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UNIVERSITY OF ALBERTA

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

By

Antonio Angelo Luciano Viganó 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

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The undersigned certify that they have read, and recommend to the Faculty of Graduate studies and research for acceptance, a thesis entitled. *Survival Predictors In Advanced Cancer Patients* submitted by Antonio Angelo Luciano Viganó in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences–Public Health Sciences.

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Date: April 17, 1998

DEDICATION

To my wife, Francesca, for having always granted me trust, support and love.

To our son, Claudio, for having added extra meaning and joy to our busy lives.

To my family in Italy and in Heaven, for being always with me in thoughts and prayers.

To my family in Canada, for having shared my difficulties and success.

ABSTRACT

Objective To evaluate the relevance of bed-side prognostic factors in terminal cancer patients.

Methods We conducted two systematic reviews on prognostic factors for survival in patients with advanced and end-stage solid malignancies. On the basis of these reviews, we conducted a longitudinal study on a prospectively accrued inception cohort of 248 consecutive patients with cancer of the breast, gastrointestinal, lung or prostate identified at the onset of the terminal stage.

Results Presence of lung cancer, liver metastases and tumor burden along with cognitive impairment, weight loss and abnormal values of lymphocyte count, albumin and lactate dehydrogenase were confirmed as independent prognostic factors of primary importance in this patients population.

Conclusion Disease, physical and laboratory assessments are predictive of survival in patients with terminal solid malignancies. Methodological improvements in the design and data collection of survival studies may reduce prognostic uncertainty and ultimately provide better care for the terminally ill and their families.

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LIST OF ABBREVIATIONS

ASL	Albumin Serum Levels
ALT	Aspartate Amino-Transferase
AJCC	American Joint Committee of Cancer
AST	Alanine Amino-Transferase
BM	Bone Marrow
BUN	Azotemia
CA	Calcium
CA 19-9	Carcino Antigen 19-9
CCI	Cross Cancer Institute
CEA	Carcino Embroyogenic Antigen
CES	Clinical Estimation of Survival
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
DFI	Disease Free Interval
DX	Diagnosis
ECOG	Eastern Cooperative Oncology Group
EFAT	Edmonton Functional Assessment Tool
EOD	Extent of Disease
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ERlevel	Estrogen Receptor level
ESAS	Edmonton Symptom Assessment System
ESR	Erithro Sedimentation Rate
ETOH	Alcohol abuse
γ-GT	Gamma-glutamil transferase
GI	Gastrointestinal
HBSAg	Hepatitis B superficial Antigen
HGB	Hemoglobin
HR	Hazard Ratios
LDH	Lactate Dehydrogenase
KPS	Karnofsky Performance Status
MMSE	Mini Mental State Examination
5NT	5 Nucleotidase

NA	Sodium
NCI	National Cancer Institute
NSCLC	Non Small Cell Lung Cancer
PDQ	Physician Data Query
PI	Prognostic Index
PLT	Platelet
PRlevel	Progesterone Receptor level
PS	Performance Status
PT	Prothrombin Time
QoL	Quality of Life
r	Correlation Coefficients
RCT	Radomize Control Trial
SVCO	Superior Vena Cava Obstruction
TNM	Tumor Node Metastasis
TX	Therapy
VAS	Visual Analogue Scales
VDMS	Visceral Dominant Metastatic Sites
WBC	White Blood Cell Count
WL	Weight Loss
XRT	Radiotheraphy
#	Number

CHAPTER 1

INTRODUCTION

In developed countries around 30% of the population alive today will develop cancer in their lifetime (1). In approximately 50% of the patients diagnosed with cancer, active treatments (aimed primarily at a cure or prolongation of life) become at a certain point ineffective (2). Most authors have defined the period that goes from this point to the patient's death as the "terminal cancer phase" (3-7). The terminal cancer phase may last from days to several months and there are not validated criteria to make adequate predictions of its length (8-14). This prognostic uncertainty, makes clinical decisions difficult for care-givers, patient and families (15, 16), and may lead to inappropriate resource expenditure or denial of potentially beneficial therapy for the terminally ill (17, 18). In the United States (19) and in Canada (20) admission criteria to government funded hospices or some regional palliative care programs (20) require physicians to determine life expectancies of 6 months or less. In the United States a 1993 report from the National Hospice Organization showed that over 50% of terminally cancer patients were not given access to hospice services (21) or were referred too late in the course of their illness to take full advantage of the support provided by hospice programs (22). Overly optimistic survival predictions made by different health care providers have adversely affected patients referrals to hospice programs in the United States (19). On the other hand "too early" referrals to hospices or palliative care programs, could create organizational, financial, clinical and emotional problems for both caregivers and patients (23). Several studies were conducted to elucidate the role of prognostic factors for survival in advanced/terminal cancer patients. Simple bed-side assessments, which were considered minimally interfering with the quality of life of the terminally ill, received great attention. In studies which focused on prognostic factors for survival,

the length of the latter has been linked to the following indicators: a) clinical estimates of survival by experienced physicians (24 - 29); b) performance status (30 - 44); c) some physical symptoms such as dyspnea, xerostomia, dysphagia, anorexia and cachexia (14, 17, 18, 35, 37, 38, 40, 41, 45- 50); d) some biological markers such as hemoglobin, leukocyte count, albumin, sodium and calcium (32, 36, 39, 42, 51 - 60); e) some psychological such as quality of life, and level of psychosocial well-being and/or support (61-71) and socio-economic parameters such as marital status, income and/or education levels (72-74), besides tumor type and stage (18, 43, 49, 70).

Both variability and uncertainty have limited the clinical significance of these studies. Methodological issues and variations in the survival of cancer patients whose death is determined by multiple causes (75, 76) tend to reduce the predictive accuracy of potential prognostic factors. Methodological limitations include: a) sampling of terminal populations, rarely including inception cohorts (77), b) use of non-standardized measures for potential survival predictors (e.g. use of different performance status scales) (78), c) variation in the predictors across studies (79), d) use of non time-adjusted analyses (e.g. logistic rather than Cox regression) (77); e) consideration of different end-points (e.g. survival at particular times instead of considering the entire survival curve) (79).

We have conducted an inception cohort study to overcome these methodological limitations and provide a base for future studies in this research area. We pursued the following objectives:

1. Identification of important predictors for survival in advanced and terminal cancer patients through systematic reviews of the medical literature. Because of the different types of studies in the medical literature, two separate systematic reviews

were performed. The first review included studies dealing with patients with a short median survival, mainly conducted in hospices and palliative care units. The second review included studies on patients with somewhat longer survival periods. In general, these publications reported on long-term follow-up studies of patients with advanced cancer that had been included in clinical trials.

2. Definition of clinical criteria to establish the onset of the terminal cancer phase in patients with by solid malignancies.
3. Application of these criteria to accrue an inception and population-based cohort of terminal cancer patients.
4. Cross-sectional evaluation of these patients characteristics at the time of their accrual.
5. Longitudinal study of survival and its prognostic factors in this homogeneous cohort of terminally ill cancer patients.

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CHAPTER 2

BED-SIDE PROGNOSTIC FACTORS FOR SURVIVAL IN TERMINAL CANCER PATIENTS: A SYSTEMATIC REVIEW OF THE LITERATURE

2.1 INTRODUCTION

In developed countries approximately one out of three individuals will develop cancer in their lifetime, and approximately 50% of cancer patients will die from their disease (1). When the likelihood of cure is limited, a prognosis "quoad vitam" is often required for planning further medical/supportive care, counseling patients and families, and establishing patients' eligibility to undergo specific clinical trials or care programs. In the United States (2) and in Canada (3) admission criteria to some government-funded hospices and palliative care program (3) require physicians to establish life expectancies of 6 months or less. Death in cancer patients is determined by multiple causes (4,5); and common predictors for all these final events may not be apparent. Furthermore, the clinical significance of some studies may be hindered by methodological issues, such as : a) sampling, few studies have included well-defined inception cohorts (6), b) such as measurement of potential prognostic factors, which are not similar across the studies (7), c) lack of adjustment for important prognostic factors, such as performance status or tumor burden (8), d) different end-points (e.g. survival at particular times instead of considering the entire survival curve) (8).

The purpose of this systematic review was to evaluate the published medical literature concerned with the survival of patients with terminal cancer, with special emphasis on potential prognostic factors.

2.2 METHODS

2.2.1 Search strategy

Publications for this review were initially identified through MEDLINE, using a search strategy developed by an experienced librarian (Appendix 1). Years 1980 to 1997 were searched. Hand searches were also conducted by examining reference lists from selected papers. We were interested in publications dealing specifically with prognostic factors for survival in end-stage cancer patients, regardless of their original primary tumor (9).Most of the studies reported an overall median survival no longer than 12 weeks. Finally, we focused on bed-side prognosis, including only publications examining prognostic factors generally available in regular clinical practice.

2.2.2 Criteria for inclusion of publications in the review

1. Tumor type/stage: any primary tumor, or a combination of different tumors.
2. Reported median survival ≤ 12 weeks - This cut-off was chosen to evaluate studies in a homogeneous population of terminal patients.
3. One or more bed-side prognostic factors considered: clinical estimation of survival, demographics, clinical staging of the disease (number and/or site of metastasis), performance status, nutritional status assessments, presence and intensity of symptoms, traditional laboratory tests, quality of life and/or socio-economic characteristics.
4. Sample size ≥ 40 patients.

2.2.3 Publications not included in the review

1. Studies reporting incomplete data (e.g. median survival, level of significance, etc.)
2. Studies reporting survival rates only at specific end-points (e.g. 3 or 6 month survival rates), as opposed to considering the survival curve.
3. Clinical trials evaluating the effect of therapies in advanced or end-stage patients.

2.2.4 Data extraction

Data reviewed and extracted from selected papers included: sample size, median survival, type of study, sampling frame, referral pattern, predictors examined, type of statistical analysis (bivariate or multivariate), choice of models and underlying assumptions.

2.2.5 Data reporting

Because of the nature of the publications, which reported varying measures of association between prognostic factors and survival, a quantitative approach such as meta-analysis could not be conducted. Instead, a systematic review was performed reporting those design features, which are thought to be relevant for the validity of studies on prognosis (10,11,12) and the level of statistical significance for each prognostic factor. On the basis of this information and through a consensus among the authors, the reviewed prognostic factors were categorized according to their association with decreased survival as: a) probably not associated - the association with survival for these variable was consistently found to be not significant or ambiguous; b) possibly associated - the association with survival for

these variables was suggested by some authors but needs to be confirmed by more/better designed studies; c) definitely associated - the independent predictive value of these variables appears to be consistent across well designed studies.

2.3 RESULTS

The MEDLINE search identified several hundred publications. The titles and abstracts of these were examined, to select publications meeting the inclusion criteria. A total of 20 studies were finally included. Nineteen were retrieved through the electronic search; one publication (13) was found through the review of references in the selected papers. In seventeen studies, the median survival was reported to be ≤12 weeks. We included three further references: two of those indicated that approximately 85% of the patients died within 12 weeks (14,15), one of these studies (14) was also reported in a separate publication (16). The third study reported an average (as opposed to median) survival of 4 weeks, with the longest follow-up being 6.4 weeks (17).

Some studies were excluded because they did not report the median survival (18,19), and others because they did not adequately report the association between various possible predictors and survival (9,20,21).

The 20 publications included in the review considered a total number of 6580 patients; the median survival ranged from 1.8 to 11 weeks (Table 1-2). Only two studies examined specific primary tumors, such as lung and liver (31,32), while the rest considered several different end-stage malignancies. Fourteen studies had a prospective cohort design. The remaining six evaluated retrospective cohorts. The

most frequent population sampling settings were: home care programs (six studies), hospices (six studies) and palliative care units (four studies). The National Hospice Study, which provided two different publications, included terminally ill cancer patients who were in home care programs, hospices and hospital wards. Of the other two studies, one was population-based, and the other hospital-based.

Seven studies showed survival curves using Kaplan-Meier methods based on different categories or levels of the prognostic factors. All these studies reported statistical significance tests: a log-rank test was used in six studies (22-27) and Wilcoxon in one (28). Life-table methods were used in two studies (14,23), but no statistical tests were reported for differences in the cumulative survival rates. The remaining 12 studies (13,15-17,26,29-35) did not use time-adjusted analysis and only reported bivariate associations between survival and prognostic factors.

Multivariate analysis was performed in 13 studies. Cox proportional hazard regression models were used in five (23,24,26,28,32). The remaining eight studies (14,17,22,25,30,31,35,36) presented other multivariate models. Compliance with the assumption criteria for each multivariate model was stated in five studies (22,23,28,32,36); the methods used for variable selection and assessment of goodness of fit, respectively, were given in seven (22,23,25,28,31,35,36) and four (14,17,30,32) studies, respectively. A model validation sample was only used in one study (31).

One hundred and thirty-six different variables were examined as possible predictors of survival in the reviewed studies. Some variables referred to similar underlying concepts, characteristics or clinical observations, and were aggregated under a single prognostic factor. These included: abnormalities in serum hemoglobin

considered as anemia; difficulty in swallowing or eating considered as dysphagia; nutritional assessments as presence or absence of cachexia; level of appetite as presence or absence of anorexia; decreased cognitive status or disorientation considered as cognitive impairment. Eighteen possible predictors of survival were examined in at least 3 studies and were included for review (Table 2-2), ranked in descending order according to frequency starting with the most frequently reported. In three studies (14,17,32) the samples sizes were small in relation to requirements for multivariate analyses (37). In one study (28) the ratio between the number of deaths and predictor variables was impossible to determine. Table 3-2 summarizes the level of statistical significance reported for the 18 prognostic factors considered in our review. Each reference number falls in one of four different columns which reflect the type of analysis (bivariate/multivariate) and whether the prognostic factor reached statistical significance Clinical estimation of survival by treating physicians was evaluated in four studies (15,17,22,27). Although a statistically significant association was observed, it appeared to be of small magnitude.

In accordance with our criteria for association (level of scientific evidence), decreased performance status, cognitive failure, weight loss, dysphagia, anorexia and dyspnea were considered to be definitely associated with decreased survival in terminally ill patients (Table 4-2).

2.4 DISCUSSION

We conducted a systematic review of the literature on prognostic factors for survival in cancer patients who, according to their median survival, were considered to be in a terminal phase of their disease. To date there are no standard criteria to define this phase. Parkes defines the period of terminal care as the period from the end of therapy aimed primarily at prolonging life to the patient's death (38). Calman lists three conditions to be met before defining cancer as terminal disease: a firm diagnosis of progressive malignant disease, the recognition of an approaching death, and the exhaustion of all therapeutic alternatives offered by conventional anticancer therapy (39). McCusker refers to the terminal care period as the period during which there is evidence of progressive malignancy and in which therapy cannot realistically be expected to prolong life significantly (33). Saunders (40) with Twycross and Lichter (41) describe the beginning of the terminal period as the time when goals must be redefined and it is appropriate to shift from treatments aimed to the control of the tumor to treatments primarily prescribed for symptom control. Most of the studies, which included these criteria for the selection of a terminal population, reported a median survival of 3 months or less. We therefore considered a median survival of less than 12 weeks to identify studies for our review. A sample size $\geq$ 40 was chosen because 30 events are needed to detect a correlation of approximately 0.45 with a power $\geq$ 80 % and a two-tailed $\alpha \geq 0.05$.

For the majority of the studies, it was difficult to establish if their samples were truly representative of a population of terminally ill cancer patients. Few studies (26,31,33-36) provided information on patient characteristics or admission criteria to

home care programs, in-patient hospices or palliative care units. These characteristics have been shown to overly influence timing of enrolment in hospice programs (42). Enrolment usually happens late in the course of the terminal disease. Therefore, patients in hospice programs may be sicker than the general population of terminally ill patients. The major limitation of these studies appears to be the lack of well-defined inception cohorts: no studies have considered patients at specific points in the course of their terminal illness.

Kaplan-Meier and life-table methods are the techniques of choice to establish conditional survival probabilities (43), but were performed in only half of the studies. Some of the studies only considered survival rates at specific time points, which may decrease the discriminative power of the study. Thirteen of the publications included multivariate models to investigate the independent prognostic value of each variable, in some cases using Cox proportional hazard models, which provide an estimation of the risk ratios with confidence limits (44). In only five of these 13 studies did the authors explicitly state that they had verified the assumptions underlying the different regressions models (e.g., proportionality of hazards for the Cox model). When these assumptions are not satisfied, the regression models may not yield valid inferences on the significance of a prognostic factor (37). A few more papers described the methods for variable selection, but often it was difficult to establish which variables were tested in the bivariate analysis and selected for the multivariate models. None of these studies reported test for interactions among covariates. The predictive accuracy of the final models was seldom determined on the training sample (the data set from which the predictive model had been

generated), and only one study included a test sample (a new data set) to test the predictive model generated from a previous sample.

Losses to follow-up were not generally reported. We assumed, however, that these losses as well as the proportion of patients alive at time of analysis would be minimal in cohorts with very short median survival. Nevertheless, in a few studies the ratio of the number of events (deaths) to the number of potential predictors was <10. A ratio of 10 or higher has been recommended for stepwise regression analyses (10,37).

The relative value of performance status among the prognostic factors for survival in terminally ill cancer patients is confirmed by our review. However, the clinical applicability of this measurement remains unclear for the following reasons: a) use of different scales, such as the Karnofsky (45) or Eastern Cooperative Oncology Group performance status scales (46), and different collapsed versions of the same scales in various studies; b) heterogeneity in the statistical analyses and in the end-points used for survival. Although statistically significant, the association between survival and performance status appears to be of small magnitude. It has been suggested that these scales are unable to discriminate patients who are sicker and cluster at their lower ends (floor effect) (17). In addition, lower predictive accuracy has also been reported for higher scores of performance status, particularly with values beyond 50-60 on the Karnofsky scale (47). Finally, the strength of the association between performance status and survival appears to be time-dependent, being more evident in the short-medium term (3-12 weeks) rather than in the long term (3-6 months and beyond) (14,23).

The presence of weight loss, dysphagia, anorexia, xerostomia and dyspnea appeared to be among the best prognostic indicators after performance status. These findings are consistent with the terminal cancer syndrome theory, which states that symptoms such as the above mentioned, rather than disease characteristics (e.g. type of tumor or metastatization) are linked to the prognosis of patients with different end-stage malignancies (36). However, in four out of nine (44%) studies which considered the type of primary, this variable was found to be significantly correlated with survival. Lung cancers were consistently associated with more unfavorable prognoses (14,23,26). Unfortunately, inception cohort studies of terminally ill cancer patients have not been performed to clarify this issue.

Pain was not among the best prognostic factors. However, a few studies showed that severe (31) or unendurable (20) pain is associated with extremely short prognosis.

The prognostic value of the clinical estimation of survival by physicians appears similar to that of performance status. It correlates significantly with survival, but the magnitude of this association is generally low. The accuracy of the clinical estimation is reported as moderate for aggregate predictions, but very low for case-by-case survival prognosis (16,17). A limited value for physicians' clinical estimations has also been observed for patients in intensive care units (48) or with acute congestive heart failure (49). In one of the studies in the review, the clinical estimation of survival added complementary information to a predictive model, which included performance status, cognitive impairment, nutritional factors and dyspnea (22). Muers and colleagues also showed that when the physician's estimation of survival was included as a prognostic factor in a predictive model, it

further differentiated prognostic subgroups in a cohort of patients with advanced lung cancer (50). Clinical predictions of survival could perhaps be considered as one of many criteria, rather than as a unique criterion by which to choose therapeutic interventions or health care programs in the terminal cancer phase.

The presence of anemia did not seem to be associated with survival in the terminally ill. In a recent report, blood transfusions failed to improve the quality of life of cancer patients admitted to a palliative care unit (51). Low albumin was consistently associated with shorter survivals, but its independent prognostic value was not confirmed by multivariate analyses .

Abnormalities in the pulse rate appeared to be significantly and independently correlated with survival after adjustment for other factors. Dysfunctions in the autonomic nervous system are frequent in terminal cancer patients (52). Fever and nausea were not associated with survival. Although autonomic dysfunction is among the causes of nausea, the pathogenesis of this symptom remains multifactorial in these patients (53).

Marital status was linked to survival in only two studies. One of them reported significantly better outcomes for married people (31) while the other study (23) showed opposite results.

Biological and disease-related characteristics were generally not considered in the reviewed studies.

2.5 CONCLUSION

The survival of individual patients cannot be predicted with certainty. However, the recognition of predictors is essential to identify terminal cancer patients who may have significantly shorter life expectancy. To date, performance status and the presence of cognitive failure, weight loss, dysphagia, anorexia and dyspnea appear to be important prognostic factors for survival in this population. The lack of representative inception cohorts (population-based), the use of non-standardized measures, and non time-adjusted analyses, and the variability in the inclusion of predictors in the analysis decreased the generalizability of many of these studies. By considering these methodological issues, future researchers may be able to reduce the uncertainty of prognostic factors for survival in terminally ill cancer patients. Meanwhile, clinicians need to recognize the serious limitations of a "simple" clinical estimation of survival in the counseling of patients and families, and in the choice of palliative therapies such as surgery or chemotherapy. The knowledge of other important prognostic factors should improve clinical predictions and assist in establishing the eligibility of terminal cancer patients for health care programs and research studies.

Table 1-2: Methodological Features of the 20 Studies Included in the Review

Ref	Study	N	Primary	Median Survival (Wks)	Sampling Frame	Cohort Type
15	Parkes, 1972	168	All	NR	Hospice	Prospective
34	Mor, 1984	685	All	5.2	National Hospice Study	Prospective
32	Attali, 1987	127	Liver	6	Hospital	Retrospective
29	Heyse-Moore, 1987	50	All	2	Hospice	Prospective
36	Reuben, 1988	1592	All	5	National Hospice Study	Prospective
16	Forster,1988	108	All	3.5	Hospice	Prospective
14	Forster,1989	108	All	3.5	Home Care	Prospective
30	Schonwetter, 1990	172	All	3.1	Home Care	Retrospective
24	Heyse-Moore,1991	303	All	11	Palliative Care Unit	Retrospective
17	Bruera, 1992	47	All	4 (mean surv.)	Palliative Care Unit	Prospective
35	Rosenthal, 1993	148	All	2	Hospice	Prospective
33	Mckusker, 1984	144	All	6.4	Population Based	Retrospective
26	Hardy, 1994	107	All	6	Palliative Care Unit	Prospective
27	Maltoni, 1994	100	All	5	Home Care	Prospective
31	Shonwetter, 1994	310	Lung	3.9	Hospice	Prospective
22	Maltoni,1995	540	All	4.6	Home Care	Prospective
23	Allard, 1995	1081	All	1.8	Hospice	Retrospective
13	Salamagne, 1996	160	All	2.2	Palliative Care Unit	Retrospective
28	Tamburini, 1996	100	All	8	Home Care	Prospective
25	Maltoni, 1997	530	All	4.6	Home Care	Prospective

Table 2-2: The 18 Most Frequently Reported Prognostic Factors Included in the Reviewed Studies.

*Reference**	*13*	*15*	*16*	*27*	*29*	*33*	*34*	*14*	*17*	*22*	*23*	*24*	*25*	*26*	*28*	*30*	*31*	*32*	*35*	*36*
Multivariate analysis	*no*	*no*	*no*	*no*	*no*	*no*	*no*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*	*yes*
Deaths/variables ratio	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*2*	*3*	*36*	*360*	*36*	*52*	*10*	*nr*	*10.8*	*16*	*4*	*37*	*100*
*Variables**:*																				
Low Performance Status				+		+	+	+	+	+	+				+		+		+	+
Male gender						*ns*		*ns*		*ns*	+				+	*ns*	+	*ns*		*ns*
Primary[a]						*ns*		+		*ns*	+	*ns*		+	+				*ns*	*ns*
Increasing Age						*ns*				+	*ns*	*ns*			*ns*	+		*ns*		*ns*
Pain						*ns*		+	*ns*	+				+	+	*ns*	+			
Cognitive Impairment								+	+						+		+		*ns*	+
Anorexia									*ns*	+					+	+	+			+
Dyspnea									*ns*	+		+		+						+
Xerostomia									*ns*	+					+		+			+
Clin. Est. of Survival		+		+					+	+										
Hypoalbuminemia	+												+					+	*ns*	
Weight loss									+	+									*ns*	+
Dysphagia									+	+					*ns*					+
Fever										*ns*									*ns*	*ns*
Marital Status[b]											+					*ns*	+			
Nausea									*ns*						+					*ns*
Tachicardia																+	+		*ns*	
Anemia													*ns*					*ns*	*ns*	

* Listed in order of appearance in the text. ** +, Association with decreased survival; *ns*, no association with worse survival. Blank space means variable not examined. [a]Lung primary in references 14, 23, 26; gastrointestinal tumor in reference 28. [b]Married in reference 23, non-married in ref. 31.

Table 3-2: Level Of Statistical Significance Reported For The Most Frequently Studied Survival Predictors In Terminally Ill Cancer Patients

Variable	Not statistically significant in the bivariate analysis (BA)	Not statistically significant in the multivariate analysis. Significance not indicated for BA	Statistically significant in the BA not significant in the multivariate analysis (MA)	Statistically significant in the MA	No. of positive studies/ total no. evaluated	Total no. of patients evaluated
Low Performance Status			17, 27*, 28, 31, 33*, 34*	14, 22, 23**, 35**,36**	11/11	5755
Male gender	14, 22, 30, 32, 33, 36		23*, 28*, 31		3/9	4219
Primary[a]	22, 24, 33, 35, 36		14, 23*, 28*	26	4/9	4025
Increasing Age	23, 28, 32, 33, 36	24	22	30	2/8	4059
Pain	17, 33,	30	14*, 22, 26, 28	31	5/8	1528
Cognitive Impairment	35		14, 31	17, 28, 36**	5/6	2305
Anorexia	17		28, 31	22, 30, 36**	5/6	2761
Dyspnea	17			22, 24, 26, 36**	4/5	2589
Xerostomia	17		22, 28	31, 36**	4/5	2589
Clin. Est. of Survival***			15*, 17*, 27*	22	4/4	855
Hypoalbuminemia	35		13*, 25, 32		3/4	975
Weight loss	35		22	17, 36**	3/4	2327
Dysphagia	28		22	17, 36**	3/4	2279
Fever	22, 35	36			0/3	2280
Marital Status[b]	30		23*, 31		2/3	1563
Nausea	17	36	28		1/3	1739
Tachicardia	35			30, 31	2/3	630
Anemia	35, 25, 32				0/3	805

Significance at p=0.05, if not otherwise specified The prognostic factors are ranked in descending order from the most to the less frequently reported. * Significance not tested/reported for MA** Level of significance not reported for bivariate analysis*** Significance not reported for references 16 and 29. [a]Lung primary in references 14, 23, 26; gastrointestinal tumor in reference 28. [b]Married in reference 23, non-married in ref. 31.

Table 4-2: Evidence Of Association Between Decreased Survival And The Most Frequently Studied Prognostic Factors In Terminally Ill Cancer Patients.

Factors probably not associated *	*Variables possibly associated*	*Variables definitely associated*
Increasing Age	*Male Gender*	*Low Performance status*
Fever	*Primary*[b]	*Cognitive impairment*
Marital status[a]	*Pain*	*Anorexia*
Nausea	*Clinical estimation of survival*	*Dyspnea*
Anemia	*Serum albumin*	*Xerostomia*
	Tachycardia	*Weight loss*
		Dysphagia

[a]Married in reference 23, non-married in ref. 31. [b]Lung primary in references 14, 23, 26; gastrointestinal tumor in reference 28.

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CHAPTER 3

BED-SIDE PROGNOSTIC FACTORS FOR SURVIVAL IN ADVANCED CANCER PATIENTS: A SYSTEMATIC REVIEW OF THE LITERATURE

3.1 INTRODUCTION

The diagnosis of advanced/metastatic disease is a turning point for most cancer patients. Virtually all patients with advanced solid tumors, will die of their disease within a relatively short time (1). Despite this unfortunate fate, the clinical course of advanced/metastatic cancers is highly variable. Numerous investigators have examined potential prognostic factors for survival in advanced cancer patients, in order to guide treatment choices and for the counseling of patients and families. Unfortunately, the interpretation of the available literature is often difficult. There are several methodological differences that make it difficult to compare studies on prognostic factors for survival (2). The main differences are:

1. Study populations: Most studies lack inception cohorts and refer to patients enrolled in clinical trials. When data are derived from cancer registries they often consider a case-mix of patients at different stages of disease.
2. Diagnostic criteria and treatment modalities: Stage and extent of disease are not always considered according to the Tumor Node Metastasis (TNM) classification (2); patients with similar type and stage of disease may have undergone different therapeutic approaches (e.g., treatment versus no treatment) in different studies.
3. The mix of variables considered: Authors may have included in the analyses post-treatment factors (e.g., response to treatments) or excluded major prognostic factors (e.g., performance status).
4. Type of statistical analyses: Some studies have explored only bivariate associations between prognostic factors and survival or have used non-time adjusted analyses (logistic rather than Cox regression) (Chapter 2).

5. End-points for survival: Some authors have considered survival rates at particular times instead of entire survival curves .

It has been suggested that simple bed-side assessments are valid alternatives to complex staging procedures and provide valuable prognostic indications for survival in patients with advanced malignancies (3). In general non-invasive assessments are preferable in very ill patients, because they minimally impact on their quality of life and are available to a general practice.

The aims of this paper were to overcome part of the mentioned heterogeneity among studies and to examine the relevance of bed-side prognostic factors for survival in advanced cancer patients, through a systematic review of literature.

3.2 METHODS

3.2.1 Search strategy for systematic review.

Publications for this review were initially identified through MEDLINE, using a search strategy developed by an experienced librarian (Appendix 1). Years 1980 to 1997 were searched. Earlier years were not included since it was felt that diagnostic and treatment procedures for solid tumors have been evolving substantially in more recent years. Hand searches were also conducted by examining reference lists from selected papers. We were interested in publications dealing specifically with prognostic factors for survival in patients with advanced solid malignancies, who are deemed to be incurable. We excluded studies that looked at prognosis in terminal cancer patients and reported overall median survivals for their samples ≤12 weeks. Most studies that considered hospice patients, have generally looked at a population dying within two months of study

accrual. This patient population is usually not stratified according to primary tumors and is sicker than (i.e. different from) a population with advanced rather than terminal cancer (Chapter1). We were also interested to see if the strength of the association between certain prognostic factors and survival could vary according to the length of follow-up both within a certain type of tumor and across different primaries. Finally, we kept our focus on bed-side prognosis, including only those prognostic factors, generally available to regular clinical practice.

3.2.2 Inclusion criteria.

1. Tumor type/stage: small-cell (extensive disease) and non small-cell lung cancers (unresectable/metastatic), breast cancer (recurrent/metastatic), gastrointestinal cancers (unresectable metastatic) and prostate cancers (unresectable, metastatic).
2. Statement or graphical indication of the overall median survival for the study sample.
3. One or more bed-side prognostic factors considered: clinical estimation of survival, demographics, clinical staging of the disease (number and/or site of metastasis), performance status and nutritional status assessments, presence and intensity of symptoms, traditional laboratory tests, quality of life and socio-economic characteristics.
4. Sample size ≥ 40 patients.

3.2.3 Exclusion criteria

1. Lack of reported associations between candidate prognostic factors and survival
2. Only specific survival rates reported: 3 or 6 months survival rates, as opposed to overall survival.
3. Intervention studies with a major focus on treatment outcomes instead of prognostic factors for survival.

3.2.4 Data extraction

Data reviewed and extracted from selected papers included: reported sample size, median survival and censored fraction, type of study and sampling frame, variables mix considered in each study, and level of statistical significance reported for bivariate and multivariate analyses.

3.2.5 Data reporting

Because of the nature of the publications, which reported unstandardized measures of association between prognostic factors and survival (e.g., similar variables were categorised differently and/or heterogeneous lengths of follow-up were considered among studies), a quantitative approach such as meta-analysis could not be applied. Instead, a systematic review was performed. The characteristics and the results of the selected studies were summarised in synoptic tables. First, we reported those design features which are thought to be relevant for the validity of studies on prognosis (4,5,6), and the level of statistical significance found in the reviewed studies for each prognostic factor (Tables 1-3, 3-3, 4-3, 6-3). High numbers of different prognostic factors were studied for each primary tumor site, but significantly fewer variables were reported frequently enough to provide a general impression of their prognostic importance. Some

variables referred to similar underlying concepts, characteristics or clinical observation, and were aggregated under a single prognostic factor. These included: presence of metastases, considered as stage of disease; number of cancerous lesions considered as tumor burden; nutritional status characterised as presence or absence of cachexia.

On the basis of this information and through a consensus of the authors, the reviewed prognostic factors were defined as follows: a) probably not important if the association with survival for these variable was found consistently not significant or ambiguous; b) possibly important if the association with survival for these variables was suggested by some authors but needs to be confirmed by more or better designed studies; c) definitively important, if the predictive value of these variables appears confirmed by a certain number of statistical analyses (i.e., by at least 80% of bivariate analyses and 40% of multivariate models) in well designed studies (i.e., where samples were derived from cancer registries rather than clinical trials) (Tables 2-3, 5-3, 7-3). In the last synoptic table (Table 8-3), we examined a proportion of studies reporting independent correlations with survival for the important prognostic factors, in samples with median survivals of six, twelve, twenty-one, and over twenty-two months. These ranges correspond roughly to 6-month intervals and are well suited to the distribution of the reviewed studies.

3.3 RESULTS

3.3.1 Studies in patients with advanced breast cancer

Ten articles (7-16) that presented analyses of prognostic factors for survival in patients with metastatic or recurrent breast tumors were reviewed. Nine titles were retrieved

through electronic searching of the MEDLINE database and one paper (10) was found in the lists of references.

The reviewed papers considered a total number of 4723 patients; the median survival of samples ranged from 8.5 to 32.4 months (Table 1-3). All studies considered retrospective cohorts of patients. In only three (8,9,15) out of ten studies (30%) inception cohorts could be identified. One hundred and fifty-eight different variables were examined as possible predictors of survival in these ten studies. No demographic variable was reported significantly and consistently associated with survival across these studies. Among clinical characteristics, six out of ten (60%) studies (7-9,11-16) that looked at the disease-free interval (DFI) found its greater length significantly associated with better survival both in bivariate (7,12,16) and multivariate analysis (8,9,15). Higher performance status and higher estrogen receptor levels were found both significant predictors of better survival in four (7,8,11,13 and 9,11,13,15) out of five multivariate analyses (80%). Among treatments received prior to study accrual, the presence of adjuvant chemotherapy had a negative significant prognostic value in five (9,11,13,14,16) out of seven studies (71%). Among disease-related characteristics, high tumor burden was found to be a significant and negative survival predictor in five (7-9,13,16) out of six studies (83%), whereas visceral dominant metastatic sites (VDMS) were found to be independent, poor prognostic factors in four (8,11,14,15) out of six studies (66%). According to the mentioned criteria, low performance status, low estrogen receptor status, high tumor burden, presence of liver/visceral metastases, and visceral dominant metastatic status (VDMS) appeared as variables of definitely and adverse prognostic importance in the reviewed studies (Table 2-3). All these variables, with the

exception of the presence of liver/visceral metastases, appeared better predictors for median survivals ≥22 months. (Table 8-3).

3.3.2 Studies in patients with advanced gastrointestinal cancers.

Nineteen articles (17-36), that examined prognostic factors for survival in patients with inoperable, metastatic or recurrent gastrointestinal tumors, were reviewed. Fourteen titles were retrieved through the electronic search of MEDLINE database, whereas five papers (21,22,27-29) were found through the review of references in the selected papers.

A total number of 3103 patients were considered; the median survivals of samples ranged from 3.3 to 18 months (Tables 3-3 and 4-3). All studies except one (33) considered retrospectives patient cohorts. In six (22,25,27,30,33,34) out of nineteen (32%), inception cohorts could be identified. One hundred and fifty-seven different variables were examined as possible predictors of survival in the reviewed studies. Demographic characteristics were again found of no prognostic significance in these patients population. Seven (18,19,24,31,33,32,35) studies out of eleven (64%), found high performance status (PS) significantly linked with better survival, while a greater amount of weight loss appeared to be significant and negative prognostic factor in three (18,25,27) out of three studies. The length of disease free interval (DFI) was found positively and independently associated with survival in two (31, 32) out of four studies (50%). Among disease characteristics, the percentage of secondary liver involvement and tumor burden were found to be significantly associated with survival in six (17,23,25,26,33) out of six studies, and in six (18,19,20,25,31,33) out of seven studies. Among laboratory parameters, bilirubin and alkaline phosphatase were examined in

eleven and twelve studies respectively: both variables were found to be significant predictors of worse survival in nine studies (18-20,22,25,26,30,32,33 and 17,19,20,25,26,28,30,32,33). Four (20,25,30,35) out of five studies (80%) found low levels of albumin significantly associated with worse survivals whereas carcino-embriogenic antigen was significantly correlated with survival in five (18,19,28,33,35) out of seven studies (71%). In summary, definitely important predictors of worse survival in advanced gastrointestinal cancer patients included: low performance status, high percentage of liver replacement/involvement, high bilirubin and alkaline phospatase and low albumin serum levels (Table 5-3). All of these prognostic factors, with the exception of percentage of liver replacement/involvement, seem to loose prognostic significance with increasing survivals (Table 8-3).

3.3.3 Studies in patients with advanced cancer of the lung

A total of ten studies (36-46) were selected and reviewed for patients with advanced cancer of the lung (Table 6-3). Eight titles were retrieved through the electronic search of MEDLINE database, whereas two articles (43,44) were found by reviewing the references of the selected papers. None of the studies, which looked at patients with small-cell lung cancer, was found complying with our selection criteria. Main reasons for exclusion of the latter were lack of appropriate stratification, lack of stated median survivals for the overall sample, and main focus of the study being treatment outcomes instead of survival analysis.

The ten reviewed papers for non-small lung cancers considered a total number of 5668 patients; the median survival of samples ranged from 4 to 10.6 months (Table 6-3). All studies considered retrospective cohorts of patients. In none of the studies an inception

cohort could be recognized. One hundred and fifty eight different variables were examined as possible predictors of survival in these studies. Among the characteristics related to patients, male gender appeared to be independently correlated with worse survival in six studies (36,40-42,44,46). Performance status was the most frequently studied variable: it appeared as an independent survival predictor in ten out of ten multivariate models with lower functional stata correlating with worse survivals (36,37,39-46). Among the most frequently studied analytical variables, both high levels of lactate dehydrogenase (36,37,40-45) and low serum albumin (38,41,43-46) were found always associated with worse survival and overwhelmingly in an independent fashion. Among disease characteristics, tumor burden appeared always associated with survival in five studies (36,37,40,41,43) mostly in multivariate models. In summary, male gender, low performance status, high tumor burden, low serum albumin and high lactate dehydrogenase serum levels, may be considered to be definitely important prognostic factors for advanced lung cancer patients (Table 7-3). Temporal trends in the association between these variables and survival were not clearly identified in the reviewed studies (Table 8-3).

3.3.4 Studies in patients with advanced prostate cancer.

Ten studies dealing with prognostic factors for survival in patients with advanced cancer of the prostate (47-56) were identified complying with most of our selection criteria, but only in one study (56) the median survival of the sample was indicated. The results of these studies were not summarised in a table as for other three types of primary tumors. Nevertheless it was felt that some prognostic factors for patients with advanced prostate cancer were worth mentioning. Among patient related characteristics, performance

status appeared to be an independent survival predictor in five (47,49,50,51,56) out of seven studies (71%), whereas three (47,49,55) out of four studies (75%) showed the amount of weight-loss to be a significant and adverse prognostic factor. The presence or the intensity of pain were significantly correlated with survival in five (49,50,52,54,55) out of six studies whereas anorexia appeared negatively correlated with survival in three out of three samples (47,49,55). Among disease related characteristics, tumor burden and grade were significantly associated with survival in two (54,55) out of three studies and three (48-50) out five studies respectively. Among analytical parameters, low levels of haemoglobin predicted worse survival in five (49-51,54,55) out of seven studies, whereas alkaline phosphatase (49-52,55,56) was found to be an independent and adverse predictor of survival in six out of six studies.

3.4 DISCUSSION

To better understand the relevance of prognostic factors for survival in patients with advanced solid malignancies, we conducted a systematic review of the literature. This approach stands between the qualitative method of the classic overview of the literature and the quantitative evaluation of meta-analysis. The former method is often biased by the authors' subjectivity in selecting, describing and criticising papers and lacks quantitative evaluations. A meta-analysis for prognostic factors was not possible due to the heterogeneous nature of the patient population, assessments, outcomes and analysis.

We identified all the available literature on prognostic factors for survival in advanced cancer patients and we selected those studies where enough information was provided to evaluate the validity of their conclusions (6).

The category of patients with advanced solid malignancies is very broad. Even excluding the terminally ill, cancer patients may live from few months (e.g., pancreatic cancer patients) to several years (e.g., metastatic prostate cancer patients) after they have been diagnosed with an incurable stage. This survival variability is particularly evident even within similar types and stages of tumors (e.g., metastatic breast cancer) as was shown by our data (see below). Part of the variability reported in the reviewed papers is probably related to the absence of inception cohorts: most studies included patients at different times in the course of their advanced diseases. To account for this phenomenon and ascertain if the association between certain prognostic factors and survival could vary according to lengths of median survivals (or follow-ups), a stated median survival was a major inclusion criteria. Most of the studies on prognostic factors for survival in advanced prostate cancer did not report the latter information and were not reported in synoptic tables.

A sample size ≥ 40 was arbitrarily chosen because 30 events are needed to detect a correlation of approximately 0.45 with a power ≥ 80 % and a two-tailed $\alpha \geq 0.05$.

We excluded studies which considered survival rates at individual points, because the latter may not be good estimates of the true underlying survival (57).

Studies that looked mainly at intervention outcomes through multivariate survival analyses, to adjust for pre-treatment variables of prognostic significance, were excluded. Results from these studies may be overly influenced by post-treatment characteristics (e.g., response to treatments) (2), and usually provide scarce methodological details

(e.g., which variables were tested/significant in the bivariate analysis and selected/significant for the multivariate models).

Half of the reviewed studies considered samples which were assembled for randomized controlled trials. It has been shown that less than 10% of the cancer population is actually enrolled in clinical trials and this proportion may not be truly representative of the rest of cancer patients (58). In only one study (33) of the forty reviewed were data prospectively collected. Retrospective studies are easier to conduct and less weighted by selection/observer bias than prospective studies (59) However data from the former are limited to variables recorded for purposes other than the study (e.g., for a clinical trial or a cancer registry) and often do not consider specific prognostic factors (e.g., quality of life issues) or potential confounders of their association with survival (e.g., clinical variables) (60).

The censored fraction information relates to both the percentage of patients still alive at the end of the study period and to the percentage of cases lost to follow-up. Although the classical survival analyses (e.g., Kaplan-Meier or Cox regression) account for the former patients, high censored fractions may indicate that follow-ups were too short for the development of the outcome of interest (e.g., death in survival studies). A high percentage of patients lost to follow-up could invalidate the study results in case of extreme scenarios, where all these patients were dead or all were alive (6). Since most of the studies indicated only the overall censored fraction, we used this information as an indirect parameter for both maturity and completeness of follow-ups among the reviewed studies. The reported censored fractions varied between 5 and 40%, but the majority of the reviewed studies had over 80% of their follow-ups completed.

On the basis of the reviewed papers, a number of clinical and laboratory variables appear to be important prognostic factors for survival in advanced cancer patients. Tumor burden as represented by the number of cancerous lesions appears to be a definite survival predictor in breast and lung cancer, whereas its role in gastrointestinal patients needs further confirmation. The prognostic importance of presence and/or level of liver involvement appears established in breast and gastrointestinal tumors, while for lung cancer patients it is not as clear. Abnormally high levels of serum alkaline phosphatase and lactate dehydrogenase generally reflect the presence of liver disease, but have also been correlated with the tumor bulk (61, 62). The prognostic importance of serum albumin, confirms the negative correlation between poor nutritional status and survival in advanced and end-stage cancer patients (38,63). Performance status appears as the most important survival predictor in the reviewed papers. The clinical significance, however, of this measure remains difficult to interpret for the following reasons: a) use of different scales, such as Karnofsky (64) or Eastern Cooperative Oncology Group (65) performance status scales or different collapsed versions of the same scales in various studies; b) time-dependency in the strength of the association between performance status and survival as demonstrated in breast and gastrointestinal patients. Two major KPS-ECOG scale equivalencies have been proposed previously: one by the American Joint Committee of cancer (AJCC) (66) and the other by Minna and associates in a classic oncology textbook (67). More recently Buccheri and colleagues proposed and prospectively validated in a cohort of lung cancer patients a simpler conversion table (2). In the latter patients with KPS = 100, 90, 80 and ECOG PS = 0, 1 were considered in grade 1: patients are still able to work in spite of various degrees of limitations; some signs and/or symptoms of disease may be present. Patients with KPS

= 70, 60 and ECOG = 2 were considered in grade 2: subjects are totally unable to work, but still able to care for themselves; low to moderate levels of assistance are needed. In grade 3, patients unable to care for themselves and with KPS ≤ 50 and ECOG 3, 4, were finally considered. The same authors also demonstrated the superiority of ECOG PS scoring as compared to KPS in discriminating survivals for lung cancer patients. A time dependency in their association with survival appears as a common characteristic to other important prognostic features such as the presence of liver metastasis for breast patients, and the abnormal values of alkaline-phospatase and bilirubin levels for gastrointestinal patients. Although this observation needs to be confirmed by more numerous and prospective studies, our data show that the predictive power of certain prognostic factors may vary according to the duration of follow-ups (see below). As suggested by other studies (68; 69), clinicians may consider different prognostic factors when looking at different lengths of survival (e.g., six months versus one year survival) in patients affected by same types of malignancies.

The prognostic role of subjective measurements, such as symptoms assessments, appears limited to patients with advanced prostate cancers. In the latter patient group, the onset of symptoms and particularly of pain, was clearly associated with worsening prognosis. Symptom appearance has been proposed as a major criterion to define the onset of terminal phases in patients with advanced cancer of the prostate (70). In the majority of the reviewed studies, the association between symptoms such as anorexia, dysphagia, dyspnea or cognitive failure and survival was not measured. This is probably due to the retrospective nature of the studies and the fact that unfortunately, symptoms are not routinely assessed in advanced cancer patients (71). The absence of evidence for an association between symptom distress and survival, can never be considered as

evidence for an absence of such association. Future studies should address the prognostic role of symptom distress.

With the exception of the studies in breast cancer patients, the prognostic role of prior specific treatments was not particularly investigated in the reviewed studies.

The prognostic importance of the length of disease free interval is strongly suggested by a few studies of advanced breast and gastrointestinal cancers, but further evidence is needed. The same consideration applies to the role of differential blood counts (particularly leukocytes and lymphocytes) in gastrointestinal and lung patients. Race age and gender were commonly studied but only gender appears of definitive prognostic importance in patients with lung cancer. Among common and non significant prognostic factors, presence of lung metastases in breast and gastrointestinal patients and tumor histology subtypes in colo-rectum and lung cancers are worth mentioning.

The prospective collection of data from inception and population-based cohorts is paramount to better understand the association between certain variables and survival in patient with advanced solid malignancies. The recording of recommended measurements for each type of primary and a standardised categorisation of variables will allow a better comparison of future studies. The association with survival of a new prognostic factor should be adjusted for variables that were previously established of definite prognostic importance for certain type of primaries and/or survival terms. All these methodological issues should be addressed in future studies.

3.5 CONCLUSIONS

The recognition of valuable pointers to survival is essential to provide accurate information to patients and families, to plan therapeutic interventions, and for planning of the health care system. A number of clinical and laboratory variables such as performance status, tumor burden, liver metastasis, and serum albumin levels were found as common, important survival predictors for advanced cancer patients. The strength of the association between the majority of these variables and survival was found to vary with length of follow-up. The percent of liver replacement in gastrointestinal cancer patients and the above-mentioned prognostic factors in lung cancer patients were the only variables that did not show clear temporal trends in their association with survival. Other survival predictors in these types of tumors, could not be adequately evaluated for the following main reasons: a) lack of representative inception cohorts; b) use of a wide variety of variables which were categorized in non-standardized ways; c) the inclusion of a mix of variables in the statistical analyses.

Knowledge of these methodological issues will allow a better comparison of future studies, the validation of the results of this literature review and more definite conclusions about prognostic factors in advanced cancer patients.

Table 1-3: Studies On Prognostic Factors For Survival In Patients With Advanced Breast Cancer

Author, year of publication	N	Survival (months)	Censored fraction(%)	Frame	Inception cohort	Non significant	Significant	
						Univariate/multivariate analysis	Univariate analysis	Multivariate analysis
Hortobagyi, 1983 (7)	619	22.7	15	RCT*	No	Age, menopause, liver & soft mets, stage at first dx., prior hormotx. surgtx & chemotx, no. +nodes at dx.	Race, DFI, WL, HGB, prior response to hormotx., WBC, lymphoc., PLT, bilirub., AST, album, CA	PS, lung mets, tum. burden, prior XRT, LDH, alk.phos
Falkson, 1986 (8)	1168	22.7	NR	RCT	Yes	prior surgtx & XRT, skin, breast,bone, lung & brain mts, tx. type	liver mets	age, menopause, DFI prior resp to hormotx., PS, VDMS, tum. burden, node mts
Clark, 1987 (9)	1015	23	40	Registry	Yes	age, tum.burden, menopause, soft mets, prior hormotx.	tum.size, prior chemotx & XRT, tum. burden, breast mets	no.+node at dx. ERlevel, DFI, brain, liver, lung, bone mets
Brada,1990 (10)	85	8.5	NR	Registry	No	age, stage at study entry, DFI, soft. mts		symptoms, bone & visc. mets, CA
Falkson,1990 (11)	378	28	15	RCT	No	tum. burden, prior surg & XRT, skin, bone, lung,brain mts, DFI, institution		PS, VDMS, age, Erlevel, breast, node mts.,prior chemo
Leivonen, 1991 (12)	131	32.4	25	Registry	No	tum. size, tx type, VDMS	stage at dx, mts. sites, DFI	
Falkson, 1991 (13)	501	20.9	15	RCT	No	age, menopause, PS, lung, node,breast mts, DFI, prior hormotx,surgtx & XRT		ERlevel, prior chemotx tum. burden, liver mts
Rabinovich, 1992 (14)	362	21	5	Registry	No	age, menopause, stage at dx, no.+nodes at dx, DFI chemo. dose, HGB, lymphoc., PLT, alk.phos	prior chemotx & XRT, WBC, AST, ALT	PS, VDMS
Vogel,1992 (15)	193	26	20	Registry	Yes	prior chemotx & XRT, stage at dx, race, income	menopause	DFI, ERlevel, VDMS
Dunphy,1994 (16)	80	16.5	15	RCT	No	bone,node, lung mets menopause, ERlevel PRlevel, race	DFI, tum. burden	liver & soft mets, prior chemotx.

* List of abbreviations: RCT= randomized controlled trial, NR: not reported; DFI: disease free interval; WL: weight-loss; HGB: hemoglobin; PS: performance status; WBC: white blood cell; PLT: platelets count; XRT: radiotherapy; LDH: lactate dehydrogenase; AST: aspartate transaminase; VDMS: visceral dominant metastatic site; Erlevel: estrogen receptor level; CA: calcium.

Table 2-3: Prognostic Importance Of The Most Frequently Studied Predictors For Survival In Advanced Breast Cancer Patients.

Variables probably not important *	*Variables possibly important*	*Variables definitively important*
Age	*Response to hormonal tx.*	*Performance status*
Race	*Disease free interval*	*Estrogen receptor status*
*Stage**	*Adjuvant chemotherapy**	*Tumor burden*
*Number of + axillary nodes**	*Soft tissue metastases*	*Liver/visceral metastases*
*Type of surgical treatment**	*Nodal metastases*	*Visceral dominant met. Site (VDMS)*
Lung metastases	*Bone metastases*	
Brain metastases	*Breast metastases*	

* At the time of first diagnosis

Table 3-3: Studies On Prognostic Factors For Survival In Patients With Advanced Gastrointestinal Cancers

Author, year of publication	N	Histology	Survival (MOS)	Censored fraction(%)	Frame	Inception cohort	Non significant Univariate/multivariate analysis	Significant Univariate analysis	Significant Multivariate analysis
Bengtsson, 1981 (17)	155	colo-rectum	4.5	5	registry	no	age	alk.phos, percent of liver replacem.	N/A
Lavin, 1982 (18)	322	stomach	5.3	NR	RCT	no	sex, race, comorb, HGB, dysphagia, protein aversion, node, lung, skin & bone mts.,grade,	tumor size, nausea, vomiting, anorexia, tum. burden, WBC, CEA, alk.phos, liver mts.	treat. type, granuloc., lymphoc., monocyte, bilirubin, protein, PS, AST,WL,visc. mts
Goslin, 1982 (19)	125	colo-rectum	12.5	15	registry	no	age, sex, histol, DFI	PS, WL, grade, tum.burden, hepatomeg., AST, LDH, alk.phos., bilirubin, visc. mts, CEA	N/A
Lahr, 1983 (20)	174	colo-rectum	6.1	5	registry	no	race, γ-GT, histol., CEA, age, contiguous & visc. mts, tum. size, grade, syncron liv. mts	LDH, tum.burden, PT, sex, symptoms,	bilirubin, prior surgery, alk.phos., site of liv. mts, albumin, chemother., no. metast. nodes
Nagasue, 1984 (21)	100	liver	3.5	5	registry	no	sex, tum.type, cirrhos	clinical type, jaundice, stage, clinical stage,ascites	N/A
Chlebowski, 1984 (22)	121	liver	4.5	5	registry	yes	treat.type, PS, sex, race, alk.phos., AFP, HbSAg	age, AST,	bilirubin, lung mts
Fortner, 1984 (23)	109	colo-rectum	11.5	NR	RCT	no	age, sex, PS, CEA, 5NT, LDH, alk.phos, bilirubin, visc. mts, DFI, histol, grade		prior chemoth, percent. of liver replacem., node mts, AST
Kaiser, 1985 (24)	182	pancreas	8.2	20	RCT	no	sex, back pain, histol, age, jaundice, tum.location, grade, cachexia		PS, race, abdom.pain
		pancreas	2.5				race, abdom.pain, back pain, histol, age, jaundice, tum.location, grade, cachexia		PS, sex,
Finan, 1985 (25)	90	colo-rectum	10.3	5	registry	yes	age, sex, presentation mode, sympt.duration, HGB,	anorexia, bilirubin, WBC, prior surg., contiguous mts, tum.burden	WL, hepatomeg., alk.phos, albumin, stage, grade, percent. of liver replacem.,
Ekberg, 1986 (26)	73	colo-rectum	11	5	RCT	no	histol, stage, tum.burden, vascularity, lung mts	stage	percent. of liver replacem., site of liver mts, bilirubin, alk.phos

Table 4-3: Studies On Prognostic Factors For Survival In Patients With Advanced Gastrointestinal Malignancies.

Author, year of publication	N	Histology	Survival (MOS)	Censored fraction(%)	Frame	Inception cohort	Non significant Univariate/multivariate analysis	Significant Univariate analysis	Significant Multivariate analysis
De Brauw, 1987 (27)	83	colo-rectum	8.4	5	registry	Yes	age, comorb, hepatomeg., jaundice, ascites, alk.phos, LDH, γ-GT	fatigue, WL, 5NT	
Chang, 1989 (28)	67	colo-rectum	15.1	25	RCT	No	AST, ALT, obstruction sympt., syncron. mts, prior surg., perforation, albumin, PT, tum.location, age, stage, grade, site of liver mts, bilirubin, mts grade, DFI	LDH, EOD, sex, CEA,	alk.phos., percent. of liver replacem.
Kellokumpu-Lehtinen, 1990 (29)	106	esophagus	8	5	registry	No	age	sex	N/A
Calvet, 1990 (30)	206	liver	3.3	15	registry	Yes	sex, ETOH, HbSAg, liver disease,GI bleeding, CNS disease, hepatomeg, glicemia, AST, ALT, cholest, tryglic, γ-globulin, grade, cirrhos, treat. type	jaundice, alk.phos., AFP, PT, creat., hematocr, HGB, PLT, albumin	stage, ascites, cachexia, NA, bilirubin, tum. size, BUN, γ-GT, age
Graf et al., 1991 (31)	340	colo-rectum	18*	6	RCT	No	sex, GI bleeding, contiguous, lung & node mts, age	histol, pain, fatigue, nausea, liv. mts, visc. mts, tum.burden	prior surgery, DFI, PS, symptom no., HGB, treat. type
Graf et al. 1994 (32)	198	colo-rectum	16*	10	RCT	No	sex, histol, prior surgery, tum.burden, chemoth., creat	no. of symptoms, PLT, bilirubin, alk.phos, ALT	age, PS, DFI, HGB, WBC, AST
Stangl et al., 1994 (33)	484	colo-rectum	7.5	5	registry	Yes	year of diagnosis, sex, age, histol, syncron mts.	PS, surgery, pos. margin of resect., hepatomegal, site of liver mts, tum. burden, alk.phos, bilirubin, LDH, CEA, WBC	node mts, grade, perc. of liver involvm., extrahepatic mts.
Farley et al. 1995 (34)	103	cholangioca.	12	5	registry	Yes	PS, symptoms duration, Rh factor, grade, tum.location, jaundice, histol, contigous & node mts	age, blood group, sex,	palliative therapy, treat. type,
Ishii et al., 1996 (35)	65	pancreas	3.9	5	RCT	No	age, sex, year of treat., smoking, pain, bilirubin, HGB, cholest., tum. location	albumin, CA19-9	PS, CEA, stage

List of abbreviations for Tables 3-3 and 4-3

* Median follow-ups; N/A: not applicable; NR: not reported. Comorb: comorbidity level; HGB: hemoglobin; WL: weight loss; WBC: white blood cell count; CEA: carcino embriogenic antigen; LDH: Lactate dehydrogenase; DFI: disease free interval; γ-GT: gamma glutamil transaminase; AST: aspartate transaminase; Alk.phos: alkaline phosphatase; 5NT: 5'nucleotidase; ALT: alanine transaminase; EOD: extent of disease; HbSAg: antibody for surface antigen of hepatitis B; PS: performance status; BUN: azotemia; ETOH: positive history of alcohol abuse; PT: prothrombin time.

Table 5-3: Prognostic Importance Of The Most Frequently Studied Predictors For Survival In Patients With Advanced Gastrointestinal Cancer.

Variables probably not important	***Variables possibly important***	***Variables definitively important***
Age	*Weight-loss*	*Performance status*
Gender	*Disease free interval*	*Percent of liver replacement*
Race	*Hepatomegaly*	*Bilirubin*
Jaundice	*Stage*	*Alkaline phosphatase*
Grade	*Node metastases*	*Albumin*
Histology	*Location of liver metastases*	
Lung metastases	*Hemoglobin*	
Tumor location	*Carcino embriogenic antigen*	
Alanine amino transferase	*Lactate dehydrogenase*	
Gamma-glutammil-transferase	*Leucocyte counts*	
	Tumor burden	
	Aspartate amino transferase	

Table 6-3: Studies On Prognostic Factors For Survival In Patients With Advanced Lung Cancers.

Author, year of publication	N	Histology	Survival (months)	Censored fraction(%)	Frame	Inception cohort	Non significant Univariate/multivariate analysis	Significant Univariate analysis	Significant Multivariate analysis
O'Connell,1986 (36)	378	NSCLC	8	30	RCT	No	liver & brain mts,histol, prior XRT & surg., WL	stage	PS, sex,tum.burden,LDH, bone mts,
Sorensen, 1989 (37)	259	NSCLC	7.2	5	RCT	No	histol, grade, age,sex, tum.size, complicat., EOD, PLT,alk.phos.,pulm. symptoms,node & BM mts.	WL,brain & bone mts, WBC, HGB,PT,symptoms pres., tum.burden	PS, prior surg.,liver mts, stage,AST,LDH
Fatzinger,1984 (38)	59	NSCLC	5.8	NR	registry	No	stage	albumin	N/A
Kaasa, 1989 (39)	102	NSCLC	10	10	RCT	No	treat. type, activity	WL	PS,stage,sympt.score, wellbeing,functioning
Albain, 1991 (40)	2531	NSCLC	5.1	NR	RCT	No	race,smoking,CA	treat. year, WL, tum.burden,HGB,LDH,alk .phos	sex, PS, age, treat. type
Shinkai, 1992 (41)	192	NSCLC	10	10	RCT	No	age,histol,lymphoc., cholest. CEA, treat. type	WL,stage,EOD, brain, liver & bone mts, HGB, alk.phos.	sex,PS,tum.burden, albumin, LDH
Paesmans, 1995 (42)	1052	NSCLC	7.2	10	RCT	No	histol,prior treat, tum.size, alk.phos,bilirub,creat, lung mts	WL, WBC,PLT,HGB,LDH, liver, bone, adrenal & brain mts	sex, age, PS, EOD, neutroph.,CA, skin mts
Espinosa, 1995 (43)	292	NSCLC	7	10	RCT	No	age,sex,stage,histol, treat. type	WL, lymphoc, bone mts	PS, ESR,LDH, albumin,tum.burden
Hespanhol, 1995 (44)	411	NSCLC	4.3	5	registry	No	hemoptysis, SVCO, COPD, histol, trach.obstr, age	symptoms pres.,HGB,WBC, neutrophyl, alk.phos, protein	PS,sex, hoarseness, stage,WL, lymphoc,LDH,albumin
Takigawa, 1996 (45)	185	NSCLC	10.6	15	registry	No	sex, age, histol, brain & lung mets, BUN, creat, cholest, CEA, treat.type	WL,bone & liver mts, WBC, alk.phos, albumin, cholinest., LDH	PS,stage,HGB,CA
Muers, 1996 (46)	207	NSCLC	4.8	10	registry	No	age, anorexia	NA, alk.phos.	sex, stage, PS, hoarseness, malaise, CES, lymphoc, albumin

List of abbreviations: XRT: radiotherapy; PS: performance status; LDH: lactate dehydrogenase; PLT: platelets count; WBC: white blood cell count; PT: prothrombin time; EOD: extent of disease; BM: bone marrow metastases; CA: calcium; HGB: hemoglobin; alk.phos: alkaline phosphatase; CES: clinical estimation of survival; ESR: erithro-sedimentation rate.

Table 7-3: Prognostic Importance Of The Most Frequntly Studied Predictors For Survival In Advanced Lung Cancer Patients.

*Variables probably not important **	*Variables possibly important*	*Variables definitively important*
Histology	*Age*	*Gender*
Treatment type	*Weight-loss*	*Performance status*
	Alkaline phosphatase	*Tumor burden*
	Hemoglobin	*Lactate dehydrogenase*
	Leukocyte	*Albumin*
	Lymphocyte	
	Stage	
	Extent of disease	
	Brain metastases	
	Liver metastases	
	Bone metastases	

Table 8-3: Temporal Trends In The Association Between Survival And Main Prognostic Factors

	3-6 month survival			6-12 months survival			13-21 months survival			≥ 22 months survival		
Tumor Groups	N*	Significant		N	Significant		N	Significant		N	Significant	
Variables		Bivariate analysis	Multivariate analysis		Bivariate analysis	Multivariate analysis		Bivariate analysis	Multivariate analysis		Bivariate analysis	Multivariate analysis
Breast	0			1			3			6		
Performance status								1 / 2	1 / 2		2 / 2	3 / 3
Estrogen receptor status								0 / 2	1 / 2		2 / 2	3 / 3
Tumor burden								1 / 2	1 / 2		3 / 4	2 / 3
Liver/visceral metastases					1 / 1	1 / 1		2 / 2	2 / 2		2 / 4	2 / 5
Visceral Dominant Metastatic Site (VDMS)								1 / 1	1 / 1		1 / 3	3 / 3
Gastrointestinal	6			10			3					
Performance status		2 / 3	3 / 4		2 / 3	1 / 4		1 / 2	2 / 2			
Percent of liver replacement		1 / 1	-		3 / 3	4 / 4		1 / 1	1 / 1			
Bilirubin		3 / 4	3 / 4		4 / 4	2 / 5		1 / 2	0 / 2			
Alkaline-phosphatase		3 / 4	1 / 4		4 / 4	3 / 5		2 / 2	1 / 2			
Albumin		2 / 2	0 / 2		2 / 2	2 / 2		0 / 1	0 / 1			
Lung	4			7								
Performance status		3 / 3	3 / 3		6 / 7	7 / 7						
Tumor burden		1 / 1	0 / 1		4 / 4	3 / 4						
Albumin		3 / 3	2 / 2		3 / 3	2 / 3						
Lactate dehydrogenase		2 / 2	1 / 2		5 / 6	4 / 6						

* Number of studies

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CHAPTER 4

THE TERMINAL CANCER SYNDROME: MYTH OR REALITY

4.1 INTRODUCTION

In spite of the number of publications concerned with factors related to survival in advanced or terminal cancer patients, there has been little discussion as to what clinically constitutes terminal illness (1). It has been suggested that patients with different types of end-stage malignancies go through a common clinical pathway that has been defined as "terminal cancer syndrome" (2). This syndrome is characterized by decreased performance status with signs and symptoms of malnutrition and is uniformly associated with shorter survival (3). Clinical recognition of this syndrome could assist physicians in the decision-making processes for patient management. To date, this theory has not been confirmed by prospective studies considering well-defined inception cohorts of terminally ill cancer patients. Terminal cancer patients cannot be staged using criteria normally used for oncological patients (4), and the literature indicates conceptual rather than practical rules to define the onset of the terminal phase in cancer (Chapter 2). Finally, both cross-sectional and longitudinal studies have considered mainly patients recruited in hospices or palliative care programs.

The objective of our study was to assess clinical differences and/or similarities in a population-based cohort of patients entering the terminal phase of their disease, according to specific criteria and grouped according to their primary tumor.

4.2 PATIENTS AND METHODS

Patient accrual to this study took place between July 3, 1996 and April 31, 1997 at the Cross Cancer Institute (CCI), Edmonton, Alberta. The Institute is the only referral

centre for oncological treatment in northern Alberta and has a catchment population of approximately 1.5 million people. During the accrual period, 270 patients who were seen in the outpatient department or admitted as inpatients were potentially eligible for the study. Patient accrual was consecutive within each tumor group. Patients were eligible if older than 18 years and with terminal cancer of the lung, breast, gastrointestinal system, or prostate. These tumors were chosen because they rank in the first four places for both incidence and death rates in developed countries (1). A disease was defined as terminal at the time when further attempts to arrest or control its progression were deemed unavailable (5). We developed specific criteria derived from the Physician Data Query statements for health professionals (6) and reached by consensus by oncologists at the Cross Cancer Institute. Patients with solid malignancies entered a terminal phase if presented with certain histologies and stages and had received/failed the treatments reported in Table 1-4.

Patients with breast cancer were considered as terminal if their disease was progressive after the failure of second-line chemotherapy and/or hormonotherapy given for metastatic disease. These patients could be accrued also if they were recently diagnosed with brain metastases. Patients with gastrointestinal cancers were eligible for the study if they presented with inoperable primaries and/or unresectable metastatic lesions. Because of the small, but significant, survival advantage demonstrated for chemotherapy, patients with unresectable gastric malignancies (6) and stage 3 or 4 non-small cell lung cancer who were to receive chemotherapy could be accrued at the end of this treatment. Otherwise, patients with inoperable non-small cell lung cancer and recurrent small cell lung cancer could be accrued in the study in spite of any oncological treatment. Patients with prostate tumors were considered as

terminal if they had progressive disease after optimal androgen blockade (as shown by very low or absent serum testosterone levels), with rising levels of prostatic specific antigen, worsening bone scan and presence of symptoms (e.g., pain, weakness, decreasing performance status etc.). These criteria could be overridden if, according to the clinical judgment of the treating oncologists: a) patients had particularly aggressive disease; b) patients were considered unsuitable for any specific treatment when first diagnosed with cancer; c) there were coexisting medical conditions which precluded any therapeutic attempts to prolong life. Patients were considered eligible for the study if they entered the terminal phase within 30 days of their possible enrolment in the study. Eligible patients were identified and screened by the principle investigator, through a daily review of medical records of patients who were scheduled for certain outpatients clinics, or were admitted at the CCI.

Of the 270 patients who met the inclusion criteria, 248 (92%) agreed to participate in the study. After the study began, It appeared to us that the treatment of prostate cancer was not centralized exclusively at the CCI, as was the case for patients with the other three primaries. The accrual of patients with prostate cancer was stopped towards the end of 1996 since the population seen at the CCI could not be assured to be representative of patients with terminal prostate cancer in the community.

Patients were given an initial assessment followed by monthly telephone interviews throughout the course of their disease until death occurrence or end of study.

The following data were recorded at baseline:

1. Demographic and socio-economic data, including age, sex, race, approximate levels of individual and family income, level of education, presence and level of social support as measured by the Older Americans' Resources and Services

Multidimensional Functional Assessment Questionnaire (7,8). The section of this questionnaire which explores the individual's functioning in the social dimension looks at three components: extent of contact with others, family satisfaction with contact, and availability of help (Appendix 2).

2. Primary and secondary tumor sites.
3. Last and concurrent treatments (surgery, chemotherapy, radiotherapy, hormonotherapy, or no treatment).
4. Tumor burden expressed as the total number of cancerous lesions (9) for all primary tumor types except prostate.
5. Performance status according to Karnofsky (KPS) (10), Eastern Co-operative Oncology Group (ECOG) (11), and Edmonton Functional Assessment Tool (EFAT) (12). The EFAT assesses the status of ten functions, namely: communication, pain, mental status, dyspnea, sitting or standing balance, mobility, walk or wheelchair locomotion, activities of daily living, fatigue, motivation. In addition, an eleventh item asks for an overall judgement of functional performance. Each item in the EFAT is evaluated by four-point rating scale from 0-3 (0=functional independent performance; 3=total loss of functional performance. A total possible score on the EFAT is 30 plus 3 for global performance status rating.
6. Physical indicator of nutritional status (weight loss in the previous 6 months, triceps skinfold thickness as measured by the Baseline Skinfold Caliper, Fabrication Enterprise Incorporated, New York 10533, USA).
7. Type and intensity of symptoms experienced at the time of patient enrolment and in the previous seven days, as recorded through the Edmonton Symptom

Assessment Scale (ESAS) (13) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Quality of Life Core Questionnaire (14), respectively. The ESAS tool consists of nine visual analogue scales (VAS) which include pain, shortness of breath, nausea, depression, activity, anxiety, well being, drowsiness and appetite. The patient draws a mark along the 10 cm line of the VAS, the left side indicating the least degree of symptoms (e.g., 'no pain') and the right side indicating the worst degree of symptoms (e.g., 'worst possible pain'). For each patient, the overall mean intensity of all the symptoms recorded through the ESAS was calculated to determine a "distress score." The EORTC QLQ-C30 questionnaire includes five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life (QoL) scale, and six single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties). All of the scales and single-item measures range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item, represents increased symptoms. As for the ESAS, one overall average score for symptoms scales/items and one overall mean score for functional scales were calculated for each patient.

8. Concurrent diseases as recorded using the Charlson comorbidity score (15). This score ranges from 0 to a theoretical maximum of 33 and is based on the presence of certain diseases with assigned values or weights. We developed an

adjusted Charlson score, which excluded the diagnosis of cancer, since our intention was to measure conditions other than the patient's principal diagnosis.

9. Cognitive status as measured by Folstein's Mini Mental State Examination (16). It measures orientation in time and space, immediate recall, short-term memory, calculation, language and construct ability. The maximum score is 30, with a score of 23 or less generally accepted as indicating the presence of cognitive impairment.
10. Serum and hematological parameters, including levels of albumin, sodium, calcium, alkaline phosphatase, lactic dehydrogenase, hemoglobin, cell blood counts and differentials. These were only measured in 165 patients because of ethical concerns for the remaining patients.

These variables were selected because they have previously been shown to be of prognostic significance in terminal cancer patients and they are simple and reproducible at the bedside and outpatient settings.

4.2.1 Statistical analysis

One-way analysis of variance (ANOVA) was done to test differences among mean values of continuous variables among the 248 patients grouped according to their type of primary tumor. The Bonferroni test was applied for multiple comparison procedures. A chi-square test was used to assess differences among categorical data. The Kruskal-Wallis rank test was used when the assumptions regarding the equality of variances (homoscedasticity) were not met (17). The survival curve for the overall sample was estimated through the Kaplan-Meier method. Statistical significance was set at $p \leq 0.05$.

4.3 RESULTS

At the time of analysis (December 1997), 218 patients (87.9%) had died. No patient was lost to follow-up. The estimated medial survival time of the group was 15 weeks, with a 95% confidence interval of 12-16 weeks. The 2-month, 4-month and 6-month survival rates as calculated through the Kaplan-Meier method were 67.7%, 47.6% and 33.5%, respectively (Figure 1-4).

Patient characteristics are shown in Table 2-4. The mean age of the patients was 62 years, with breast cancer patients being significantly younger and prostate cancer patients significantly older than the rest. The majority of patients were married and Caucasian; no differences were observed among tumor types. Less than a quarter of the patients reported problems in their social support; no tumor-specific differences were found in this regard. One-third of the patients had some form of post-secondary education, with breast cancer patients having a higher education level than lung and prostate cancer patients. Although there were some differences among the four primaries in terms of individual income, family incomes appeared to be similar. Residence in rural areas and in major cities was similar across groups.

Disease-related characteristics are shown in Table 3-4. Statistically significant differences were observed across the primary sites. Less than one-third of the patients had moderate to severe comorbidity (adjusted Charlson index ≥ 3); patients with lung or prostate cancer more often had moderate or severe comorbidity. The tumor burden as measured by the number of cancerous lesions was significantly higher in breast cancer patients, with increased lung and bone metastatic lesions.

Patients with lung or gastrointestinal cancer were significantly more affected by brain and liver metastases, respectively. In significantly higher percentages, gastrointestinal patients could not receive any tumor-directed treatment at the time of first diagnosis, or these treatments were discontinued after the onset of the terminal phase. Most patients had specific therapies initiated or continued in the terminal phase, with breast and lung cancer patients receiving more chemotherapy and radiotherapy, respectively.

Clinical and laboratory parameters according to the primary site are shown in Table 4-4. Most patients had adequate cognitive status. A lower cognitive status was observed in prostate and lung cancer patients. Performance status differed across groups, for both the Karnofsky and the EFAT, but not for the Eastern Cooperative Oncology Group performance assessment. Most patients, at the onset of the terminal phase, were capable of self-care and bed-ridden for $\leq$ 50% of their daily time.

Almost 70% of the patients had a triceps skinfold measurement below the 50th percentile for North American normal standards (adjusted for gender and age distribution) (18). The average weight-loss in the previous 6 months was close to 19 pounds. Some laboratory parameters differed according to tumor. Lung and prostate cancer patients had higher percentages of hyponatriemia. Half of the patients had hypoalbuminemia and over 40% had higher levels of lactate dehydrogenase. Abnormal leukocyte and granulocyte counts were relatively uncommon and were similar across the four primaries. Half of the patients presented low lymphocyte counts; the proportion of gastrointestinal patients with this characteristic was significantly lower. Some laboratory measurements were not reported because they

had either >15% of missing data (e.g., alkaline phosphatase), or <15 cases with abnormal values (e.g., serum calcium).

A comparison of subjective evaluations of symptoms and quality of life measures at the time of the onset of the terminal phase is presented in Tables 5-4 and 6-4. Patients reported an overall mild to moderate intensity for most of the symptoms recorded through the Edmonton Symptom Assessment System (ESAS). Fatigue, anorexia, and poor well-being showed the worst scores (approximately 4 on a VAS 0-10). Pain and poor well-being were statistically different across the four groups, but the magnitude of the differences was small. Patients experienced an average of six symptoms at the time of their assessment. When interviewed through the EORTC-C30 questionnaire, which examines symptoms experienced over the week prior to the interview, patients reported slightly higher intensities than the ones recorded through the ESAS. Fatigue, anorexia, pain and insomnia represented the highest scored symptoms (Table 6-4). Most statistically significant differences in symptom intensities still appeared of little clinical value. Patients with gastrointestinal tumors consistently had lower symptom intensity and better functioning according to most scales.

4.4 DISCUSSION

Most longitudinal studies on terminally ill cancer patients are limited by a focus on patients from hospice or palliative care programs and their sampling methods. Generally, these studies include prevalent ("convenience") cohorts, as opposed to well-defined inception cohorts. Our study describes the characteristics of patients

with terminal breast, gastrointestinal, lung, or prostate malignancies who were seen in a provincial cancer referral centre. Patient accrual took place at the onset of their terminal phase, defined according to tumor type and stage and previous treatments received. Because of the referral patterns from the community to this institution, the study can be considered as population-based.

To our knowledge this represents the first attempt to establish inception criteria in terminally ill cancer patients. We acknowledge several limitations in these criteria. Our classification may require revisions according to the progress of scientific knowledge and/or according to different therapeutic schemes (e.g., treatment of advanced breast cancer may not contemplate chemotherapy sequential trials). Furthermore, it does not clearly differentiate between patients whose disease is considered to be "terminal" when initially diagnosed, from patients whose cancer becomes uncontrollable after the failure of certain tumor-directed treatments. Finally, our criteria rely on the time of consultation to a treating physician: a disease recurrence which was discovered in a six-month follow-up and labelled a patient as terminal could have been found earlier (e.g., with a three-month follow-up).

Our criteria nevertheless provide common "landmarks" for the classification of patients with advanced solid malignancies by defining the onset of their terminal phase. Other researchers have proposed a classification of terminally ill case mix based on quality of life parameters (4). Both researchers and clinicians may find our criteria easier to use in general practice and probably more specific to identify a precise inception point for longitudinal studies in this group of patients.

As expected, the four groups of patients differed in terms of age, gender and level of education, with lung and prostate cancer patients being older and less educated as

compared to breast and gastrointestinal cancer patients. Data on personal and family income were similar to the figures reported for the general population in Alberta (19).

The higher comorbidity levels recorded for lung and prostate cancer patients could be related to their more advanced age. Tumor and treatment related characteristics were quite different in the four primaries groups. The availability of a greater number of treatments which were considered able to arrest or control breast cancer (6) may explain why these patients had more extensive involvement. Characteristic metastatic patterns were confirmed for lung and gastrointestinal tumors, which presented higher prevalence of brain and liver metastases, respectively. The source of referrals also varied, with patients with breast and gastrointestinal cancer mostly seen within medical oncology services, and lung and prostate patients being referred mainly from radiotherapy services.

Tumor-directed treatments were continued in two-thirds of the patients, and almost half of these received radiotherapy treatments despite patients being considered to be in their terminal phase. The terminal cancer phase begins when patients are still being seen in cancer center, particularly radiotherapy departments: in these environments issues such as patient's declining health, symptom management and possibly approaching death need to be considered by both patients and oncologists.

Only 17 (7.6%) out of 248 patients presented cognitive failure as demonstrated by a <23 score on Folstein's Mini Mental State Questionnaire. More than half of these cases were represented by lung patients, who also had higher percentages of brain metastases and hyponatriemia. The most common cause of cognitive failure in cancer patients remains delirium, which is often determined by the presence of brain

metastases and electrolytes imbalances (20). Although cognitive impairment is not frequent at the onset of the terminal phase, its frequency increases as death approaches (21). Our data show that the onset of the terminal phase is characterized by multiple, but not devastating, symptoms with a low prevalence of cognitive failure. Health care providers, patients and families in this phase could gain experience in the early detection of changes in cognition and other symptoms to prevent further distressing consequences from mishandling a likely worsening situation. Levels of performance status did not differ in clinical meaningful ways across the four primaries, but the overall findings are suggestive of a quite physically impaired population. Almost two-thirds of our patients were only capable of self-care and had to spend a good portion of their day in bed. Two thirds of patients showed also signs of malnutrition, as demonstrated by low triceps skinfold measurements. The average weight loss was 18.6 pounds and almost 50% of the patients presented serum albumin levels of <35g/L. Declining performance and nutritional status have been commonly described in terminal cancer patients (22). Our data confirm that advanced tumors with different primaries and metastatic burdens, determine syndromes characterized by similar levels of functional impairment and malnutrition. Both leucocytosis (23) and high levels of lactate dehydrogenase have been associated with the presence of metastases (24,25).

Most studies have reported symptom prevalences rather than symptom intensity in terminal cancer patients (2,3,22). Since few patients in our sample have reported zero values in the different symptom scales, it was difficult to compare tumor groups on the base of symptoms prevalence, and we therefore examined intensity levels as well. When patients were asked to report on their symptoms at the time of

assessment, anorexia, fatigue, and poor well-being were the highest scored symptoms, but the mean scores remained clinically moderate (4-5 on a 0-10 VAS) and did not significantly differ in four tumor groups. Fatigue, anorexia, pain and insomnia were also reported as the main symptoms experienced in the week prior to the interview. The scoring of these symptoms fell into the moderate range, although mean fatigue in lung cancer patients was more severe (66 on a 0-100 VAS). Anorexia, asthenia and weight loss are the hallmarks of the cachexia syndrome (26). Our data and the review of the literature confirm that this syndrome is very common in advanced cancer patients and represents an important survival indicator in this population (Chapter 2).

Patients with gastrointestinal tumors presented a slightly better clinical picture as shown by symptom and functional scales. This phenomenon may be explained by the fact that lower percentage of these patients received tumor-directed treatments. Cancer patients at the onset of their terminal phase present a variety of problems, as shown by the high number of symptoms reported and by the multiple aspects of the quality of life impaired in our sample. Multiple problems require multiple assessments of symptom and functional stata. Visual analogue scales (VAS), numerical scales, verbal descriptors appear to be highly effective assessment systems in this population (13) and correlate well with each other, as demonstrated in the present study.

4.5 CONCLUSIONS

Our study demonstrates that loss of function, malnutrition and a variety of symptoms characterize the last part of disease trajectories in cancer patients. The similarity of this syndrome across different primaries at the onset of the terminal phase, supports the terminal cancer syndrome theory.

Standardized criteria to identify the onset of this phase in each tumor type, should allow patients, families and heath-care providers to deal proactively with quality of life issues such as symptoms palliation and end-of-life decisions.

The above-mentioned criteria should also be used to accrue similar inception cohorts, to validate our observations both in cross-sectional and longitudinal (e.g., survival) studies.

Table 1-4: Criteria To Define As Terminal Patients With Common Solid Malignancies.

HISTOLOGY	STAGE (T.N.M.)	TREATMENTS TO BE FAILED OR COMPLETED
BREAST		
All	Recurrent/metastatic	II line hormonotx and/or II line chemotx
LUNG		
Mesothelioma	All except solitary/resectable	Surgery for solitary
Small-cell (SCLC)	Recurrent	N/A*
Non small-cell (NSCLC)	Stage IIIA	Chemotherapy
	Stage IIIB	Chemotherapy
	Stage IV	Chemotherapy
	Recurrent	N/A
GASTRO-INTESTINAL		
Esophagus	All except I and II	N/A
	Recurrent	N/A
Stomach	Stage IV	Chemotherapy
	Recurrent	N/A
Liver	Non resectable	N/A
	Recurrent	N/A
Gallbladder	Non resectable	N/A
	Recurrent	N/A
Extra-hepatic bile ducts	Non resectable	N/A
	Recurrent	N/A
Exocrine pancreas	Non resectable	N/A
	Recurrent	N/A
Small intestine	Non resectable	N/A
	Recurrent	N/A
Colon	Stage IV with non resect. mets.	N/A
	Recurrent & non resect.	N/A
Anus-rectum	Stage IV with non resect. mets.	N/A
	Recurrent & non resect.	N/A
PROSTATE		
All	Metastatic/progressive with rising levels of P.S.A., worsening bone scan & presence of symptoms.	Orchiectomy or complete androgen blockade**

*N/A: For this particular type and stage of tumor there are not treatment that are considered life-prolonging.
** As demonstrated by absent levels of circulating serum testosterone.

Table 2-4: Demographic Characteristics Of Patients According To Primary Tumor.

Tumor Group	*Breast*	Gastrointestinal	*Lung*	*Prostate*	*P value*	*Total*
	N = 70	*N = 80*	*N = 77*	*N = 21*		
Variables						
Age (mean±SD)	*55.9±13.4*	*62±12.9*	*63±9.8*	*73±7.4*	*<.0001*	*61.8±12.6*
Female n(%)	*70 (100)*	*33 (41.3)*	*42 (54.5)*	*0 (0)*	*<.0001*	*145 (58.5)*
Married n(%)	*51 (72.9)*	*52 (65.0)*	*56 (72.7)*	*19 (90.5)*	*.14*	*178 (71.8)*
Non white n(%)	*9 (12.9)*	*6 (7.5)*	*4 (5.2)*	*0 (0)*	*.16*	*19 (7.7)*
Impaired social support	*15 (21.4)*	*15 (18.8)*	*17 (22.1)*	*3 (14.3)*	*NS*	*50 (20.2)*
School > 12 years n (%)	*31 (44.3)*	*25 (31.3)*	*16 (20.8)*	*5 (23.8)*	*.02*	*77 (31.0)*
Individual yearly income*	*19.2±18.0*	*28.2±19.7*	*18.0±19.3*	*27.5±24.4*	*.01*	*22.5±20.0*
Family yearly income **	*48.2±26.8*	*43.3±22.6*	*35.4±23.3*	*42.0±28.8*	*.12*	*42.2±24.9*
Rural residence n(%)	*32 (45.7)*	*34 (42.5)*	*45 (58.4)*	*12 (57.1)*	*.18*	*123 (49.6)*

* *Mean±SDx1000; 46 cases missing*
** *Mean±SDx1000; 109 cases missing*

Table 3-4: Comparison Of The Four Groups Of Patients With Breast, Gastrointestinal, Lung And Prostate Cancers On Disease-Related Characteristics.

Tumor Group	*Breast*	*Gastrointestinal*	*Lung*	*Prostate*	*P value*	*Total*
	N = 70	*N = 80*	*N = 77*	*N = 21*		*N = 248*
	n (%)	*n (%)*	*n (%)*	*n (%)*		*n (%)*
Variables:						
Comorbidity (≥3 Charlson Index)	*15 (21.4)*	*15 (18.8)*	*33 (42.9)*	*7 (33.3)*	*.004*	*70 (28.2)*
Tumor burden (> 5 lesions)	*62 (88.6)*	*50 (62.5)*	*40 (51.9)*	*N/A*	*<.0001*	*152 (67.0)*
Brain metast.*	*23 (32.9)*	*0 (0)*	*34 (44.2)*	*N/A*	*<.0001*	*57 (25.1)*
Lung metast.*	*36 (51.4)*	*16 (20.0)*	*32 (41.6)*	*N/A*	*<.0001*	*84 (37.0)*
Liver metast.*	*25 (35.7)*	*38 (47.5)*	*11 (14.3)*	*N/A*	*<.0001*	*74 (32.6)*
Bone metast.*	*47 (67.1)*	*3 (3.8)*	*26 (33.8)*	*21 (100)*	*<.0001*	*97 (39.1)*
Type of treatment received in the terminal phase:						
No treatment	*16 (27.1)*	*47 (58.8)*	*18 (23.4)*	*N/A*	*<.0001*	*81 (37.5)*
Chemotherapy	*21 (35.6)*	*10 (12.5)*	*3 (3.9)*	*N/A*		*34 (15.7)*
Radiotherapy	*22 (37.3)*	*23 (28.8)*	*56 (72.7)*	*N/A*		*101 (46.8)*
Treatment choice in the terminal phase:						
No treatment	*0 (0)*	*14 (17.5)*	*6 (7.8)*	*0 (0)*	*<.0001*	*20 (8.1)*
Treat. stopped	*16 (22.9)*	*33 (41.3)*	*12 (15.6)*	*3 (14.3)*		*64 (25.8)*
Tx start/contin.	*54 (77.1)*	*33 (41.3)*	*59 (76.6)*	*18 (85.7)*		*164 (66.1)*
Referral **	*54 (77.1)*	*50 (62.5)*	*20 (26.0)*	*5 (23.8)*	*<.0001*	*129 (52.0)*

** Presence of metastatic lesions in the indicated sites*

*** Medical oncology (vs. radiotherapy oncology)*

Table 4-4: Clinical And Laboratory Parameters According To Primary Tumor.

Tumor Group	*Breast*	*Gastrointestinal*	*Lung*	*Prostate*	*P value*	*Total*
	N = 70	*N = 80*	*N = 77*	*N = 21*		
	n(%) or mean±SD	*n(%) or mean±SD*	*n(%) or mean±SD*	*n(%) or mean±SD*		*n(%) or mean±SD*
Variables:						
Cognitive failure^	*2 (3.2)*	*3 (4.0)*	*9 (13.2)*	*3 (15.8)*	*.05*	*17 (7.6)*
MMSE score	*123.1*	*122.2*	*96.5*	*97.0*	*.006*	
ECOG^^ PS 0-1	*22 (31.4)*	*40 (50.0)*	*28 (36.4)*	*8 (38.1)*	*.15*	*98 (39.5)*
2	*25 (35.7)*	*25 (31.3)*	*21 (23.6)*	*5 (23.8)*		*76 (30.6)*
3-4	*23 (32.9)*	*15 (18.8)*	*28 (36.4)*	*8 (38.1)*		*74 (29.8)*
KPS^^^	*62.4±14.2*	*71.0±17.0*	*62±18.1*	*60±20.0*	*.001*	*64.8±17.3*
EFAT* scale	*7.5±4.70*	*4.7±4.0*	*8.0±5.6*	*9.1±6.5*	*<.0001*	*6.9±5.2*
Weight-loss (lbs.)	*18.4±13.8*	*19.8±16.4*	*17.0±15.4*	*21.5±13.5*	*NS*	*18.6±15.2*
Triceps skinfold **	*47 (71)*	*49 (63.6)*	*56 (74.7)*	*7 (36.8)*	*.01*	*159 (67.1)*
Na (<135 mmol/L)	*10 (18.7)*	*8 (13.8)*	*24 (33.8)*	*6 (31.6)*	*.04*	*48 (23.9)*
Albumin (<35g/L)	*28 (42.4)*	*30 (46.2)*	*40 (57.1)*	*11 (55.0)*	*NS*	*109 (49.3)*
LDH (>618 U/L)	*34 (53.1)*	*27 (42.2)*	*24 (35.3)*	*8 (40.0)*	*NS*	*93 (43.1)*
Hgb (<113g/L)	*16 (23.9)*	*25 (34.2)*	*15 (20.5)*	*7 (36.8)*	*.19*	*63 (27.2)*
Leucocyte ($>11x10^9$/L)	*10 (14.7)*	*15 (20.5)*	*23 (31.5)*	*3 (15.8)*	*.09*	*51 (21.9)*
Granulocyte ($.>7.5x10^9$/L)	*13 (19.4)*	*15 922.4)*	*30 (43.5)*	*4 (25)*	*.008*	*62 (28.3)*
Lymphocyte ($<1x10^9$/L)	*41 (61.2)*	*24 (35.3)*	*39 (58.2)*	*11 (64.7)*	*.007*	*115 (52.5)*

*^ according to Folstein's Mini Mental State Examination (MMSE); ^^ Zubrod scale; ^^^ Karnofsky Performance Status; * Edmonton Functional Assessment Tool; ** < 50^{th} normal percentile.*

Table 5-4: Comparison Of The Four Groups Of Patients With Breast, Gastrointestinal, Lung And Prostate Cancers On Subjective Symptoms As Recorded Through The Edmonton Symptom Assessment System*.

Tumor Group	*Breast*	*Gastrointestinal*	*Lung*	*Prostate*	*P value*	*Total*
	N = 70	*N = 80*	*N = 77*	*N = 21*		
	mean±SD	*mean±SD*	*mean±SD*	*mean±SD*		*mean±SD*
VAS scale for:						
Pain	*3.1±2.7*	*2.4±2.4*	*2.4±2.6*	*4.5±3.0*	*.004*	*2.8±2.6*
Fatigue	*4.5±2.7*	*3.6±2.8*	*4.4±3.1*	*4.0±2.2*	*.16*	*4.1±2.8*
Nausea	*2.0±3.1*	*1.4±2.6*	*1.0±2.0*	*1.2±1.6*	*.10*	*1.4±2.6*
Depression	*1.8±2.6*	*1.9±2.5*	*1.4±2.3*	*1.5±2.1*	*NS*	*1.7±2.4*
Anxiety	*2.7±2.8*	*2.1±2.5*	*2.3±2.7*	*1.5±2.3*	*NS*	*2.3±2.7*
Anorexia	*4.2±3.2*	*4.1±3.3*	*4.7±3.7*	*3.8±3.0*	*NS*	*4.3±3.4*
Wellbeing	*5.0±2.7*	*3.7±2.9*	*4.6±2.8*	*4.3±2.0*	*.02*	*4.3±2.8*
Dyspnea	*2.2±3.1*	*1.5±2.6*	*2.4±2.9*	*2.4±2.6*	*.18*	*2.1±2.8*
Drowsiness	*2.9±3.1*	*2.2±2.7*	*3.0±3.2*	*2.2±2.3*	*NS*	*2.6±3.0*
Distress score	*2.7±1.5*	*2.1±1.5*	*2.4±1.6*	*2.2±1.5*	*.15*	*2.4±1.5*
Symptom number	*6.2±2.4*	*5.6±2.7*	*5.6±2.5*	*6.0±2.3*	*NS*	*5.7±2.5*

* Nine Visual Analogue Scales (VAS): 0=no symptom;10=worst possible symptom.

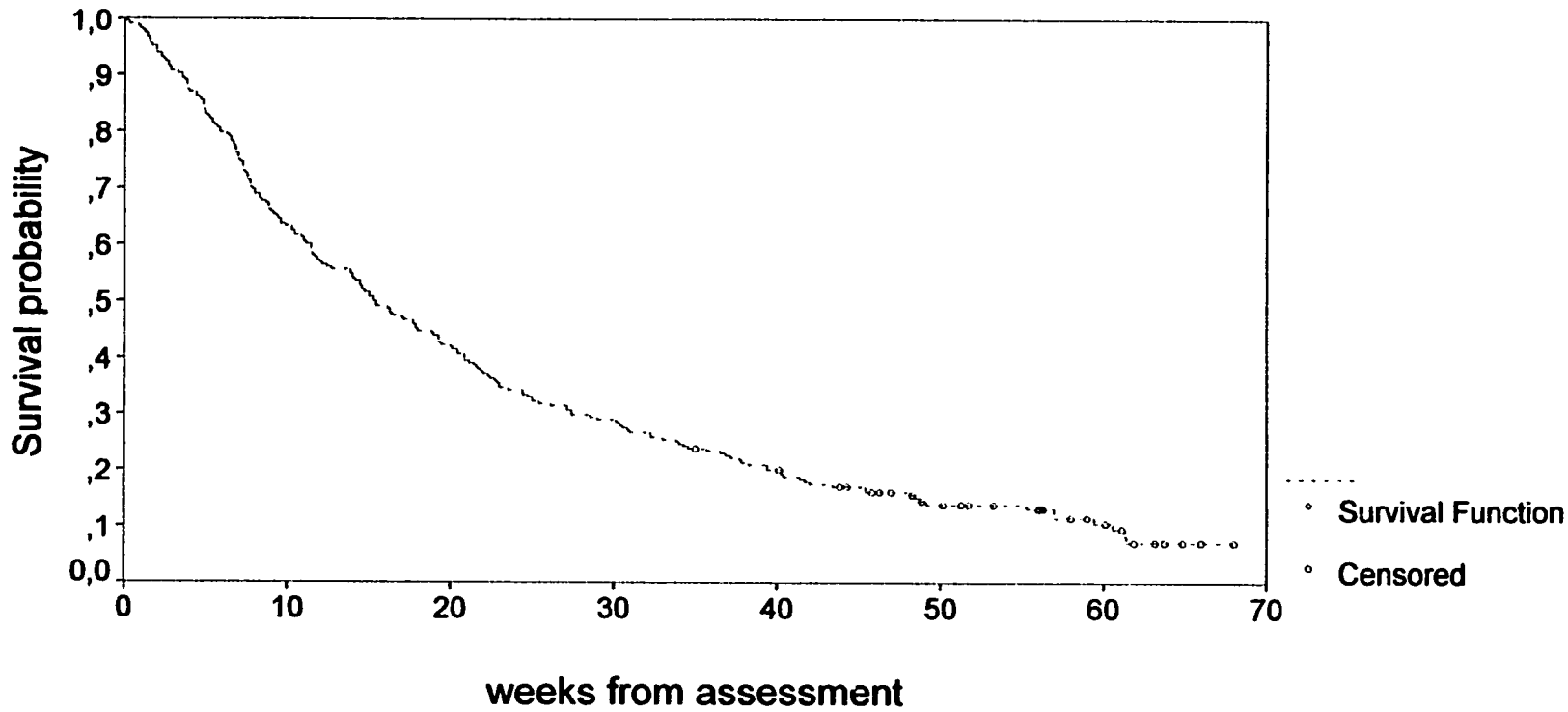
Table 6-4: Comparison of the four groups of patients with breast, gastrointestinal, lung and prostate cancers on quality of life measures as recorded through the EORTC 30*.

Tumor Group	*Breast*	*Gastrointestinal*	*Lung*	*Prostate*	*P value*	*Total*
	N = 70	*N = 80*	*N = 77*	*N = 21*		
	mean±SD	*mean±SD*	*mean±SD*	*mean±SD*		*mean±SD*
Symptoms scales*:						
Anorexia	*45.0±37.8*	*42.1±40.0*	*53.1±40.1*	*43.0±36.7*	*NS*	*46.3±39.4*
Constipation	*38.2±37.2*	*26.2±34.6*	*42.8±36.6*	*57.1±33.6*	*.002*	*37.4±36.8*
Diarrhea (rank)	*134.2*	*125.4*	*113.5*	*123.8*	*NS*	
Dyspnea	*33.8±34.5*	*16.2±26.5*	*32.5±32.3*	*38.1±33.8*	*.001*	*28.1±32.4*
Insomnia	*42.0±35.5*	*38.3±34.4*	*41.1±36.2*	*42.8±36.7*	*NS*	*40.6±35.3*
Fatigue	*63.6±28.7*	*50.8±30.6*	*66.4±29.6*	*60.0±23.1*	*.006*	*60.0±29.8*
Nausea & vomit.	*33.3±34.9*	*20.2±28.1*	*18.6±25.2*	*24.6±31.0*	*.01*	*23.7±30.1*
Pain	*44.7±32.3*	*32.7±33.6*	*45.0±33.9*	*57.1±37.1*	*.01*	*42.0±34.2*
Functional scales*						
Role funct n(%)	*35 (50)*	*26 (32.5)*	*41 (53.2)*	*11 (52.4)*	*.04*	*28.2 (45.6)*
Cognitive funct.	*67.4±28.4*	*80.6±24.1*	*61.0±33.0*	*66.7±31.2*	*.01*	*69.6±29.8*
Physical funct.	*38.0±32.7*	*60.2±34.5*	*40.8±34.8*	*39.0±31.3*	*<.001*	*46.1±35.1*
Social funct.	*48.8±34.6*	*66.9±34.7*	*57.8±34.4*	*51.6±29.3*	*.01*	*57.7±34.7*
Emotional funct	*65.3±25.2*	*75.7±22.2*	*67.8±26.4*	*72.2±24.5*	*.06*	*70.1±24.8*
Finance probl. n(%)	*22 (31.9)*	*15 (18.8)*	*17 (22.1)*	*7 (33.3)*	*NS*	*61 (24.7)*
Quality of life	*44.8±22.8*	*51.3±25.4*	*41.3±25.2*	*42.1±19.3*	*.06*	*45.6±24.4*
Overall sympt.	*40.5±18.1*	*31.6±19.0*	*41.2±21.2*	*43.8±17.1*	*.003*	*38.1±19.7*
Overall funct.	*49.1±21.7*	*65.9±23.0*	*51.7±23.6*	*51.6±23.7*	*<.001*	*55.6±23.9*

* Higher score = worse symptom
** Higher score = better functional level

Figure 1-4: Cumulative survival probability

Overall sample: 248 patients



Overall median survival: 17 weeks (95% C.I.: 12, 18)

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CHAPTER 5

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

5.1 INTRODUCTION

About one-third of the population in developed countries today will develop cancer in their lifetime (1). In approximately 50% of the patients diagnosed with cancer, active treatments aimed at prolonging survival will not be effective (2). Most authors have defined the period that goes from this point to the patient's death as the "terminal cancer phase" (3-7). The terminal cancer phase may last from days to months and there are not validated criteria to make adequate predictions of its length (8-14). This prognostic uncertainty makes clinical decisions difficult for care-givers, patient and families (15, 16) and may lead to inappropriate resource expenditure or denial of potentially beneficial therapy for the terminally ill (17, 18). In United States (19) and in Canada (20) admission criteria to government-funded hospices or some regional palliative care programs (20) require physicians to estimate life expectancies of 6 months or less. In the United States a 1993 report from the National Hospice Organization showed that over 50% of terminally cancer patients were not given access to hospice services (21) or were referred too late in the course of their illness to take full advantage of the support provided by hospice programs (22). Overly optimistic survival predictions made by different health care providers have adversely affected patients referrals to hospice programs in the United States (19). On the other hand "too early" referrals to hospices or palliative care programs, could create organizational, financial, clinical and emotional problems for administrators, health care providers and patients (23). Several studies have been conducted to elucidate the role of prognostic factors for survival in advanced/terminal cancer patients, including simple, non-invasive and clinically

based assessments. In studies focusing on prognostic factors for survival, the length of survival has been associated with: a) clinical estimates of survival by experienced physicians (24-29); b) performance status (30-44); c) some physical symptoms (14,17, 18, 35, 37, 38, 40, 41, 45- 50); d) some biological markers (32, 36, 39, 42, 51 - 60); and e) some psychological (61-71) and socio-economic parameters (72-74), besides tumor type and stage (18, 43, 49, 70).

Variation in the causes of death of terminal patients (75,76) may reduce the predictive power of some prognostic factors. This area of research also presents several methodological problems, including the choice of well-defined inception cohorts (77), use of clinically relevant measures (78,79), and the use of appropriate statistical analyses adjusting for the length of survival and for confounding factors (77,79).

The objective of this study was to evaluate the association of various clinically based prognostic factors with the survival of terminally ill cancer patients.

5.2 PATIENTS AND METHODS

Patients for this study were recruited at the Cross Cancer Institute (Edmonton, Alberta) between July 3, 1996, and December 31, 1997. The institute represents the only referral centre for oncological treatment in northern Alberta and has a catchment population of approximately 1.5 million people.

Details concerning eligibility criteria for patient accrual have been provided in the previous chapter (80).

Of the 270 patients who met the criteria, 248 (92%) agreed to participate in the study. After the study began, It was felt that the treatment of prostate cancer was not centralised and done exclusively at the CCI as for the other three primaries. The accruement of these patients may perhaps not be representative of this province population and was stopped towards the end of year 1996.

Survival was recorded from the date when patients were accrued into the study. All patients were followed until December 23, 1997, or death, thus providing a minimum follow-up time of approximately eight months.

Patients underwent an initial, in-person assessment followed by monthly phone interviews throughout the course of their disease until death occurred. The following data were recorded at baseline:

1. Demographic data including age, sex, race, approximate levels of individual and family income, level of education, presence and level of social support as measured by the Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire (81,82). The part of this questionnaire, which explores the individual's functioning in the social dimension, looks at three components: extent of contact with others, family satisfaction with contact, and availability of help (appendix2).
2. Primary and secondary tumor sites.
3. Last and concurrent treatments (surgery, chemotherapy, radiotherapy, hormonotherapy, or no treatment).
4. Tumor burden expressed as the total number of cancerous lesions (83) for all primary tumor types except prostate.

5. Performance status according to Karnofsky (KPS) (84), Eastern Co-operative Oncology Group (ECOG) (85), and Edmonton Functional Assessment Tool (EFAT) (86). The EFAT assesses the status of ten functions, namely: communication, pain, mental status, dyspnea, sitting or standing balance, mobility, walk or wheelchair locomotion, activities of daily living, fatigue, motivation. In addition, an eleventh item asks for an overall judgement of functional performance. Each item in the EFAT is evaluated by four-point rating scale from 0-3 (0=functional independent performance; 3=total loss of functional performance. A total possible score on the EFAT is 30 plus 3 for global performance status rating.
6. Physical indicators of nutritional status (weight-loss in the previous 6 months, triceps skinfold thickness as measured by the Baseline Skinfold Caliper, Fabrication Enterprise Incorporated. New York 10533 USA).
7. Type and intensity of symptoms experienced at the time of patient enrolment using the Edmonton Symptom Assessment Scale (ESAS) (87). The ESAS tool consists of nine visual analogue scales (VAS) which include pain, shortness of breath, nausea, depression, activity, anxiety, well being, drowsiness and appetite. The patient draws a mark along the 10 cm line of the VAS, the left side indicating the least degree of symptoms (e.g.:'no pain') and the right side indicating the worst degree of symptoms (e.g.: 'worst possible pain'). For each patient, the overall mean intensity of all the symptoms recorded through the ESAS was calculated to determine a "distress score".
8. Concurrent diseases recorded with the Charlson comorbidity score (88). This score ranges from 0 to a theoretical maximum of 33 and is based on the

presence of certain diseases with assigned values or weights. We developed an adjusted Charlson score, which excluded the diagnosis of cancer, since our intention was to measure conditions other than the patient's principal diagnosis

9. Cognitive status as measured by the Folstein's Mini Mental State Examination (89). The MMSE measures orientation to time and place, immediate recall, short-term memory, calculation, language and construct ability. The maximum score is 30, a score of 23 or less generally accepted as indicating the presence of cognitive impairment.
10. Serum and hematologic parameters including level of albumin, sodium, calcium, alkaline phosphatase, lactate dehydrogenase, haemoglobin, cell blood counts and differentials.

These variables were selected because they were found to be of prognostic significance in terminal cancer patients (Chapters 1 and 2) and were felt to be easy to record and reproducible and detectable even in seriously ill patients.

5.2.1 Statistical analysis

Bivariate analysis

Forty-seven variables were initially considered for bivariate association with survival (Tables 1-5 to 6-5). Continuous variables were evaluated without categorization, dichotomized, and as quartiles. The first category was used as the reference category for each of the other categories. The cut-off points for continuous, ordinal and categorical variables, were chosen according to: a) reference intervals for all laboratory variables; b) description in other studies; c) distribution of cases; d) clinical meaningfulness; e) biological plausibility.

Only patients with tumors other than prostate and without missing data were initially included in the analyses. There were no significant differences in survival between patients with tumors of the breast and gastrointestinal cancer, but lung cancer patients had significant poorer survivals (p-value <.05; log rank test) (; Table 3-5; Figure 1-5). Therefore, tumor type was considered as a dichotomous variable (non-lung, lung) for all analyses. For the heterogeneity of cancer treatments in the four primaries (Chapter 3), a classification proposed by McKusker was adopted (6): patients who entered their terminal phase without ever receiving any tumor-directed therapy (e.g. for poor medical conditions or too advanced stages of diseases); with their cancer treatments discontinued (e.g. for disease progression or recurrence); and patients for whom those therapies were started (e.g. for symptom palliation) were considered (Table 1-5).

The literature does not offer specific indications for categorization of the intensity of symptoms (Chapter 2) and, patients similar to our population, may present comorbidities and mild symptoms unrelated to their cancer. Therefore, for comorbidity and symptom levels, cut-off points between absent-to-mild and moderate-to-severe were used.

Functioning levels as measured by the Zubrod/ECOG and Karnofsky performance status scales were recoded in three comparable categories, according to the simple conversion table recently proposed by Buccheri and colleagues (90).

Other cut-off points were based on mean values (e.g. personal and family incomes), median values (e.g. distress score, symptom number and weight-loss) and median for the normal population (e.g. triceps skinfold measurements).

Kaplan-Meier survival curves (product limit procedure) were constructed for the estimated survival probabilities for each categorical variable (91). The statistical significance of differences among survival curves was determined by two-tailed log-rank test (92). The Cox regression method (93) was also used for exploratory bivariate analyses, in which each single variable was examined.

Multivariate analysis

Multivariate analysis was performed using Cox proportional hazard regression models. The Cox model is a semi-parametric regression model that evaluates the effect of independent variables (covariates) on the dependent variable (e.g. survival), taking into account censored observations (cases for which the event of interest, such as death, has not yet occurred).

Provided that the most strict assumption of this model (i.e., changes in hazard of dying of any patient over time will always be *proportional* to changes in the hazards of any other patients and to changes in the underlying hazard over time) is fulfilled, the Cox regression model has the form:

$$h(t) = [\, h_0(t) \,] e^{(b_1 X_1 + b_2 X_2 + \ldots\ldots + b_p X_p)}$$

where : X_1 to X_p are the covariates and b_1 to b_p are the regression coefficients.

$h_0(t)$ is the underlying hazard function

Thus h(t) is the hazard at time *t* after a defined starting point (diagnosis, study accrual) for an individual with variables (covariates) $x = x_1 \ldots\ldots x_p$. h(t) is dependent on (explained or predicted by) $h_0(t)$, and the covariates x_1 to x_p (recorded at time 0), multiplied by their corresponding regression coefficient b_i. The underlying hazard $h_0(t)$, may be considered a "reference" hazard from which the hazard h(t) at time *t* of

a given subject may be obtained by multiplication with a factor, namely the exponential function *e* of the subject's variables, "weighted" by the regression coefficients. Formally, in an individual whose x_i's are all zero, $h_0(t)$ is equal to h(t) and closely corresponds to the cumulative survival function, as calculated with the Kaplan-Meier method (without taking into account any covariate).

Through the Cox regression method, we wanted to investigate whether simple clinical and demographic characteristics had any prognostic value in terminal cancer patients, when adjusted for other variables of major prognostic significance. Variables that achieved a conservative statistical significance of p-value ≤ 0.20 in the bivariate analysis, fulfilled the proportionality assumption and were felt of particular interest, were examined in multivariate models. The proportionality of hazards associated to each predictor, was checked by visual inspection of log minus log survival plots. Demographics, patient and disease related characteristics that had shown some degree of correlation with survival in our data set and or were previously found to be important prognostic factors were screened by multivariate analysis. These included:

- Education level.
- Personal yearly income.
- Tumor type.
- Brain and liver metastases.
- Tumor burden.
- Comorbidity level.
- Antineoplastic treatments (never received/discontinued prior to study accrual vs. continued/initiated after study accrual).
- Asthenia.
- Depression.

- Anorexia.
- Nausea.
- Anxiety.
- Dyspnea.
- Pain.
- Well-being.
- Weight loss.
- Cognitive status.
- Serum albumin.
- Serum lactate dehydrogenase.
- Hemoglobin.
- Leukocyte, granulocyte and lymphocyte counts.

In the first model (M1), patient and disease related variables were adjusted for subjective assessments, as recorded through the Edmonton Symptom Assessment System (ESAS). Stepwise forward regression procedures based on the partial likelihood ratio were applied to determine factors of prognostic importance from M1. Variables were entered in the model if they were associated with p-values ≤ 0.06 and retained if they had observed significance levels ≤ 0.10, after the addition of new variables to the model. Unselected variables, including age and sex, were singularly added to M1, to detect any significant contribution to M1 main-effect model. Performance status could not be included in the model as an independent variable because it violated the proportionality assumption (Figure 2-5). Variables selected by M1 were therefore subsequently examined in two models (M2 & M3) that considered the sample stratified according to two levels of performance status (M2=ambulatory; M3=bedridden).

Separate regressions were estimated for the laboratory parameters because of missing data in 62 patients. No values were imputed to missing data and to preserve an adequate sample size, laboratory parameters were not included in the stepwise regression procedures. Significant laboratory variables in the bivariate analyses (p-value $\leq$ 0.20) were added to a model (M4) that included variables selected in M1. Two other models were finally obtained (M5 and M6) that included the significant variables of M4 in the sample stratified according to performance status.

Meaningful interaction terms (e.g. between weight loss and type of primary, serum albumin and weight loss, lactate dehydrogenase and tumor burden, tumor burden and weight loss, albumin and tumor burden) were also examined in final models. In models 1 and 4, outliers as detected from plots of Martingale residuals (94), and overly influential observations, as identified from plots of DfBeta (95) , were inspected for each significant covariate.

Through Cox regression models, for each patient it is possible to calculate a prognostic index (PI). According to this score, the patient can be "reclassified" in prognostic sub-groups. The PI is obtained from the sum of all the product terms between the regression coefficients of the variables in the final model and the value of these variables recorded in the individual patients. In our data set PI were calculated for each patient using both M1 and M4, and patients were divided into six equal-sized groups with 'better', 'medium' or 'worse' prognosis (i.e. three prognostic groups for each one of two models). Kaplan-Meier survival curves were traced for these prognostic groups and their comparison was based on the log-rank test. Power estimates were performed "a priori," using both the method of Schoenfield

(96) and the Egret Size software program (97). In both methods, albumin serum levels (ASL) were considered as the main exposure. This variable was dichotomized as "high/normal" (i.e. ASL ≥35g/L) and "low" (ASL <35g/L). A sampling fraction of 46% of patients (51,98), and a conservative hazard ratio for the risk of dying ranging between two and three were assigned to the low ASL group (99). Both methods agreed in indicating that a sample of approximately 80 patients could provide a power of at least 80%, for a hazard ratio of 2.0 and an alpha of 0.05 (two-sised).

The SPSS 6.0 statistical software package (100) was used for all other statistical analyses.

5.3 RESULTS

Table 1-5 shows selected demographic and clinical characteristics of the 248 patients who were accrued in the study. At the time of analyses (December 23, 1997) 218 patients (87.9%) had died, 30 (12.1%) were alive, and no patient was lost to follow-up. The estimated median survival time of the overall group was 15 weeks, with a 95% confidence interval of 12-18 weeks. The 2-month, 4-month and 6-month survival rates calculated by Kaplan-Meier methods were 67.7%, 47.6% and 33.5%, respectively (Figure 3-5).

Bivariate survival analysis showed a statistically significant association ($P < 0.01$, log-rank test) between decreased survival and the following baseline characteristics (Tables 1-5 to 6-5): education level ≤12 years of schooling; lung cancer; liver metastasis; more than 5 cancerous lesions; moderate or severe comorbidity; cognitive impairment; weight loss above the 50th percentile of the sample; triceps

skinfold measurements less than the 50th for a standard population of North American men and women of the same mean age as our sample (101); lower performance status; fatigue, nausea, drowsiness, and distress score and number of symptoms, as measured by the Edmonton Symptom Assessment System (ESAS); and serum sodium, albumin, granulocyte and lymphocyte absolute counts, lactate dehydrogenase (LDH), and alkaline phosphatase beyond normal ranges. Other variables that were also discriminant for worse survival (with associated P-values between 0.01 and 0.05) were: married or common-law marital status, brain metastases, dyspnea and impairment in well-being (as measured by the ESAS); high leukocyte absolute counts. No statistically significant factors associated with survival were found for age, gender, race, personal and family yearly income, impairment in social support, tumor staging, bone, lung, lymphonodal, skin and visceral metastases, pain and anxiety, serum calcium and hemoglobin with platelets absolute counts.

Multivariate regression analyses were used to examine the joint effects of selected variables. The hazards ratio of dying within 18 months in the overall sample (excluding prostate cancer patients and cases with missing data, N=203), ambulatory (ECOG 0-1, N=90), and bedridden patients (ECOG 2-4, N=113) are presented in Tables 7-5 to 9-5. Table 7-5 shows the significant variables in the Cox regression model (M1) that considered patient, disease, and symptom characteristics as recorded through the ESAS. All variables showed hazard ratios between 1.5 and 3.0. The highest hazard ratios were associated with disease-related characteristics and cognitive status, whereas the lowest were found associated with nausea and number of symptoms. Tables 8-5 and 9-5 show the

results stratified by performance status. Table 8-5 includes the model assessed for ambulatory patients. Again, hazard ratios ranged from 1.5 to 3.9, with lung cancer and tumor burden having greater impact on survival. Bedridden patients (Table 9-5) showed decreased survival associated with the presence of liver metastasis, tumor burden and cognitive status. In Tables 10-5 to 12-5 the significant factors in M1 were adjusted for serum albumin, lymphocyte counts and lactate dehydrogenase in the overall sample (N=165) and in ambulatory (ECOG 0-1, N=75) and bedridden (ECOG 2-4, N=90) patients. In Table 10-5 hazard ratios ranged from 1.1 to 3.6. The most significant hazard ratios remain those associated with lung cancer, presence of liver metastases and tumor burden. In ambulatory patients (Table 11-5), hazard ratios showed a wider range, from 1.3 to 6.0. The most important prognostic variables were, again, lung cancer, presence of liver metastases and lymphocyte count. In bedridden patients (Table 12-5), hazard ratios had a smaller range (1.5 to 2.5) and indicated the highest prognostic importance for lung cancer, tumor burden and serum albumin.

Variables that were statistically significant (p-value ≤ 0.05) in M1 and M4 did not grossly violated the proportionality assumption, as shown by Figures 4-5 to 14-5. Variables that were not selected by M1 were also tested by adding each one of them at the time to the main effect final model (M1), but they resulted still insignificant (p-value ≥ 0.05 Wald statistics and log-likelihood ratio test). Examination of the outliers (Figures 15-5 and 16-5) did not show particular trends and an overall satisfactory goodness of fit. Data for two outliers (cases 208 and 3) were found also to be overly influential with respect to the coefficients estimated for laboratory parameters, symptoms, disease related variables (Figures 17-5 to 27-5). These

observations were closely examined, found correctly recorded and kept in the database. Independent prognostic factors were reassessed for their bivariate association with survival, by Cox regression on the same sample of the final model (Table 13-5). No significant interaction terms among M1 and M4 factors were detected.

All analyses were repeated with the inclusion of prostate patients for M1 and M4, and similar results were obtained (data not shown).

Prognostic indexes were calculated for each patient using the significant variables (p-value ≤ 0.05) in models M1 and M4. Patients were stratified into three groups for both models that included patients with better, medium and worse prognoses. The survival curves traced through the Kaplan-Meier method for each of these prognostic groups are depicted in Figures 28-5 & 29-5. The Kaplan Meier findings are consistent with good prognostic discrimination of the two models. A better separation of the survival curves in M4 (clinical and laboratory data) than in M1 (clinical data only) is evident.

5.4 DISCUSSION

Our study was designed to identify survival predictors in terminally ill patients affected by solid malignancies. To our knowledge, no previous attempts have been made to evaluate the independent value of prognostic factors for survival in a population-based and prospectively accrued inception cohort of terminal cancer patients. A major difficulty in this type of study arises from the lack of clinical criteria to define the onset of the terminal phase in these patients (Chapters 1 and 3). We

established simple criteria to define the onset of the terminal stage in patients with breast, lung, gastrointestine and prostate cancers. These criteria present certain limitations: they rely on specific therapeutic schemes (e.g.: treatment of advanced breast cancer may not contemplate chemotherapy sequential trials); they may change according to the state of the art in the management of neoplastic diseases and they are influenced by the time patients seek cancer care (e.g.: disease progression may be discovered earlier through a three months instead of six month follow-up). However, they provide benchmarks by which to enroll patients at common points in the course of their terminal disease that would be otherwise difficult to define (Chapter 3). Furthermore, the lack of significant differences in survival between patients that either discontinued or continued/initiated treatments in the terminal phase, confirm that our sample complied with most "theoretical" definitions of terminal cancer patients (Chapter 2).

The median survival in our sample was 15 weeks (95%, C.I. 12-18), which is longer than that observed in studies of end-stage patients (Chapter 2), but shorter than that reported for advanced cancer patients (Chapter 3). However, our study population was not accrued within hospice care facilities or for clinical trials, as in most studies included in the systematic reviews. All patients were examined while seeking regular cancer care in the referral centre for oncological treatment in northern Alberta.

The purpose of our study was to investigate whether simple subjective assessments, demographic and socioeconomic characteristics had any prognostic value in the survival of terminal cancer patients.

The bivariate analysis showed that multiple variables had prognostic significance (Tables 1-5 to 6-5). However, in the multivariate analyses only biological

characteristics (lung cancer, liver metastases, tumor burden and level of comorbidity) along with a few clinical features (amount of weight loss and cognitive status) and laboratory parameters (albumin, lymphocyte counts and lactate dehydrogenase), remained as strong, independent survival predictors in terminal cancer patients.

Our results appear to be generally consistent with the literature on survival predictors in end-stage and advanced cancer patients (Chapters 2 and 3). Symptoms such as anorexia and dyspnea were not found as independent prognostic factors as previously shown in end-stage cancer patients. On the other hand, nausea and number of symptoms remained independently correlated with survival in most models, whereas these parameters were either not particularly studied (number of symptoms) or considered to be unlikely important survival predictors (nausea) in the reviewed literature. However, the hazard ratios associated with these variables were of small magnitude. The onset of the terminal phase seems characterized by multiplicity rather than intensity of symptoms (Chapter 4) and this finding may as well be of prognostic value. Although the pathogenesis of nausea remains multifactorial in terminal cancer patients (102), this symptom frequently reflect dysfunctions in the autonomic nervous system of this population (103). The latter sign has been associated with malnutrition and is involved in the pathogenesis of the cachexia syndrome, that appears quite prevalent in advanced cancer patients (Chapter 4). Our data may support an early and independent prognostic role of autonomic dysfunctions in the terminal cancer phase that could not be previously identified in both advanced or end-stage cancer patients.

Performance status is well recognized as an important prognostic factor for survival in both end-stage and advanced cancer patients (Chapters 2 and 3). However, the strength of the association between performance status and survival seems to vary with length of follow-ups. In addition, lower predictive accuracy has been reported with higher scores of performance status, particularly with values beyond 50-60 on the Karnofsky scale, in end-stage cancer patients (Chapter 2). These observations were confirmed in our sample where the association between performance status and survival appeared strong but time dependent (Figure 2-5). The latter variable could not be included in Cox's regression models but was examined as a stratification factor. As expected, the magnitude of the coefficients of the independent variables appeared to be generally lower in bedridden patients compared to those who were ambulatory.

Greater hazards ratios and relatively stable p-values throughout the different models confirm in our data the high prognostic relevance of tumor related characteristics, namely the presence of lung malignancies, liver metastases and high tumor burdens. These data are consistent with the reviewed literature on prognostic factors in advanced and end stage cancer patients (Chapters 2 and 3). Although, symptomatically, patients appear to have similar features in the terminal phase ("common terminal syndrome"), individual survival is highly variable and is dependent on disease-specific features. Survival in our patients was greatly influenced by the type of primary tumor, site of metastases and by the extent of tumor burden. The consistent suggestion of an association between lung cancer and more unfavorable prognoses in end-stage cancer patients is confirmed by our study. This association is not clearly explained either by the clinical characteristics

of lung patients in our sample (e.g. by more evident signs or symptoms; Chapter 4) or by significant interaction terms between variables in the final model. The presence and level of metastatic liver involvement has shown to be of definite prognostic importance in patients with advanced breast and gastrointestinal cancer. Similarly, in advanced breast, lung and possibly gastrointestinal cancers, tumor burden has been found significantly correlated to survival (Chapter 3).

Weight loss and cognitive impairment are common signs in end-stage cancer patients and were related to shorter survival, as previously described in Chapter 2. All patients with impaired cognitive status in our sample were at least partially bedridden, and the prognostic value of the former variable could not be established for ambulatory patients.

Serum albumin levels <35g/liter, serum lactate dehydrogenase concentration > 618 U.I./liter, and lymphocyte counts <1 x 10^9/liter, were all found significantly and independently correlated with decreased survival. The prognostic importance of low serum albumin levels was well recognized in patients with advanced lung and gastrointestinal tumors (Chapter 2). By measuring indirectly the amount of body protein stores, serum albumin represents an important and simple nutritional assessment in cancer patients (104). The prognostic value of this variable confirms the association between malnutrition, disease progression and survival in the terminally ill.

The association between lactate dehydrogenase and survival was clear in studies of patients with advanced lung cancer and only suggested for patients with incurable gastrointestinal malignancies (Chapter 3). Interestingly, the prognostic relevance of

lactate dehydrogenase did not vary with the extent of tumor burden as demonstrated by the lack of statistical significance of their interaction term.

A small number of studies have investigated lymphocyte counts as prognostic factors in incurable lung cancer, suggesting an association with survival. This is confirmed by our data and could be explained by the relationship between low lymphocyte counts, impairment of the immunity system, and poor nutritional status in patients with advanced cancer.

Good prognostic discrimination was observed for groups of patients with "good," medium" or "worse" prognoses, as calculated by the regression-derived prognostic indices (Figure 16-5). The greater discriminatory power obtained for model predictions after adjustment for laboratory parameters (M4), was tempered by a reduction in sample size. This situation may reflect the reality of palliative care, where even simple laboratory assessments are not always feasible or ethical.

Our study findings had some limitations. Characteristics and survival patterns for prostate patients undergoing the terminal phase could not be examined appropriately. The recruitment of these patients was felt to be not representative for this province population and was discontinued prematurely. Future studies should consider these patients in primary or secondary health care facilities rather than in a single tertiary institution. The sample sizes used in the multivariate models were smaller because of missing data in the laboratory assessments and also had to be stratified according to performance status. Stratification was considered to be a simple and clinically meaningful way to control our results for a variable of essential prognostic value such as performance status, given the violation of the proportionality assumption in the Cox regression. The prognostic relevance of each

covariate after stratification needs to be considered relative to the non-stratified models. In the latter, sample sizes were adequate in most cases to guarantee enough power for the estimated hazards ratios considered clinically meaningful. Finally, the magnitude of the coefficients or hazard ratios, rather than p-values (which may vary according to sample sizes), were focused in our analyses.

Our study results have to be validated in an independent data set gathered on similar patients. It was felt that the relatively small sample sizes obtained for our models would not allow meaningful split-sample or cross-validation techniques (105).

5.5 CONCLUSION

Prognostic uncertainty in terminal cancer will be always a reality for health care providers, patients and families. The result of this study however indicate that primary lung cancer, presence of liver metastases, tumor burden, cognitive status, amount of weight-loss, lactate deydrogenase, albumin, and lymphocytes count are important factors to reduce this uncertainty. Other prognostic factors of secondary importance appear to be nausea intensity and the number of symptoms experienced at the onset of the terminal phase. No other symptoms (e.g. dyspnea or anorexia) or socioeconomic characteristics such as social support, education and income level appeared as independent survival predictors when adjusted for other major prognostic factors. On the contrary, our data suggest that simple disease and physical assessments may be useful to appraise patient survival at the onset of their terminal stages. This estimate can be refined by examining certain routine

laboratory parameters, but the need for such investigation in palliative care patients should be evaluated case by case because of ethical concerns.

Table 1-5: Selected Demographic And Clinical Characteristics Of The 248 Patients

Overall survival (median):	15 weeks (95% C.I.=12-18)		
Age (median):	62 yr. (range 29-92)		
		N	(%)
Gender:	Males	103	42
	Females	145	58
Race:	Caucasian	229	92
	Non-Caucasian	19	8
Residence:	City	125	50
	Rural	123	50
Primary site:	Breast	70	28
	GI	80	32
	Lung	77	31
	Prostate	21	9
Tumor-directed treatments in the terminal phase:			
No treatment ever received*		20	8
Treatments were discontinued		64	26
Treatment were started/continued		164	66

* Patients could not receive any specific treatment either prior or post the beginning of the terminal phase.

Table 2-5: Median Duration Of Survivals And Log-Rank Test For Overall Survivals: Influence Of Demographics And Socio-Economic Variables.

Variable	Categories	# of patients	Median survival (weeks)	P-value (Log-rank)
Gender				
	Male	82	13	>.20
	Female	145	15	
Age				
	≥65	94	14	>.20
	<65	133	16	
Race				
	Caucasians	208	15	>.20
	Others	19	21	
Marital status				
	Single, widow, separated/divorced	68	18	.05
	Married, common-law	159	14	
Education level				
	>High school	72	19	.007
	≤ High school	155	14	
Personal yearly income*				
	≥22.500	71	20	.08
	<22.500	115	14	
Family yearly income**				
	≥42.200	65	15	>.20
	< 42.200	63	14	
Social support***				
	No impairment	180	15	>.20
	Impairment	47	15	

* Average for the sample; 46 cases with missing data (overall sample)

** Average for the sample; 109 cases with missing data (overall sample)

*** As measured through the Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire

Table 3-5: Median Duration Of Survivals And Log-Rank Test For Overall Survivals: Influence Of Tumor Related Variables.

Variable / Categories	# of patients	Median survival (weeks)	P-value (Log-rank)
Primary tumor site			
Breast (0)	70	18	0 1 2
Gastrointestinal (1)	80	19	1 .43
Lung (2)	77	11	2 .02 .003
Prostate (3)	21	18	3 .62 .29 .32
Staging			
Inoperable	34	17	.07
Recurrent/Metastatic	193	15	
Bone metastases			
Absent	151	15	>.20
Present	76	15	
Brain metastases			
Absent	170	15	.02
Present	57	13	
Lymphonodal metastases			
Absent	148	15	>.20
Present	79	15	
Liver metastases			
Absent	153	18	.0002
Present	74	8	
Lung metastases			
Absent	143	16	>.20
Present	84	14	
Skin metastases			
Absent	217	15	>.20
Present	10	8	
Visceral metastases			
Present	195	15	>.20
Absent	32	12	
Specific treatments in terminal phase (t.p.):			
No treatments given prior/into t.p., 0	20	8	0 1
Cancer treatments discontinued, 1	64	21	1 .03
Cancer treatments continued/started, 2	147	14	2 .02 >.20
Tumor burden			
≤ 5 lesions	75	23	.0002
> 5 lesions	152	12	

Table 4-5: Median Duration Of Survivals And Log-Rank Test For Overall Survivals: Influence Of Clinical (Objective) Variables.

Variable	Categories	# of patients	Median survival (weeks)	P-value (Log-rank)		
Level of comorbidity*						
	Absent-mild	164	19	.001		
	Moderate-severe	63	11			
Cognitive status**						
	Normal	192	17	.0002		
	Abnormal	13	7			
ECOG/Zubrod performance status scale						
	0-1(0)	90	24		0	1
	2 (1)	71	12	1	<.001	
	3-4 (2)	66	8	2	<.001	.08
Karnofsky performance status scale						
	≥80 (0)	64	24		0	1
	70-60 (1)	106	15	1	.001	
	≤50 (2)	57	7	2	<.001	.04
EFAT performance status scale***						
	≤ 5[a]	113	22	.0001		
	> 5	114	10			
Weight-loss						
	≤ 18 lbs.[a]	117	19	.0004		
	> 18 lbs.	109	10			
Triceps Skinfold						
	≥ 11 mm (males), 25 mm (females)[b]	66	24	.002		
	≥ 11 mm (males), 25 mm (females)	152	12			

* According to modified Charlson Index score; cut-off point = 2

** According to Folstein's mini mental status evaluation; cut-off point = 24

*** Edmonton Functional Assessment Tool.

[a] 50th percentile for the sample.

[b] 50th percentile for a normal population of North American with same gender distribution and average age then our sample.

Table 5-5: Median duration of survival And Log-Rank Test For Overall Survivals: influence of clinical (subjective) variables as measured through the Edmonton Symptom Assessment System (ESAS).

Variable	Categories	# of patients	Median survival (weeks)	P-value (Log-rank)
Pain				
	Absent-mild	123	16	>.20
	Moderate-Severe	103	14	
Anxiety				
	Absent-mild	138	18	.13
	Moderate-severe	88	10	
Fatigue				
	Absent-Mild	70	19	.01
	Moderate-Severe	156	14	
Nausea				
	Absent-Mild	176	17	.006
	Moderate-Severe	50	10	
Depression				
	Absent-mild	167	16	.04
	Moderate-severe	59	11	
Drowsiness				
	Absent-Mild	127	19	.01
	Moderate-Severe	98	11	
Anorexia				
	Absent-Mild	84	20	.03
	Moderate-Severe	141	11	
Impairment in well-being				
	Absent-Mild	65	20	.02
	Moderate-severe	155	12	
Dyspnea				
	Absent-mild	151	19	.03
	Moderate-severe	74	11	
Distress-score*				
	≤ 3 [a]	112	20	.006
	> 3	115	11	
Number of symptom**				
	≤ 6 [a]	129	20	.0002
	> 6	95	10	

* Overall intensity for symptoms reported by each patient (VAS 0-10).** Overall number of symptoms reported by each patient. [a] 50th percentile for the sample.

Table 6-5: Median Duration Of Survival And Log-Rank Test For Overall Survivals: Influence Of Measured Laboratory Variables.

Variable	Categories	# of patients	Median survival (weeks)	P-value (Log-rank)
Serum Sodium				
	≥135 mmol/L	140	19	.001
	<135	42	7	
Adjusted serum Calcium				
	≤ 2.65mmol/L	182	15	.09
	> 2.65 mmol/L	13	5	
Serum Albumin				
	≥ 35 g/L	112	23	<.0001
	< 35 g/L	109	9	
Serum Hemoglobin				
	≥ 120 g/L	157	16	.09
	< 120 g/L	56	11	
Leukocyte count				
	≥ 11 x 10^9/L	166	18	.04
	> 11 x 10^9/L	48	8	
Granulocyte count				
	≥ 7.5 x 10^9/L	145	20	.009
	> 7.5 x 10^9/L	58	9	
Lymphocyte count				
	≥ 1 x 10^9/L	98	25	<.0001
	< 1 x 10^9/L	104	10	
Platelets count				
	≥ 450.000	180	15	>.20
	> 450.000	32	15	
Serum lactate dehydrogenase				
	≤ 618 U/L	111	21	<.0001
	> 618 U/L	85	10	
Serum alkaline phospatase				
	≤ 130 U/L	78	22	.0006
	> 130 U/L	53	9	

Table 7-5: Model 1(M1): Significant Variables In The Cox Regression Model* That Considered Patient, Disease And Symptoms Characteristics, As Recorded Through The Edmonton Symptom Assessment Tool (ESAS).

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	1.1	.19	3.0	2.0-4.2	<.0001
Liver metastases	(absent)					
	Present	.89	.18	2.4	1.7-3.5	<.0001
Tumor burden	(presence of <5 lesions)					
	Presence of ≥5 lesions	.91	.20	2.5	1.7-3.6	<.0001
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.69	.18	2.0	1.4-2.8	.0002
Amount of weight-loss	(≤ 18 lbs. [a])					
	> 18 lbs.	.69	.16	2.0	1.4-2.8	<.0001
Cognitive status	(normal [b])					
	impaired	1.0	.32	2.8	1.5-5.2	.002
Symptoms number	(≤ 6 [a])					
	> 6	.42	.18	1.5	1.1-2.1	.02
Nausea	(absent-mild)					
	Moderate-severe	.50	.21	1.6	1.1-2.5	.02

* Stepwise forward selection (p entry: ≤ 0.06; p elimination: > 0.10); N = 203.** ≤ 2 modified Charlson index. [a] 50th percentile for the sample.[b] Folstein's Mini-mental State Questionnaire ≥ 24. HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval

Table 8-5: Model 2 (M2): Significant Variables Of Model 1 Were Considered In Ambulatory Patients Only*.

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	1.4	.33	3.9	2.0-7.4	<.0001
Liver metastases	(absent)					
	Present	.93	.32	2.5	1.4-4.7	.003
Tumor burden	(presence of < 5 lesions)					
	Presence of ≥ 5 lesions	.98	.29	2.6	1.5-4.7	.0007
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.42	.32	1.5	.8-2.8	.18
Amount of weight-loss	(≤ 18 lbs.[a])					
	> 18 lbs.	.78	.28	2.2	1.2-3.7	.006
Cognitive status [b]	(normal)					
	impaired	--	--	--	--	--
Symptoms number	(≤ 6 [a])					
	> 6	.39	.32	1.5	.8-2.8	>.20
Nausea	(absent-mild)					
	Moderate-severe	.73	.52	2.1	.8-5.7	.16

* Eastern Cooperative Oncology Group (ECOG) Performance status scale 0-1; N = 90 ** ≤ 2 modified Charlson index. ***. [a] 50th percentile for the sample. [b] No patient in this stratum had a Folstein's Mini-mental State Questionnaire score < 24; HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval.

Table 9-5: Model 3 (M3): Significant Variables Of Model 1 Were Considered In Bedridden Patients Only*.

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	.78	.23	2.2	1.4-3.4	.001
Liver metastases	(absent)					
	Present	1.0	.24	2.8	1.7-4.4	<.0001
Tumor burden	(presence of < 5 lesions)					
	Presence of ≥ 5 lesions	.88	.27	2.4	1.4-4.1	.001
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.69	.25	2.0	1.2-3.2	.005
Amount of weight-loss	(≤ 18 lbs.[a])					
	> 18 lbs.	.23	.23	1.2	.8-2.0	.32
Cognitive status	(normal [b])					
	impaired	.88	.33	2.4	1.3-4.6	.008
Symptoms number	(≤ 6 [a])					
	> 6	.29	.22	1.3	.9-2.0	.19
Nausea	(absent-mild)					
	Moderate-severe	.19	.26	1.2	.8-2.0	>.20

* Eastern Cooperative Oncology Group (ECOG) Performance status scale 2-4; N = 113 ** ≤ 2 modified Charlson index. ***. [a] 50th percentile for the sample. HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval

Table 10-5: Model 4 (M4): significant variables of model 1 were adjusted for laboratory parameters*.

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	1.3	.22	3.6	2.4-5.5	<.0001
Liver metastases	(absent)					
	Present	.87	.22	2.4	1.6-3.6	.0001
Tumor burden	(presence of < 5 lesions)					
	Presence of ≥ 5 lesions	.81	.23	2.2	1.4-3.6	.0005
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.60	.22	1.8	1.2-2.8	.005
Amount of weight-loss	(≤ 18 lbs. [a])					
	> 18 lbs.	.85	.20	2.3	1.6-3.4	<.0001
Cognitive status	(normal [b])					
	impaired	.72	.39	2.0	1.0-4.3	.07
Symptoms number	(≤ 6 [a])					
	> 6	.08	.21	1.1	.6-1.6	>.20
Nausea	(absent-mild)					
	Moderate-severe	.69	.22	2.0	1.3-3.0	.02
Serum albumin	(≥35g/liter [c])					
	< 35 g/liter	.63	.20	1.9	1.2-2.8	.002
Lymphocytes	(≥ 1 x 10^9/liter [c])					
	< 1 x 10^9/liter	.71	.20	2.0	1.4-3.0	.0004
Lactate dehydrogenase	(≤ 618 U/liter [c])					
	> 618 U/liter	.52	20	1.7	1.1-2.5	.008

* Overall sample; N = 165.** ≤ 2 modified Charlson index. [a] 50th percentile for the sample.[b] Folstein's Mini-mental State Questionnaire ≥ 24. [c] Upper/lower cut-off points for normal value in our laboratories
HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval

Table 11-5: Model 5 (M5): significant variables in M4 were considered in ambulatory patients only*.

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	1.8	.38	6.0	2.9-12.6	<.0001
Liver metastases	(absent)					
	Present	1.4	.39	4.3	2.0-9.1	.0002
Tumor burden	(presence of < 5 lesions)					
	Presence of ≥ 5 lesions	1.2	.38	3.2	1.6-6.8	.002
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.27	.36	1.3	.6-2.7	>.20
Amount of weight-loss	(≤ 18 lbs. [a])					
	> 18 lbs.	1.09	.31	3.0	1.6-5.5	.0004
Cognitive status [b]	(normal)					
	impaired	--	--	--	--	--
Nausea	(absent-mild)					
	Moderate-severe	1.32	.50	3.7	1.4-10.0	.008
Serum albumin	(≥35g/liter [c])					
	< 35 g/liter	.78	.34	2.2	1.1-4.3	.02
Lymphocytes	(≥ 1 x 10^9/liter [c])					
	< 1 x 10^9/liter	1.19	.30	3.3	1.8-6.0	.0001
Lactate dehydrogenase	(≤ 618 U/liter [c])					
	> 618 U/liter	.62	.30	1.8	1.0-3.4	.008

* Eastern Cooperative Oncology Group (ECOG) Performance status scale 0-1; N = 75.** ≤ 2 modified Charlson index. [a] 50th percentile for the sample.[b] No patient in this stratum had a Folstein's Mini-mental State Questionnaire score < 24. [c] Upper/lower cut-off points for normal value in our laboratories HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval.

Table 12-5: Model 5 (M5): variables selected in M4 were considered in bedridden patients only*.

Predictor	(reference category)	B	SE	HR	95% CI	P value
Primary tumor site	(breast, gastrointestinal)					
	Lung	.92	.28	2.5	1.4-4.3	.0009
Liver metastases	(absent)					
	Present	.56	.28	1.7	1.0-3.0	.05
Tumor burden	(presence of < 5 lesions)					
	Presence of ≥ 5 lesions	.74	.31	2.1	1.2-3.8	.02
Level of comorbidity	(absent-mild**)					
	Moderate-severe	.67	.27	1.9	1.1-3.3	.02
Amount of weight-loss	(≤ 18 lbs. [a])					
	> 18 lbs.	.62	.27	1.8	1.1-3.2	.02
Cognitive status	(normal [b])					
	impaired	.44	.36	1.6	.8-3.2	>.20
Nausea	(absent-mild)					
	Moderate-severe	.39	.27	1.5	.9-2.5	.16
Serum albumin	(≥35g/liter [c])					
	< 35 g/liter	.75	.27	2.1	1.2-3.6	.006
Lymphocytes	(≥ 1 x 10^9/liter [c])					
	< 1 x 10^9/liter	.43	.28	1.5	.9-2.7	.12
Lactate dehydrogenase	(≤ 618 U/liter [c])					
	> 618 U/liter	.47	.26	1.6	1.0-2.6	.07

* Eastern Cooperative Oncology Group (ECOG) Performance status scale 2-4; N = 90.** ≤ 2 modified Charlson index. [a] 50th percentile for the sample.[b] Folstein's Mini-mental State Questionnaire score ≥ 24. [c] Upper/lower cut-off points for normal value in our laboratories HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval.

Table 13-5: Hazard ratios (HR) in bivariate and multivariate Cox regression models for significant variables in the final main effect model (M2) and the model adjusted for laboratory parameters (M3).

		Bivariate Analysis			Multivariate Analysis		
Predictor	(reference category)	HR	95% CI	P value	HR	95% CI	P value
Primary tumor	(breast, gastrointestinal)						
	Lung	1.8	1.3-2.6	.001	3.5	2.3-5.3	<.0001
Liver metastases	(absent)						
	Present	1.7	1.2-2.5	.002	2.4	1.5-3.6	.0001
Tumor burden	(presence of < 5 lesions)						
	Presence of ≥ 5 lesions	2.0	1.4-3.0	.0006	2.2	1.4-3.6	.0005
Level of comorbidity	(absent-mild**)						
	Moderate-severe	1.7	1.1-2.4	.009	1.9	1.2-2.9	.003
Amount of weight-loss	(≤ 18 lbs.[a])						
	> 18 lbs.	1.8	1.3-2.5	.0009	2.2	1.5-3.4	.0001
Cognitive status	(normal [b])						
	impaired	2.6	1.3-5.4	.008	2.0	.9-4.4	.08
Symptoms number	(≤ 6 [a])						
	> 6	1.8	1.3-2.6	.0004	1.1	.7-1.6	>.20
Serum albumin	(≥35g/liter[c])						
	< 35 g/liter	2.4	1.7-3.4	<.0001	1.8	1.2-2.8	.002
Lymphocytes	(≥ 1 x 10^9/liter[c])						
	< 1 x 10^9/liter	2.3	1.6-3.2	<.0001	2.0	1.4-3.0	.0004
Lactate dehydrogenase	(≤ 618 U/liter[c])						
	> 618 U/liter	2.3	1.6-3.2	<.0001	1.7	1.1-2.5	.01

* N = 165.** ≤ 2 modified Charlson index. [a] 50th percentile for the sample. [b] Folstein's Mini-mental State Questionnaire score ≥ 24.[c] Upper/lower cut-off points for normal value in our laboratories. HR: Hazard ratio. B: regression coefficient. SE: standard error. CI: confidence interval.

Figure 1-5: Primary tumor sites

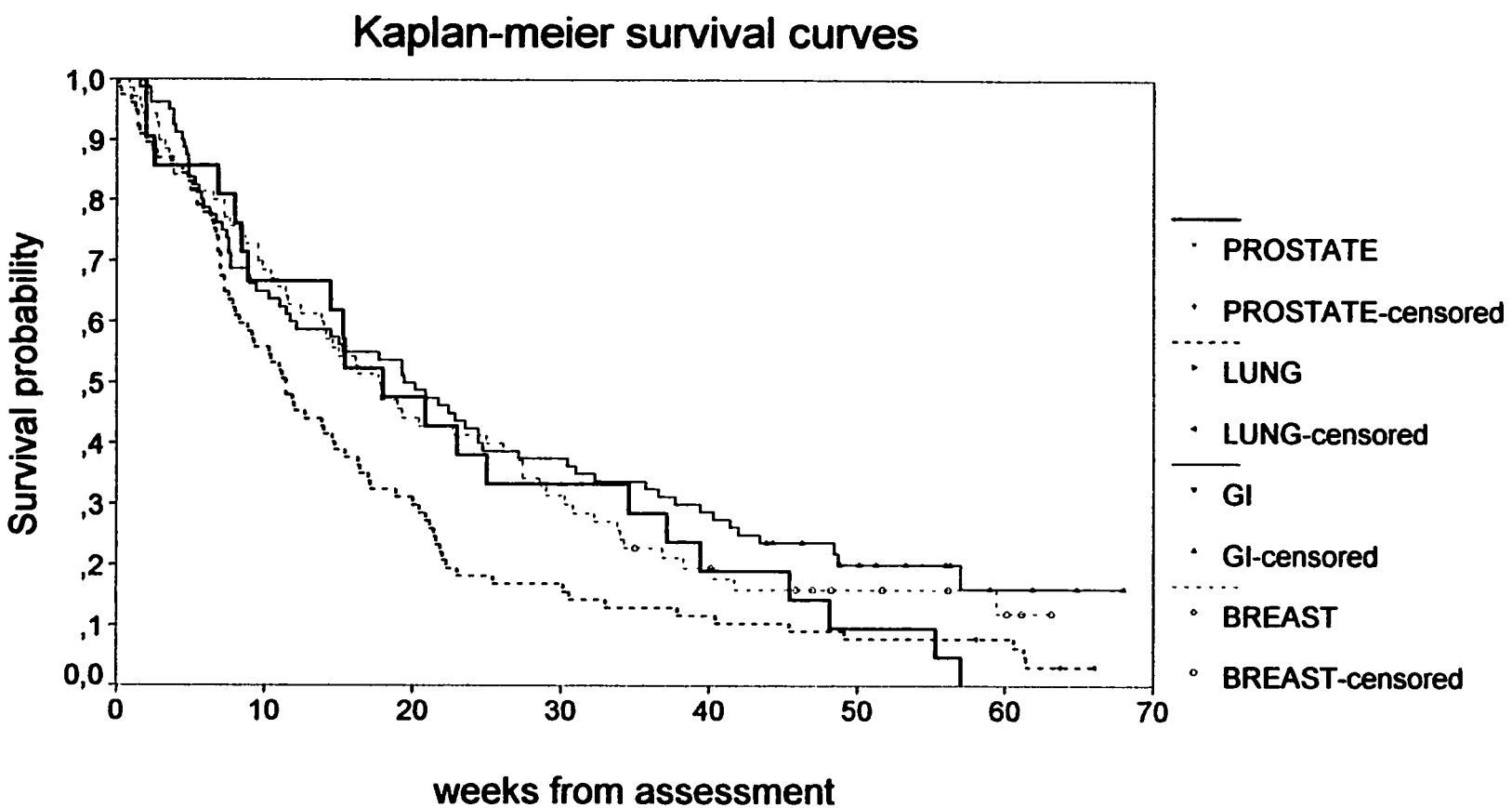
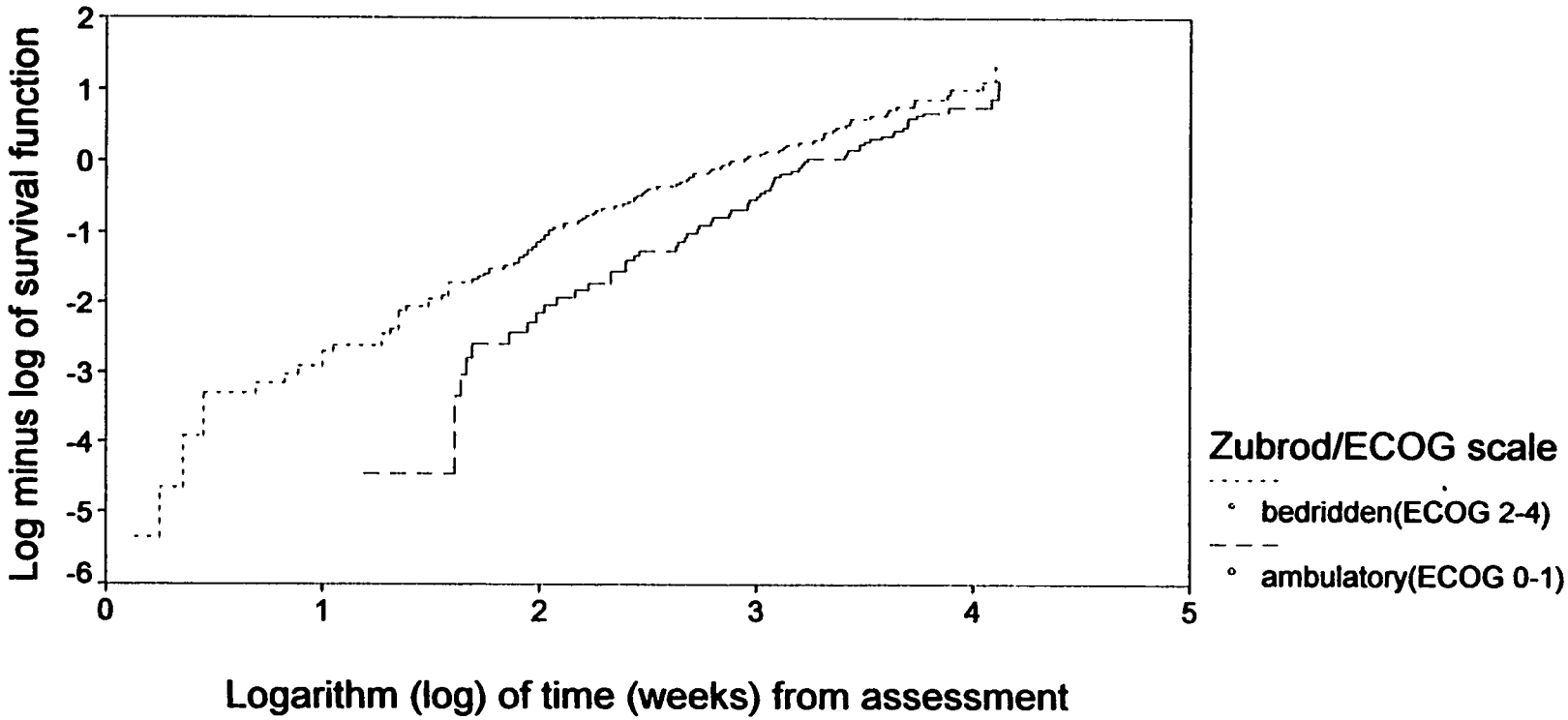


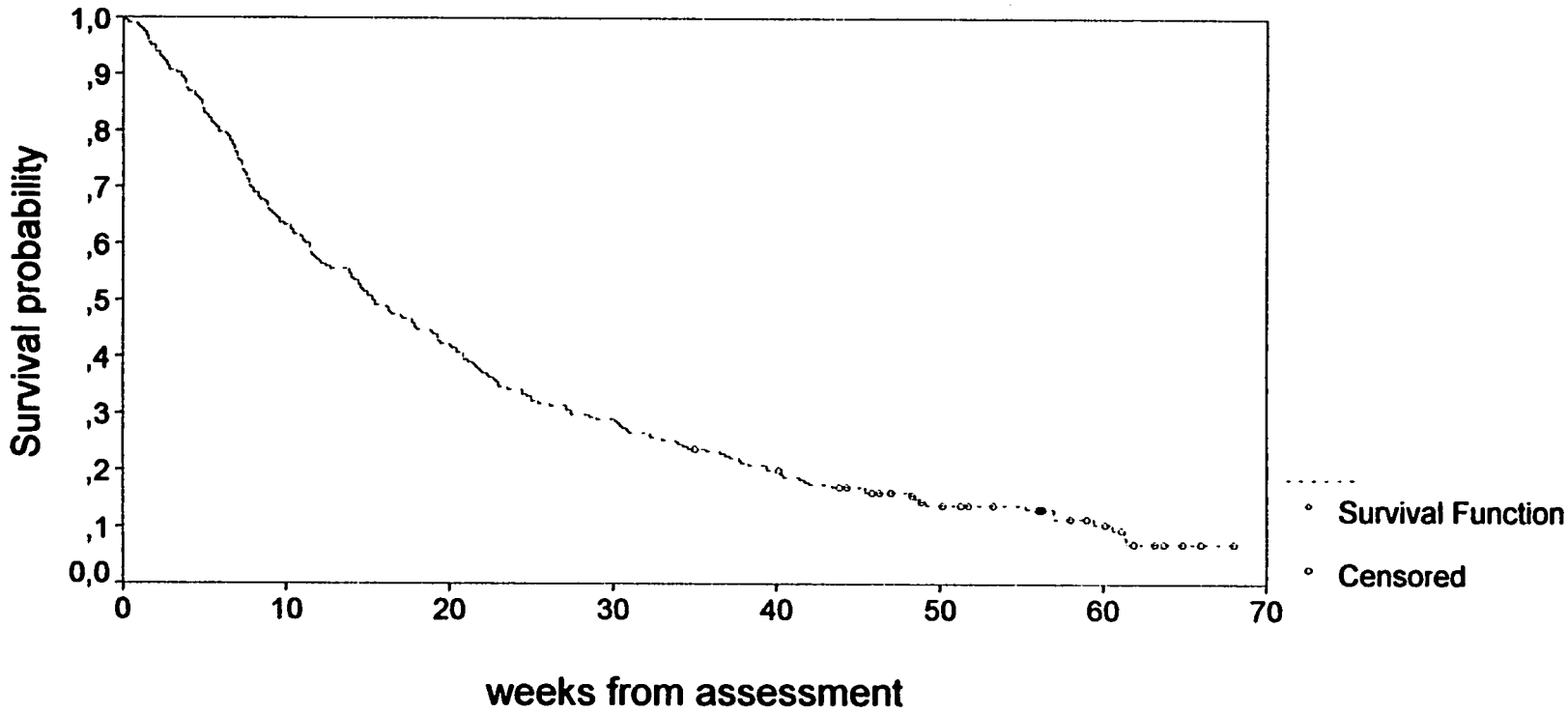
Figure 2-5: LML graph by Performance Status for Model 1*



* Model unadjusted for laboratory variables

Figure 3-5: Cumulative survival probability

Overall sample: 248 patients



Overall median survival: 17 weeks (95% C.I.: 12, 18)

Figure 4-5: LML graph by primary tumor type for Model 1

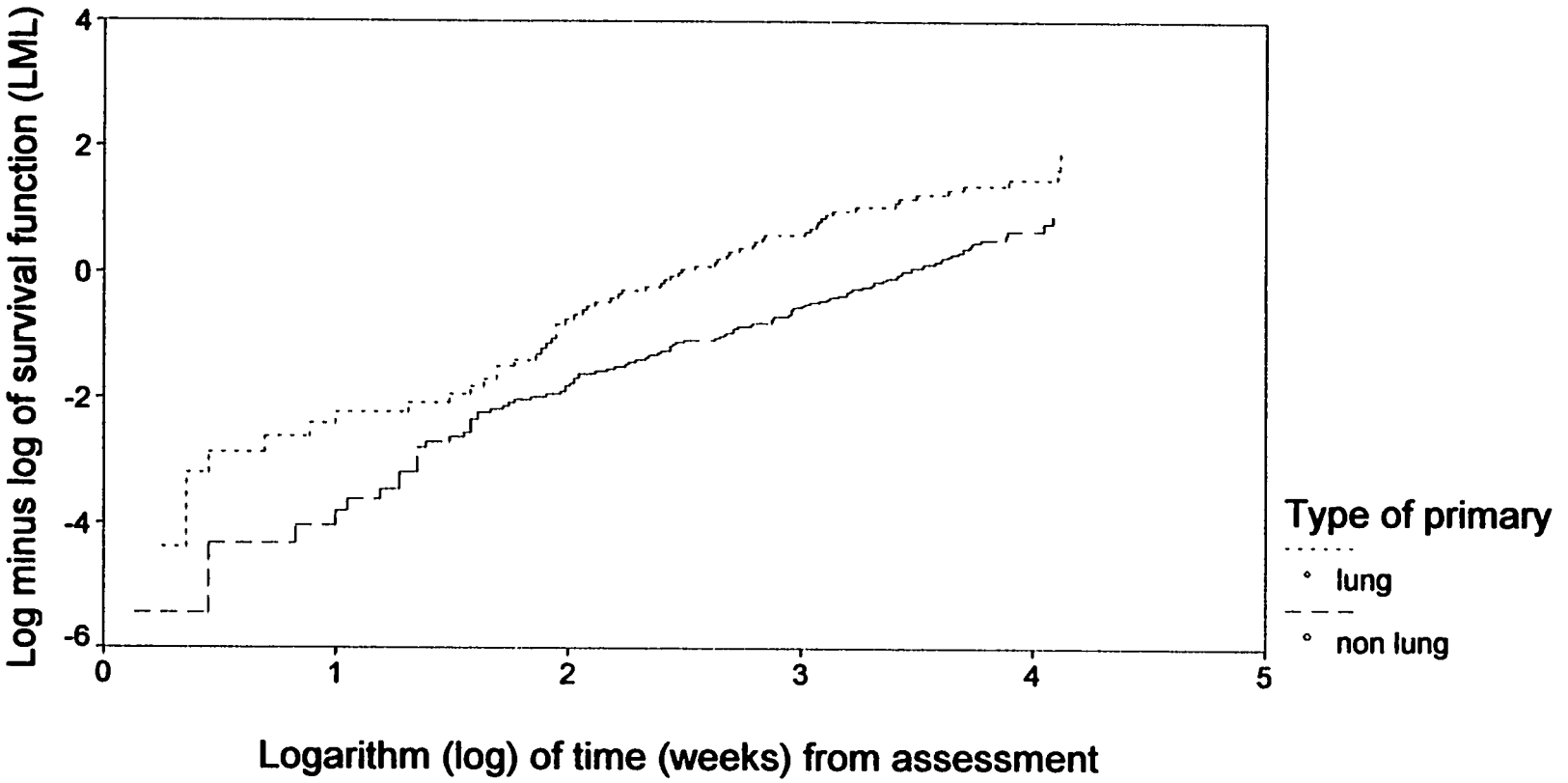


Figure 5-5: LML graph by liver metastases for Model 1

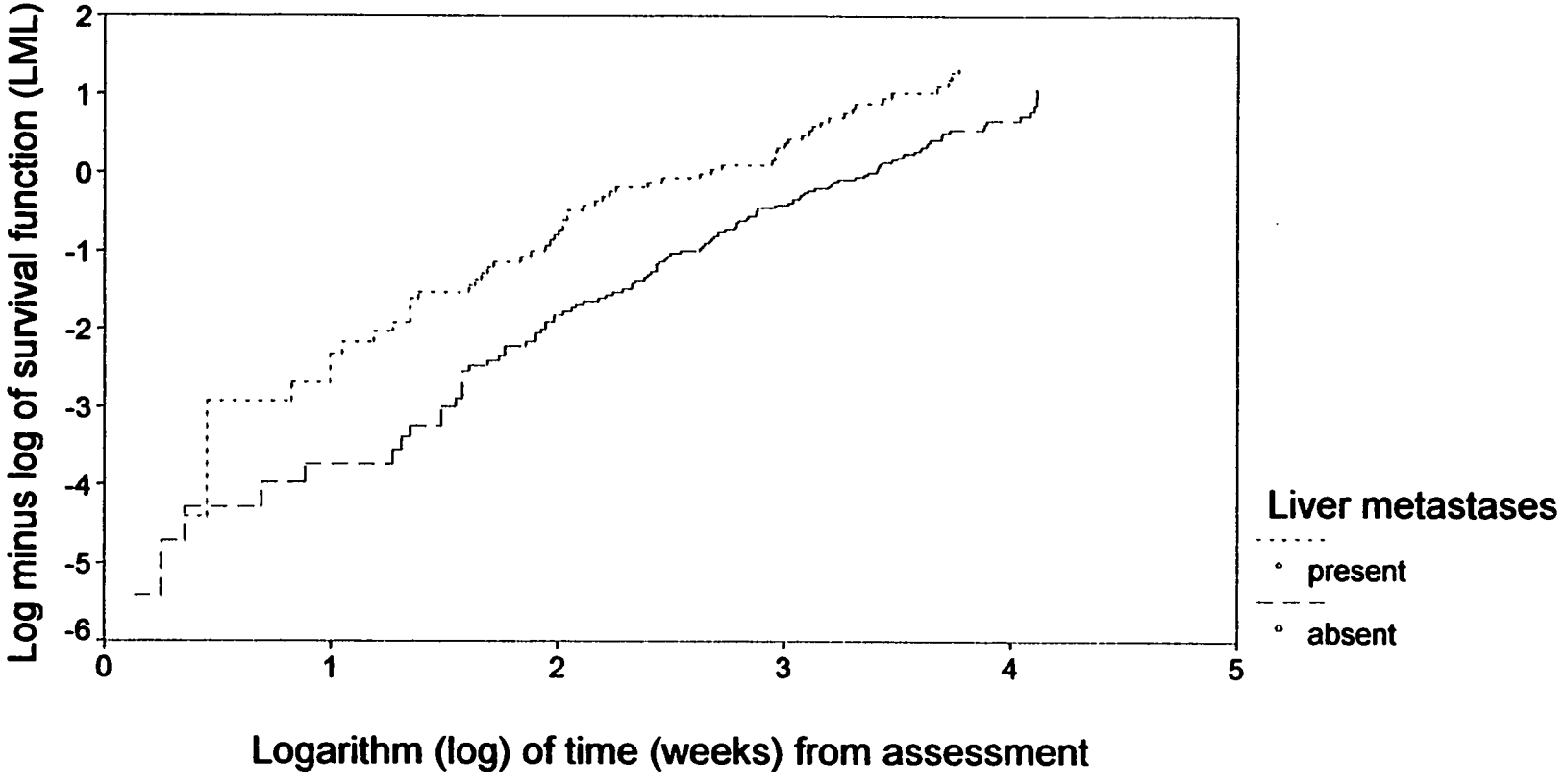


Figure 6-5: LML graph by tumor burden for Model 1

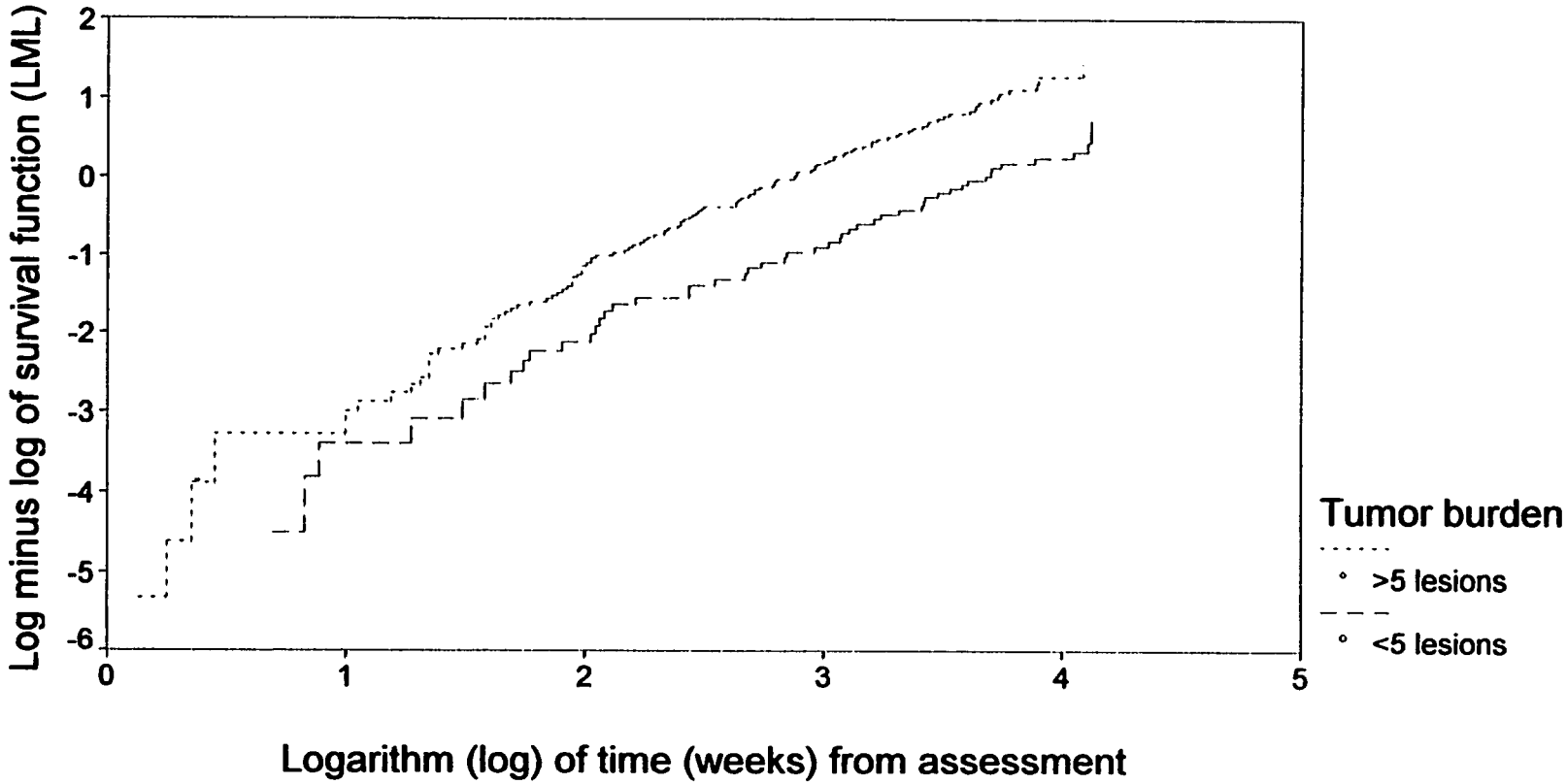


Figure 7-5: LML graph by comorbidity level for Model 1

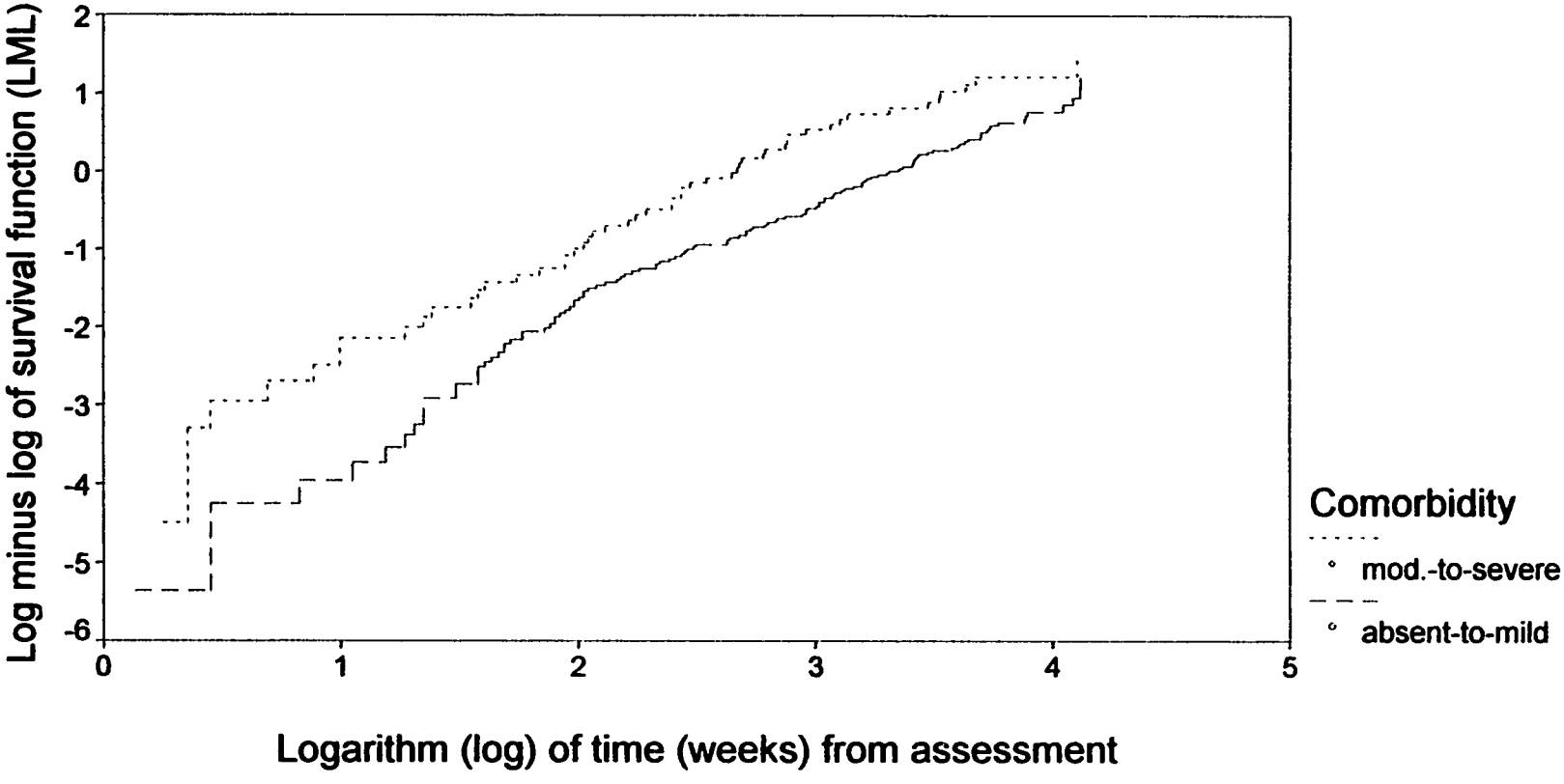


Figure 8-5: LML graph by cognitive status for Model 1

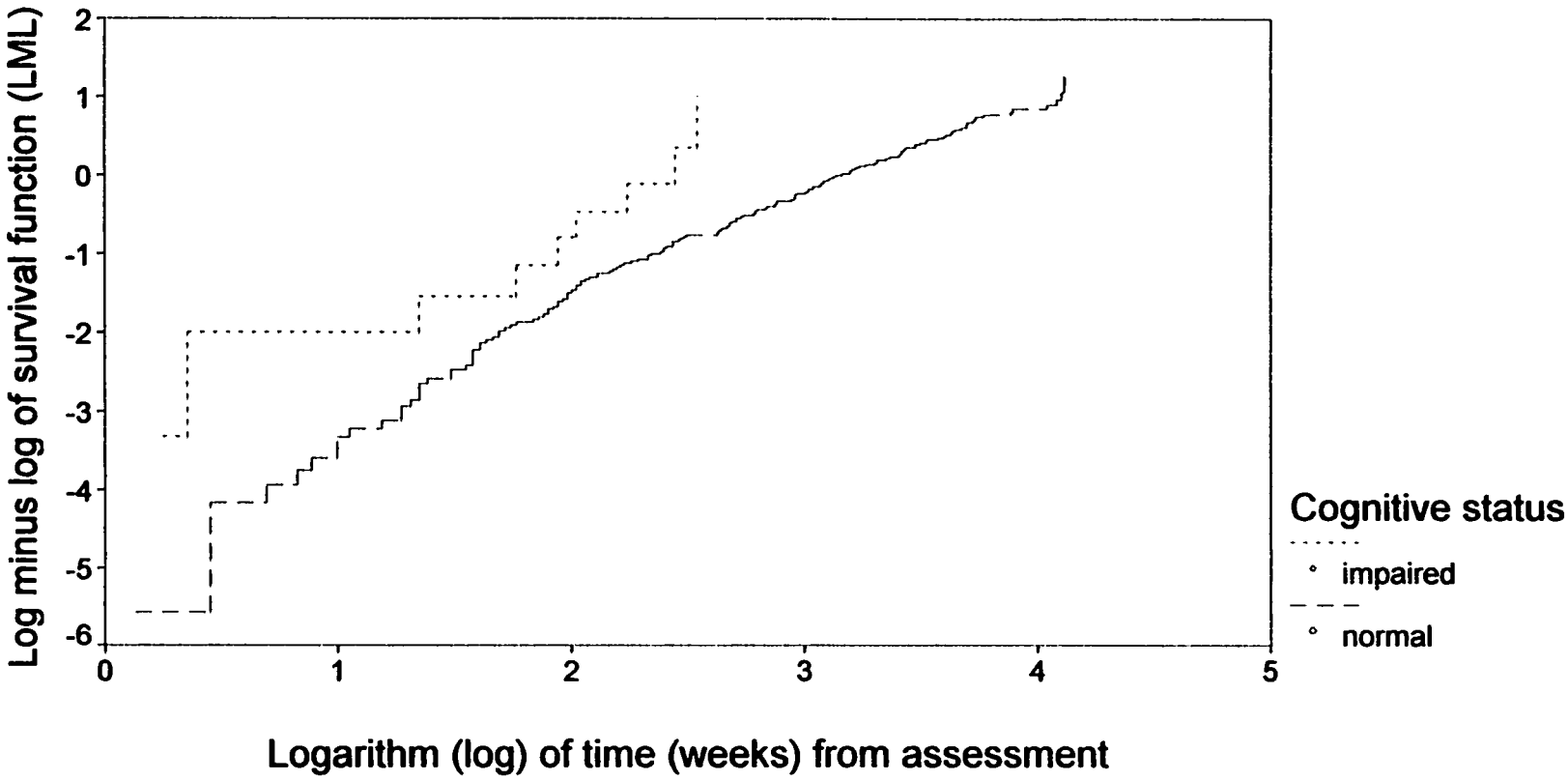
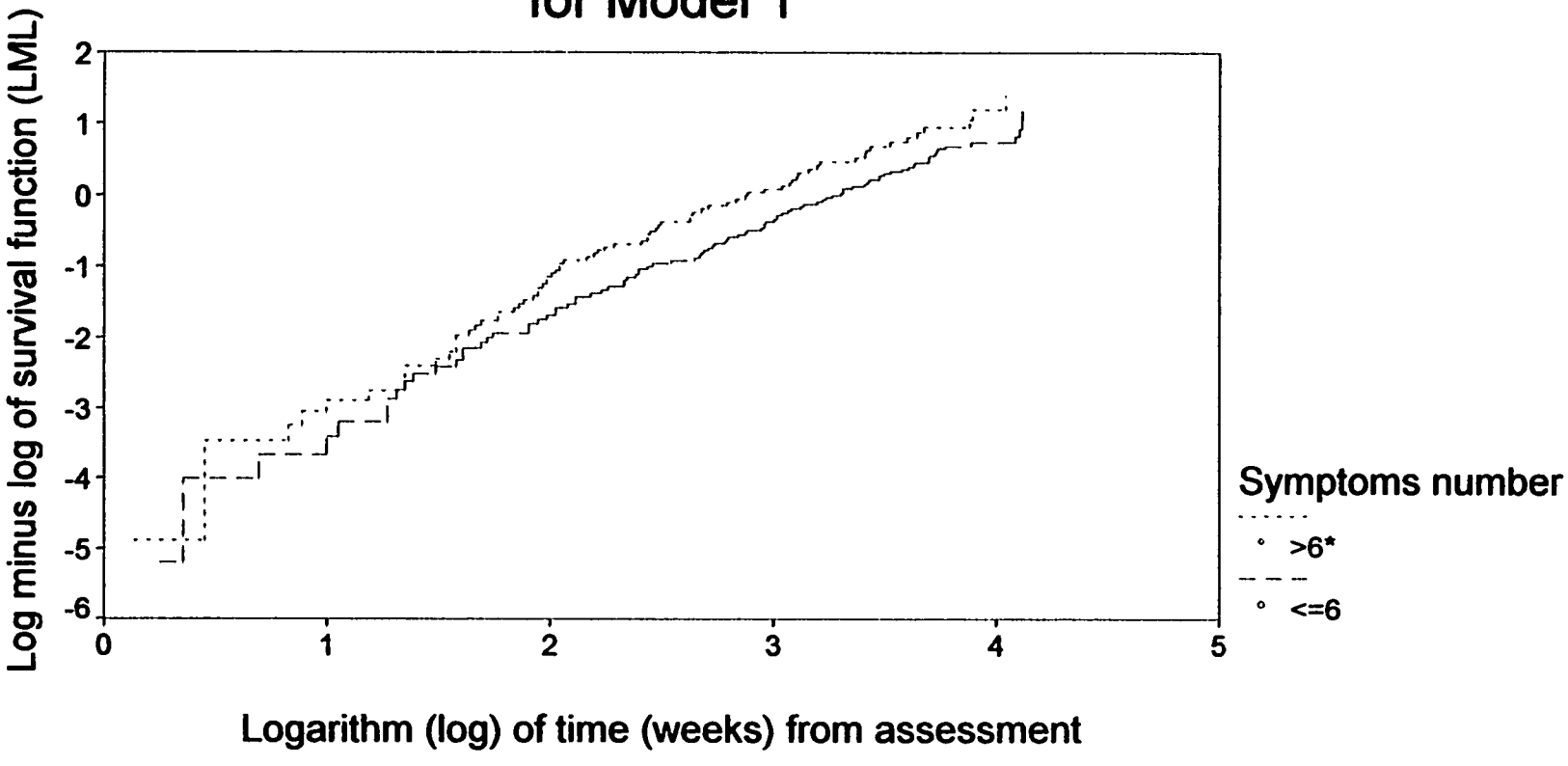


Figure 9-5: LML graph by symptoms number for Model 1



* 50th percentile for the sample

Figure 10-5: LML graph by nausea intensity for Model 1

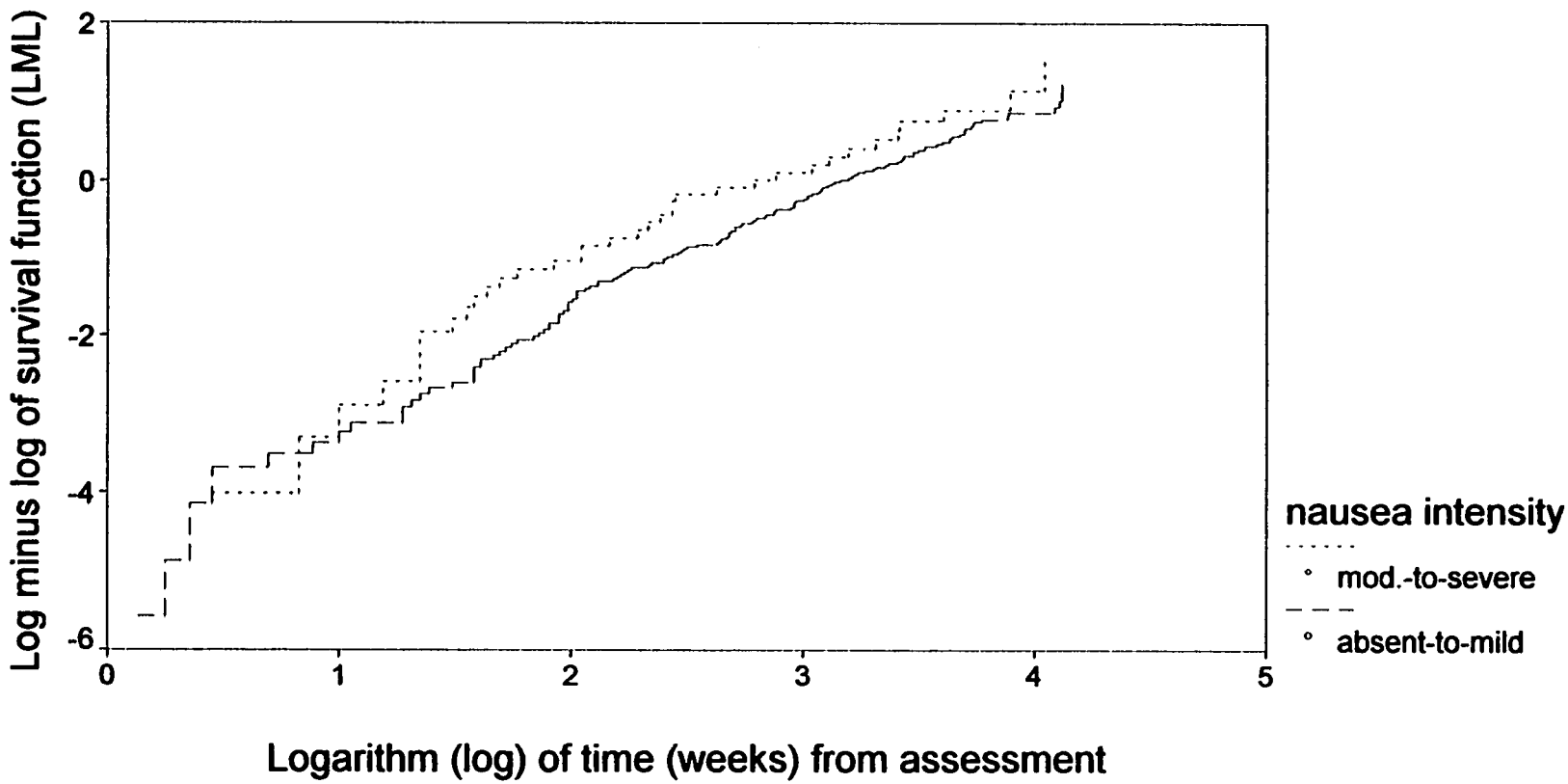
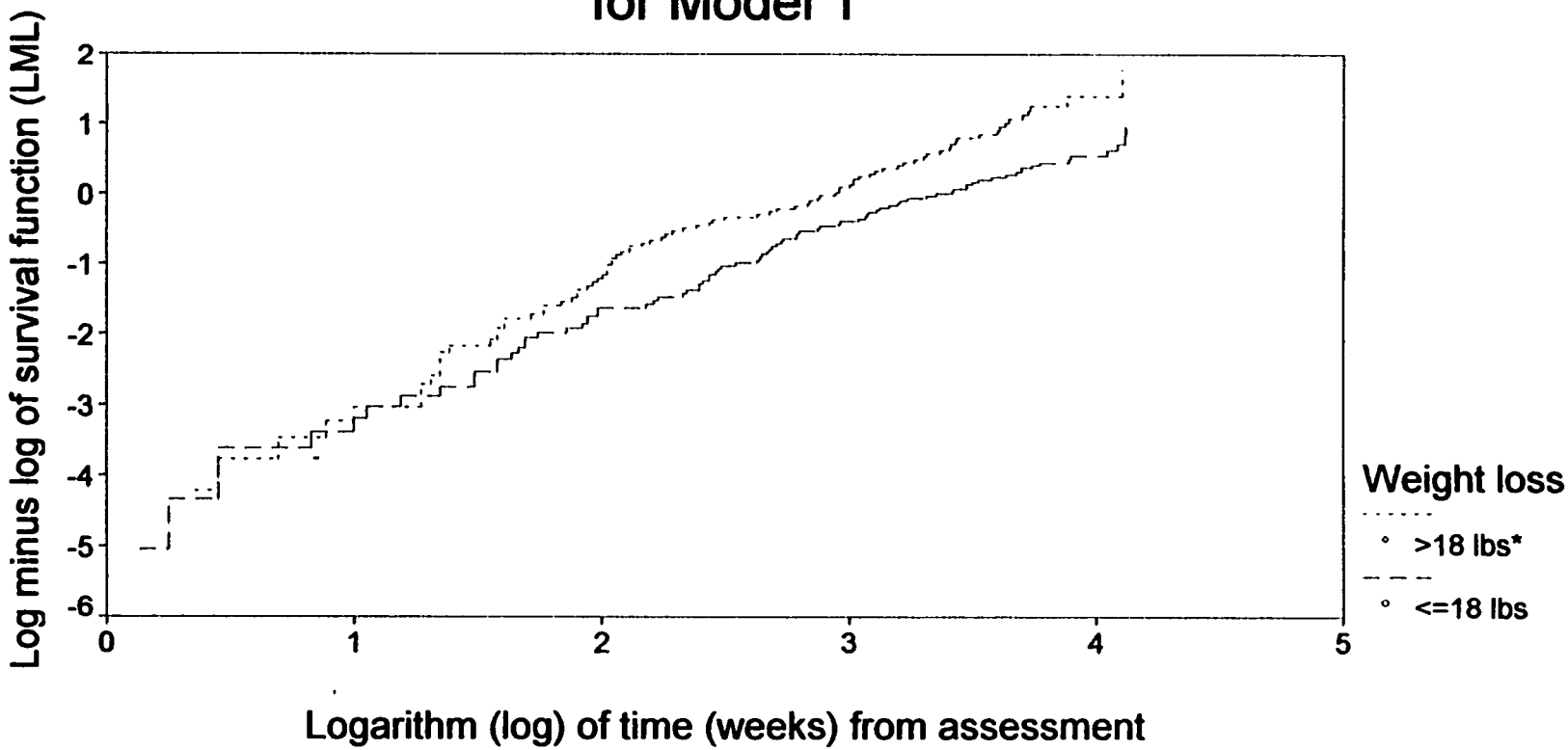
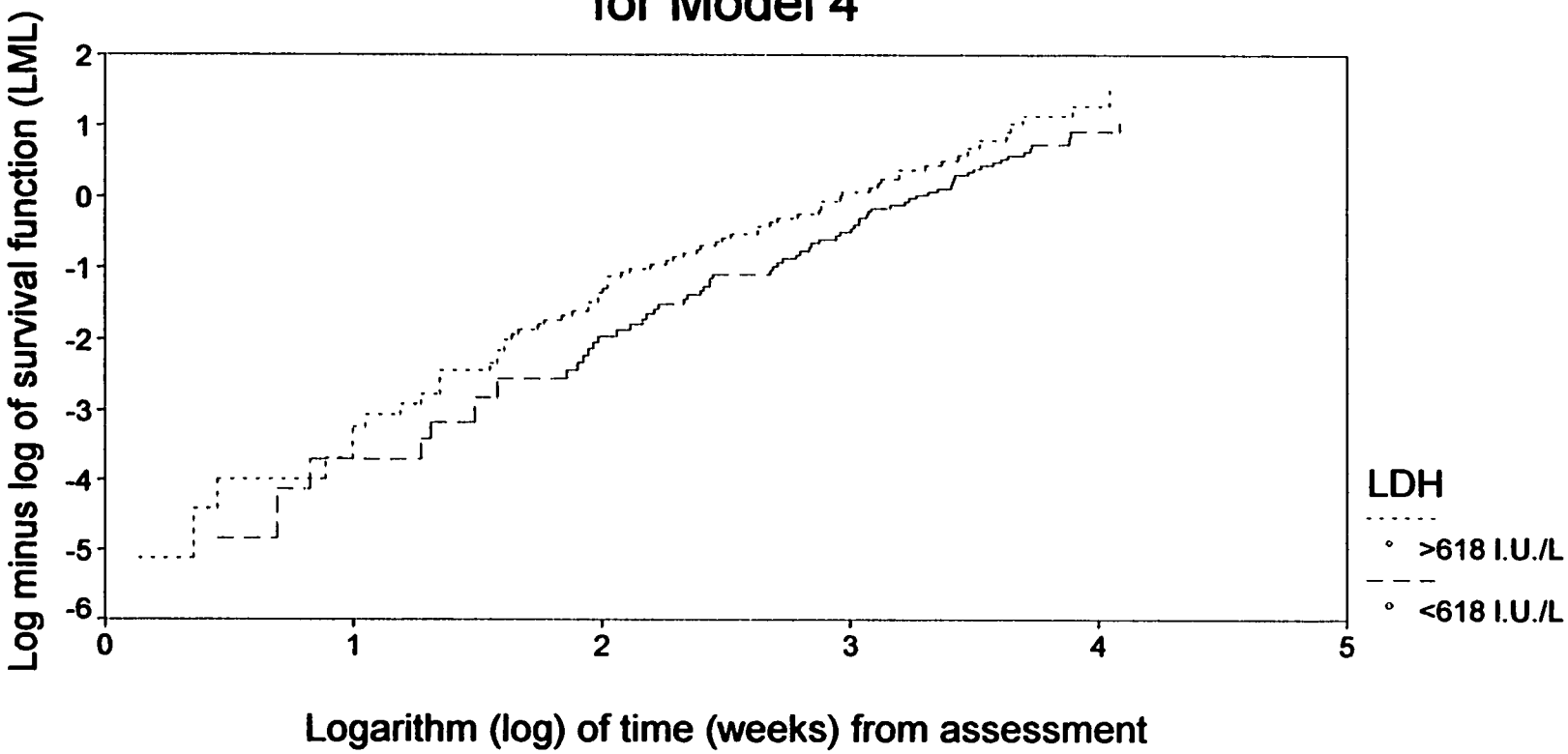


Figure 11-5: LML graph by weight loss for Model 1



* 50th percentile for the sample

Figure 12-5: LML graph by LDH* for Model 4



* Lactate dehydrogenase

Figure 13-5: LML graph by lymphocytes count for Model 4

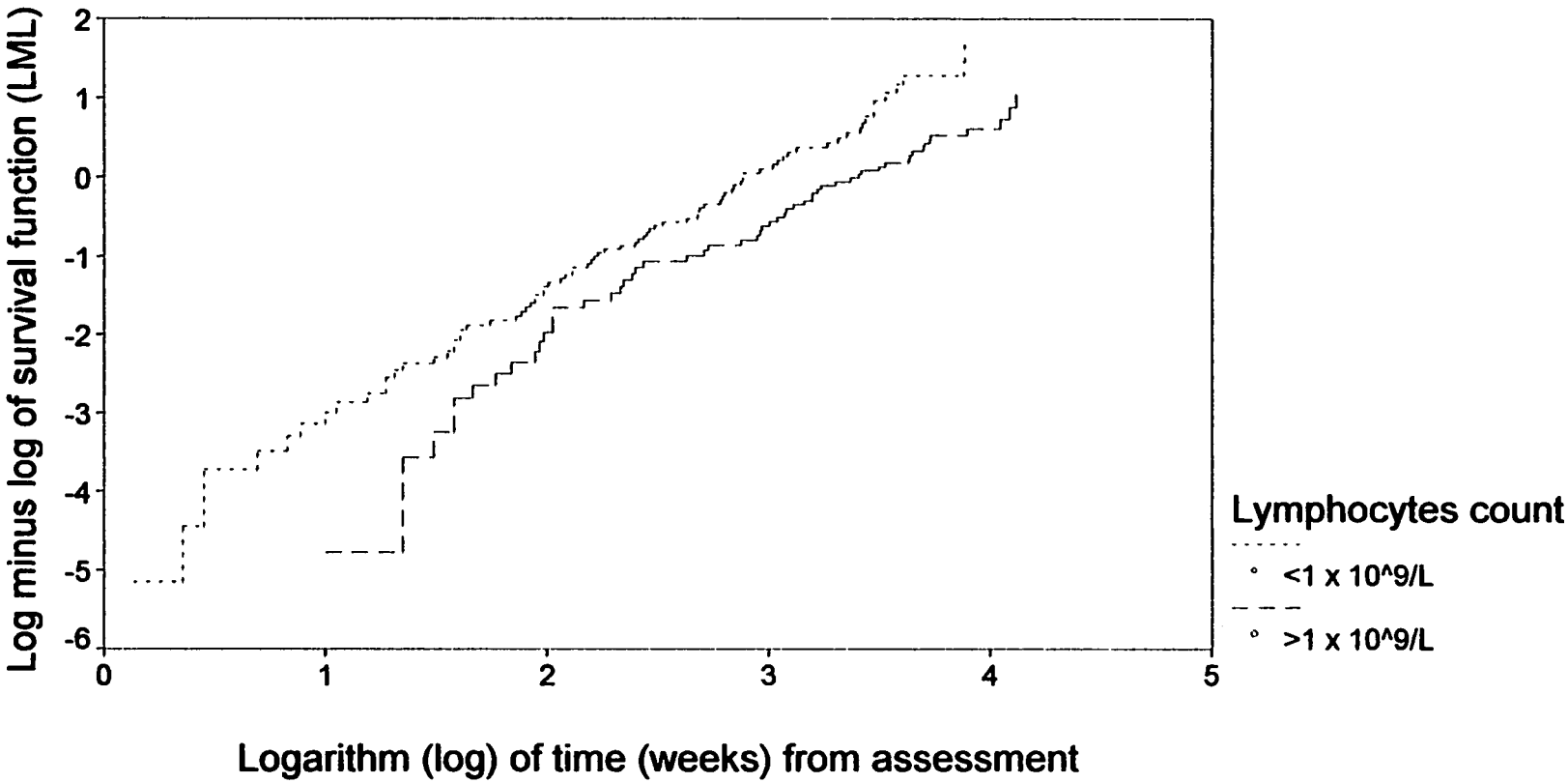


Figure 14-5: LML graph by albumin for Model 4

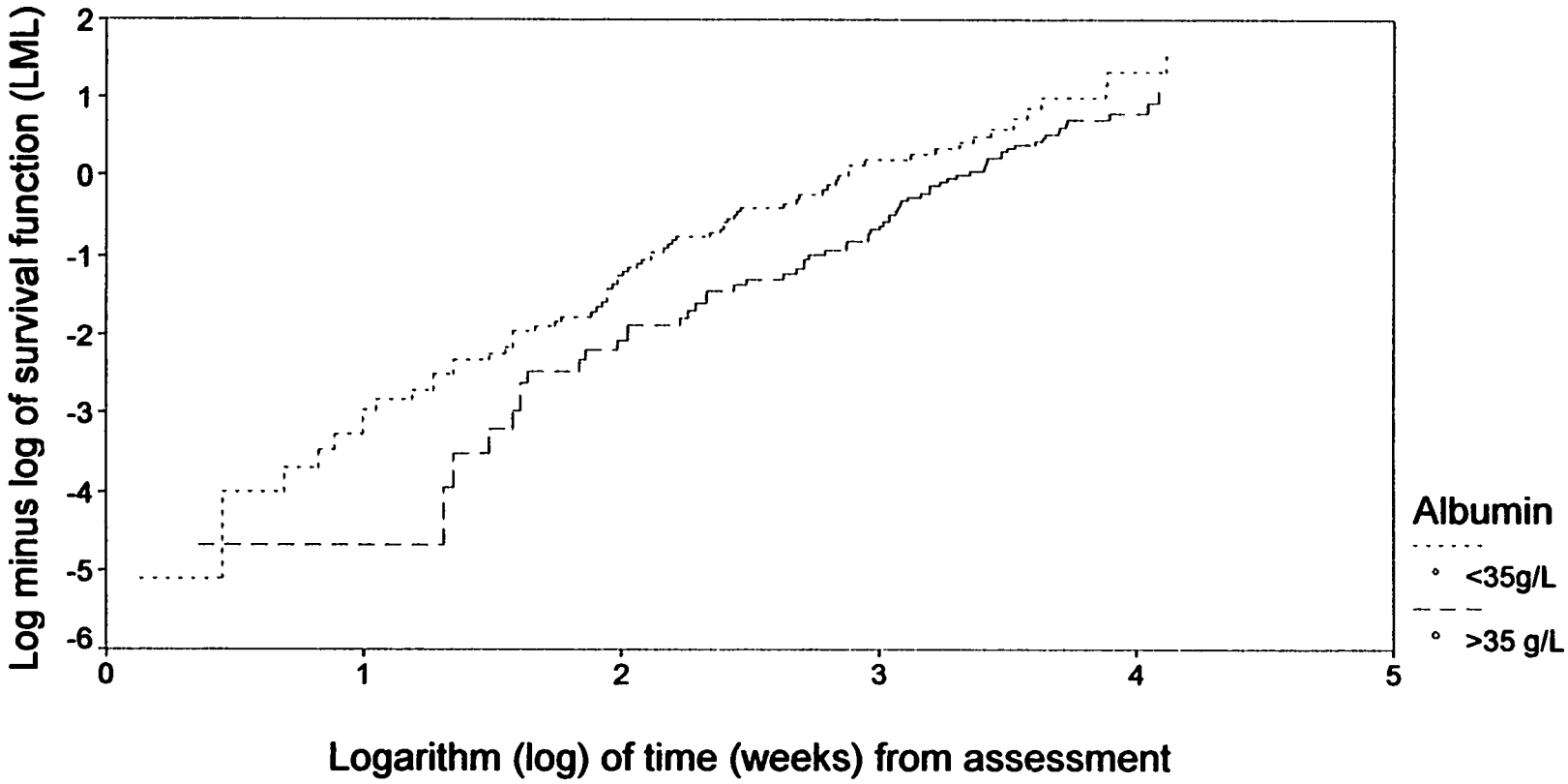


Figure 15-5: Martingale residuals plot for Model 4*

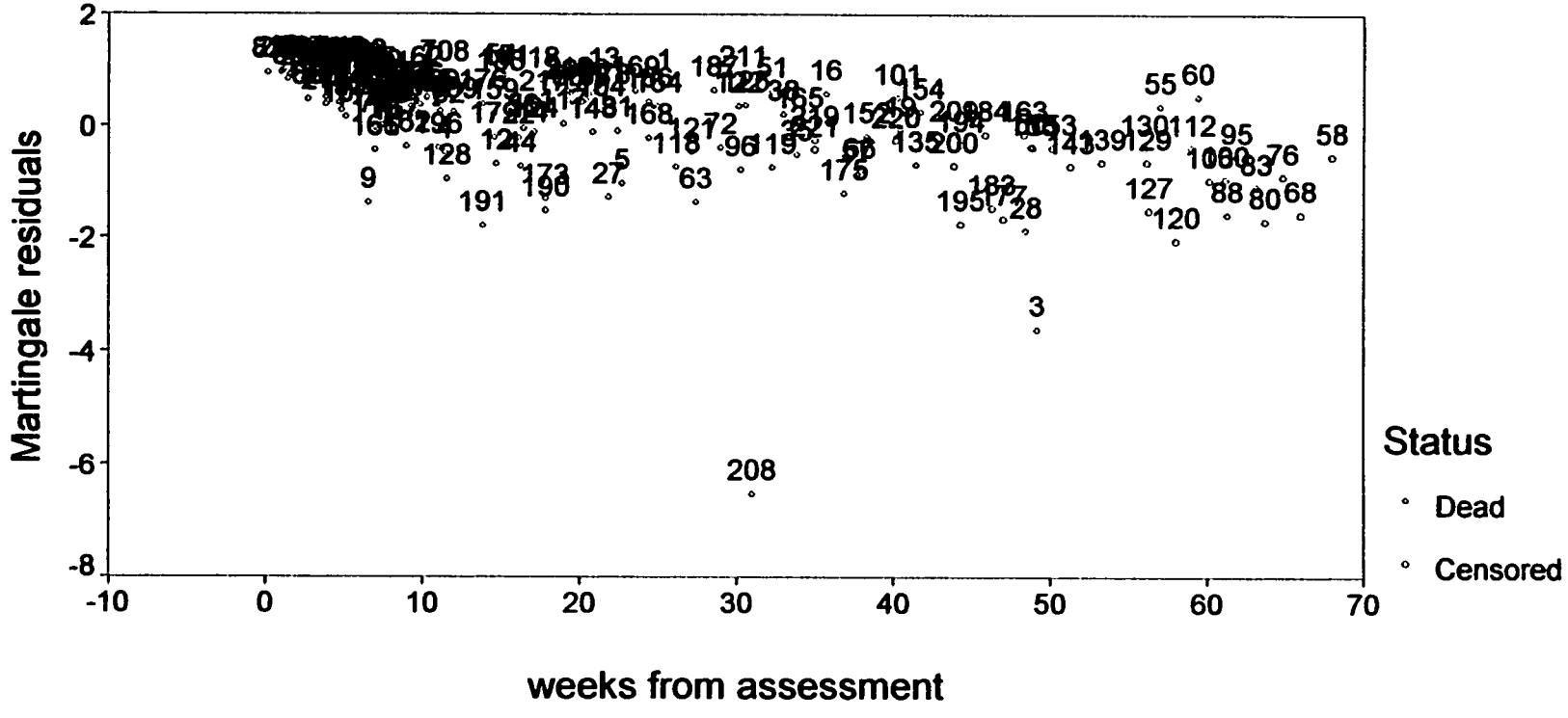


Figure 16-5: Martingale residuals plot for Model 4*

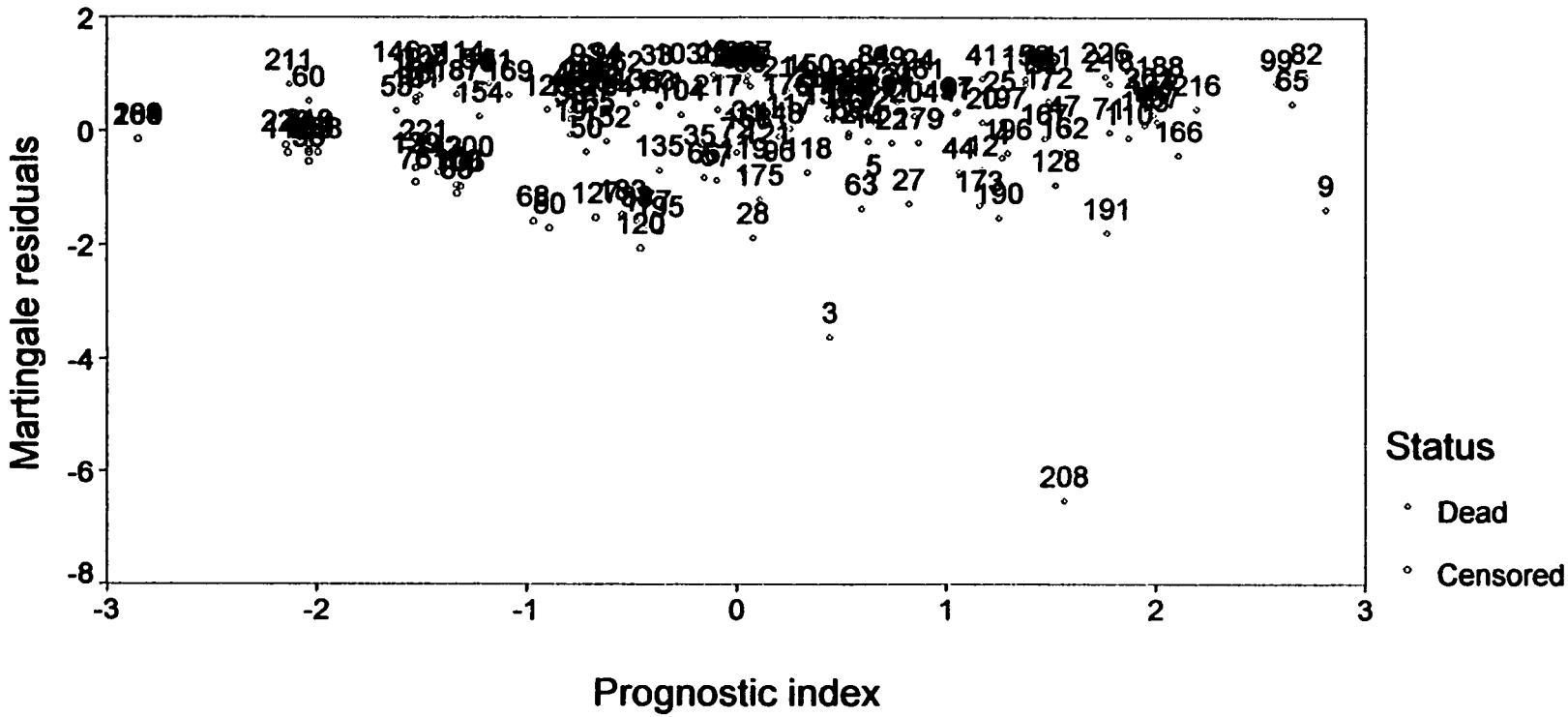


Figure 17-5: DfBeta plot for primary tumor site for Model 4

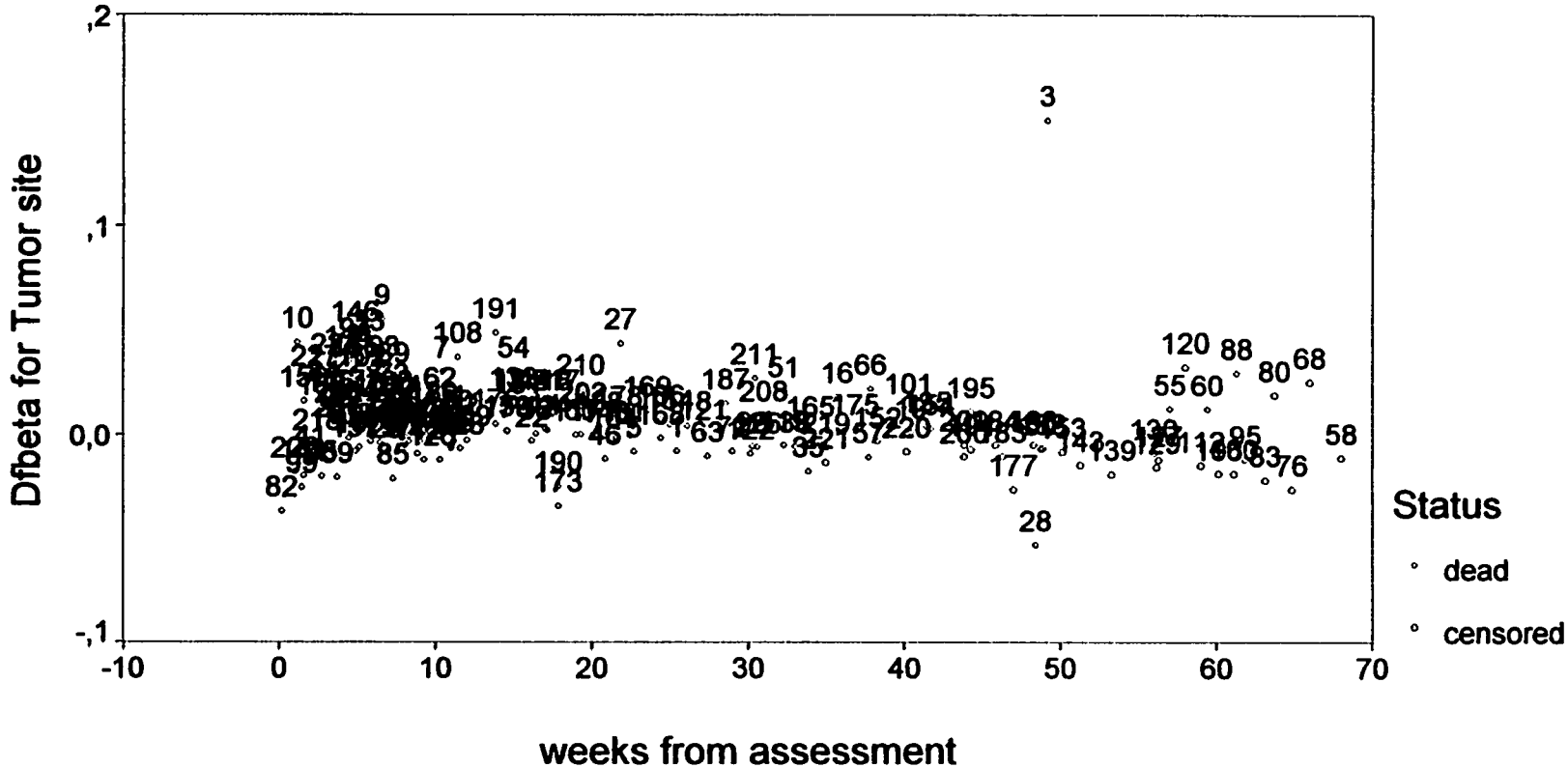


Figure 18-5: DfBeta plot for liver metastases for Model 4

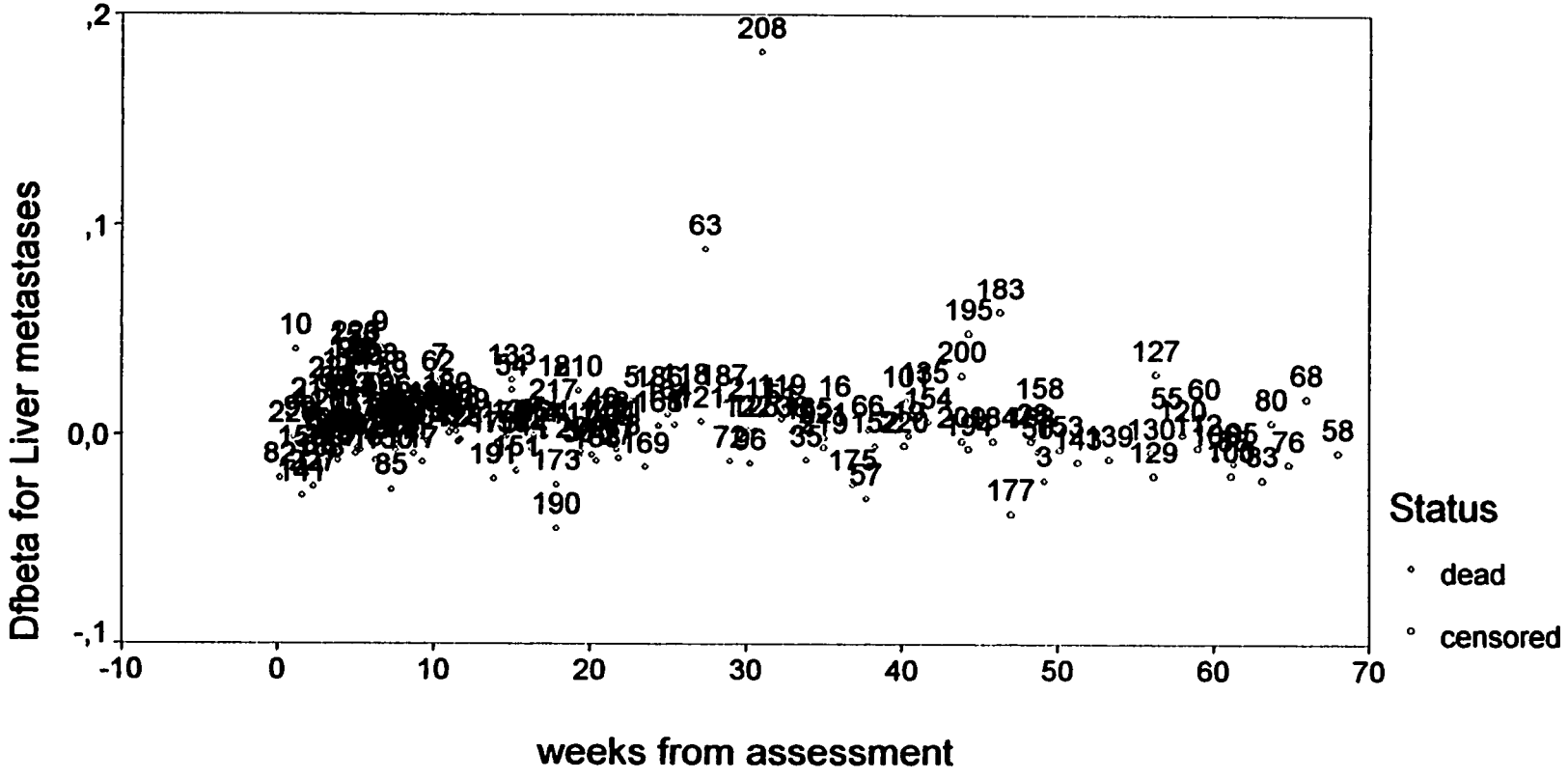


Figure 19-5: DfBeta plot for tumor burden for Model 4

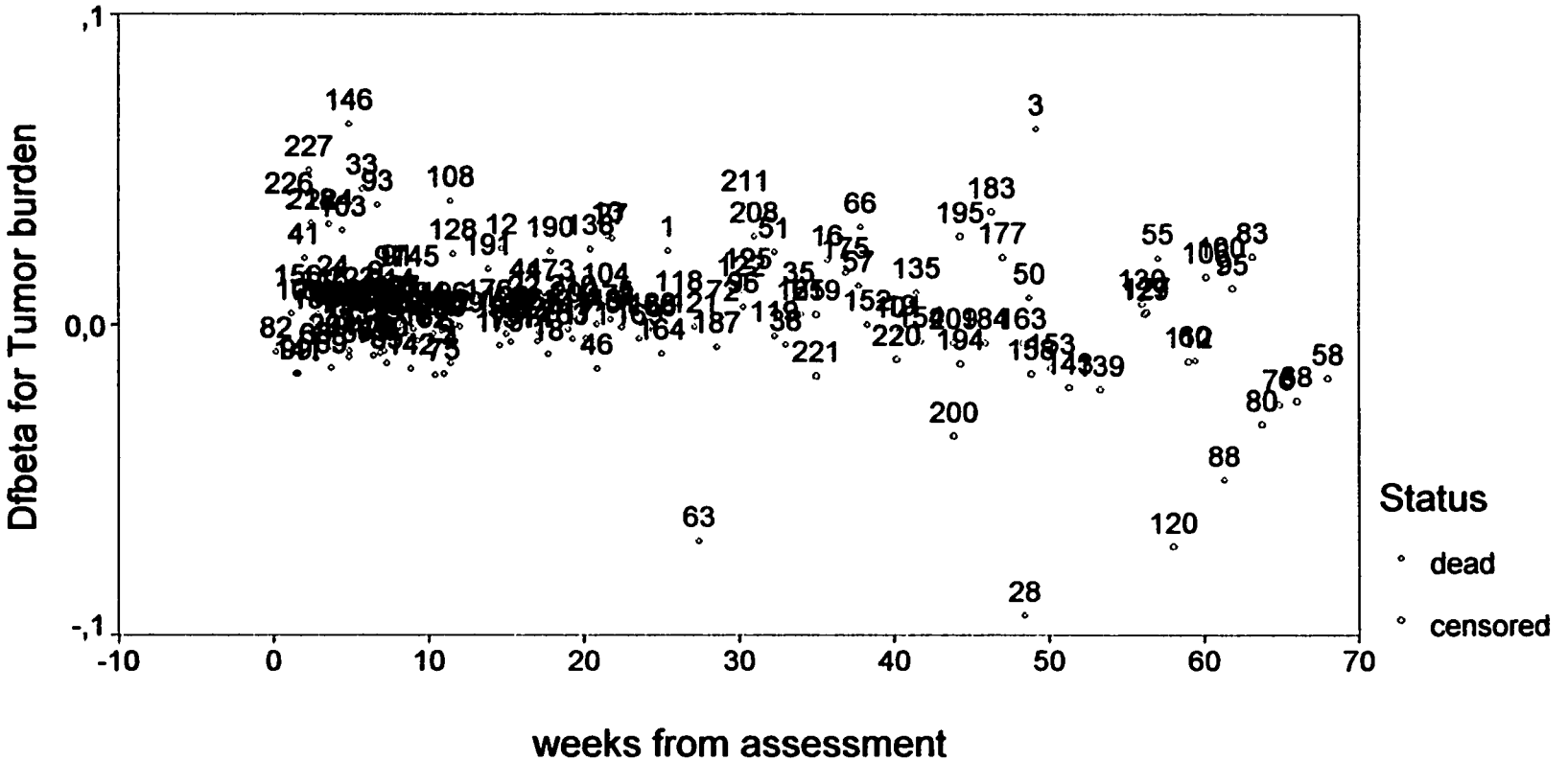


Figure 20-5: DfBeta plot for comorbidity level for Model 4

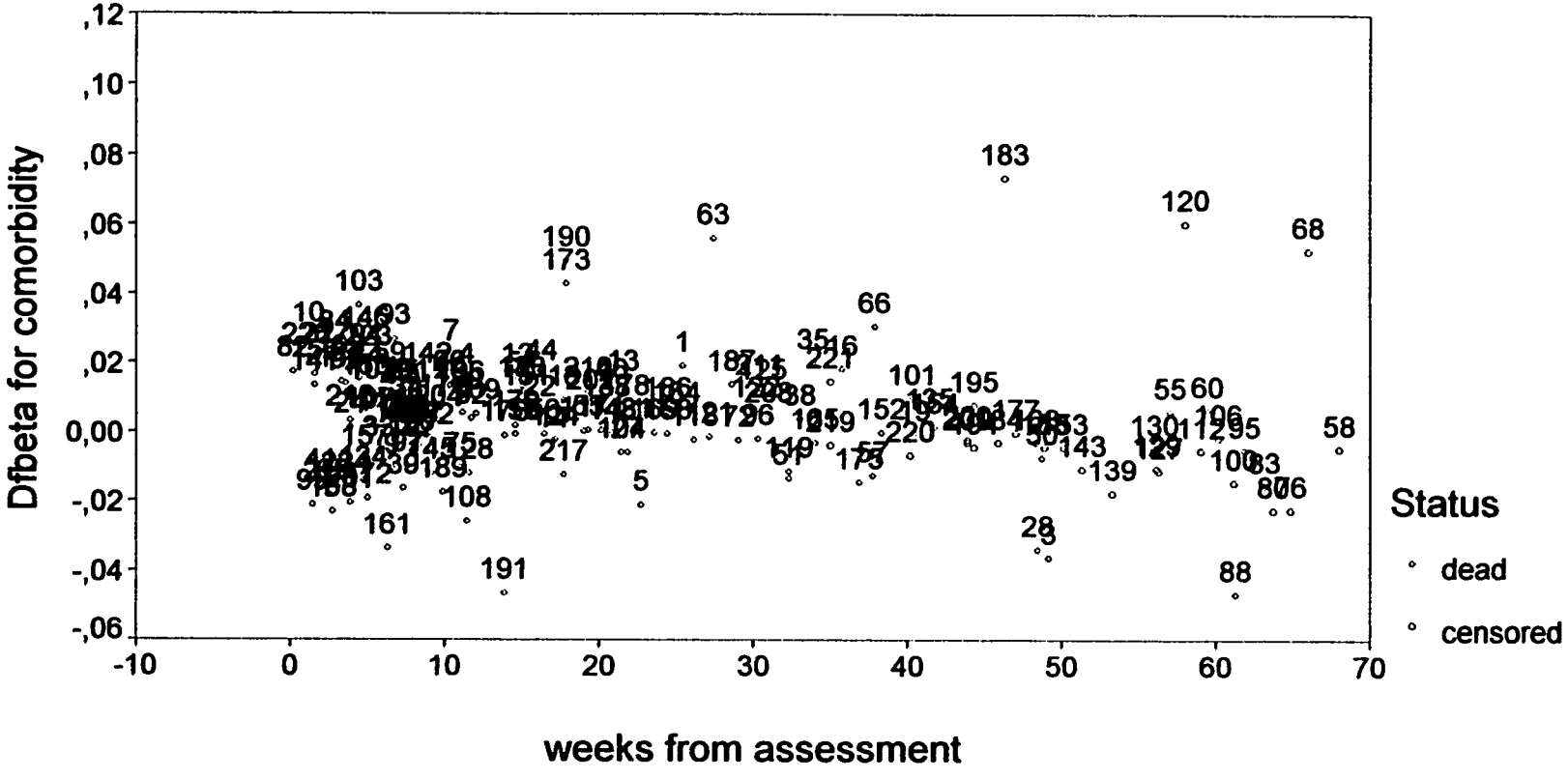


Figure 21-5: DfBeta plot for nausea intensity for Model 4

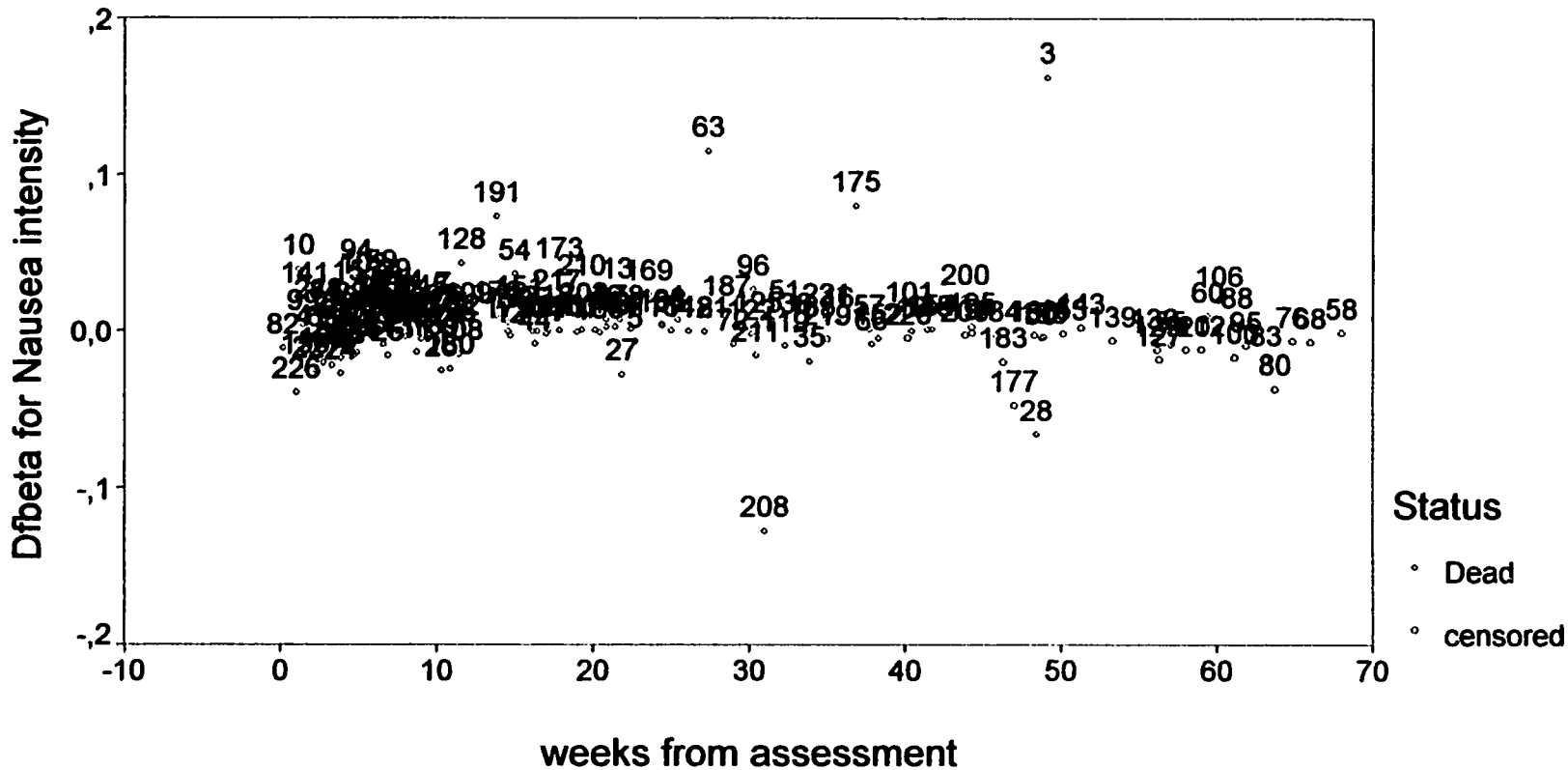


Figure 22-5: DfBeta plot for weight loss for Model 4

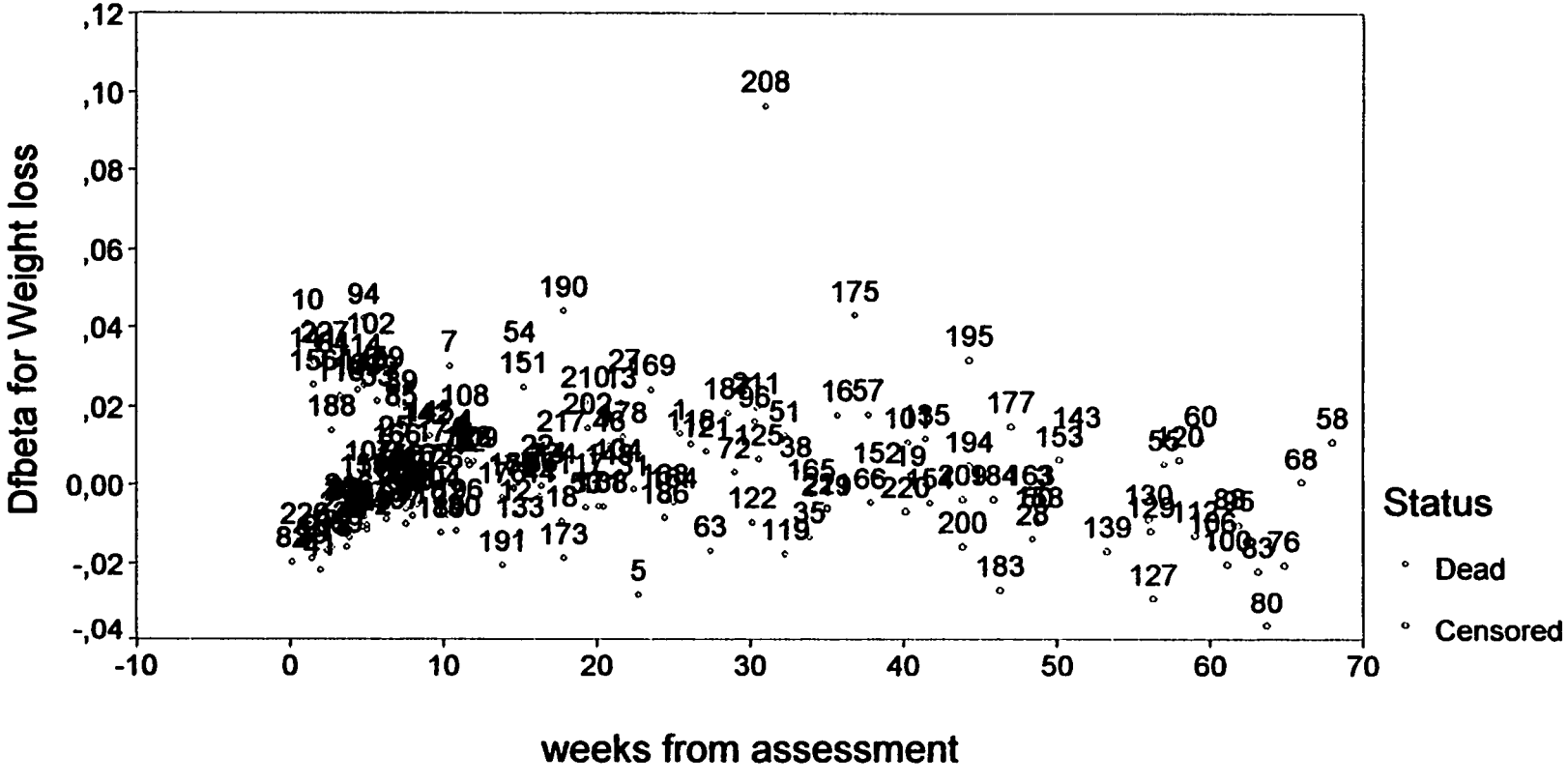


Figure 23-5: DfBeta plot for cognitive status for Model 4

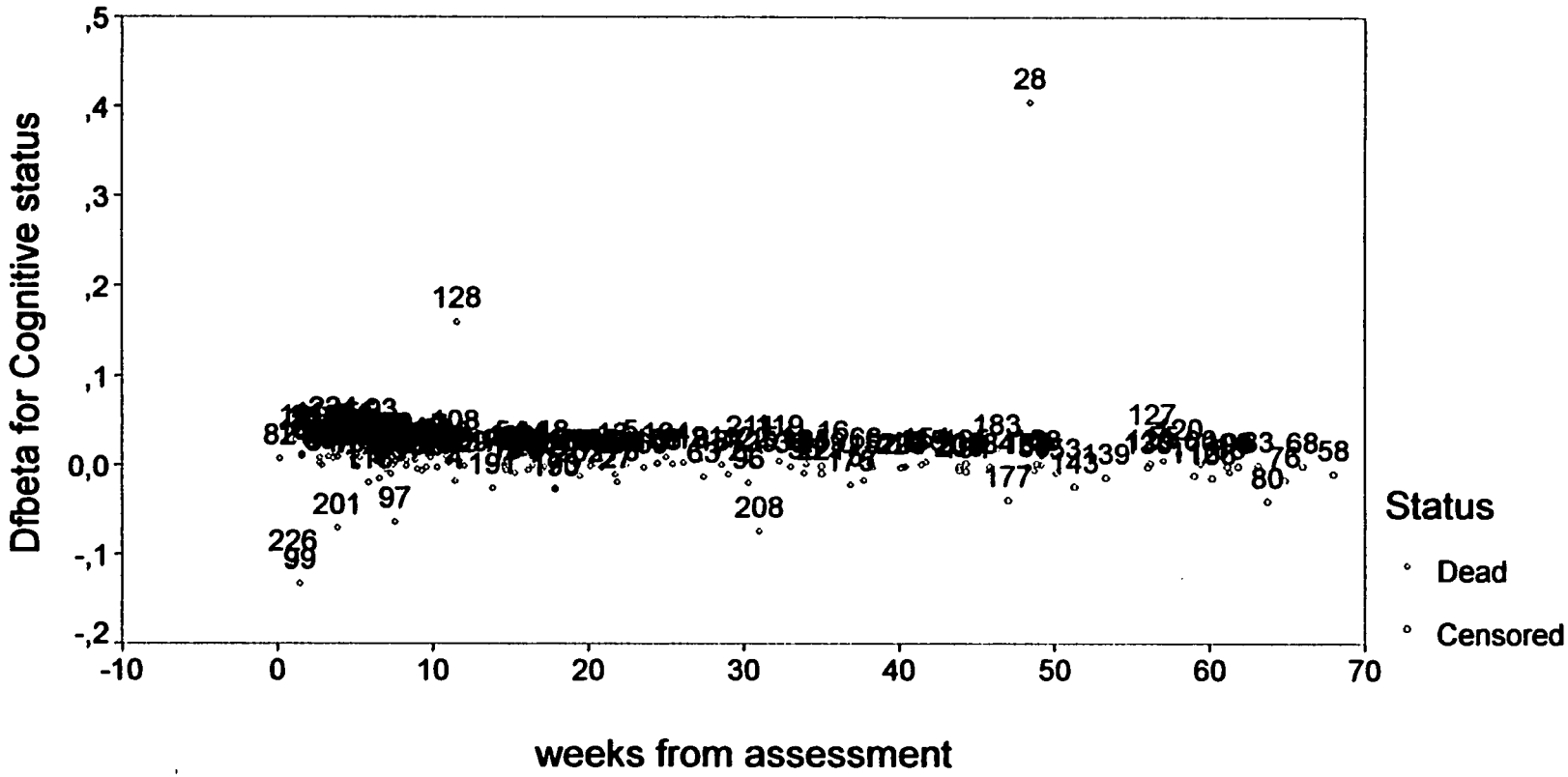


Figure 24-5: DfBeta plot for symptoms number for Model 4

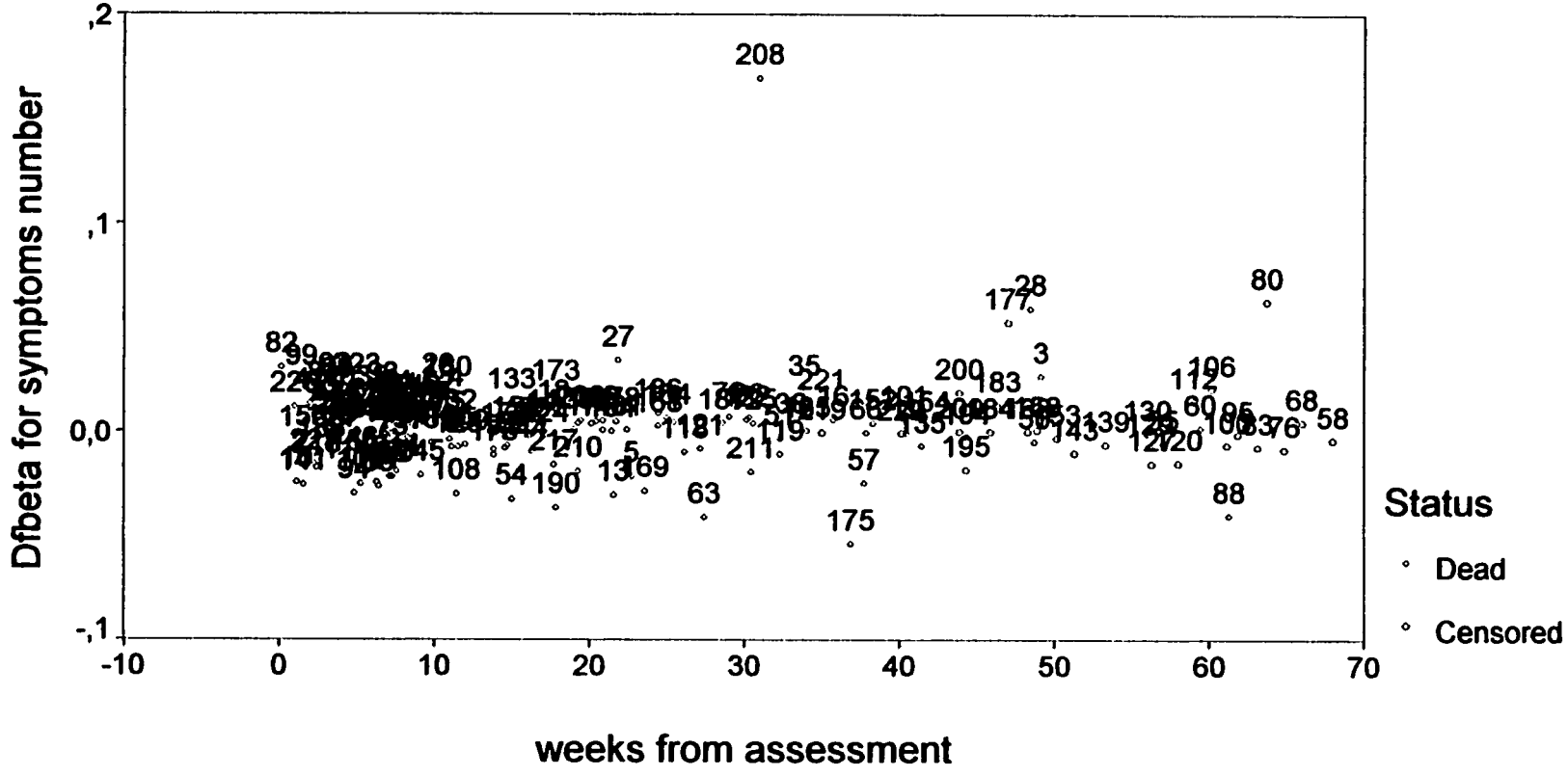
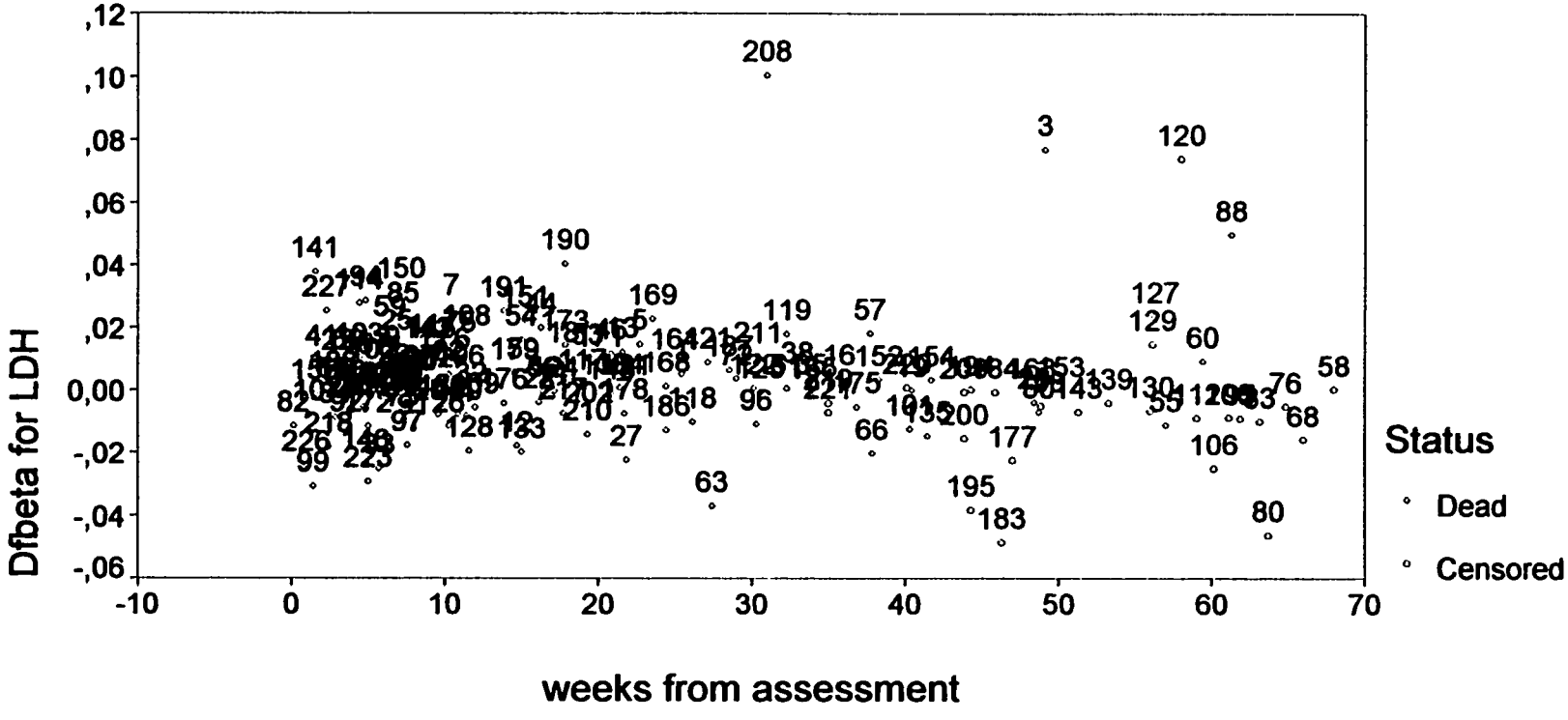


Figure 25-5: DfBeta plot for LDH* for Model 4



* Serum lactate dehydrogenase

Figure 26-5: DfBeta plot for lymphocytes count for Model 4

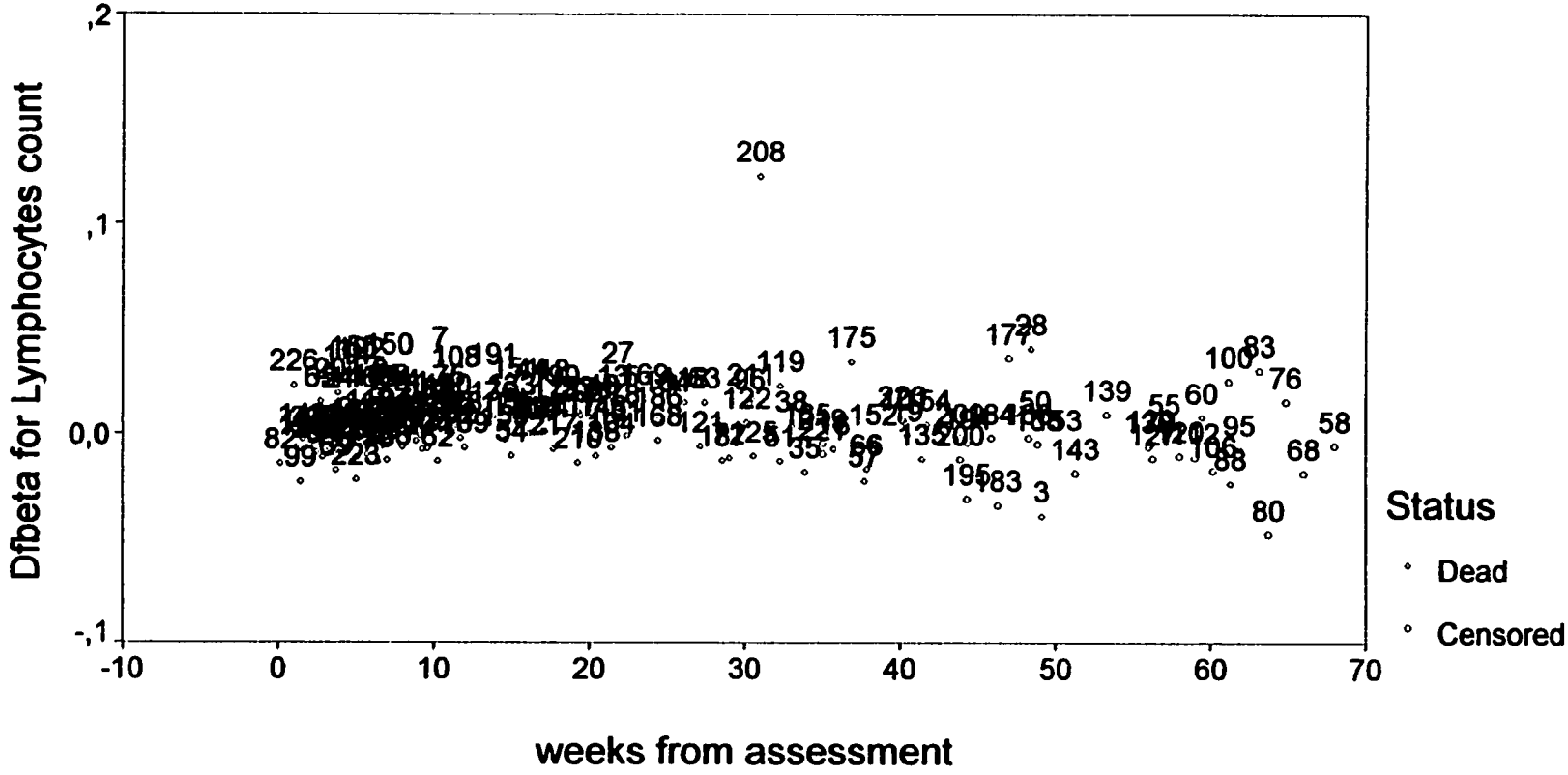


Figure 27-5: DfBeta plot for albumin for Model 4

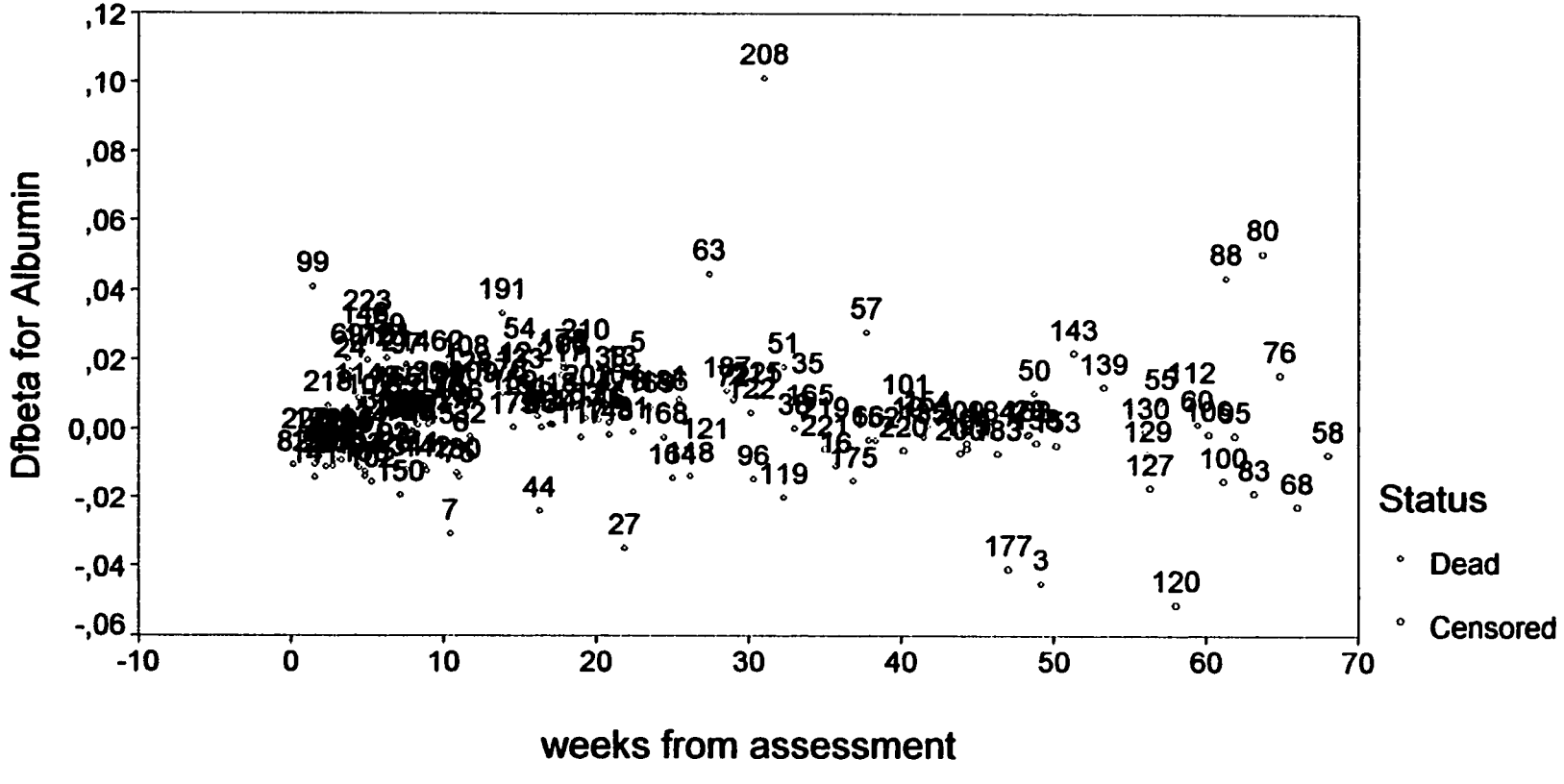
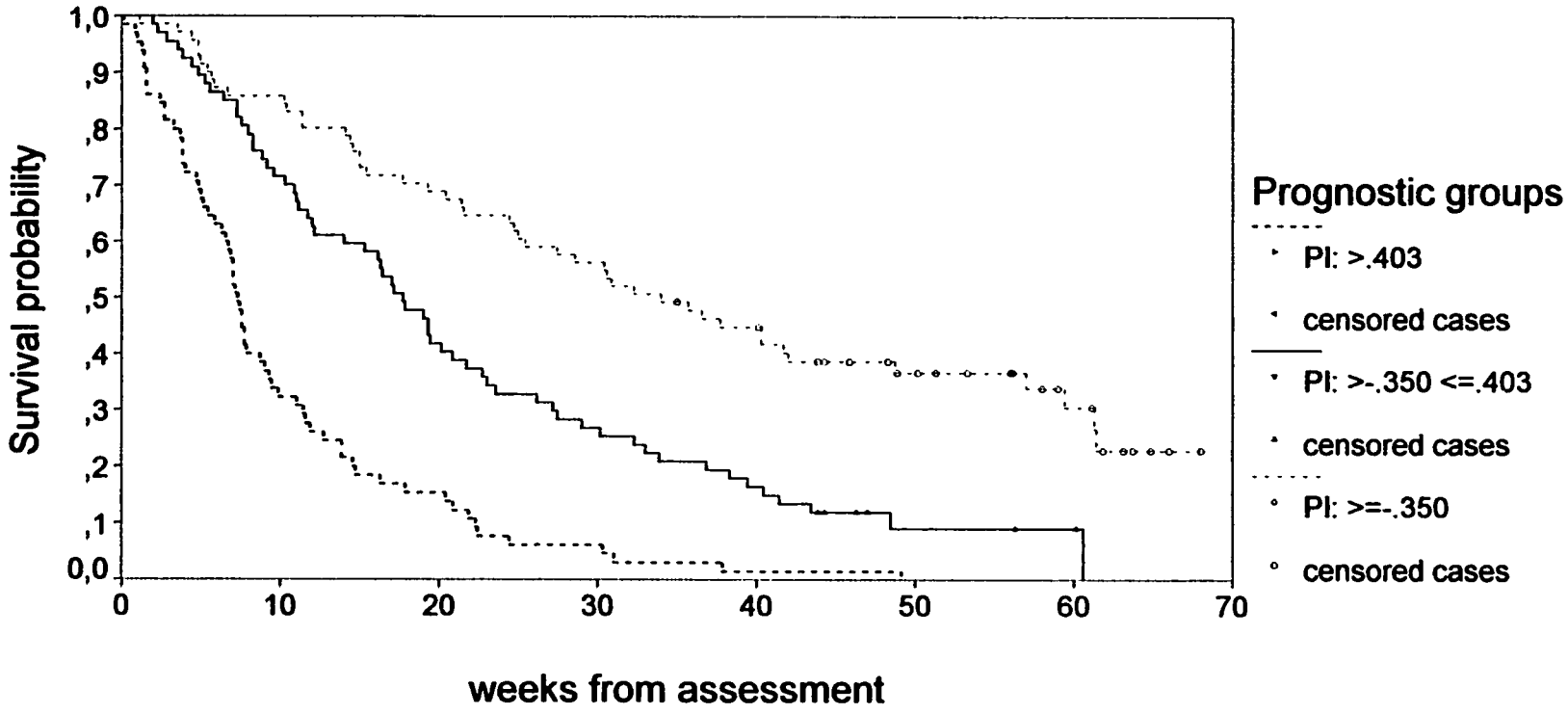
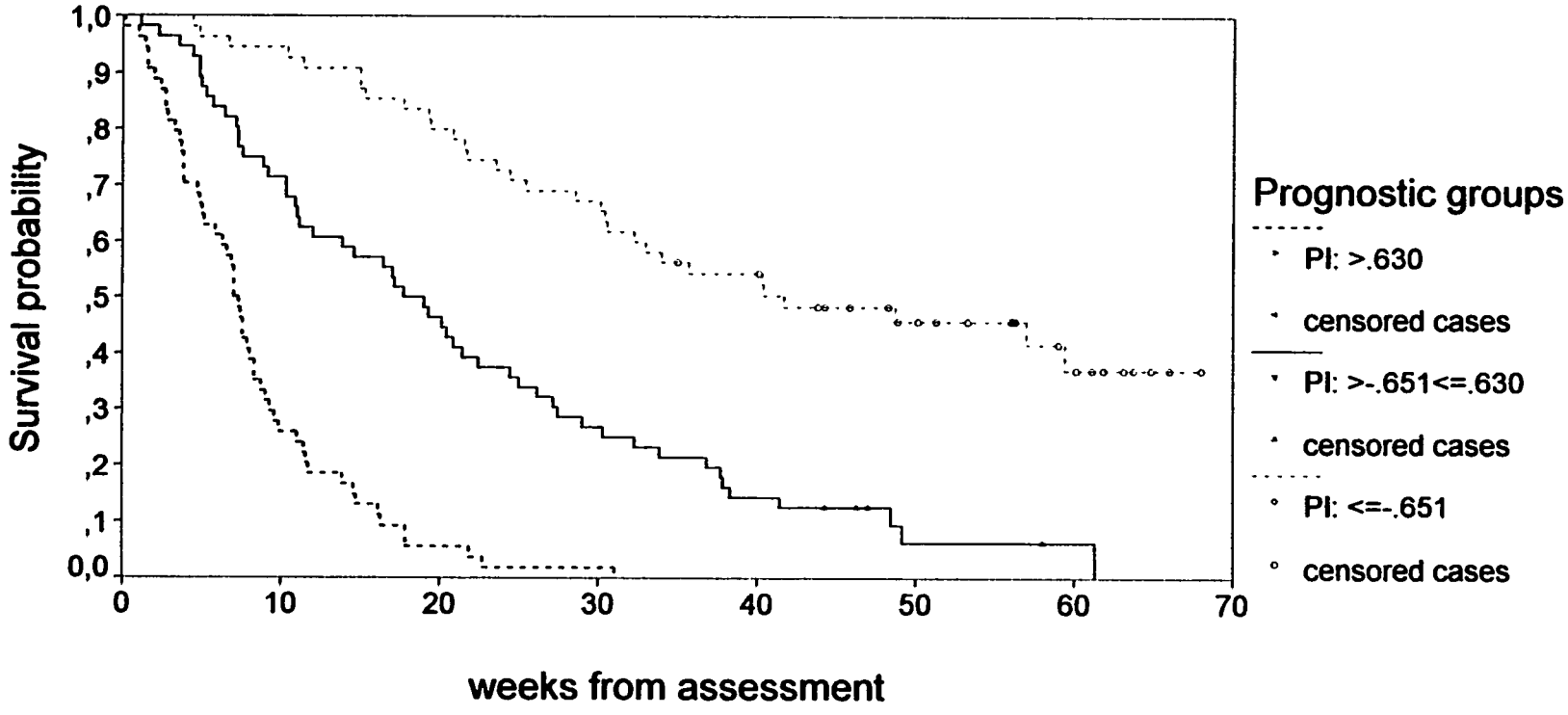


Figure 28-5: survival curves by prognostic groups for Model 1*



* Model unadjusted for laboratory variables

Figure 29-5: survival curves by prognostic groups for Model 4*



* Model adjusted for laboratory variables

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CHAPTER 6

CONCLUSIONS

6.1 SYSTEMATIC REVIEWS

To date performance status and the presence of cognitive failure, weight loss, dysphagia, anorexia and dyspnea appear to be definite prognostic factors for survival in end-stage cancer patients. Low performance status, high tumor burden, liver metastasis, and low serum albumin levels were found to be common and important survival predictors for patients with advanced breast, lung and gastrointestinal cancers. The lack of representative inception cohorts, the use of non-standardized measures and inclusion of different variables in the statistical analyses and the retrospective nature of most studies, make the clinical significance of these predictors still uncertain.

Arbitrary criteria were used for both paper selection and appraisal, in the systematic reviews of the literature on prognostic factors for survival in advanced and end-stage cancer patients. Most studies lack inception cohorts and the identification of papers dealing with homogeneous group of patients was our main focus. Papers dealing with advanced small cell lung and prostate cancer did not stratify patients appropriately or reported essential informations on this regard (e.g. overall median survival) and were discarded from a detailed review. In the absence of a validated quality score for study on prognosis, we appraised the selected articles on the base of simple epidemiological and statistical characteristics, which are deemed important to evaluate studies "validity." Because of the nature of the publications, which reported unstandardized measures of association between prognostic factors and survival, a quantitative approach such as meta-analysis could not be applied. Instead, qualitative systematic reviews were performed. Characteristics and results

of the selected studies were summarized in synoptic tables. Due to the variety of prognostic factors examined in these studies, we reported and/or discussed only those variables that were used frequently enough to provide a general impression of their prognostic importance.

6.2 LONGITUDINAL STUDY

The aim of our study was to overcome the above-mentioned methodological limitations, and better clarify the prognostic role of certain clinical and demographics characteristics in terminal cancer patients. Lung cancer, liver metastases, tumor burden, cognitive status, amount of weight-loss, lactate deydrogenase, albumin, and lymphocytes count were primarily important survival predictors in patients with breast, gastrointestinal and lung cancer, at the onset of their terminal phase. Loss of functional independence, malnutrition and multiplicity of symptoms, appeared as common clinical features in this population and in prostate patients. The latter observation may partially support the terminal cancer syndrome theory. However, the hypothesis that the length of survival for patients in their terminal phase is not influenced by disease characteristics such as tumor type and burden, is definitively contradicted by our longitudinal data.

Our longitudinal study had some limitations. Characteristics and survival patterns for prostate patients undergoing their terminal phase could not be examined appropriately. The sample sizes implemented in the modeling procedures were greatly impacted by missing data in the laboratory assessments and by stratification according to levels of performance status. It was felt by both patients and

investigators that in certain cases even routine blood-works were not either acceptable or indicated beyond the study purposes. Stratification represented a simple and clinically meaningful way to control our results for a variable of essential prognostic value such as performance status. The prognostic relevance of each covariate after stratification, need to be considered relatively to the non-stratified models. In the latter, sample-sizes resulted in most cases adequate to guarantee enough power for the estimated hazard ratios.

Inception criteria and results of this study need to be validated on new and independent data sets. Multicentric rather than single center studies are also needed to further increase generalizability and minimize selection biases in prospective studies.

6.3 STUDY IMPLICATIONS

The exact survival of cancer patients may never be a measurable or predictable entity. However, valuable predictors of survival can complement the simple clinical predictions made by health professionals and assist in establishing the eligibility of terminal cancer patients for research studies or access to health care programs.

Our data suggest that simple disease characteristics, physical and laboratory assessments are useful to aid in the prediction of survival in patients with solid malignancies at the onset of their terminal stages. Methodological improvements in the design and implementation of survival studies may reduce prognostic uncertainty and ultimately provide better care for the terminally ill and their families.

APPENDIX 1:

Search strategy for literature review

Appendix 1: MEDLINE Search Strategy For Systematic Literature Review

1. exp neoplasms/
2. 1 and cancer$. ti,ab,sh.
3. 2 and (metast$ or recurr$ or end-stage or advanced or nonresect$ or unresect$) ti,ab,sh.
4. exp terminally ill/
5. exp terminal care/
6. exp hospices/
7. exp palliative care/
8. (4 or 5 or 6 or 7)
9. exp prognosis or prognos$/
10. exp survival/
11. exp survival analysis/
12. exp longevity/
13. exp life expectancy/
14. 9 or 10 or 11 or 12 or 13 or (time factors sh)
15. (3 or 8) and 14
16. exp tumor markers, biological/
17. exp interleukins/
18. exp growth substances/
19. exp antigens, neoplasm/
20. exp cytological techniques/
21. exp cytogenetics/
22. exp pathology, clinical/
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 15 not 23
25. limit 24 to human
26. limit 25 to english language
27. limit 26 to yr=80-97

APPENDIX 2:

Data collection forms

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

PATIENT IDENTIFICATION FORM

Patient ID#: _ _ _ _ _ _ _ _ Patient initials: _ _ _ (F M L)

Patient Name: _____ _____
(Please print) Last Name Given Names

Date of birth: /_ _/_ _/_ _ _ _/ (dd mm yy) Gender:_____

_____ _____
Apt. No. Street Postal Code

_____
Town/City Province

Telephone: Home _ _ _-_ _ _-_ _ _ _

Health Insurance #: _____

Family Physician: _____ Nurse in charge:_____

Contact Person: _____ _____
(Close family member or friend) Last Name Given Names

_____ _____
Apt. No. Street Postal Code

_____
Town/City Province

Relationship to Patient: _____

Telephone: Home _ _ _-_ _ _-_ _ _ _

Office _ _ _-_ _ _-_ _ _ _

Date form completed: /_ _/_ _/_ _ _ _/ (dd mm yy)

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

BASELINE FORM

ID #: _ _ _ _ _ _ _ _ Patient initials: _ _ _
F M L

A. DEMOGRAPHIC CHARACTERISTICS

How old are you?: (years)___

What is your gender?: ___

Which is your race?:
1 white (caucasian)
2 black:
3 oriental
4 Canadian indian/ Native person
5 East Indian
6 Other - not answered ___

How far did you go in school?
1 0-4 years
2 5-8 years
3 High school incomplete
4 High school completed
5 Post high school, business or trade school
6 1-3 years college
7 4 years college completed (University)
8 Post graduate college (University)
- Not answered ___

NOTES:

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

ID #: _ _ _ _ _ _ _ _ _ Patient initials: _ _ _ (F M L)

B. SOCIAL RESOURCES QUESTIONNAIRE

I would like to ask you some questions about your family and friends. Please circle only the number that best applies to you in each question.

Are you single, married, never married, widowed, divorced or separated ?

1 Single (never married)
2 Married
3 Widowed
4 Divorced
5 Separated
6 Common law
- Not answered

Who lives with you (you may circle more than one number for this question)

	no	yes
No one	0	1
Husband or wife	0	1
Children	0	1
Grandchildren	0	1
Parents	0	1
Grandparents	0	1
Brothers and sisters	0	1
Other relatives (does not include in-laws covered in the above categories)	0	1
Friends	0	1
Non-related paid helper (includes free-room)	0	1
Other(specify):_____	0	1

_____

How many people do you know well enough to visit in their homes?

3 Five or more
2 Three to four
1 One or two
0 None
- Not answered ____

About how many times did you talk to someone - friends, relatives, or others on the telephone in the past week (either you called them or they called you) ? (if subject has no phone, question still applies).

3 Once a day or more
2 2-6 times
1 Once
0 Not at all
- Not answered ____

How many times during the past week did you spend some time with someone who does not live with you; that is you went to see them or they came to visit you, or you went out to do things together ?

3 Once a day or more
2 2-6 times
1 Not at all
- Not answered

Do you have someone you can trust and confide in?

1 Yes
0 No
- Not answered _____

Do you find yourself feeling lonely quite often, sometimes, or almost never?

0 Quite often
1 Sometimes
2 Almost never
- Not answered _____

Do you see relatives and friends as often as you want to, or not?

1 As often as I want to
0 No as often as wants to
- Not answered _____

Is there someone who would give you any help at all if you were sick or disabled, for example your husband/wife, a member of your family, or a friend?

1 Yes
0 No one willing and able to help
- Not answered _____

if "yes" please answer to a and b questions

a. Is there someone who would take care of you as long as needed, or only for short time, or only someone who would help you now and then (for example, taking you to the doctor, or fixing lunch occasionally, etc.)?

3. Someone who would take care of subject indefinitely (as long as needed)
2. Someone who would take care of subject for a short time (a few weeks to six months)
1. Someone who would help the subject now and then (taking him to the doctor or fixing lunch, etc.)
- Not answered _____

b. Who is this person?
Name_____
Relationship_____
(Code: Spouse=1, Sibling=2, Offspring=3, Grandchild=4, Other Kin=5, Friend=6, Other=7)

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

ID #: _ _ _ _ _ _ _ _ Patient initials: _ _ _
F M L

C. QUALITY OF LIFE QUESTIONNAIRE

We are interested now in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you.

	no	yes
Do you have any trouble doing strenuous activities, like carrying shopping bag or a suitcase?	1	2
Do you have any trouble taking a long walk?	1	2
Do you have any trouble taking a short walk outside of the house?	1	2
Do you have to stay in bed or chair for most of the day?	1	2
Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
Are you limited in any way in doing either your work or doing household jobs?	1	2
Are you completely unable to work at a job or to do household jobs?	1	2

DURING THE PAST WEEK

	Not at all	A Little	Quite a Bit	Very Much
Were you short of breath?	1	2	3	4
Have you had pain?	1	2	3	4
Did you need to rest?	1	2	3	4
Have you had trouble sleeping?	1	2	3	4
Have you felt weak?	1	2	3	4
Have you had lack of appetite	1	2	3	4

	Not at all	A Little	Quite a Bit	Very Much
Have you felt nauseated?	1	2	3	4
Have you vomited?	1	2	3	4
Have you been constipated?	1	2	3	4
Have you had diarrhea?	1	2	3	4
Were you tired?	1	2	3	4
Did pain interfere with your daily activities?	1	2	3	4
Have you had difficulties in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
Did you feel tense?	1	2	3	4
Did you worry?	1	2	3	4
Did you feel irritable?	1	2	3	4
Did you feel depressed?	1	2	3	4
Have you had difficulties in remembering things?	1	2	3	4
Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING QUESTIONS, PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

How would you rate your overall physical condition during the past week?

1 2 3 4 5 6 7

Very poor Excellent

How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

ID #: _ _ _ _ _ _ _ _ _ Patient initials: _ _ _
F M L

D. ECONOMIC RESOURCES QUESTIONNAIRE

Some studies in literature have suggested a correlation between the annual income level and both the place of care and the length of survival in advanced cancer patients. Therefore we are collecting this information, which similarly to your other records, will be kept strictly confidential . Please show your family and individual gross yearly income by circling the numbers which identifies the appropriate ladder.

Family yearly income before taxes for 1995	**Individual yearly income before taxes for 1995**	
01	01	<10.000
02	02	10.000 - 15.000
03	03	15.000 - 20.000
04	04	20.000 - 25.000
05	05	25.000 - 30.000
06	06	30.000 - 35.000
07	07	35.000 - 50.000
08	08	50.000 - 60.000
09	09	60.000 - 70.000
10	10	70.000 - 80.000
11	11	80.000 - 90.000
12	12	90.000 - 100.000
13	13	>100.000

Not answered: ___ Not answered: ____

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

BASELINE FORM

ID #: _ _ _ _ _ _ _ _ Patient initials: _ _ _ (F M L)

E. TUMOR RELATED CHARACTERISTICS

Primary tumor site: _____

Secondary tumor sites:	Single	Multiple
Liver:	___	___
Lung:	___	___
Brain:	___	___
Bone:	___	___
Other:	___	___

Last protocol implem.: _____

Concurrent treatments: _____

Tumor burden (= estimation of clinical tumor mass):

0 No lesions
1 One lesion < 5 cm in any diameter
2 One lesion > 5 cm in any diameter up to 2 lesions
3 Between three and five lesions
4 More than five lesions

Date of terminal illness dx.: /_ _/_ _/_ _/

Clinical estimation of survival: months: _
weeks: _
days: _

SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

BASELINE FORM

ID #: __ __ __ __ __ __ __ Patient initials: __ __ __ (F M L)

F. BASELINE MEASUREMENTS

Nutritional Status:

Weight loss in the previous 6 mos.: (kg) __

Triceps skin fold: __ __ __

Mean: __

Laboratory measurements:

Na: _____ mmol/l Ca: _____ mmol/l
Albumin: _____ mmol/l LDH: _____ I. U./L
Hemoglobin: _____ gm/l Alkaline Phos. __ I.U/L
Leucocyte count: ___
Granulocyte count: __
Lymphocyte count: ___

Weighted Index of Comorbidity

Assigned weights for diseases	Conditions		
1	Myocardial infarct	yes	no
	Congestive heart failure	yes	no
	Peripheral vascular disease	yes	no
	Cerebrovascular disease	yes	no
	Dementia	yes	no
	Chronic pulmonary disease	yes	no
	Connective tissue disease	yes	no
	Ulcer disease	yes	no
	Mild liver disease	yes	no
	Diabetes	yes	no
2	Hemiplegia	yes	no
	Moderate or severe renal disease	yes	no
3	Moderate or severe liver disease	yes	no
6	AIDS	yes	no

Total: ___

Note: the total equals the score. Example: chronic pulmonary (1) and hemiplegia (2) = total score (3)

Date form is completed: /__ __/__ __/__ __/

ID #: _ _ _ _ _ _ _ _ _ Patient initials: _ _ _ (F M L)

MINI-MENTAL STATE (FORM A)

MAXIMUM SCORE	SCORE	
5		What is the (year) (season) (day) (month) (date)?
5		Where are we: (province) (country) (town) (hospital) (floor)?
3		Name three objects: glass blanket pencil
5		Serial 7"s. Alternately spell "World" backwards.
3		Ask for the 3 objects repeated above.
2		Name a pencil and watch.
1		Repeat the following "No if's, ands or buts".
3		Follow a 3-stage command: "take a paper in your right hand, fold it in half, and give it to me."
1		Read and obey the following: CLOSE YOUR EYES
1		Write a sentence.
1		Copy a design.
30		TOTAL SCORE

Assess level of consciousness along a continuum

Alert Drowsy Stupor Coma

ID #: _ _ _ _ _ _ _ _ _ Patient initials: _ _ _ (F M L)

SCORING OF KARNOFSKY PERFORMANCE INDEX

Based on interviewer judgment of patient:

Coding

100 Normal, no complaints, no evidence of disease
90 Able to carry on normal activity, minor signs or symptoms of disease
80 Normal activity with effort, some signs or symptoms of disease
70 Cares for self, unable to carry on normal activity or to do work
60 Requires occasional assistance from others but able to care for most needs
50 Requires a considerable assistance from others but able to care for most needs
40 Disabled, requires special care and assistance
30 Severely disabled, hospitalization indicated, death not imminent
20 Very sick, hospitalization necessary, active supportive treatment necessary
10 Moribund
0 Dead

Source: Karnofsky DA, Abelman WH *et al*: The use of nitrogen mustards in palliative treatment of carcinoma. Cancer 634: 56, 1948.

Performance Status Scale		
ECOG (Zubrod)†	*Karnofsky*	*Definitions*
0	100	Asymptomatic
1	80–90	Symptomatic, fully ambulatory
2	60–70	Symptomatic, in bed <50% of day
3	40–50	Symptomatic, in bed >50% of day but not bedridden
4	20–30	Bedridden

*Stanley KE: Prognostic factors for survival in patients with inoperable lung cancer. JNCI 65:25–32, 1980.

†Eastern Cooperative Oncology Group (ECOG) or Zubrod performance status score.

ID#:_____ Patient initials: ___

EDMONTON SYMPTOM ASSESSMENT SYSTEM (E.S.A.S.)

Please circle the number that best describes:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Fatigue	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Fatigue
Not Nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
Not Depressed	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
Not Anxious	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Not Drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
Best Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Appetite
Best Feeling of Well-being	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Feeling of Well-being
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
Other Problem	0	1	2	3	4	5	6	7	8	9	10	

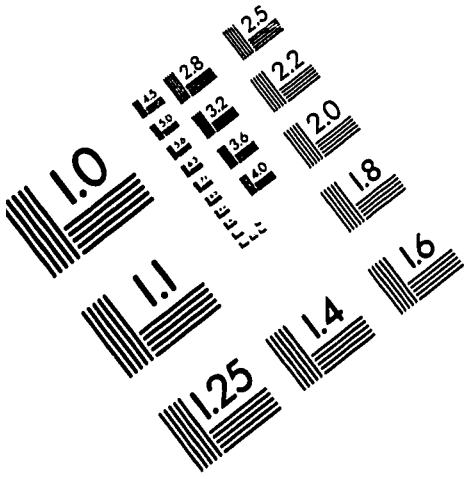
SURVIVAL PREDICTORS IN ADVANCED CANCER PATIENTS

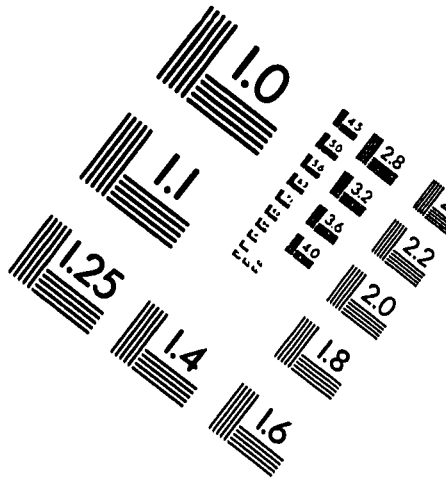
ID #: _____ Patient initials: _____ (F M L)

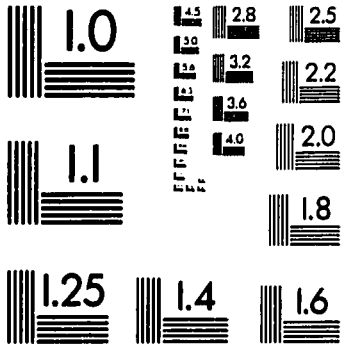
KARNOFSKY FUNCTIONAL ASSESSMENT TOOL

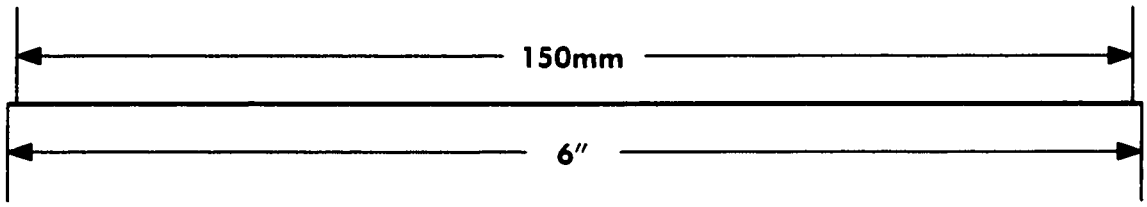
	0 Functional	1 Min Dysfunction	2 Mod Dysfunction	3 Severe Dysfunction	Data
Communication	Independent with all aspects of communication	Requires glasses, hearing aid(s) or communication device	Communicates effectively <50% of time	Unable to communicate	
Mental Status *	Oriented x 3 Memory intact	Impair 2/6 orientation/memory. Follows simple commands	Impair 3-4/6 orientation/memory. Requires intermittently re-orient, explain, assists	Impair 5-6/6 orientation/memory or unresponsive to verbal commands	
Pain	None or occ. pain. Pain does not impact function'	Pain limits some activity. Inhibits function minimally	Pain prevents all the time. Inhibits function mod.	Unable to do any activities because of pain	
Dyspnea *	No dysfunction	Urgency = commitg or SOBOE or intermittent	1 extra breath with counting or O_2 at 1-3 liters	≥ 2 breaths with counting or O_2 at ≥ 4 liters	
Balance * Sit Stand	Normal Balance	Unable balance. Attain/maintain position with equip or 1 person. Min. safety risk	Unable balance. Maintain position with mod. assist 1 or more. Risk of fall	Maintain position with max assist 1-2 persons or unable to evaluate	
Mobility *	Controls/moves all limbs at will. Performs safely and independently	Controls/moves all limbs but degree of limitation. 1 assist to move/safety	Can assist another person who initiates movement. Requires 2 persons assist for safe transfer	Unable to assist with position change. Mechanical lift to transfer	
Locomotion ** With Wheelchair	Walks unassisted or independently to lead up and propelling	Walks with 1 person assist / 1 walk aid or supervision with lead up	Walks with 2 person assist short distance or requires assist with lead up/propel wheelchair	Unable to walk. WB for transfer. Dependent W/C management	
Fatigue ***	Rarely needs to rest	Rest <50% of day	Rest >50% of day	Prohibitive due to fatigue	
Motivation ***	Wants to participate despite limitations	Active/passive participant >50% of time	Active/passive participant <50% of time	No desire to participate in activity	
ADL	Independent	Independent using adaptive equipment	Manual assist of 1, verbal cueing/supervision to complete task	Total assist with ADL	
Performance Status	Independent in room or unit	Independent with minimal assist of 1	Total assist of 1 person room/unit	Assist of 1-2 persons in room	

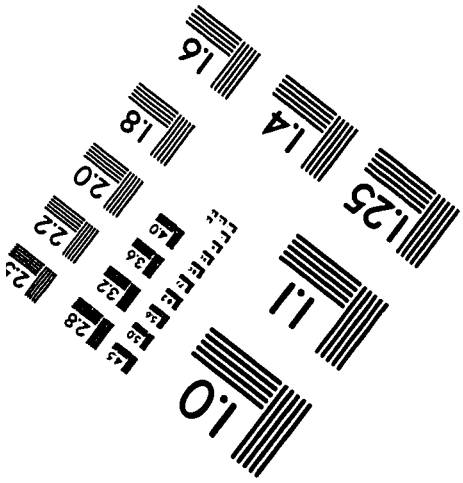
IMAGE EVALUATION
TEST TARGET (QA-3)











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