cancer patients in primary care.

In Chapter 7 the relationship between unbearable suffering and requests for EAS is reported. In the interview study of 64 patients who were followed up until death an explicit request for EAS occurred in 27% (n=17); EAS was performed in 8% (5 patients). The final SOS-V interview per patient was analyzed. Unbearable suffering related to symptoms was present in 94% of the patients with an explicit request for EAS and in 87% of the patients without an explicit request, a non significant difference. Categorical analysis of the qualitative descriptions of unbearable suffering demonstrated no differences between patients with and without a request for euthanasia for the various categories in which suffering may occur (which included such categories as physical suffering, loss of meaning, loss of autonomy, loss of dignity and experiencing to be a burden to others). An advance euthanasia directive (77% versus 9%)
and higher education (35% versus 13%) were significantly more frequent in the patients with an explicit request for euthanasia. It was concluded that in a population of end-of-life cancer patients cared for in primary care no differences in unbearable suffering were found between patients with and without explicit requests for euthanasia. The study results raise the question whether unbearable suffering is the dominant motive to request for EAS. Most patients suffered from unbearable symptoms, indicating that the compulsory criterion of unbearable suffering may be met a priori in most end-of-life cancer patients dying at home, whether they request EAS or not.

Chapter 8 is the general discussion in which the development and psychometric qualities of the SOS-V and the main results of the study are discussed. The importance of comprehensive investigation of suffering to understand and recognize suffering is discussed. Possible directions for interventions to relief suffering are discussed in relationship to the study outcomes. Considering the absence of differences in unbearable suffering between the patients with a request for EAS and the patients without a request for EAS it is questioned whether unbearable suffering, one of the pillars of Dutch legalization of EAS, actually is the dominant motive to request for EAS. Other motives to request for EAS are discussed. Patients depend upon responses of physicians. A tradition of research which investigates effectiveness of palliative interventions to reduce the suffering of end-of-life cancer patients hardly exists. Therefore not much is known about the effectiveness of interventions to relief the suffering of end-of-life cancer patients also in the primary care setting. The high prevalence of unbearable symptoms in end-of-life cancer patients in primary care (comparable figures for end-of-life cancer patients in secondary care are not available) is an instigation for better substantiated palliative interventions. Meanwhile even less is known about the care and interventions which may result in reduction of requests for euthanasia and physician-assisted suicide. The strengths and limitations of the study are discussed. Implications of the study for the medical education curriculum and GP education curriculum are presented. Conceptual confusion which may arise related to the definition of suffering is discussed in relationship to two commonly employed definitions of suffering. Finally direction for further research is presented.