LOCALIZED PROSTATE CANCER AND QUALITY OF LIFE

Screening, treatment and methodological issues

Ida Korfage

Acknowledgements

The work presented in this thesis was conducted at the Erasmus MC, department of Public Health. The author gratefully acknowledges the collaboration with the departments of urology of St. Franciscus Gasthuis, Medical Center Rotterdam Zuid, locations 'Clara' and 'Zuider', and Erasmus MC; the collaboration with the department of general practice, Erasmus MC; the patients and other participants, and the Dutch Cancer Society, Amsterdam, who funded the studies (EUR 2000-2329 and EUR 95-11.43).

The printing of this thesis was supported by Erasmus MC, by the department of Public Health and by the Dutch Cancer Society.

Cover design: Anna Bosselaar (anna@zoiets.com)

Front cover photo: courtesy Siep van den Akker

Back cover photo: courtesy Ed de Jong (www.eddejong.nl).

Printed by Optima Grafische Communicatie, Rotterdam

ISBN: 90-9019970-5

ISBN per 1st of January 2007: 90-9789090199702-5

Localized prostate cancer and quality of life. Screening, treatment and methodological issues.

IJ Korfage

E-mail: i.korfage@erasmusmc.nl

LOCALIZED PROSTATE CANCER AND QUALITY OF LIFE

Screening, treatment and methodological issues

GELOKALISEERDE PROSTAATKANKER EN KWALITEIT VAN LEVEN

Screening, behandeling en methodologische kwesties

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 23 november 2005 om 11.45 uur

door

IDA JOANNA KORFAGE

geboren te Pijnacker.

PROMOTIECOMMISSIE

Promotor:
Prof.dr. J.D.F. Habbema

Overige leden:
Prof.dr. F.H. Schröder
Prof.dr. J. Passchier
Prof.dr. G.J. Bonsel

Copromotoren:
Dr. M.L. Essink-Bot
Dr. H.J. de Koning

CONTENTS

STATUS OF MANUSCRIPT

Chapter 2	Impact of radical prostatectomy and primary radiotherapy for localized prostate cancer on quality of life'. Essink-Bot ML, Korfage IJ, de Koning HJ. In: Bangma CH, Newling DWW, editors. Prostate and renal cancer, benign prostatic hyperplasia, erectile dysfunction and basic research. An update.: The Parthenon Publishing Group; 2003. p. 14-21.
Chapter 3	Measuring disease specific quality of life in localized prostate cancer: the Dutch experience. Korfage IJ, Essink-Bot ML, Madalinska JB, Kirkels WJ, Litwin MS, de Koning HJ., Qual Life Res 2003;12(4):459-64.
Chapter 4	Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Korfage IJ, Essink-Bot ML, Borsboom GJJM, Madalinska JB, Kirkels WJ, Habbema JDF, Schröder FH, de Koning HJ. Int J Cancer 2005;116(2):291-6.
Chapter 5	Five-year follow-up on anxiety and depression before and after primary prostate cancer treatment. Korfage IJ, Essink-Bot ML, Janssens ACJW, Schröder FH, de Koning HJ Submitted 2005.
Chapter 6	Patients' perceptions of the side effects of prostate cancer treatment – a qualitative interview study. Korfage IJ, Hak T, de Koning HJ, Essink-Bot ML, submitted 2005.
Chapter 7	Side-effects of prostate cancer treatment: comparison of valuations by patients and healthy men. Korfage IJ, de Koning HJ, Habbema JDF, Essink-Bot ML, submitted 2005.
Chapter 8	Receiving a prostate cancer diagnosis: the impact on patients' mental health. Korfage IJ, Essink-Bot ML, Roobol M, Schröder FH, de Koning HJ, submitted 2005.
Chapter 9	Including the quality of life effects in the evaluation of prostate cancer screening: expert opinions revisited? Essink-Bot ML, Korfage IJ, de Koning HJ, BJU Int 2003;92 Suppl 2:101-5.

CHAPTER 1

General introduction

In Western countries prostate cancer is the most prevalent malignancy in males (Parkin, Bray et al. 2001). Early stage prostate cancer usually does not cause any pain or other symptoms. By the time symptoms are experienced, prostate cancer has often reached an advanced stage in which cure is not possible anymore. Prostate cancer can be detected early by testing for prostate-specific antigen (PSA), a biologic tumour marker. Since its introduction in the 1980s general practitioners and urologists have applied the PSA-test at an increasing scale, resulting in a substantially higher proportion of prostate cancers being diagnosed in early stages than before, and causing an increased prevalence of prostate cancer (Etzioni, Penson et al. 2002; 2004). Overdiagnosis, defined as the detection and subsequent treatment of prostate cancer through PSA-testing that otherwise would not have been diagnosed within the patients' lifetime, is considered a major potential drawback of PSA-testing (Etzioni, Penson et al. 2002).

Several intentionally curative therapies for localized prostate cancer are available. Most commonly radical prostatectomy (surgery) and external radiotherapy are applied, less often brachytherapy. A novel approach is 'active surveillance' or 'watchful waiting', which entails the monitoring of men with well differentiated prostate cancer by periodically assessing the PSA-level and prostate biopsies. If indicated by the rise in the PSA-level and/or the results of biopsy, treatment is subsequently applied. The increase in the number of men being treated for prostate cancer is associated with a proportional rise in the prevalence of side effects of primary treatment, mainly erectile and urinary dysfunction after radical prostatectomy, and erectile and bowel dysfunction after external radiotherapy (Madalinska, Essink-Bot et al. 2001).

Introduction of population-based prostate cancer screening has so far not taken place in the Netherlands. First early detection followed by appropriate treatment should have shown to reduce prostate cancer-specific mortality. This is currently being assessed in two large randomised controlled screening trials: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the U.S.A. (Andriole, Levin et al. 2005), and the European Randomized Screening study for Prostate Cancer (ERSPC) in Europe (de Koning, Auvinen et al. 2002). Outcomes on prostate-cancer specific mortality are not expected before 2007 (de Koning, Liem et al. 2002). Further conditions for the introduction of population-based screening concern costs and the unfavourable side effects in the different phases of the screening process. The total costs of a screening programme depend upon the screening policy, such as the age ranges of men who

will be screened, the length of the interval between screening rounds, and the PSA-level above which biopsy will be indicated. Introduction of screening may entail additional treatment costs and savings, for example in the stage of advanced disease. The cost-effectiveness of prostate cancer screening, defined as cost per life-year gained, can be estimated when results of the ERSPC-trial on prostate cancer-specific mortality are available.

Unfavourable side effects may occur in the process of screening and diagnosis itself, for example pain or discomfort and feelings of uncertainty and anxiety (Essink-Bot, de Koning et al. 1998). Unfavourable side- effects will certainly arise in the treatment phase, such as sexual, urinary, and bowel dysfunctions. Systematic PSA-testing advances diagnosis with on average 11 years compared to a situation without PSA-testing (Draisma, Boer et al. 2003) and leads to overdiagnosis (Etzioni, Penson et al. 2002). During these 'extra' years men are labelled and followed up as cancer patients. At the population level, cancer screening will thus lead to an increased number of life-years lived with side effects of primary treatment. However, if screening results in reduced prostate cancer mortality, the incidence of end-stage prostate cancer will decrease accordingly. From a prostate cancer-specific perspective, the prevention of the advanced disease phase, which involves substantial morbidity and impairment, can be regarded as a favourable effect of screening (Essink-Bot, de Koning et al. 1998). From a general health perspective this advantage is only relatively favourable, since people will eventually die of an alternative cause of death, which not necessarily involve a less painful end-stage of disease.
The effects of screening and earlier treatment on prostate cancer mortality and on quality of life all have to be taken into account in the evaluation of public health effects of prostate cancer screening.

This thesis focuses on the effects of prostate cancer diagnosis and primary treatment on quality of life (QoL). In this thesis 'quality of life' will be restricted to 'health-related quality of life' or 'health status', defined as quality of life relating to disease and/or treatment. Three types of measures are available to assess QoL: generic, disease-specific, and domain-specific. Generic measures are comprehensive and non-disease specific. They are applicable in a wide range of populations, health conditions and treatments and enable the comparison of QoL results across these populations. Generic measures are either health profiles or preference-based measures. Health profiles stem from a psychometric tradition, usually contain several items per scale, and result in a description of someone's health status. Preference-based

measures originate from an economic tradition, typically contain 1 item per dimension, and result in a health status' classification that can be used to compose health state descriptions (see below). An often-applied preference-based measure is the EuroQol (EQ-5D) (Brooks 1996).

Disease-specific measures aim at assessing the consequences of a specific disease or treatment for the patients' health status. Disease-specific measures were mainly developed for (types of) cancer, but are also available for other diseases, ranging from diabetes and migraine to depression and rhinitis, etc.

Domain-specific measures, finally, focus at assessing a patient's function and well being in a specified domain of health status irrespective of the presence of disease, e.g. on fatigue.

All 3 types of QoL measures usually combine items on function (e.g. 'Did you experience difficulties in performing X in the past four weeks?'), with items on bother (e.g. 'Overall, how big a problem was it for you during the last 4 weeks to experience difficulties in performing X?').

Data on patients' QoL are often collected through self-assessment questionnaires, i.e. booklets containing a combination of measures and items to be completed by the respondent him or herself.

If health outcomes are to be compared to enable a judgment on which specific health outcomes are more or less preferred than others - for example in cost-effectiveness analysis – the preferences for health states may be obtained from an appropriate panel, e.g. patients, doctors or members form the general public. The preferences for each health state are usually expressed in numbers between 0 (least preferred) and 1 (most preferred); some models allow for negative numbers indicating health states considered worse than death (Brooks 1996). By multiplying the preference number for each health state, and the number of years lived in that health state, so-called standard quality adjusted life years (QALYs) can be calculated. The standard QALY-concept assumes that a health state's value (preference) is independent of what preceded and what will follow, and that valuation is independent of the duration of the health state (Weinstein and Stason 1977).

QoL data can be obtained in a quantitative or a qualitative way. Quantitative data-collection involves the measurement of quantity or amount, often using statistical techniques. Qualitative data-collection is aimed at revealing motives and reasoning, for example why does someone decide to participate in a screening programme.

Several issues complicate the assessment of QoL in (prostate cancer) patients. Typically, patients report very good QoL in responding to the EQ-5D and SF-36 after primary prostate cancer treatment. Several explanations for this phenomenon have been suggested. First, generic QoL measures may be unresponsive to changes in health status occurring after diagnosis or treatment. In that case respondents' functioning may actually differ from their functioning pre-diagnosis or pre-treatment, but according to generic QoL scores nothing has changed. Second is 'response shift', which denotes adaptation to changing health (Schwartz and Sprangers 2000). Adaptation can be described as a mean of coming to terms with the consequences of a disease or health condition; after diagnosis and/or treatment of a serious disease, someone's internal standards of what constitutes 'normal' life, for example with regard to 'social activities', 'work' or 'other regular daily activities' may change. Adaptation to a changed health condition can be beneficial for patients. In the assessment of QoL, however, it may lead to a shift in their interpretation of response-categories and thus to data interpretation problems.

Content of the thesis

This thesis addresses the following research questions:

Q1. What is the burden of long-term sexual, urinary and bowel dysfunction after radical prostatectomy and external radiotherapy in men with localized prostate cancer for the population?

Q2. How anxious and depressed are men in the years following diagnosis and treatment of localized prostate cancer?

Q3. When asking patients, how important are side effects after primary prostate cancer treatment for them?

Q4. What mental impact does early prostate cancer diagnosis through screening have on symptomless men?

Structure of the thesis

Part I (chapter 2) provides a literature overview of long-term health related quality of life after primary prostate cancer treatment.

Part II (chapter 3-5) is based on a prospective cohort study in localized prostate cancer patients from pre-treatment till 4 to 5 years afterwards. Chapter 3 concerns the development of the prostate cancer specific part of the questionnaire that was used in the cohort study.

Chapter 4 focuses on generic health-related quality of life in the cohort and the prevalence of side effects after primary treatment (research question 1). Chapter 5 deals with the prevalence of anxiety and feelings of depression in the cohort in the years following diagnosis and primary treatment (research question 2).

Part III (chapter 6-8) contains an exploration of the study results as described in Part II. We explored the importance of sexual, urinary and bowel dysfunctions after primary prostate cancer treatment to patients (research question 3, chapter 6); we compared how men with and without prostate cancer valued health states that were associated with prostate cancer treatment (research question 3, chapter 7); and we measured the mental impact of early prostate cancer diagnosis through screening on men who typically did not experience any pain or other symptoms (research question 4, chapter 8).

In part IV (chapter 9-10) we discuss screening, treatment and methodological implications that our study results may have, and we present the conclusions and recommendations.

CHAPTER 2

The impact of radical prostatectomy and primary radiotherapy for localised prostate cancer on quality of life

Essink-Bot ML, Korfage IJ, de Koning HJ. In: Bangma CH, Newling DWW, editors. Prostate and renal cancer, benign prostatic hyperplasia, erectile dysfunction and basic research. An update.: The Parthenon Publishing Group; 2003. p. 14-21.

Abstract

Purpose Review of longitudinal prospective cohort studies on quality of life (QoL) in patients with localised prostate cancer treated with radical prostatectomy (RP) or external beam radiotherapy (ER)

Methods A PubMed search identified 5 cohort studies that included a pre-treatment assessment. A population-based study was added.

Results The cohort studies confirm findings from previous cross-sectional studies with respect to the patterns of side effects of RP and ER on urinary, bowel and sexual function. Direct numerical comparison of published QoL results was difficult. After adjustment for baseline characteristics, most studies did not show differences in generic QoL between the ER and RP groups at 12 months after diagnosis. Generic QoL scores showed small changes, if any, after 12 months, if compared to pre-treatment scores.

Discussion Possible explanations of the findings, including response shift and / or insensitivity of generic QoL measures to the consequences of RP and ER, are discussed. These issues, as well as symptoms and QoL in the longer term after primary treatment for prostate cancer, are currently being investigated in the Rotterdam QoL study.

Introduction

External beam radiotherapy (ER) and radical prostatectomy (RP) have been the most common primary treatments for localised prostate cancer. There is no convincing evidence available to show that either treatment is more effective in saving quantity of life than the other. A recent report of a trial comparing RP and expectant management showed a significant reduction of prostate cancer mortality after RP, but a trial comparing RP and ER is not yet available(Holmberg, Bill-Axelson et al. 2002). Quality of life (QoL) issues become decisive in this situation.

Among the first QoL studies of primary treatment for localised prostate cancer, that of Litwin and colleagues found no differences in general QoL between groups of men who had previously been treated by RP or ER, but the groups differed from men without prostate cancer regarding sexual, urinary and bowel function (Litwin, Hays et al. 1995). Fowler and associates also reported similar general QoL and different patterns of side-effects in men after ER and RP (Fowler, Barry et al. 1996). The findings of such cross-sectional studies need to be confirmed by prospective longitudinal comparative studies, preferably randomised controlled clinical trials. Prospective observational cohort studies provide the next best information: if a pretreatment assessment is included, it is to some extent possible to adjust the results after RP or ER for pretreatment differences between treatment groups in terms of background characteristics (e.g. age), disease characteristics (e.g., cancer stage) and functional aspects of QoL (e.g., urinary or sexual function).

We conducted a search of the published literature to identify observational cohort studies with a pretreatment assessment comparing QoL in RP and ER. The designs and results have been compared with each other and with those of the Prostate Cancer Outcomes Study, a large population-based observational study with a retrospective pretreatment assessment (Potosky, Legler et al. 2000).

Methods

Quality of life

Health-related QoL is the variable complementary to survival in studies of patient outcome. QoL is commonly defined as physical, psychological and social functioning and well being. Medical and clinical variables (such as tumour stage and symptoms) are indispensable for the interpretation of QoL scores.

The common approach to empirical QoL assessment includes combining generic and condition specific measures. Generic measures determine QoL in general terms, thus allowing for comparisons across disease (including 'no disease') and treatment groups. The Short Form-36 (SF-36) is an example of a generic QoL measure. The specific consequences of localised prostate cancer and its various treatments are in the areas of urinary, bowel and sexual functioning. Prostate cancer specific QoL measures address these areas, preferably in terms of functioning and experienced bother. Typically, a variable such as 'urinary functioning' is measured by multiple items that are combined into a scale score. This approach is psychometrically superior to single-item questions, because a more reliable overall score is provided. However, the interpretation of such a scale score depends on the item content of the scale.

Literature search

We performed a PuBMed search in May 2002. We used the following search strategy: 'Prostatic neoplasms [majr] AND quality of life [majr] AND Prostatic Neoplasms/therapy [MAJR] AND 1998/1/1 [mhda]:2002/5/29[mhda]'. This resulted in 111 references. Two of the authors (M.L.E.-B., I.J.K.) independently selected on the basis of the abstracts the papers that met the following criteria:

1. Empirical QoL study of patients with localised prostate cancer, comparing treatment by RP or ER in the same study;

2. Prospective longitudinal design, including a pre-treatment assessment of at least sexual and urinary function, or, in a population-based study, at least a retrospective pre-treatment assessment;
3. Including generic and prostate cancer specific QoL assessments in follow-up;
4. Published in English.

Five published cohort studies were identified (Clark, Rieker et al. 1999; Galbraith, Ramirez et al. 2001; Lee, Hall et al. 2001; Madalinska, Essink-Bot et al. 2001; Schapira, Lawrence et al. 2001). Because most of these appeared to refer to relatively small and selected patient samples, the Prostate Cancer Outcomes study was added (Potosky, Legler et al. 2000).

Selected studies

The study reported by Talcott's group included 287 from 398 eligible American men with localised prostate cancer diagnosed in 1990-94. These men were treated at various centres, including non-teaching hospitals. We used mainly two publications from this study. The 1998 publication focused on comparing frequencies of urinary, bowel and sexual dysfunction before and after RP and ER until 12 months after the start of treatment (Talcott, Rieker et al. 1998). In the article published in 1999 the relationship between generic QoL (SF-36) scores and the occurrence of urinary, bowel or sexual dysfunction was analysed in a subsample of 125 men from the original cohort (Clark, Rieker et al. 1999). Table 2.1 provides further details.

Schapira and colleagues reported a study including 122 men (from 274 eligible; response rate 45%) with localised prostate cancer, recruited from 4 academically affiliated US hospitals, treated with RP, ER or expectant management. Differences in change scores over time in prostate cancer-specific scale scores and SF-36 scale scores between treatment groups were analysed, with adjustments for age, comorbidity, and other covariates (Schapira, Lawrence et al. 2001).

The article of Galbraith and co-workers reported a cohort selected from a US tertiary care facility. Five groups of patients were included of 24-59 men each: watchful waiting, prostatectomy, conventional ER, proton-beam radiotherapy, and combined conventional / proton-beam ER. The statistical methods are not quite clear, but consisted mainly of comparisons of SF-36 scale scores and prostate cancer-specific scale scores per two treatment groups per assessment moment (Galbraith, Ramirez et al. 2001).

Lee and associates compared the QoL after RP, ER and interstitial brachytherapy in a prospective cohort study among 90 patients treated at a US teaching hospital in 1998-1999.

Analysis focused on QoL (as measured mainly with the Functional Assessment of Cancer Therapy (FACT) scales) changes over time within each treatment group, but included a covariance analysis with adjustment for age, tumour characteristics, baseline QoL scores, and other confounders (Lee, Hall et al. 2001).

Our group reported on the first part of the ongoing Rotterdam QoL study that started in 1996, hence representing the only European study. The Rotterdam QoL study is a side study to the European Randomized Screening study for Prostate Cancer (ERSPC) trial (de Koning, Auvinen et al. 2002) and aims at providing a detailed description of the QoL effects of primary treatments for localised prostate cancer, to enable inclusion of these effects in the overall evaluation of population-based prostate cancer screening. Data from 278 (out of 299) patients treated in Erasmus MC (University Hospital Rotterdam) or one of 3 general Rotterdam hospitals by RP or ER in 1996 – 1998 were included in the analysis reported by Madalinska and colleagues. This analysis focused on post-treatment differences between the treatment groups, using covariance analysis with age and baseline QoL as covariates (Madalinska, Essink-Bot et al. 2001).

The Prostate Cancer Outcomes study PCOS (Potosky, Legler et al. 2000; Stanford, Feng et al. 2000; Hamilton, Stanford et al. 2001) aimed at obtaining longitudinal, community-based estimates of health outcomes in men diagnosed with prostate cancer. From their various publications, we refer mainly to Potosky (Potosky, Legler et al. 2000). A total of 5672 US men with biopsy-proven prostate cancer in 1994-95 were eligible for the PCOS. Of them, 62% (n = 3533) participated in surveys at 6, 12 and 24 months after diagnosis. The 6-month survey included retrospective questions on urinary, bowel and sexual functioning ‘just before’ the prostate cancer diagnosis. All assessments included current urinary, bowel and sexual functioning, and 5 SF-36 scales. Data from 1591 men aged 55-74 years were used for the comparison of RP (n=1156) and ER (n=435). This study compared health status outcomes at 24 months after diagnosis with statistical correction (propensity score) for pre-treatment differences between treatment groups in age, baseline functioning, race, comorbidity and educational attainment.

Results

Characteristics of the studies

Table 2.1 indicates study characteristics and some characteristics of the patients included in the 5 cohort studies. In all studies, ER patients were older than RP patients. Mean age of the RP patients ranged from 61 in Talcott’s and Lee’s studies to 65 in Galbraith’s study.

Table 2.1 Characteristics of published studies on Quality of Life (QoL) in localised prostate cancer. The first five are cohort studies with a pretreatment assesment. The last column refers to a population-based longitudinal study with a retrospective pretreatment assessment.

Characteristic	Clark (1999) Talcott (1998)	Schapira (2001)	Galbraith (2001)	Lee (2001)	Madalinska (2001b)	Potosky (2000)
Total n reported	125 (Clark) / 279 (Talcott)	122	185	90	278	1591
n RP	125	42	59	23	107	1156
n ER	135	51	96	23	171	435
Age (years): mean (range)	RP 61 (41-72) ER 68 (49-86)	RP 64 (58-68) ER 73 (68-75)	RP 65 ER (68-71) (3 types)	RP 61 ER 69	RP 63 (50-73) ER 68 (50-82)	? (55-74) RP 48%>65 ER 78%>65
TNM state (%)						
T1	RP / ER 18 /	RP / ER 55 / 43	not reported	RP/ ER 83 / 52	RP / ER 17 / 11	not reported
T2	RP / ER 73 /	RP / ER 45 / 57	not reported	RP / ER 17 / 48	RP / ER 67 / 61	not reported
PSA at enrollment: median / mean	RP 8.2 / 15.3 ER 8.3 / 13.0	RP 7.6* ER 7.1*	RP 9.8† ER 14.1 – 22.8†	RP 6.2* ER 8.1*	RP 8.2 / 5.6 ER 15.2 / 8.7	RP 28% PSA > 10 ER 36% > 10
Assessments	pre-Tx, 3m, 12m	pre-Tx, 3m, 12m	pre-Tx, 6m, 12m,18m	pre-Tx, 1m, 3m, 12m	pre-Tx, 6m, 12m	6m, 12m, 24 m
Generic Qo L measures	SF-36	SF-36	SF-36, QLI	FACT-G	SF-36, EQ-5D	SF-36 (5 scales)
Prostate cancer–specific QoL scales	SWOG (PTSS?)	UCLA PCI	PTSS (SWOG)/ BSRIS	FACT-P, IPSS	UCLA PCI + sex items	Urinary, bowel, sexual function and bother scales

*Median; † mean; RP, radical prostatectomy; ER, external-beam radiotherapy; TNM, tumour, node, metastasis; PSA, prostate-specific antigen; Tx, treatment; m, months; SF-36, Short Form-36; QLI, Quality of Life Index; FACT-G, Functional Assessment of Cancer Therapy - General form; EQ-5D, EuroQol measure for health-related quality of life; SWOG, Southwest Oncology Group; PTSS, Prostate Treatment Specific Symptoms Measure; UCLA PCI, University of California, Los Angeles Prostate Cancer Index; BSRI-s, Berm Sex-role Inventory – Short form; FACT-P, Functional Assessment of Cancer Therapy – Prostate cancer form; IPSS, International Prostate Symptom Score.

Schapira's study included the oldest ER group. Patients in the studies published by Lee and Schapira showed more favourable distributions of TNM (tumour, node, metastasis) stages than did the other studies.

Symptoms

Frequencies of selected single symptoms of urinary, bowel and sexual dysfunction were reported in 4 studies. For Table 2.2 we selected symptom variables from the reports that seemed to be defined similarly across studies, but we cannot be sure that definition differences partly explain different results.

Wearing of incontinence pads is infrequent preceding treatment for localised prostate cancer. One year after treatment, the frequency was higher among RP patients (27% (PCOS) – 44% (Schapira)) than among patients treated with ER (1% (PCOS) – 8% (Schapira and Madalinska)).

Table 2.2 Frequencies (percentages) of selected urinary, bowel and sexual dysfunction symptoms pretreatment and at 12 and 24 months (m) after treatment

	Wearing pads*			Bowel urgency†			Erectile dysfunction‡		
Study	Pre	12m	24m	Pre	12m	24m	Pre	12m	24m
Talcott (1998)									
RP	3	35	-	7	6	-	32	93	-
ER	1	5	-	1	28	-	45	58	-
Schapira (2001)									
RP	2	44	-	not	not	-	35	89	-
ER	4	8	-	repor-	repor-	-	61	75	-
				ted	ted				
Madalinska (2001b)									
RP	3	35	-	7	6	-	12	87	-
ER	1	8	-	11	30	-	26	52	-
PCOS									
RP (Potosky, 2000;	2	27	28	-	-	15	16	72	80
Stanford, 2000)									
ER (Potosky, 2000;	2	1	3	20	36	36	42	54	62
Hamilton, 2001)									

*Talcott: 'wearing pads'; Schapira: 'use of ≥ 1 pad a day for control of urine'; Madalinska: 'use of ≥ 1 pad a day for control of urine'; PCOS: 'wearing pads to stay dry'

†Talcott: 'bowel urgency or tenderness (at least mild)'; Madalinska: 'bowel urgency(> 3 stools a day), a few times a week or more often'; PCOS: 'frequency of urgent bowel movements, some days or almost every day'

‡Talcott: 'no erections or erections usually inadequate for sexual intercourse'; Schapira: 'not having an erection firm enough for sexual intercourse'; Madalinska: (almost) always problems with getting erections; sum of numbers of men reporting being sexually active and having erectile problems, and of numbers of men reporting not being sexually active because of erectile problems'; PCOS: 'erections not firm enough for sexual intercourse'

Bowel urgency preceding treatment was somewhat more frequent than wearing of urine pads. Twelve months after treatment, bowel urgency was reported more often in ER (28 (Talcott) – 36% (PCOS)).

Erectile dysfunction was more frequent than urinary leakage or bowel urgency preceding treatment, and it was uniformly more frequent among patients who were to undergo ER (reflecting probably partly the fact that ER patients are older). Preceding treatment, the percentages of men reporting erectile dysfunction ranged from 12% (Madalinska) to 35% (Schapira) in the RP group, and 26% (Madalinska) to 61% (Schapira) in the ER group. At 12 months after treatment, the frequency of erectile dysfunction was higher among RP patients ((72 (PCOS) – 93% (Talcott)) than among ER patients (52 (Madalinska) – 75% (Schapira)).

Prostate cancer specific QoL

The University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) was employed in the studies reported by Schapira and Madalinska. It includes scales on urinary, bowel and sexual function, complemented by items on the level of bother in each of these areas. Madalinska's group used items on sexual functioning and bother from another source (Korfage, Essink-Bot et al. 2002). The PCOS study used PCI-like scales. Talcott did not use scales, and Lee's and Galbraith's studies employed other prostate cancer-specific scales. Numerical comparison of scale scores from different studies is difficult if different scales were used. Furthermore, some studies that used the PCI reported figures adjusted, for example age, whereas others reported unadjusted figures or difference scores. Therefore, the comparison across studies was limited to verbal interpretation of the results.

All studies found good urinary function preceding treatment. At 12 months, urinary function had declined significantly in all RP groups studied, and the amount of bother experienced was significant. Urinary functioning in the ER groups was generally reported as little changed. Bowel functioning was generally good preceding treatment. At 12 months, bowel functioning had declined in the ER groups, but not in the RP groups. Preceding treatment, sexual dysfunction was more common than urinary or bowel dysfunction. Although not all men with sexual dysfunction after treatment reported high bother scores, the amount of bother due to sexual dysfunction was significant, especially in the RP groups. Subgroup analyses on the level of bother experienced by men with erectile problems after treatment but with good erectile function preceding treatment were not reported in the selected studies.

Generic QoL

The SF-36 was employed in 5 of the 6 studies selected, hence providing theoretically good opportunities for comparison. However, direct comparison of scale scores on the basis of published figures was not possible due to different reporting of the results.

Madalinska and Schapira reported pre-treatment SF-36 scores per treatment group. RP patients were healthier and younger than ER patients, and this was reflected by better generic SF-36 scores preceding treatment. Madalinska concluded that the ER group's scores were similar and the RP group's scores better than age-and sex-adjusted reference scores from the Dutch general population.

The studies from Galbraith, Madalinska, Talcott (SF-36), Lee (FACT scales), and Potosky (5 SF-36 scales) reported analyses of differences in generic QoL after treatment between the RP and ER groups, with adjustment for baseline characteristics (age in all studies; baseline QoL in Madalinska and Lee; tumour characteristics and/or various demographic characteristics in Lee, Talcott and PCOS). Only Madalinska found significant differences between the treatment groups, for 4 SF-36 scales (Role-Physical, Bodily Pain, General Health Perceptions, Role-emotional), all with better scores for the RP group. In the other studies differences were statistically insignificant after adjustment for baseline characteristics.

Schapira and Lee additionally tested between-group differences in score patterns over time. Schapira found no significant differences in change scores between the RP and the ER groups. Lee found in both groups significant (but similar) decreases in functional and physical well-being, but increases in emotional well-being. Analyses of within-group changes over time from the Rotterdam QoL study were not yet published.

Talcott's group used the SF-36 data from their study to analyse the relationship between generic QoL (SF-36 scale scores) and symptoms (sexual, urinary or bowel) (Clark, Rieker et al. 1999). In a cross-sectional analysis, five out of 8 scales registered diminished scores in men with urinary, bowel or sexual dysfunction. From their longitudinal analyses it appeared that SF-36 scores in the mental, role performance and social domains of men who had no lasting side effects of primary treatment *improved* from baseline to 12 months after the start of treatment, whereas the scores of men with side effects remained stable. Scores in the physical domain were stable for both groups. Despite this complicated pattern, the observed changes in SF-36 scores were rather small.

Discussion

We are aware that our comparison of published cohort studies on QoL in localised prostate cancer may not do justice to the special qualities of each individual study. These studies were designed to provide answers on specific research questions, not for mutual comparability. However, the comparison adds to the body of knowledge and provides guidelines for further investigations.

With the necessary precautions regarding dissimilarities in definitions and selection of patients, about 30% men in the available empirical cohort studies reported wearing urinary incontinence pads 12 months after surgery. When asked specifically, urinary incontinence was perceived as a problem. Symptoms of incontinence were infrequent after ER. However, the case may be that ER patients experience other urinary symptoms than leakage, especially irritative symptoms. The original UCLA PCI has been extended with items on for example, urinary urgency to accommodate for this omission (Wei, Dunn et al. 2000).

Twelve months after ER, approximately 30% of men experienced bowel problems. Sexual function showed the biggest decline, especially in RP. At 12 months after RP, only about 10% of men reported erections firm enough for intercourse. Many, although not all, men with sexual dysfunction after treatment for prostate cancer reported this as a major problem. Whether urinary dysfunction after treatment causes more or less bother than either bowel or sexual dysfunction is not clear, because the studies did not provide separate figures for the groups with good function preceding treatment but with dysfunction afterwards. Cross-sectional studies showed a relatively strong association between bowel dysfunction and bowel bother, a somewhat less strong association between urinary dysfunction and bother, whereas sexual dysfunction is a relatively weak predictor of sexual bother (Litwin, Flanders et al. 1999; Bacon, Giovannucci et al. 2002).

At 12 months, the total side effects of ER seem to be less frequent and less burdensome than those of RP. However, there is evidence to suggest that the situation at 12 months can be subject to change (Litwin, Flanders et al. 1999; Litwin, Pasta et al. 2000; Potosky, Legler et al. 2000; Galbraith, Ramirez et al. 2001). Side effects of RP may still improve, and side effects of ER can become incident or get worse after 12 months. We need results from prolonged follow-up studies, such as the Rotterdam study (Korfage, Essink-Bot et al. 2002).

Most studies reported differences in urinary, bowel and sexual functioning and associated bother between RP and ER, but these were not reflected by generic QoL differences between the groups. If between-group differences in generic scores were found, these were attributable to pretreatment differences between the treatment groups, especially in age. Moreover,

changes in generic QoL over time from pretreatment to 12 months afterwards appeared to be small, if any. On the basis of these findings, generic QoL scores in localised prostate cancer patients have been regarded as rather uninformative, but this conclusion may be premature.

First, the observation that generic QoL 12 months after treatment for localised prostate cancer is generally good is in accordance with common knowledge. These men seem to function relatively well. They may have symptoms of urinary, bowel or sexual dysfunction, but in general they can live with these. Naturally, this is not meant to trivialise the side effects of primary treatment.

Second, men may have adapted to their situation. They may regard the side effects of treatment as 'all in the bargain', as the price paid for the treatment they underwent in order to get rid of their prostate cancer and to improve their chances of survival.

Third, we may use the wrong measure for measuring generic QoL. We say that the effects of prostate cancer treatment on generic QoL are small, which is in fact generic QoL *as defined by the SF-36* and similar measures. The situation may be similar to the mythic Pygmalion, who took the marble statue of the girl he loved for 'the real thing'. If urinary, bowel or sexual dysfunction has an effect on generic QoL, the question is whether the SF-36 is able to pick it up. On inspection of the SF-36 items, it is not quite clear which are relevant for respondents to express the effects of physical symptoms other than pain. And respondents are asked to rate limitations 'as a result of your physical health' – but whether, as an example, men who complete the questionnaire generally regard urinary or sexual dysfunction as an element of their physical health is not known. Qualitative research of the meaning of SF-36 items to respondents, as ongoing in the Rotterdam QoL study, may provide some answers.

From scarce longitudinal analyses in the data from the selected studies there is the suggestion of an improvement of mental health between the pre-treatment assessment and 12 months later, with stable general physical functioning. This suggested finding focuses on the fact that the pretreatment assessment is not a real 'baseline' assessment. At the time of the pre-treatment assessment the men have recently been told the diagnosis of prostate cancer. The two events (being diagnosed with cancer and the subsequent primary treatment) probably both have their specific effects afterwards. We hypothesise that the real stressor is the diagnosis, not the treatment, and that the treatment reduces the distress. In the Rotterdam QoL study this hypothesis is being investigated by including a pre diagnosis QoL assessment in the screening phase.

After completion of the review in 2003 an update on the population-based study with similar findings was published in 2004 (Potosky, Davis et al. 2004).

CHAPTER 3

Measuring disease specific quality of life in localized prostate cancer: the Dutch experience.

Korfage IJ, Essink-Bot ML, Madalinska JB, Kirkels WJ, Litwin MS, de Koning HJ.,
Qual Life Res 2003;12(4):459-64.

Abstract

Objective We aimed at developing and testing a Dutch health-related quality of life measure for localized prostate cancer patients.

Methods Scales on urinary and bowel function and bother from the UCLA Prostate Cancer Index (PCI) underwent formal linguistic and cultural translation. PCI sexual scales were replaced by an existing Dutch sexual activities module (SAc). After qualitative pilot testing 389 patients with localized prostate cancer (mean age 67 years ± 7 years) completed the measure before and at 2 time points after primary treatment. Psychometric properties (feasibility, score distribution, reliability, construct validity and responsiveness to change) of the new instrument were analyzed.

Results Response rates ranged from 93% at baseline to 87 % after treatment. Urinary and bowel function scales showed Cronbach's alphas > 0.7. Urinary function and bother, and bowel function and bother were significantly correlated. Pre- versus post-prostatectomy effect sizes were > 0.9 only for urinary scales; while pre- versus post-radiotherapy effect sizes were > 0.75 only for bowel scales. Six months after baseline erectile dysfunction was reported by 64% of respondents, either as a problem in sexual activity or as a reason for not being sexually active.

Conclusion The Dutch PCI and SAc performed well in men treated for early stage prostate cancer.

Introduction

Within the framework of the European Randomized Study of Screening on Prostate Cancer (ERSPC) a longitudinal study on the health-related quality of life (QoL) effects of primary therapy in localized prostate cancer has been ongoing in Rotterdam since 1996 (Madalinska, Essink-Bot et al. 2001a; Madalinska, Essink-Bot et al. 2001b; de Koning, Auvinen et al. 2002). The principal aims of this quality of life study were first to assess the frequency of side effects of primary therapy for localized prostate cancer, and secondly to determine their effects on QoL, defined as patient's physical, psychological and social functioning. QoL was measured with generic and prostate cancer specific instruments.

Confronted with the choice of an appropriate prostate cancer specific instrument preceding the start of data collection in 1996, we defined the following criteria:

1. the instrument was to be complementary to the RAND 36-item Short-Form Health Survey (SF-36) (Ware and Kosinski 2001) and the EuroQol classification (EQ-5D) (Dolan 1997);

2. the instrument had to be applicable and valid for patients with different primary treatment modalities (prostatectomy, external beam radiotherapy, watchful waiting) and thus encompass the urinary, bowel and sexual domains;
3. the instrument was to contain items on function and bother;
4. the instrument had to be comprehensible for unselected prostate cancer patients ;
5. the instrument had to enable differentiation among various physical and non-physical causes of sexual inactivity after prostate cancer treatment.

By reviewing literature and contacting researchers we identified 7 instruments. We decided to adapt the UCLA Prostate Cancer Index (PCI), as this instrument met most of the predefined criteria (Litwin, Hays et al. 1998). The PCI contains 6 scales on urinary, bowel and sexual function and bother and was originally constructed to be complementary to the SF-36. A shortcoming of the PCI was its inability to differentiate among the causes of sexual inactivity. We chose to adapt 4 PCI scales into Dutch: urinary function (5 items), bowel function (4 items), urinary bother (1 item) and bowel bother (1 item). Each item contains 3-5 answer categories. Scales are transformed linearly to ranges of 0-100, with higher scores representing better QoL. The PCI sexual function and bother scales were replaced by a Dutch module on sexual activity (SAc) consisting of 12 single items that do not add up to a scale. Each item contains 3 to 5 answer categories. A skip pattern enables differentiating in sexually active versus inactive men. Sexually inactive men were asked why they were inactive (no desire; no partner; partner had no desire; erectile dysfunction or other reasons), while sexually active men were asked whether erectile dysfunction (problems with getting or maintaining erections) had occurred. Items on the presence of spontaneous erections were added to assess physical erectile ability (Slob, Blom et al. 1990).

This brief communication first addresses the development and testing of the Dutch PCI, after which the questionnaire on sexual activity (SAc) is discussed.

Materials and methods

Independent forward and backward translation procedures were applied for the 4 PCI scales (urinary function, bowel function, urinary bother and bowel bother). Respondents were to receive the first questionnaire between diagnosis and start of treatment. To ensure that the respondents' answers indeed referred to this specific period the original time frame of the PCI was adjusted from 4 weeks to one.

The Dutch PCI and the SAc were qualitatively pilot tested in 12 recently treated prostate cancer patients. Prostate cancer patients from 4 Rotterdam hospitals subsequently completed

questionnaires at baseline (after diagnosis, preceding treatment, T1) and at 6 (T2) and 12 months (T3) following treatment. The design of this study is described in more detail elsewhere (Madalinska, Essink-Bot et al. 2001b). Unless otherwise indicated reported results relate to the T2 assessment. We evaluated feasibility (response rates, percentages of missing items, compliance with skip patterns, remarks of respondents), score distribution, reliability (Cronbach's coefficient alpha for multi-item scales) and construct validity (product-moment correlations among the 4 PCI and 8 SF-36 scales). We expected a change in urinary function and bother in prostatectomy patients and a change in bowel function and bother in radiotherapy patients. Responsiveness to these changes of PCI scales was measured with an effect size statistic, D/SD, which divides the mean difference by the standard deviation at baseline (Staquet, Hays et al. 1998) and can be interpreted as follows: 0.2 <D/SD< 0.5 indicates a small, $0.5 \leq D/SD < 0.8$ a moderate and $D/SD \geq 0.8$ a large effect size .

The association between the presence of spontaneous erections and sexual activity was measured with a chi-square test.

Results

A total of 389 respondents with a mean age of 67 years (SD 7) participated in the study.

Patients were treated by radical prostatectomy (n=128), primary radiotherapy (n=188), watchful waiting (n=25) or androgen deprivation treatment for advanced disease (n=48).

Response rates were high (T1-T3: 93 to 87%). Due to respondents' mistakes in a preceding skip pattern (n=10) and inadvertent gluing of 2 pages of the questionnaire (n=5), the ranges for missing values in urinary modules were high in T3 (6.0-8.5%) in comparison to T1 (2.1-3.1%) and T2 (0.5-1.6%). After correction for this, ranges for missing values in the 3 questionnaires were 0.5-3.5% (urinary function), 1.6-4.3% (urinary bother), 0.5-1.9% (bowel

Table 3.1 Descriptive Statistics and Reliability of the Dutch PCI scales at T2

Module (no. of items)	n	Mean scale score (SD)	% Min score	% Max score	Cronbach's alpha*)	Skewness of scale (SE)
Urinary Function (5)	366	85.0 (22.4)	0	53	.83	-1.55 (0.13)
Bowel Function (4)	368	86.6 (18.6)	0	37	.79	-2.06 (0.13
Urinary Bother (1)	369	80.5 (30.7)	7	63	-	-
Bowel Bother (1)	374	87.0 (24.4)	2	72	-	-

*) Cronbach's alpha cannot be determined for single-item modules.

Table 3.2 Product-moment correlations between the PCI- and SF-36-scales

	UF	BF	UB	BB
PCI				
Urinary Function (UF)	1.00			
Bowel Function (BF)	0.04	1.00		
Urinary Bother (UB)	0.67*	0.10**	1.00	
Bowel Bother (BB)	0.03	0.73*	0.13**	1.00
SF-36				
Physical Functioning	0.09	0.32*	0.13**	0.28*
Role Limitations-Physical	0.11**	0.32*	0.14*	0.29*
Bodily Pain	-0.01	0.42*	0.09	0.28*
General Health	0.00	0.36*	0.14*	0.31*
Vitality	0.09	0.35*	0.14*	0.30*
Social Functioning	0.19*	0.39*	0.19*	0.28*
Role Limitations-Emotional	0.13**	0.36*	0.10	0.24*
Mental Health	0.10	0.42*	0.17*	0.33*

* $p < 0.05$ level (2-tailed); ** $p < 0.01$ level (2-tailed)

function), 0.3-0.5% (bowel bother) and 1.4-7.7% (SAc). A quality check of 100 randomly selected questionnaires (50 copies of T1, 50 copies of T2) showed that 87% of respondents correctly performed skip patterns in the SAQ. The respondents' remarks suggested a good understanding and general acceptance of the questionnaire. At T2, the range of mean PCI scale scores was 80-87. Cronbach's alpha coefficients were 0.83 (urinary function) and 0.79 (bowel function) (Table 3.1). As shown in Table 3.2, urinary function and bother and bowel function and bother correlated significantly ($r = 0.67$; $p < 0.001$ and $r = 0.73$; $p < 0.001$ respectively). Urinary function showed significant correlations with 3 out of 8 SF-36 scales and urinary bother with 6 out of 8. Bowel function and bother showed significant correlations with all SF-36 scales ($p < 0.01$ for all values).

Table 3.3 Effect sizes from T1 to T2 for pre-/post-prostatectomy and pre-/post radiotherapy

	Treatment	
	Prostatectomy	**Radiotherapy**
Urinary function	1.51	0.16
Bowel function	-0.10	0.81
Urinary bother	0.92	0.16
Bowel bother	0.01	0.77

Effect size: > 0.2= small effect; > 0.5= medium effect; > 0.8= large effect.

Effect sizes (Table 3.3) for pre- and post-prostatectomy urinary function and bother were 1.51 and 0.92 respectively, for pre- and post-radiotherapy these were both 0.16. Effect sizes for pre- and post-prostatectomy bowel function and bother were -0.10 and 0.00 respectively, for pre- and post radiotherapy these were 0.81 and 0.77.

Figure 3.1 shows the results regarding the sexual activity and erectile dysfunction in the respondents at T2. Of the 226 men reporting no sexual activity during the previous fortnight 132 (58%) reported erectile dysfunction as a reason for sexual inactivity. Eighty eight out of 138 sexually active men reported problems with achieving erections (64%). Thirteen men who had no problem with getting an erection did report problems with maintaining their erections. At T2, 233 respondents (64%) reported experiencing erectile dysfunction.

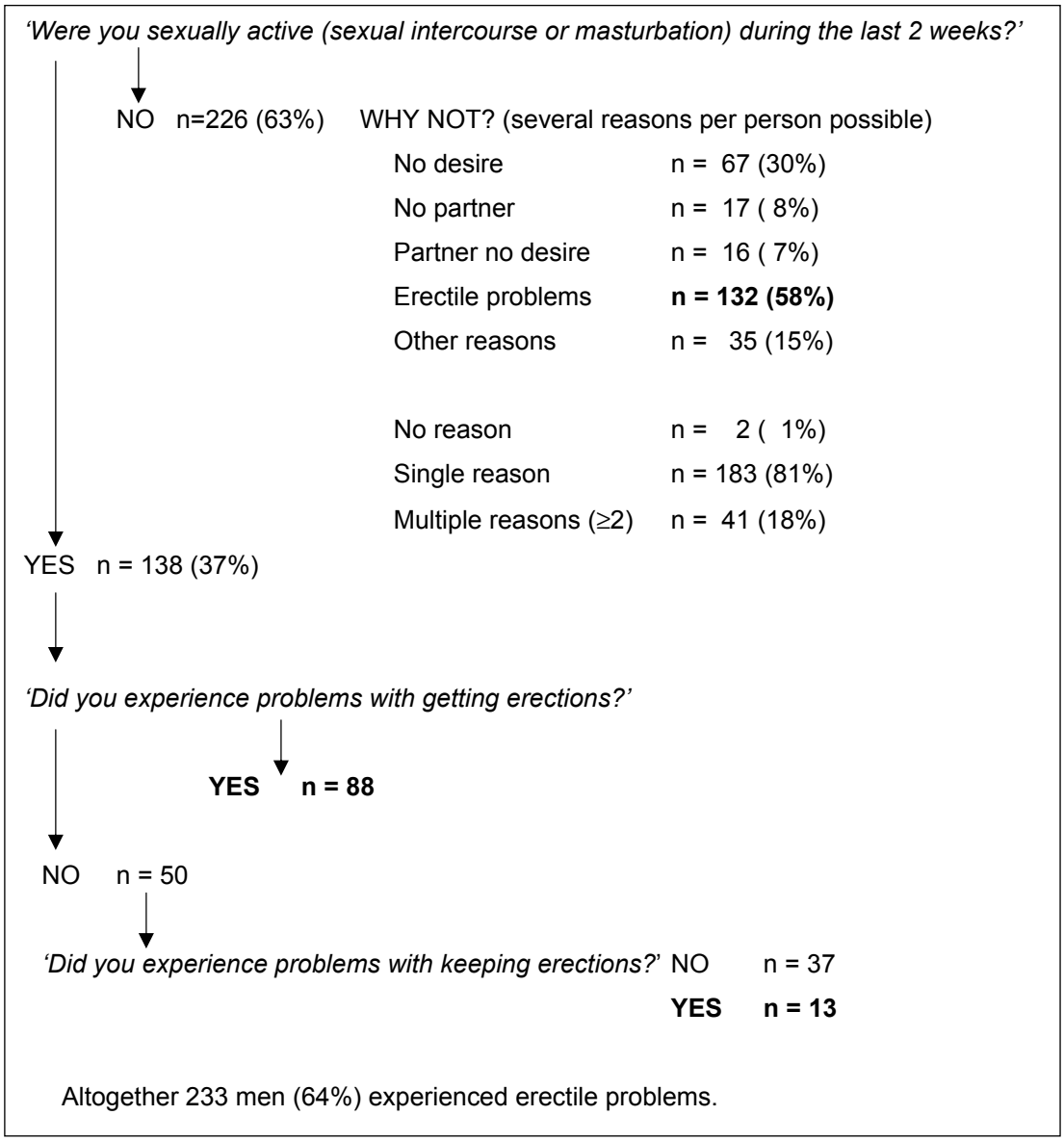


Figure 3.1 Sexual activity and erectile dysfunction in study respondents at T2 (n = 364)

Table 3.4 Association* between sexual activity (sexual intercourse, masturbation) and presence of spontaneous erections at T2, n = 364

	Spontaneous erections	
	present	absent
Sexually active	78 (22%)	58 (16%)
Sexually inactive	41 (11%)	185 (51%)

* significant at $p < 0.001$, χ^2-test

An item on the occurrence and the frequency of spontaneous erections was used to distinguish between physical and non-physical causes of erectile dysfunction. A total of 58 out of 243 men without spontaneous erections (24%) reported sexual activity. The presence of spontaneous erections was associated significantly ($p < 0.001$) with sexual activity (Table 3.4).

Discussion

The results of the present study indicate a good feasibility, reliability and construct validity for the Dutch PCI. The questionnaire caused no objections or high percentages of missing values, which implies that the instrument is comprehensible to and well accepted by respondents. When asked at T3, a high proportion of respondents (>80%) agreed to participate in a follow-up study illustrating the value attached to -studies into- these aspects of QoL. Means and standard deviations of scale scores were comparable to those found by Litwin in a sample of 255 U.S. prostate cancer patients (mean age 73 years) (Litwin, Hays et al. 1998). Correlations of Dutch bowel modules with SF-36 scales were comparable to Litwin's. The number of significant correlations between Dutch SF-36 and the PCI urinary scales was lower than Litwin reported for the US (Litwin, Hays et al. 1998). This may be due to differences between the populations or to the translation of either SF-36 or PCI.

As would be expected clinically, urinary function and bother scores, but not bowel function and bother scores, change significantly from pre- to post surgery. The opposite pattern (significant change in bowel function and bother scores, but not in urinary function and bother scores) holds for pre- versus post-radiotherapy. This shows the instruments' responsiveness.

The Dutch SAc allowed for assessment of erectile dysfunction in sexually active and sexually inactive men. Although sexual activity was reported by a number of men without spontaneous erections, sexual activity was associated significantly with the presence of spontaneous erections ($p < 0.001$, Table 3.4). We wanted respondents to refer to the period between diagnosis and treatment in answering the questionnaire. That is why the sexual activity of the

respondents was assessed over a period of 'the previous fortnight'. A longer time frame may have resulted in higher numbers of sexual activity in respondents.

The SAc in its present form merely consists of a number of items. Efforts are currently ongoing to combine the existing items into scales. In the course of our study, Rosen's International Index of Erectile Function (IIEF) (Rosen, Riley et al. 1997) and the Expanded Prostate Cancer Index Composite (EPIC, an adapted version of the PCI) were published (Wei, Dunn et al. 2000). Unfortunately, no differentiation among the causes of sexual activity is possible with either instrument.

Conclusion

We conclude that the Dutch adaptation of PCI's urinary and bowel modules is suitable for further use in men treated for early stage prostate cancer. The SAc is useful in identifying men experiencing erectile dysfunction, regardless of whether they are sexually active or inactive. A statistically significant association between presence of spontaneous erections and sexual activity was demonstrated. Distinction between organic and non-organic causes of erectile dysfunction merits further attention, although possibilities to make this distinction by questionnaire are only limited.

Acknowledgement

We thank the men who, by participating in this study, have contributed to the development of the Dutch PCI. We thank the Dutch Cancer Society for funding our study.

CHAPTER 4

Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer therapy

Korfage IJ, Essink-Bot ML, Borsboom GJJM, Madalinska JB, Kirkels WJ, Habbema JDF, Schröder FH, de Koning HJ. Int J Cancer 2005;116(2):291-6.

Abstract

Although with earlier detection of prostate cancer more men face the long-term consequences of primary treatment, studies on the impact of treatment on long-term health-related quality-of-life (QoL) are scarce. We followed 314 men with newly diagnosed localised prostate cancer from 1 month before until 5 years after radical prostatectomy (n = 127) or external beam radiotherapy (n = 187) (median follow-up 52 months). Questionnaires addressing disease-specific (UCLA PCI) and generic (SF-36, EQ-5D) QoL were sent 1 month before, and 6, 12 and 52 months after treatment. Repeated-measures modelling was used to study QoL over time. Regular urinary leakage was reported by 12% of prostatectomy patients before treatment and by 31% at the 52-month assessment. Erectile dysfunction before treatment was reported by 31% of prostatectomy patients and by 40% of radiotherapy patients; at the 52-month assessment, these percentages were 88% and 64%, respectively. Erectile dysfunction present at 1 year post-treatment can be considered permanent. Prostatectomy patients reported better generic functioning both before and after treatment than radiotherapy patients, who were on average 5.9 years older and had more comorbid conditions. General physical functioning of prostatectomy patients slightly improved over time, but declined in radiotherapy patients. The relation between age and physical scores was found to be non-linear. The long-term physical decline in radiotherapy patients partly resulted from aging and its non-linear impact on health, although treatment effects cannot be excluded. Scores of both patient groups remained above those of norm populations. Innovative graphs describing disease-specific and generic functions after treatment can help patients and physicians in their treatment choices.

Introduction

In Western countries, prostate cancer is the most prevalent malignancy in males (Parkin, Bray et al. 2001). Due to early detection and treatment, the number of men with long post-treatment survival of localized prostate cancer is increasing. However, the growing tendency for prostate screening and the concomitant overdetection and overtreatment (Draisma, Boer et al. 2003) warrant careful evaluation of treatment effects on health related quality of life (QoL). Prostatectomy is reported to lead to better disease-specific survival than watchful waiting (Holmberg, Bill-Axelson et al. 2002), but data are lacking concerning radical prostatectomy versus external beam radiotherapy, which are the most commonly used primary therapies. A randomised controlled treatment trial in the United Kingdom is currently comparing survival

and QoL after radical prostatectomy, external beam radiotherapy and monitoring (Donovan, Mills et al. 2002).

While awaiting results from randomised trials, longitudinal studies with long-term follow-up are important to assess the effects of treatment on QoL, defined as a patient's physical, psychological and social functioning and well being. A longitudinal prospective cohort study on the effects of primary therapy in localized prostate cancer was started in the Netherlands in 1996: the Rotterdam study (Madalinska, Essink-Bot et al. 2001), within the context of the European Randomized study of Screening for Prostate Cancer (ERSPC) (de Koning, Auvinen et al. 2002). The principal aims of the Rotterdam study were to assess the frequency of side effects of primary therapy and to determine QoL in men with localized prostate cancer up to 5 years after primary treatment with radical prostatectomy or external beam radiotherapy.

Patients and methods

Patients

Prostate cancer patients from 4 hospitals (University Medical Center Rotterdam; St. Franciscus Gasthuis; Medical Center Rotterdam Zuid, locations 'Clara' and 'Zuider') participated in the Rotterdam study. Patients were enrolled between June 1996 and January 1999, on average 1 month before the start of non-randomly allocated primary treatment, consisting of radical prostatectomy (intentionally nerve-sparing) or external beam radiotherapy (comprising an average of 33 radiation sessions over 7 weeks). For details of patient recruitment and first-year results see Madalinska *et al*. (Madalinska, Essink-Bot et al. 2001). Written informed consent was obtained from all respondents. The Medical Ethical Committees of all 4 hospitals approved the study design.

Quality of Life measures

Respondents completed postal self-assessment questionnaires on 4 occasions: 1 month before, and 6, 12 and 52 months after treatment. The following disease-specific and generic (i.e. comprehensive and non-disease specific) QoL measures were used:

One, the University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) measures disease-targeted QoL in men treated for early-stage prostate cancer (Litwin 1999). Following formalized procedures, 4 of its 6 scales were adapted for use in Dutch: urinary function (5 items, including frequency of urinary leakage, number of pads used to control leakage), bowel function (4 items, including frequency of rectal urgency and of crampy pain in abdomen or pelvis), urinary bother, and bowel bother (1 item each). Psychometric

properties (feasibility, score distribution, reliability, construct validity and responsiveness to change) of the Dutch version of the UCLA PCI have been described earlier (Korfage, Essink-Bot et al. 2003). SF-36 missing item procedures were used for imputation of missing responses in PCI items (Ware, Snow et al. 1993). Each scale is scored from 0 to 100, with higher scores representing better outcomes. Differences of more than 5-10 points are considered clinically meaningful (Litwin, Flanders et al. 1999).

Two, sexual function was defined as regularly or often having problems in achieving or maintaining an erection if wished to, or not being sexually active because of erectile problems. This was measured with 12 Dutch single items derived from Slob *et al*. (Slob, Blom et al. 1990; Korfage, Essink-Bot et al. 2003).

Three, generic QoL was measured with the RAND 36-item Short-Form Health Survey (SF-36) and the EuroQol classification (EQ-5D). Both measures are available in over 50 languages and are considered applicable in a wide range of populations, health conditions and treatments. The SF-36 consists of 8 scales: physical functioning (10 items), role limitations due to physical problems (role-physical, 4 items), bodily pain (2 items), general health perception (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (role-emotional, 3 items), and mental health (5 items). Scales are transformed to ranges of 0-100 with higher scores indicating better functioning (Ware and Kosinski 2001). Differences of at least 6.5 points in the physical dimensions and 7.9 points in the mental dimensions are considered clinically meaningful (Norman, Sridhar et al. 2001). Procedures concerning imputation of missing responses in SF-36 items were conducted according to the guidelines of the SF-36 Health Survey Manual (Ware, Snow et al. 1993).

The EQ-5D classification consists of 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) complemented by a visual analogue scale (VAS) for valuation of own health. Classification scores can be linked to a utility score (Dolan 1997).

Additionally, information on age, marital status, educational level and profession was obtained. Educational level was classified as low (primary school or lower technical education), high (college/university degree) or intermediate. To assess co-morbidity, respondents were also asked which of 28 chronic conditions on a standardized list they were experiencing or had experienced over the past year (Dutch Health Interview Survey, Statistics Netherlands).

Baseline clinical information on tumour stage (Tumor-Node-Metastasis clinical classification) (Hermanek and Sobin 1992), histopathologic tumour (biopsy) grade and urologic treatment history was obtained from the Regional Cancer Registry. Data on the clinical or biochemical

progression at the time of the respondent's long-term QoL assessment were obtained from the treating physicians. Biochemical recurrence was defined as a prostate specifice antigen (PSA) level of at least 0.2 ng/mL after prostatectomy, confirmed on repeat testing, or a rise in PSA level of at least 0.5 ng/mL after radiotherapy, confirmed on a repeat testing.

Statistical analysis

Between-group differences in background characteristics and descriptive statistics for the QoL scales were calculated using SPSS for Windows, release 10.0.7. A *p*-value less than 0.01 (referring to 2-sided statistical tests) was considered significant. The chi-square test was used for categorical variables and the Mann Whitney U test for continuous variables.

The development over time of disease-specific and generic function scores in the 2 groups was analysed with repeated-measures analysis of variance (ANOVA) using proc mixed from the SAS system for Windows release 8.2. Random intercept models were applied that allowed for the use of all available data, including incomplete records. The models comprised the main effects of treatment and time and the interaction between treatment and time. Time was included as a factor with 4 levels (1 for each assessment) to account for possible non-linearity's in the development of QoL scores. A non-response analysis was performed; details on this are available from the authors.

Results

Cohort characteristics

Between June 1996 and January 1999, 415 eligible men were identified, of whom 387 consented to participate in this study (Figure 4.1). Primary treatment consisted of prostatectomy (n = 127) or radiotherapy (n = 187). Men referred to watchful waiting (n = 25) or advanced disease therapy (n = 48) were excluded from analysis.

There was a significant difference in age, co-morbidity and average PSA levels between the 2 treatment groups. Compared to radiotherapy patients, prostatectomy patients were on average 5.9 years younger ($p < 0.01$, Table 4.1), had on average 0.4 fewer co-morbid conditions ($p < 0.01$) and had a lower PSA level ($p < 0.01$). TNM stages were more favourable in prostatectomy patients ($p = 0.06$).

The overall response rate to all 4 questionnaires was 76%, representing 224 of 294 men still alive at the 52-month assessment. Median and mean time to long-term follow-up was 52 months (range, 45-58 months).

Figure 1 Profile of study population

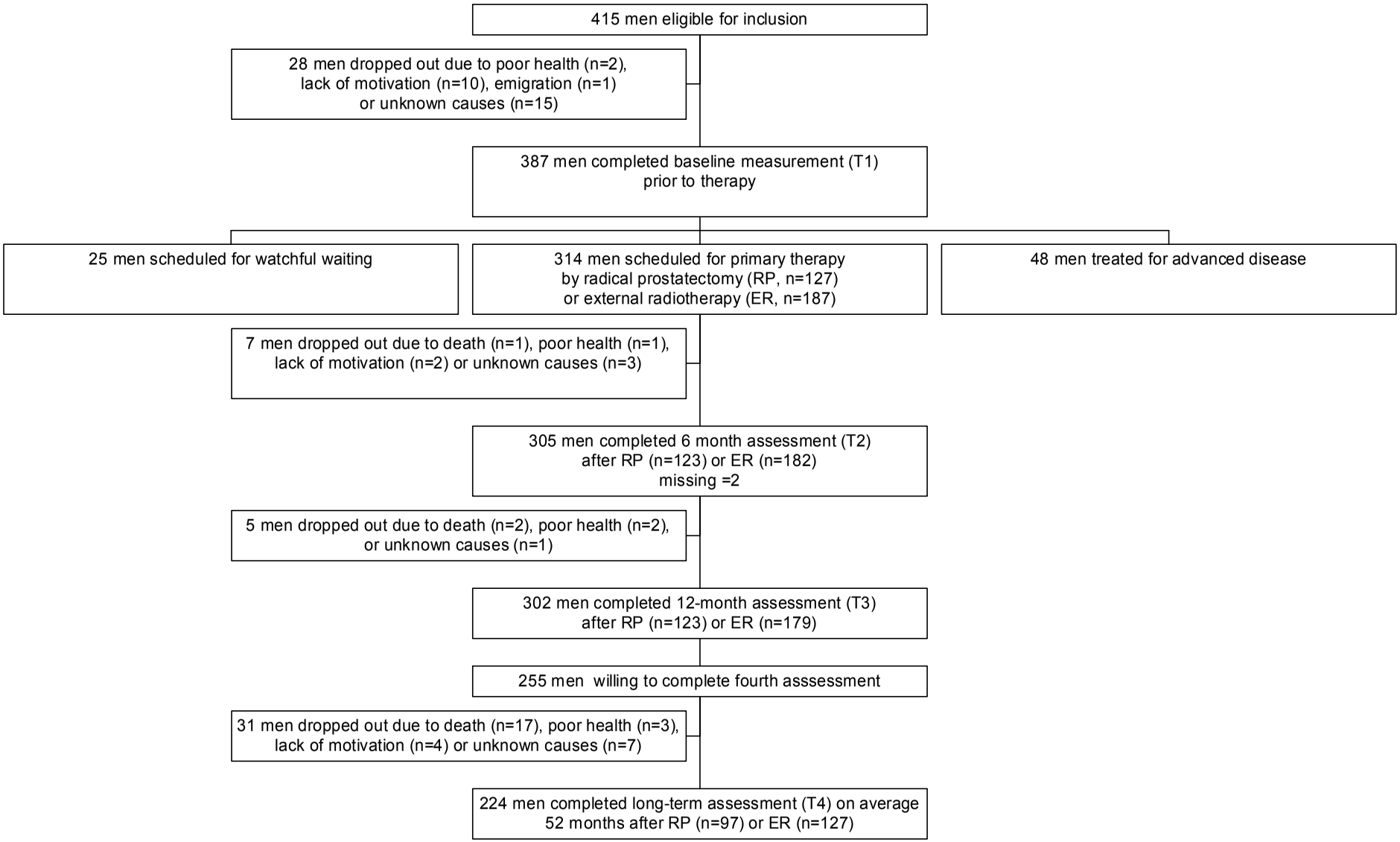


Table 4.1 Characteristics of the participants

	Prostatectomy (n = 127)	**Radiotherapy** (n = 187)	***P*-value**
Age at baseline (years)			0.00
Average ± SD (range)	62.3 ± 5.2 (49-74)	68.2 ± 5.8 (49-82)	
Educational level (%)			0.08
Low	30%	38%	
Intermediate	55%	54%	
High	15%	8%	
Marital status (%)			0.92
Married or cohabiting	87%	87%	
Divorced / single	13%	13%	
Comorbidity			0.00
Average number of conditions	0.6	1.0	
PSA level before treatment, ng/mL			0.00
Average ± SD	9.6 ± 15.6	15.4 ± 24.3	
Tumour stage before treatment			0.06
T1	18%	12%	
T2	67%	61%	
T3	15%	26%	
T4	0	1%	
Tumour grade before treatment			0.84
G1	51%	50%	
G2	38%	37%	
G3	11%	13%	
Detection mode			0.46
Screen-detected	60%	56%	
Clinically diagnosed	40%	44%	

Information on recurrence was available for 94% of the 52-month respondents. There was clinical evidence of recurrence in at least 7% (7/97) of the prostatectomy patients and in 22% (28/127) of the radiotherapy patients.

Age

Average age differed considerably between treatment groups (±6 years). Because the relation between age and the physical functions in particular was found to be non-linear (as the decline with ageing was generally steeper for older subjects than for younger ones), age

Table 4.2. Mean values (SD) of Prostate Cancer Specific Functioning: UCLA PCI Urinary and Bowel Scales, and Erectile Dysfunction, and frequencies (%) of symptoms

	Radical Prostatectomy				External Beam Radiotherapy			
	pretreatment	**6 months**	**12 months**	**52 months**	**pretreatment**	**6 months**	**12 months**	**52 months**
	n=127	n=123	n=123	n=97	n=187	n=182	n=179	n=127
Urinary Function (±SD)	**93 (±16)**	**70 (±27)**	**77 (±24)**	**79 (±24)**	**95 (±12)**	**92 (±15)**	**93 (±15)**	**91 (±16)**
Urinary leakage								
Every day	10 (8%)	46 (37%)	28 (23%)	23 (24%)	7 (4%)	12 (7%)	12 (7%)	5 (4%)
Several days a week	5 (4%)	14 (11%)	18 (15%)	7 (7%)	8 (4%)	11 (6%)	9 (5%)	12 (9%)
Urinary control								
No control	3 (2%)	7 (6%)	5 (4%)	2 (2%)	3 (2%)	3 (2%)	1 (1%)	3 (2%)
Frequent dribbling	4 (3)	19 (15%)	14 (11%)	10 (10%)	11 (6%)	11 (6%)	10 (6%)	11 (9%)
Use of pads								
3 or more pads a day	3 (2%)	21 (17%)	12 (10%)	7 (7%)	1 (1%)	3 (2%)	2 (1%)	5 (4%)
1-2 pads a day	6 (5%)	42 (34%)	30 (24%)	17 (18%)	1 (1%)	11 (6%)	11 (6%)	3 (2%)
Urinary Bother (±SD)	**90 (±23)**	**71 (±36)**	**79 (±31)**	**82 (±28)**	**89 (±24)**	**85 (±27)**	**89 (±24)**	**86 (±25)**
Big problem	3 (2%)	17 (14%)	10 (8%)	4 (4%)	4 (2%)	7 (4%)	4 (2%)	3 (2%)
Moderate problem	4 (3%)	6 (5%)	5 (4%)	4 (4%)	8 (4%)	9 (5%)	7 (4%)	6 (5%)

Bowel Function (±SD)	**90 (±16)**	**91 (±15)**	**90 (±16)**	**89 (±13)**	**91 (±12)**	**81 (±22)**	**81 (±21)**	**84 (±19)**
Loose or liquid stools								
Always	1 (1%)	1 (1%)	1 (1%)	-	1 (1%)	9 (5%)	4 (2%)	-
Usually	4 (3%)	3 (2%)	6 (5%)	2 (2%)	8 (4%)	19 (10%)	13 (7%)	10 (8%)
Crampy pain								
Several times a day	1 (1%)	1 (1%)	2 (2%)	2 (2%)	3 (2%)	11 (6%)	6 (3%)	3 (2%)
About once a day	6 (5%)	1 (1%)	3 (2%)	2 (2%)	3 (2%)	4 (2%)	5 (3%)	3 (2%)
Bowel Bother (±SD)	**94 (±18)**	**94 (±19)**	**93 (±20)**	**95 (±14)**	**95 (±17)**	**81 (±27)**	**78 (±29)**	**81 (±29)**
Big problem	1 (1%)	2 (2%)	2 (2%)	-	2 (1%)	6 (3%)	9 (5%)	4 (3%)
Moderate problem	4 (3%)	4 (3%)	3 (2%)	1 (1%)	3 (2%)	9 (5%)	10 (6%)	10 (8%)
Erectile Dysfunction (ED)								
Sexually active and ED	32 (25%)	39 (32%)	47 (38%)	41 (42%)	40 (21%)	52 (29%)	46 (26%)	36 (28%)
Sexually inactive, because of ED	7 (6%)	71 (58%)	61 (50%)	44 (45%)	34 (18%)	42 (23%)	50 (28%)	45 (35%)
Total ED*)	39 (31%)	110 (89%)	108 (88%)	85 (88%)	74 (40%)	94 (52%)	96 (54%)	81 (64%)

Higher scores indicate better functioning.

adjustment would not have been appropriate. Therefore we decided to present the QoL scores over time in graphs with the differences in age between the treatment groups presented on the x-axes.

Disease-specific scores

The impact of prostatectomy had a marked effect on urinary function, urinary bother and erectile dysfunction (Table 4.2). The proportion of prostatectomy patients experiencing regular urinary leakage (i.e. at least several days a week) was 12% (15/127) before treatment, 37% (46/123) at the 12 month-assessment, and 31% (30/97) at the 52-month assessment. Of all prostatectomy patients, 7% reported wearing pads for incontinence before treatment; this increased to 34% at the 12-month assessment and to 25% at the 52-month assessment.
Radiotherapy had a marked effect on bowel unction and bowel bother scores (Table 4.2).

Generic function

Prostatectomy patients had higher scores on all 8 SF-36 scales, higher EQ-5D utility scores and higher valuation of own health than radiotherapy patients (Table 4.3). Differences in mean scale scores between groups were smallest for nental health and largest for role-physical. Comparison with Dutch reference scores (Aaronson, Muller et al. 1998) showed that the pre-treatment SF-36 scale scores of prostatectomy patients were higher except for the mental health scores, which were significantly lower (data not shown). Radiotherapy patients had lower scores for mental health and in general health perceptions, similar scores for vitality and social functioning, and higher scores for the remaining SF-36 scales. At the 52-month follow-up assessment, the prostatectomy patients scored significantly better than the general population on all SF-36 scales, whereas radiotherapy patients scored equal to or significantly better (role-physical, bodily pain and role-emotional) than the general population. Both treatment groups scored equal to or higher than the US national age-adjusted norms for males (Ware, Snow et al. 1993) except for pre-treatment mental health (prostatectomy and radiotherapy group) and general health (radiotherapy group).

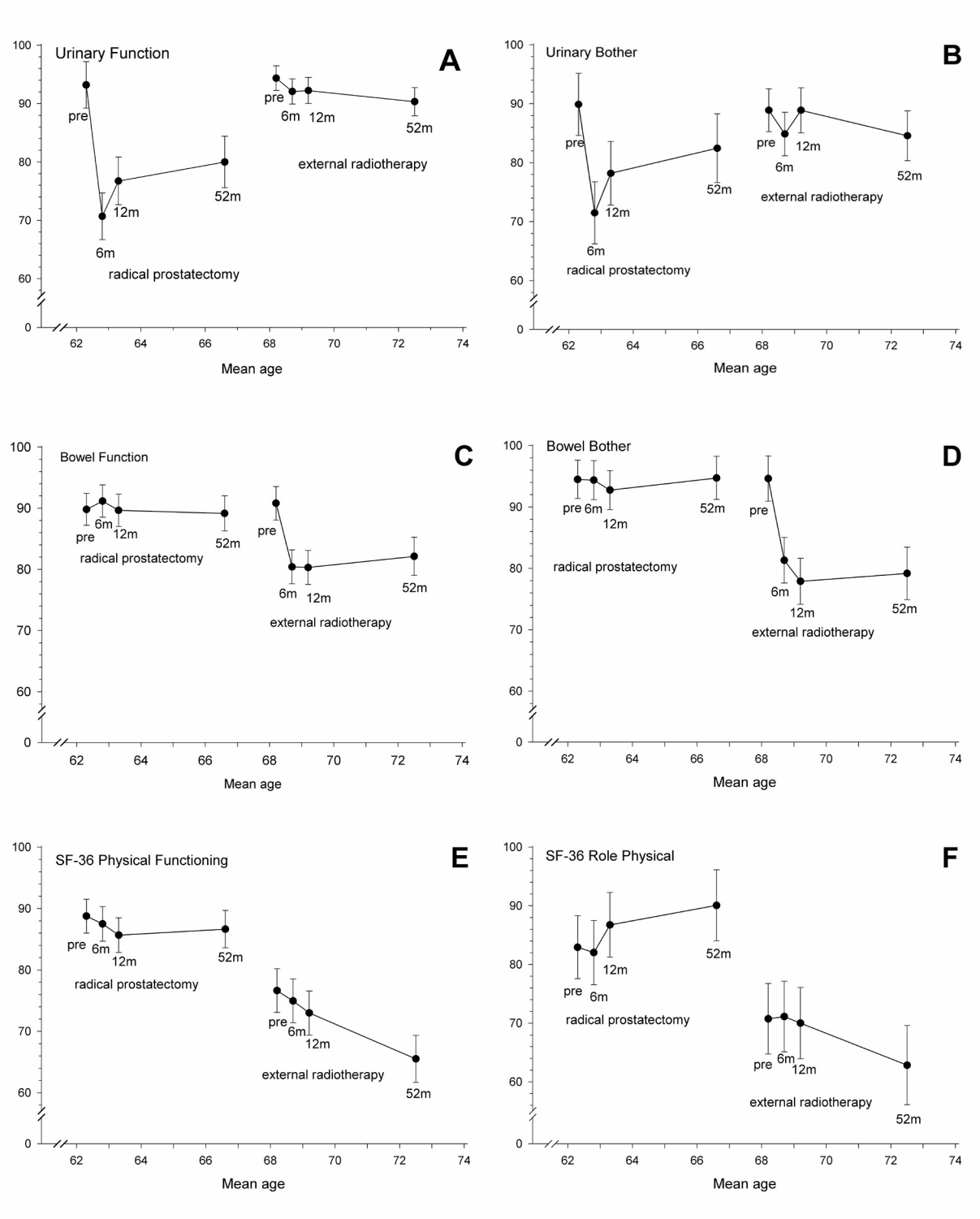
QoL over time

Results of the repeated measures model are shown in Figure 4.2. After prostatectomy, there was a steep decline in scale scores for urinary function and urinary bother (Figures 4.2A and B), and after radiotherapy, in scores for bowel function and bowel bother (Figures 4.2C and

Table 4.3 Mean values of Generic Health-Related Quality of Life Scales

	Radical Prostatectomy				External Beam Radiotherapy			
	pretreatment n=127	**6 months** n=123	**12 months** n=123	**52 months** n=97	**pretreatment** n=187	**6 months** n=182	**12 months** n=179	**52 months** n=127
SF-36								
Physical Functioning	89 (16)	87 (15)	86 (17)	87 (15)	77 (23)	76 (23)	74 (24)	68 (27)
Role-Physical	83 (33)	82 (32)	87 (30)	90 (26)	70 (40)	72 (39)	71 (41)	67 (44)
Bodily Pain	89 (18)	92 (17)	90 (17)	88 (18)	80 (25)	82 (24)	80 (24)	79 (23)
General Health	69 (17)	74 (18)	73 (17)	69 (20)	58 (18)	63 (20)	61 (19)	61 (22)
Vitality	78 (18)	75 (19)	76 (19)	76 (16)	69 (19)	69 (21)	68 (21)	67 (21)
Social Functioning	87 (19)	89 (18)	90 (19)	91 (16)	81 (23)	85 (21)	84 (23)	84 (24)
Role-Emotional	84 (32)	88 (27)	90 (25)	89 (27)	77 (36)	84 (32)	83 (32)	80 (35)
Mental Health	72 (16)	82 (18)	81 (17)	82 (16)	68 (18)	80 (19)	79 (19)	80 (19)
Physical Component Summary	53 (7)	52 (7)	52 (7)	52 (6)	48 (9)	47 (10)	46 (10)	44 (11)
Mental Component Summary	51 (9)	54 (9)	55 (9)	54 (8)	50 (10)	54 (10)	54 (10)	54 (10)
EQ-5D								
Utility	89 (15)	91 (16)	90 (17)	88 (18)	81 (20)	83 (21)	82 (20)	76 (23)
Valuation of Own Healthth	79 (17)	84 (12)	81 (13)	81 (13)	72 (17)	76 (17)	73 (16)	74 (16)

Higher scores indicate better performance



D). Generic physical function scores (Figures 4.2E and F) of radiotherapy patients declined between the 12- and 52-month assessment, whereas those of prostatectomy patients increased slightly. The scores for bodily pain and valuation of own health (Figures 4.2G and J) showed similar patterns in both treatment groups; the average scores, however, were lower in the radiotherapy group. Mental health score patterns were identical for both groups, showing no influence of either age or treatment choice (Figure 4.2H).

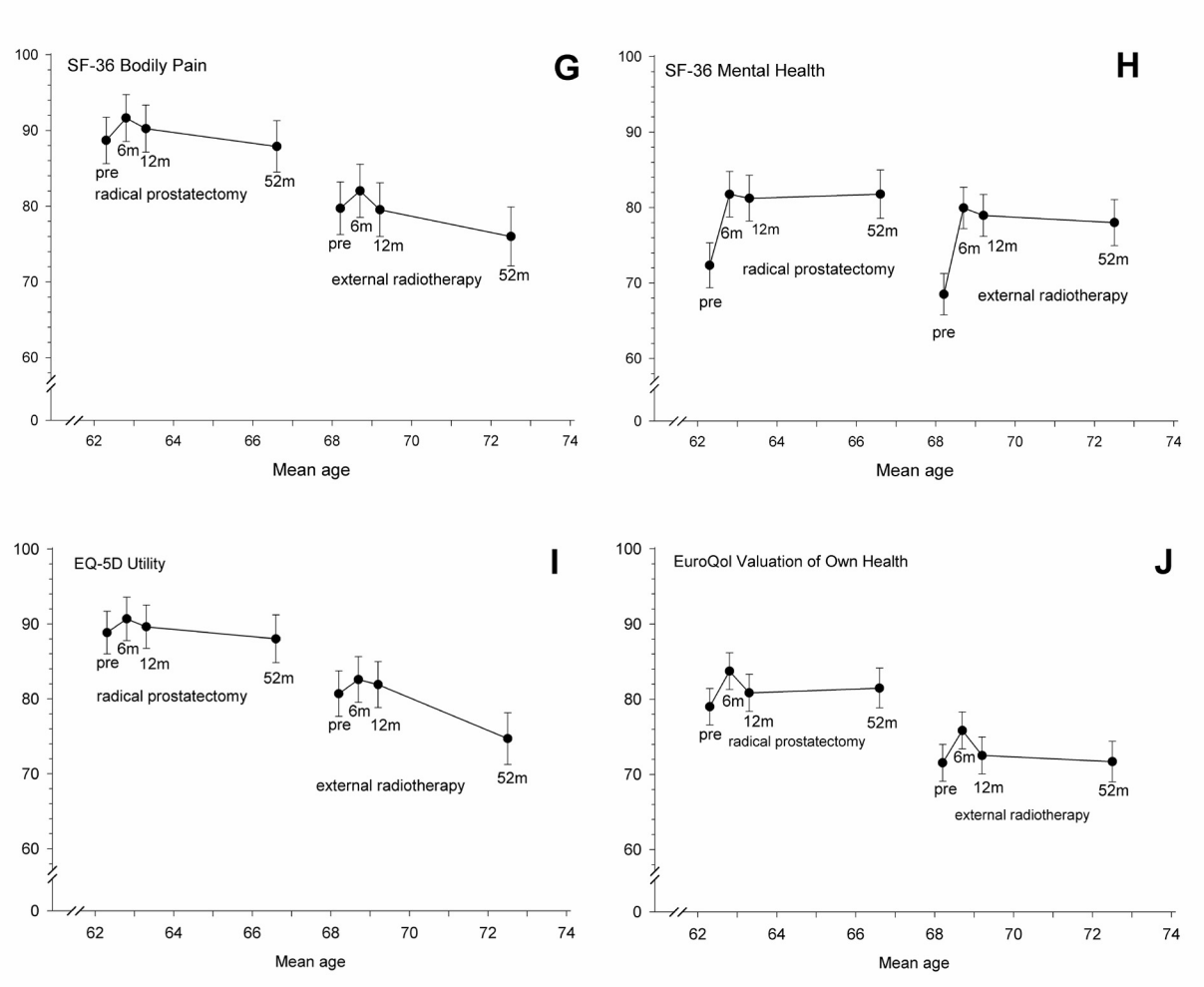


Figure 4.2 Model results showing average scale scores and 95% confidence intervals per treatment group: Dutch UCLA PCI scales of urinary (A-B) and bowel (C-D) domain, SF-36 scales (E-H) and EuroQol scales (I-J). Higher numbers indicate better functioning.

Discussion

Cross-sectional studies have shown that localized prostate cancer treatments can have serious consequences for urinary, bowel and sexual function (Penson, Litwin et al. 2003). Longitudinal follow-up studies, however, provide better insight in the effect of treatment on disease-specific and generic function than cross-sectional studies, especially when a pre-treatment assessment is included. However, the number of published cohort studies is limited (Litwin, Flanders et al. 1999), (Talcott, Rieker et al. 1998; Clark, Rieker et al. 1999; Lubeck, Litwin et al. 1999; Potosky, Legler et al. 2000; Galbraith, Ramirez et al. 2001; Lee, Hall et al. 2001; Litwin, Melmed et al. 2001; Schapira, Lawrence et al. 2001; Siston, Knight et al. 2003; Talcott, Manola et al. 2003). In the present longitudinal prospective cohort study, we followed 314 men with localized prostate cancer from pre-treatment until 5 years after treatment; the overall response rate was 76%. Average follow-up was longer and the number of patients larger than in most other prospective cohort studies. In one study on health outcomes after

prostatectomy or radiotherapy, 1,591 prostate cancer patients participated, but this study did not include a pre-treatment assessment (Potosky, Legler et al. 2000).

Previous longitudinal cohort studies found that prostatectomy mainly affected urinary and sexual functioning, whereas radiotherapy had consequences for bowel and sexual functioning. These results were confirmed by the present study.

In our study, there were some important baseline differences between the prostatectomy and radiotherapy patients. Prostatectomy patients had fewer co-morbid conditions, a lower PSA level, a more favourable TNM-stage and were on average 5.9 years younger than radiotherapy patients. These differences were due to the non-random treatment allocation. Randomised controlled trials may ensure comparable groups at baseline; however, only a selected group of prostate cancer patients will be eligible for random allocation to either treatment option.

We found a non-linear relation between age and physical function: cross-sectional QoL scores at baseline showed a steep decrease with increasing age of the patient. Assuming that the effect of illness on QoL at baseline was small and similar in both treatment groups, this decrease with age was probably the result of aging. It is likely that a similar effect of age occurred in the within-person or longitudinal changes in QoL. Such an effect, however, could have been confounded by the effects of having prostate cancer and of treatment, both of which may also vary with age. Because of this non-linear relation, adjustment for age would not have been appropriate. Therefore, we have presented the results as a descriptive analysis of the average course of QoL over age in 2 treatment groups. The innovative graphs in our study illustrate disease-specific and generic function in the years following treatment and provide a useful tool for patients and physicians in their treatment choices.

The unclear overall benefit of PSA screening and the high prevalence of side effects of primary treatment complicate decision-making about PSA testing and prostate cancer treatment. Increasing attention is currently paid to the process of shared or informed decision-making. Information on the development of disease-specific and generic functions over the years as well as the non-linear relationship with age is useful for both physicians and patients in this process of decision-making.

At the 52-month assessment, we observed a decrease in general physical function of radiotherapy patients, whereas physical function and role-physical scores of prostatectomy patients showed no decline over time in spite of aging. The decrease in radiotherapy patients may be explained by advancing age and its non-linear impact on health, but treatment effects or the higher rate of recurrence in the radiotherapy arm may also have played a role (Pietrow, Parekh et al. 2001).

In both treatment groups, mental health scale scores showed a striking increase at the 6-month assessment. At the pre-treatment assessment the men had just been informed that they had prostate cancer, whereas 6 months later, they had undergone treatment for this disease. We hypothesize that the diagnosis of prostate cancer is the main stressor (not the treatment) and that treatment reduces distress.

Another interesting finding is that the urinary and bowel scale scores before treatment in both treatment groups were better than those in an age-related sample of U.S. men without prostate cancer (n = 134; mean age 66.4 years) (Litwin 1999). SF-36 scores, both before and after treatment, were equal to or higher than Dutch and U.S. age and sex-adjusted norms. The better generic function of prostate cancer patients before treatment may be the result of selection bias, since socio-economic status is positively associated with prostate cancer incidence (Liu, Cozen et al. 2001). Possible explanations for the higher generic scores after treatment include insensitivity of generic instruments for changes induced by prostate cancer diagnosis and treatment and response shift (Sprangers and Schwartz 1999). Patients may re-evaluate the value of life itself when (after intentionally curative treatment for cancer) they are still alive and in a reasonably good functional state; i.e. they may perceive urinary, bowel or sexual dysfunction as an inevitable consequence of treatment.

Confronted with similar results, Krahn et al. concluded that although sexual, urinary, and bowel dysfunction are common and important, their impact on the health status of prostate cancer patients may be overstated (Krahn, Ritvo et al. 2003). We believe, however, that even if patients accept the side effects of treatment and are prepared to put up with them, these side effects should never be taken lightly in the context of screening evaluation. Further study is required to establish what men perceive as the benefits or disadvantages of screening.

ACKNOWLEDGEMENTS

The authors are grateful to all patients for their participation in the study. We also thank the Departments of Urology of the four participating hospitals for their cooperation, and J.H. Groenewoud for critical comments on the manuscript. This study was funded by the Dutch Cancer Society (EUR 2000-2329 and EUR 95-11.43).

CHAPTER 5

Five-year follow-up on anxiety and depression before and after prostate cancer treatment

Korfage IJ, Essink-Bot ML, Janssens ACJW, Schröder FH, de Koning HJ. Submitted 2005.

Abstract

Aims To document anxiety and depression from pre-treatment till 5-year follow-up in 299 men with localized prostate cancer and to assess if baseline scores were predictive for ongoing anxiety and depression.

Methods Respondents completed 4 assessments on anxiety, depression and mental health. Respondents were subdivided according to therapy (prostatectomy versus radiotherapy) and high versus low-anxiety.

Results Pre-treatment 28% of all patients were classified as 'high-anxiety'. In these men average anxiety scores decreased significantly post-treatment, i.e. towards less anxiety. At all assessments, high-anxiety men treated by prostatectomy reported less depression than high-anxiety men after radiotherapy. Of men treated by radiotherapy, 27% reported clinical significant levels of depression while 20% is expected in a general population. The improvement in mental health at 6-months follow-up was statistically significant and clinically meaningful in all respondent groups. Sensitivity of anxiety at baseline as a screening tool was 71% for anxiety and 60% for symptoms of depression.

Discussion We recommend clinicians to attempt early detection of patients at risk of high levels of anxiety and symptoms of depression after prostate cancer diagnosis. STAI-State can be a useful screening tool but needs further development.

Introduction

Prostate cancer is highly prevalent in most Western countries (Parkin, Bray et al. 2001). Prostate cancer can be detected early by PSA, a biologic tumour marker. Radical prostatectomy and external beam radiotherapy are the most commonly used intentionally curative primary therapies.

Being diagnosed with prostate cancer leads to anxiety, but not to the same extent in every patient (Balderson and Towell 2003; Carlson, Angen et al. 2004; Steginga, Occhipinti et al. 2004). In a recent study some 30% of the participating prostate cancer patients met criteria for general distress in the clinical range (Carlson, Angen et al. 2004). In a retrospective, cross-sectional study among men with prostate cancer who were seeking psychological support, the prevalence of severe psychological distress was 37% (35/94) (Balderson and Towell 2003). Although several longitudinal studies with a follow-up longer than 12 months have reported on mental health or emotional well-being after prostate cancer treatment (Potosky, Legler et al. 2000; Galbraith, Ramirez et al. 2001; Litwin, Melmed et al. 2001; Litwin, Lubeck et al.

2002; Korfage, Essink-Bot et al. 2005), the long-term impact of prostate cancer diagnosis and treatment on anxiety and feelings of depression in men is not known.

The high prevalence of severe distress resulted in the recommendation to target interventions at treatment decision-related distress for all men and to offer in-depth psychological support for those who experience ongoing difficulties (Steginga, Occhipinti et al. 2004). Yet, for clinicians and patients it would be useful if individual patients at risk of prolonged psychological distress could be identified shortly after diagnosis. Several instruments have been developed to identify high-anxiety men who might need psychological support, for example the MAX-PC (Memorial Anxiety Scale for Prostate Cancer (Roth, Rosenfeld et al. 2003)) or the HADS (Hospital Anxiety and Depression Scale (Nordin, Berglund et al. 2001)) . Results were promising, but follow-up relatively short (2 weeks - 6 months). We conducted a prospective study with 5-year follow-up in newly diagnosed prostate cancer patients to 1) document the course of anxiety and depression from before the initiation of treatment; and 2) evaluate the predictive accuracy of baseline scores at the individual level for anxiety and depression in the year following diagnosis.

Patients and methods

Ethics approval and informed consent

The ethics review committee of the Erasmus MC, the University Medical Center Rotterdam, the Netherlands, approved of the research protocol. All participating men gave written informed consent.

Patients and procedures

All consecutive newly diagnosed prostate cancer patients from four Rotterdam hospitals were recruited between June 1996 and January 1999. Respondents were diagnosed through the ERSPC screening trial or in a clinical setting. Exclusion criteria were 1) referral to watchful waiting or advanced disease therapy; 2) non-completion of the STAI-State score (see below), since this score was crucial in assessing the respondents' anxiety level at baseline. The prospective study consisted of 4 measurements: 1 month before the start of primary treatment, and at 6 months, 12 months and 5-year follow-up. The non-randomly allocated treatment consisted of (intentionally nerve-sparing) radical prostatectomy or external beam radiotherapy (comprising an average of 33 radiation sessions over 7 weeks). Further details on the study design and the inclusion of respondents were published previously (Korfage, Essink-Bot et al. 2005).

Patients' characteristics

Information on age, marital status, education, co-morbidity and profession was obtained from the respondents. Educational level was classified as low (primary school or lower technical education), intermediate or high (college/university degree). The prevalence of co-morbidity was assessed using a standardized list of 28 chronic conditions among which were heart failure, asthma, diabetes etc. Respondents were asked to report which condition they were currently experiencing or had experienced during the past year (Dutch Health Interview Survey, Statistics Netherlands).

Baseline clinical information on tumour stage (Hermanek and Sobin 1992), histopathologic tumour (biopsy)grade and urologic treatment history were obtained from the Regional Cancer Registry. Possible postoperative adjustments to staging in the prostatectomy group were not included to maintain comparability with the radiotherapy group. Data on the clinical or biochemical progression at the 5-year assessment were obtained from the treating physicians. Biochemical recurrence was defined as a PSA-level of at least 0.2 ng/mL after prostatectomy, confirmed at least once, or as a rise in PSA-level of at least 0.5 ng/mL after radiotherapy, confirmed at least once.

Psychological measures

The questionnaires contained 3 validated self-report psychological measures.

Anxiety was assessed by the State Trait Anxiety Inventory (**STAI-State).** This scale contains 20 items on, for instance, feeling at ease or upset (Sesti 2000). Scale scores range from 20 to 80 with higher scores indicating higher levels of anxiety (van der Ploeg, Defares et al. 1980). A STAI-State score of more than 44 defines an individual as highly anxious (Spielberger and Vagg 1984; Millar, Jelicic et al. 1995). Applying this cut-off level we defined men with pre-treatment STAI-State scores equal to or above 45 as 'high-anxiety' and those with scores equal to or below 44 as 'low-anxiety'.

The Center for Epidemiologic Studies Depression Scale (**CES-D**) was used to assess the frequency and severity of symptoms of depression. We applied the 20-item version with items relating to, for instance, feeling depressed or fearful, being happy, and enjoying life. Scores range from 0 to 60 with higher scores indicating higher levels of symptoms of depression (Radloff 1977). A score of 16 or higher suggests a clinically significant level of symptoms of depression, which does not necessarily mean that the participant has a clinical diagnosis of depression. In a general population sample 20% of the participants had a CES-D score above 16 (Bouma, Ranchor et al. 1995).

The Mental Health scale of the RAND 36-item Short-Form Health Survey (**SF36-MH**) was used as a general measure of mental health. The scale consists of 5 items on being nervous, down, peaceful, depressed and happy. Item scores are transformed to ranges of 0 to 100 with higher scores indicating better mental health (Ware, Snow et al. 1993). Differences of at least 7.9 points are considered clinically meaningful (Norman, Sridhar et al. 2001).

Procedures concerning imputation of missing items were conducted according to the respective guidelines. STAI-State, CES-D and SF36-MH scores are moderately to strongly correlated. In our study the correlations at baseline ranged from 0.71 between STAI-State and CES-D to 0.83 between STAI-State and SF36-MH.

Statistical analysis

Respondents were subdivided into 4 groups, defined by therapy (surgery or external radiotherapy) and by level of anxiety (high versus low). Between-group and within-group differences in background characteristics and descriptive statistics were calculated using SPSS for Windows, release 10.0.7. The Chi-square test was used for categorical variables, the t-test or Mann-Whitney U for continuous variables. *P*-values less than 0.05 (referring to two-sided statistical tests) were considered significant.

The course of STAI-State, CES-D and SF36-MH scores within therapy groups was analysed by repeated-measures analysis of variance (ANOVA) using proc mixed from the SAS system for Windows release 8.2. Random intercept models were applied that allowed for the use of all available data, including incomplete records. These models comprised the main effects of ‘anxiety’ and ‘time’ and the interaction between anxiety and time. Time was included as a factor with four levels – one for each assessment - to account for possible non-linearities in the course of scale scores. Co-morbidity and PSA-level were included in the models as covariates.

To compare the course of anxiety and symptoms of depression in subgroups stratified by baseline anxiety scores, we calculated mean scores at 6 and 12-months follow-up for respondents with low (≤ 44) and high (>44) anxiety scores at baseline. To evaluate the diagnostic performance of baseline anxiety screening, we calculated the sensitivity, specificity, positive (PPV) and negative predictive value (NPV) using data of patients treated by surgery (n= 91) and radiotherapy (n= 123) who completed the first 3 assessments. This complete case analysis is a valid strategy, because missing values at 1-year follow-up were not related to levels of anxiety or symptoms of depression at baseline nor to age.

Age

Average age differed considerably between treatment groups (±6 years). Because the relation between age and the physical functions in particular was found to be non-linear (as the decline with ageing was generally steeper for older subjects than for younger ones), age adjustment was not appropriate. Therefore we present the psychological scores over time in graphs with the average age of the treatment groups presented on the x-axes – analogous to earlier reported disease-specific and generic quality of life scores of the same cohort (Korfage, Essink-Bot et al. 2005).

Results

Patient's characteristics

Between June 1996 and January 1999, 415 men met the inclusion criteria, of whom 387 consented to participate (93%). Men who were referred to watchful waiting (n=25) or advanced disease therapy (n=48), or had not completed the STAI-State at the first assessment (n=15) were excluded. The final cohort consisted of 299 primary prostate cancer patients treated with radical prostatectomy (n=118) or external radiotherapy (n=181). The response rate to all four questionnaires was 78% (214 out of 275 men still alive at the 52-month assessment). Median time to long-term follow-up was 52 months, and mean time 51 months (range: 44-56 months).

Table 5.1 reports patients' characteristics for the 2 treatment groups. The table shows that the groups differed significantly in age, the number of comorbid conditions, and the PSA-level before treatment. Based on STAI-State scores at the first assessment, 25% of the prostatectomy (n=29) and 30% of the radiotherapy group (n=55) were classified as high-anxiety. Characteristics did not differ significantly between high-anxiety and low-anxiety individuals within the 2 treatment groups, except that in the radiotherapy group the percentage of singles was higher among high-anxiety men compared to low-anxiety men (26 versus 8%, p=0.003).

Information on clinical or biochemical recurrence at the 5-year assessment was available for 94% of the 5-year respondents; prostate cancer had recurred in 5% (5/91) of the prostatectomy patients and in 21% (26/123) of the radiotherapy patients.

Table 5.1 Patient characteristics at baseline

	Prostatectomy (n=118)	**Radiotherapy** (n=181)	***p*-value**
Age in years			<0.001
Average (SD, range)	62.6 (5.3, 50-75)	68.1 (5.8, 50-82)	
Educational level (%)			0.10
Low	28% (31)	38% (66)	
Intermediate	57% (62)	54% (94)	
High	15% (16)	8% (14)	
Marital status (%)			1
Married or cohabiting	87% (103)	87% (155)	
Divorced or single	13% (15)	13% (24)	
Comorbidity			<0.001
Average number of conditions	0.7	1.2	
PSA-level before treatment in ng/mL			0.002
Average (SD)	9.7 (16.3)	15.7 (24.7)	
Tumour stage before treatment			0.06
T1	18% (19)	12% (20)	
T2	67% (71)	61% (103)	
T3	15% (16)	27% (45)	
T4	-	1% (2)	
Tumour grade before treatment			0.78
G1	51% (54)	50% (86)	
G2	38% (40)	37% (63)	
G3	11% (11)	13% (23)	

Psychological measures

Pre-treatment 28% of all patients were classified as 'high-anxiety'. Average **STAI-State** scores in high-anxiety men of 52 (surgery group) and 54 (radiotherapy group) decreased significantly after treatment, i.e. less anxiety, and remained at the lower level through follow-up (Table 5.2). At all assessments, surgically treated high-anxiety men reported less anxiety than high-anxiety men treated by radiotherapy. Repeated measures analysis showed a significantly different score pattern within treatment groups (p<0.0001): although high-anxiety men improved substantially at 6-months follow-up, they still reported more anxiety than low-anxiety men (Figure 5.1a). The percentage of patients with clinical levels of anxiety

Table 5.2 Mean STAI-State, CES-D and SF36-MH by treatment and baseline anxiety level and standard deviation

	Prostatectomy[1)]		Radiotherapy[1)]	
	High-anxiety n=29	**Low-anxiety** n=89	**High-anxiety** n=55	**Low-anxiety** n=126
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
STAI- State (80-20)				
Pre-treatment	51.9 (7.8)	32.8 (7.5)	54.1 (7.7)	32.8 (6.5)
6 months	39.2 *(12.5)	29.8* (8.4)	45.6* (11.8)	30.6* (8.4)
12 months	39.1 (11.6)	30.0 (8.7)	42.9 (11.4)	30.6 (9.7)
5 year	40.2 (11.3)	30.5 (8.4)	43.0 (10.3)	31.6* (9.0)
CES-D (60-0)				
Pre-treatment	16.8 (9.0)	7.6 (5.9)	19.9 (8.7)	8.1 (5.8)
6 months	13.0 *(12.3)	5.9* (7.1)	17.3 (11.0)	6.5* (6.1)
12 months	11.6 (9.8)	5.9 (6.8)	15.0 (10.1)	6.5 (6.6)
5 year	10.8 (9.7)	6.1 (5.7)	15.5 (8.7)	7.5* (7.2)
SF36-MH (0-100)				
Pre-treatment	55.4(13.3)	78.2 (11.5)	48.8 (14.3)	77.0 (11.2)
6 months	69.6 *(24.7)	86.0* (13.9)	64.7* (22.3)	86.6* (13.3)
12 months	70.4 (21.3)	85.7 (14.2)	65.1 (20.8)	84.8 (15.4)
5 year	71.2 (19.5)	85.1 (12.9)	65.1 (21.9)	84.5 (15.7)

[1)] Differences between anxious and non-anxious groups were <0.001 for all scale scores and at all assessments.
*) Statistically different (p<0.05) from previous assessment.

(STAI-State ≥ 45) decreased from 25 to 13 in surgically treated high-anxiety men and from 30 to 13 in those who received radiotherapy.

Compared to pre-treatment, all groups except the high-anxiety men who were treated by radiotherapy reported significantly lower **CES-D** scores at 6-months follow-up, i.e. less symptoms of depression (Table 5.2). At all assessments, high-anxiety men who received prostatectomy reported less feelings of depression than high-anxiety men after radiotherapy (Table 5.2). Repeated measures analysis showed that although levels of feelings of depression differed between high- and low-anxiety men, score patterns within treatment groups did not statistically differ (Figure 5.1b).

At all assessments *lower* percentages of prostatectomy men reported clinically significant levels of symptoms of depression than the general population (9-18% versus 20%), pre-treatment and at 5-year assessments in the radiotherapy group these percentages were *higher* than 20% (27 and 22%).

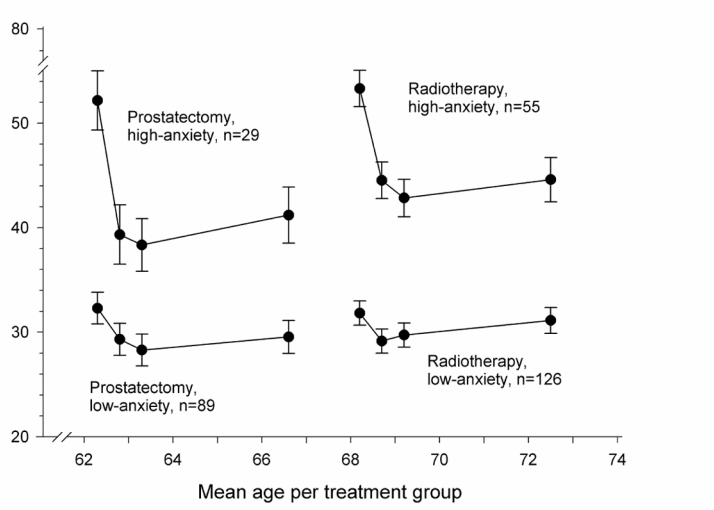


Fig. 1.a. STAI-State scores during 5-year follow-up by treatment group and baseline anxiety level.

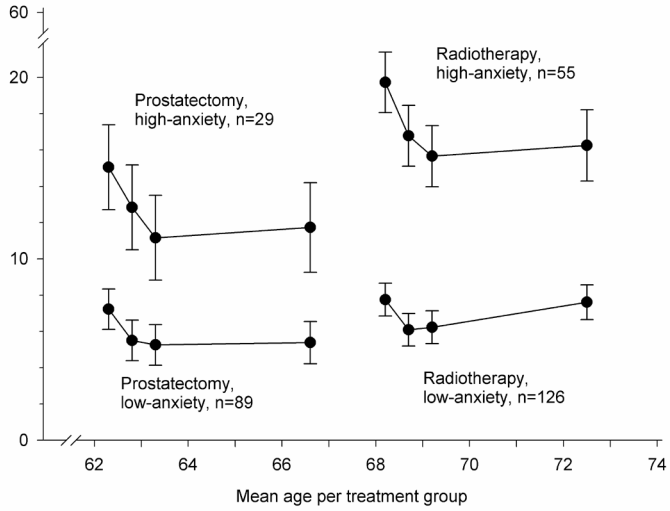


Fig. 1.b. CES-D scores during 5-year follow-up by treatment group and baseline anxiety level.

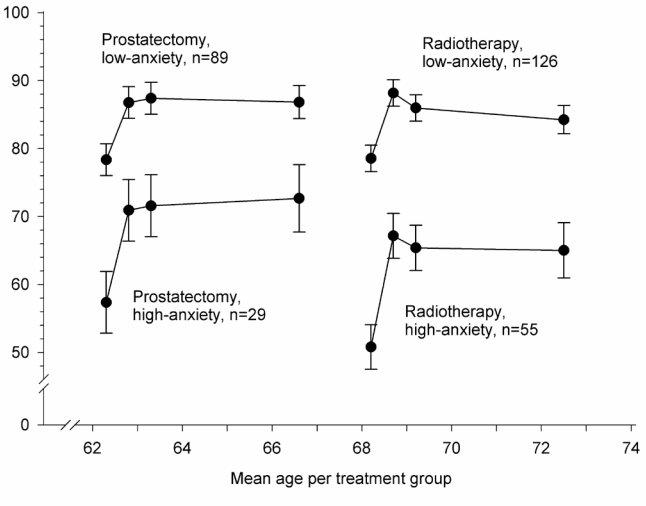


Fig. 1.c. SF-36 Mental Health scores during 5-year follow-up by treatment group and baseline anxiety level.

Table 5.3 Evaluation of baseline anxiety screening for the prediction of psychological distress at follow-up

	Anxiety score at baseline		Sensitivity	Specificity	PPV	NPV
	Low (n=193)	High (n=69)				
High anxiety score						
at 6 months	12 (6%)	29 (42%)	71%	82%	42%	94%
at 12 months	16 (8%)	26 (38%)	62%	80%	38%	92%
High depression score						
at 6 months	17 (9%)	26 (38%)	60%	80%	38%	91%
at 12 months	18 (9%)	26 (38%)	60%	80%	38%	91%
High anxiety or depression score						
at 6 months	22 (11%)	34 (49%)	61%	83%	49%	89%
at 12 months	22 (11%)	33 (48%)	60%	83%	48%	89%

Table 5.2 shows that compared to pre-treatment, the improvement in post-treatment **SF36-MH** in all four respondent groups was not only statistically significant, but also clinically meaningful (Ware, Snow et al. 1993). High-anxiety prostatectomy men reported better mental health than high-anxiety radiotherapy men (Table 5.2). Repeated measures analysis showed that although levels of SF36-MH differed between high-anxiety and low-anxiety men, score patterns within treatment groups were not significantly different between the groups (Figure 5.1c).

Predictive value of baseline scores

Table 5.3 shows the results of using the STAI-State score at baseline as a screening tool to predict high levels of anxiety and feelings of depression at the 6 and 12-months follow-up. The tool detected 71% of the patients who reported high anxiety at 6-months follow-up (sensitivity = 71%), and 60% of those reporting a clinical level of symptoms of depression (sensitivity = 60%). The probability of high anxiety scores at 6 or 12-months follow-up was 42% in patients with a high-anxiety score at baseline (PPV = 42%), and 8% in those with low-anxiety scores (NPV = 92%). The probabilities of high levels of symptoms of depression at follow-up were 38% (PPV = 38%) and 9% (NPV = 91%) in these groups.

Discussion

We performed a prospective, longitudinal study on mental health in 299 prostate cancer patients, using validated instruments. One month before treatment roughly one in every 4

patients was classified as 'high-anxiety'. Six months later, after initiation of treatment, men reported significantly less anxiety and feelings of depression and a significantly better mental health. Average scale scores remained at the improved levels through follow-up.

Before interpreting the results from a clinical perspective, 2 methodological issues have to be discussed. First, there is no unequivocal cut-off value for the STAI, with various cut-off values for high-anxiety circulating. We defined men with STAI-State scores of 45 and higher at baseline as 'high-anxiety'. This cut-off value has been reported before (Millar, Jelicic et al. 1995) (Roth, Kornblith et al. 1998) and matches almost perfectly with the validated cut-off value of the HADS (Millar, Jelicic et al. 1995). Second, non-response at 5-year follow-up was present. Repeated measures analyses can take incomplete cases into account, but in evaluating the STAI-State as a screening tool we excluded the 5-year assessment; because the non-response at 5-year follow-up was significantly lower in high-anxiety men, a complete case analysis would not be appropriate. It can be argued that a prediction of high-anxiety at 12-months follow-up is clinically more relevant, because high levels of anxiety or symptoms of depression at 5-year follow-up may be unrelated to the preceding prostate cancer diagnosis and treatment.

The average STAI-State scores at baseline in the high-anxiety groups, i.e. 52 for surgery patients and 54 for radiotherapy, can be considered high. In comparison, the mean STAI-State score in a group of males with anxiety neurosis was 45 (van der Ploeg, Defares et al. 1980). Of high-anxiety men, prostatectomy patients reported less anxiety and feelings of depression and better mental health at follow-up than radiotherapy patients. A first possible explanation is that the level of anxiety influenced the treatment decision; high-anxiety men may have perceived surgery as too frightening and therefore opted for radiotherapy. A second explanation could be that surgery led to more reassurance since – contrary to radiotherapy – the prostate actually is removed. Previous research has suggested that men may choose surgery on the basis of the lay belief that surgical removal is the most effective way to cure cancer (Steginga, Occhipinti et al. 2002). A third explanation could be age, since high-anxiety radiotherapy men were significantly older than high-anxiety prostatectomy men. However, for a number of reasons age does *not* seem to be the explanation. For instance, low-anxiety men who were treated by radiotherapy reported similar levels of anxiety and symptoms of depression as surgically treated low-anxiety men, in spite of the difference in average age. Furthermore, several studies reported an association of higher age and lower levels of anxiety. A review study, for instance, reported some evidence that ageing is associated with an intrinsic reduction in susceptibility to anxiety and depression (Jorm 2000). Furthermore, older

men reported better mental health, although higher ages were associated with worse physical health (Litwin, Lubeck et al. 2002). And finally, higher levels of anxiety were found in prostate cancer patients younger than 65 years of age (Lintz, Moynihan et al. 2003). A fourth possible explanation could be that compared to the high-anxiety surgery group, a higher percentage of men were 'single' – i.e. in most cases divorced or widowed - in the high-anxiety radiotherapy group. It has been reported before that marital status contributes to happiness (Joung, van de Mheen et al. 1994).

Our findings are in line with a cohort study on 111 prostate cancer patients with 12 months follow-up. Steginga *et al.* found that psychological and treatment decision-related distress decreased with time, independent of treatment choice. At 12 months follow-up most men experienced low levels of distress. The authors suggested that, in general, men are resilient to the experience of localized prostate cancer and adjust well psychologically. We agree that the majority of localized prostate cancer patients seems to do fine in the 1 to 5 years following treatment, but this is not the case for all patients. The challenge for clinicians is to detect those men early who will experience ongoing clinical levels of anxiety and symptoms of depression, and provide those with in-depth support. A (short) anxiety measure could be a useful tool. We applied a 20-item version of the STAI-State. Currently validated 6-item versions are available in English (Marteau, Dormandy et al. 2001) and other languages such as Dutch (van der Bij, de Weerd et al. 2003). Using the STAI-State baseline score as a screening tool resulted in the early detection of 71 respectively 60% of patients who were to experience high levels of symptoms of anxiety respectively feelings of depression at 6 or 12-months follow-up. The sensitivity might be improved by expanding the tool with disease characteristics as the Gleason score, by screening at another time point, or by applying other measures, for instance the often-used 14-item hospital anxiety and depression scale (HADS, (Zigmond and Snaith 1983)).

Treating clinicians may not always realize that, in spite of a comparably favourable prognosis, so many patients experience high levels of anxiety and symptoms of depression after a diagnosis of localized prostate cancer. We recommend clinicians to attempt early detection of patients at risk of such high levels and provide them with mental support. STAI-State can be a useful screening tool but needs further development.

Acknowledgements

We are grateful to the patients for participating in the study. We thank the departments of urology of the four participating hospitals (Erasmus University Medical Center Rotterdam, St. Franciscus Gasthuis, Medical Center Rotterdam Zuid, locations 'Clara' and 'Zuider') for their friendly cooperation. We gratefully acknowledge the Dutch Cancer Society for funding our study (EUR 2000-2329 and EUR 95-11.43).

CHAPTER 6

Patients' perceptions of the side effects of prostate cancer treatment – a qualitative interview study.

Korfage IJ, Hak T, de Koning HJ, Essink-Bot ML, submitted 2005.

Abstract

Although primary prostate cancer treatment often results in sub optimal urinary, bowel and/or sexual function, patients typically report high health related quality of life (QoL) scores. This discrepancy between disease-specific and generic results brings up the question which meaning side-effects actually have to patients. In a qualitative study we explored 2 mechanisms which could possibly explain the discrepancy: insensitivity of generic QoL measures to these specific symptoms and adaptation to changed health (response shift). In semi-structured interviews with 33 prostate cancer patients we collected data on their opinions regarding health and QoL, we observed behaviour, and solicited comments on an QoL questionnaire, its items, and face validity. We observed that patients trivialized sexual (dys) function referring to old age. We found that interviewees might consider sexual, urinary, and bowel dysfunctions as problems, but that they did not take such dysfunctions into account when completing QoL measures, because they did not view these dysfunctions as aspects of *health*. This finding revealed a so far unidentified cause of the insensitivity of generic measures. Furthermore, response shift appeared to be present: many patients accepted the side-effects as inevitable consequences of having been treated for prostate cancer, a condition they perceived as life-threatening. We conclude that generic QoL measures cannot reveal the impact of sexual, urinary and bowel dysfunctions on patients if such dysfunctions are not perceived as *health* problems. By presenting these findings we do not only want to draw attention to issues that complicate QoL assessments in general or more specifically in prostate cancer patients. We also want to show that qualitative techniques are valuable tools in the validation of self-assessment questionnaires.

Introduction

Prostate cancer is increasingly being detected in many countries, especially due to prostate-specific antigen testing of asymptomatic men. As a consequence more men receive treatment for localized prostate cancer and subsequently face the long-term side-effects of primary treatment, which mainly include urinary and sexual dysfunctions after surgery, and bowel and sexual dysfunctions after radiotherapy (Bacon, Giovannucci, 2001; Potosky, Legler, 2000; Talcott, Manola, 2003). Despite the frequency of these side-effects, prostate cancer patients repeatedly reported high generic Health Related Quality of Life (QoL) scores (Clark, Rieker, 1999; Galbraith, Ramirez, 2001; Lee, Hall, 2001; Lepore & Eton, 2000; Potosky, Legler, 2000; Schapira, Lawrence, 2001; Staff, Salner, 2003; Talcott, Rieker, 1998), which suggests the respondents are doing fine. The apparent discrepancy between high generic QoL scores

and the high prevalence of dysfunctions after treatment, brings on the question which meaning side-effects have to patients. It has been argued that high generic QoL scores weaken the argument that prostate cancer screening and treatment should be limited because of severe and debilitative side-effects (Krahn, Ritvo, 2003). It seems implausible, however, that side-effects do not matter at all to the men who experience them. Knowing the 'real' meaning of post-treatment dysfunctions to patients is of considerable importance in deciding whether or not to introduce population-based prostate cancer screening programs. A first condition for introducing such a program is that early detection followed by appropriate treatment should have shown to reduce prostate cancer-specific mortality. This is currently being assessed in two large randomised controlled screening trials. Further conditions for the introduction concern costs and the unfavourable side effects in the different phases of the screening process.

Several possible explanations for the repeatedly found discrepancy between generic and disease-specific results have been put forward. For example, a short follow-up, so that studied patients still might expect their side-effects to be temporary (Clark, Rieker, 1999). Further, the unresponsiveness of generic QoL instruments to changes perceived by men treated for prostate cancer (Clark, Rieker, 1999). Such generic QoL measures include the widely used SF-36 with 8 scales in the physical and mental domain (Ware & Kosinski, 2001), and the EQ-5D with a brief generic classification and a subjective evaluation of health (Dolan, 1997). Both measures are available in over 50 languages and claim to be applicable in a wide range of populations, health conditions and treatments. Finally, Madalinska et al. suggested that the discrepancy between disease-specific and generic results might be explained by 'response shift' (Madalinska, Essink-Bot, 2001b), which denotes adaptation to changing health (Schwartz & Sprangers, 2000). A man's internal standards of what constitutes 'normal' social activities, or 'work' or 'other regular daily activities' may have changed after the diagnosis and treatment of prostate cancer.

In this study we explored, using qualitative research methods, the discrepancy between levels of erectile, urinary, or bowel dysfunctions and generic QoL scores and paid especially attention to two mechanisms that could possibly explain it: adaptation to changed health and the insensitivity of generic QoL measures for dysfunctions that prostate cancer patients perceive after primary treatment.

Methods

Ethics approval and informed consent

The ethics review committee of the Erasmus MC, the University Medical Center Rotterdam, approved the research protocol (MEC 197.630/2000/254). All participating men gave written informed consent to be interviewed for the study.

Inclusion of patients

In a previous multi-center cohort study, linked to the European Randomized study of Screening for Prostate Cancer (ERSPC) (de Koning, Auvinen, 2002), we included 314 newly diagnosed prostate cancer patients shortly before the start of their primary treatment. These patients completed self-reported questionnaires before primary treatment, and at 6 months, 12 months and 5 year follow-up. Questionnaires consisted of disease-specific (UCLA-Prostate Cancer Index) and generic (SF-36, EQ-5D) measures. In this cohort post-treatment high levels of dysfunctions and high generic scores were reported (Madalinska, Essink-Bot, 2001), as observed before.

From the above mentioned longitudinal cohort of prostate cancer patients we recruited respondents for the presently reported interview study. Criteria for inclusion were 1) actual experience of urinary, bowel and/or sexual dysfunctions or any combination of these since – but not before – treatment; 2) a maximum age of 74 years; 3) willingness to participate. Sixty-two men fulfilled these criteria. Eighteen were randomly allocated to sample A and 16 to sample B. One man refused after initial consent. The resulting 33 interviewees were between 60 and 74 years old. The interview took place on average 5 to 6 years (range 52-80 months) after primary prostate cancer treatment, which consisted of radical prostatectomy, external radiotherapy or (in one case) brachytherapy.

In sample A, one researcher performed all 18 interviews, aiming at exploring response shift as a possible explanation for the discrepancy. The semi-structured interviews were guided by a checklist containing questions such as ‘How is your health?’, ‘Has it been affected by the prostate cancer treatment?’ ‘Ij yes, how?’, ‘How is your quality of life?’, ‘Has it been affected by the prostate cancer treatment?’ The interviewer told the respondents about the high prevalence of post-treatment dysfunction and the high QoL scores of patients in responding to the EQ-5D and the SF-36 and asked the respondents for their explanation of this phenomenon. The respondents were not explicitly asked if they had experienced response shift themselves.

The 15 interviews in sample B by researcher IK were aimed at exploring whether generic measures (SF-36 and EQ-5D) were sensitive to changes in health status after primary prostate cancer treatment. The Three-Step Test-Interview was used to reveal motives and considerations of interviewees while they responded to items in generic health measures (EQ-5D and SF-36 Role Physical, Bodily Pain, General Health, and Social Function). This method consists of the following steps: 1) concurrent thinking aloud, aimed at collecting observational data of a respondent who completes the questionnaire as if he is alone, but expressing his thoughts aloud; 2) a focused interview aimed at clarifying the interviewee's previous expressions, vocal or otherwise, while he completed the questionnaire; 3) a semi-structured interview aimed at eliciting the interviewee's experiences and opinions on the questionnaire (Hak, Van der Veer, 2004). Respondents were asked, for instance, if all items were clear to them and if they missed issues they considered as crucial in the process of diagnosis and treatment. The interviewer emphasized that the questionnaire was the subject of testing, not the respondent himself.

The interviews were performed face-to-face at the respondent's home or at the university medical center. All interviewees agreed to the audio taping of the interview. The tapes were transcribed verbatim. The data collected in this way and used for the analysis of this paper consisted of:

- Completed questionnaires;
- Observed respondent behaviour;
- 'Think Aloud' data, including patients' answers to our retrospective probes about our observations and about what they had said during the task;
- Solicited comments on the questionnaire and its items;
- Solicited comments on the face validity of the questionnaire and its items.

Two of the authors (IK, TH) each independently studied the 'verbatim' of the interviews. They interpreted the data and selected citations that in their opinion indicated the presence or absence of response shift, or adaptation to changing health. The authors compared their selections and interpretations and discussed them. The authors jointly reached final conclusions on the meaning of the data.

Results

Sexual function

The side-effects of primary prostate cancer treatment mainly concern urinary, bowel and sexual dysfunction. In analyzing our results we noticed that interviewees frequently tended to

trivialize sexual problems referring to their age. We did not observe this attitude considering bowel or urinary dysfunction. Respondent 1, 74 years of age and reporting some urinary leakage and no erectile function since treatment, was aware of his sexual problems and of prostate cancer treatment as its cause:

> Treatment of prostate cancer does have consequences for one's sexual life. But I'll soon be 75 years old, so, of course that's not a major theme anymore. I can imagine that if you're 25 years of age when you get it, that you look at it differently than if you're 75.

Respondent 2, 70 years of years and no erectile function since treatment, was also aware of his erectile problems but added that he was happy to have been 'in time':

> My only complaint is that I don't have an erection, but apart from that I don't have any complaints. I'd like to continue as long as possible like this. […] Those complaints that I have, well, they can be ignored. [….] But, I mean, you've got your age as well. I'll be 70, so I mean. It might be different when you're young, but …. no, I'm happy I was treated in time. That I could be cured and so on.

Apparently, diminishing sexual activity in the course of life was considered as more or less normal. Its decreasing significance with the increase of age may well occur in the ageing population in general.

Urinary and bowel function

Many respondents who experienced urinary leakage and/or bowel problems reported instances of how the persistent presence of these side-effects had changed their evaluation standards. Respondent 3, 66 years of age and reporting some urinary leakage, and erectile dysfunction since treatment,

> I didn't consider the consequences of prostate cancer treatment much when I answered questions about my health, because … after all those years I've got more or less used to them. […] That's just a matter of acceptance.

Respondent 4, 71 years of age and having serious urinary leakage and erectile dysfunction since treatment, recounted how he found a way to live with his handicap:

> And you learn, you're distancing yourself more and more from it, you're handling it easier all the time. You are faced with it every day, but, yes, that's already a routine in my life, that I have to change my underwear maybe once, or twice or three, four times a day. And I absolutely don't want to, not for a second, ease up on it. Not for me. Because I'm scared to death and very vain, if people....

Not all respondents reported similar experiences. Respondent 1 described an initial acceptation:

> I can explain it like this. In the beginning you feel totally relieved that the cancer has disappeared and actually you take everything that comes along as part of the deal. But in the end you start feeling the annoyance of urinary leakage and diminished erection.

At first he accepted his dysfunction out of sheer relief that the tumour had been removed; gradually, however, it started to annoy him.

A number of respondents related their acceptance of the side-effects not only to the passing of time. They associated the side-effects also with the treatment that in their opinion had been life-saving. Respondent 5, 64 years of age and experiencing serious urinary and bowel problems since treatment, and and respondent 6, 64 years of age and experiencing some urinary and bowel problems, and no erectile function since treatment, describe how their level of acceptance had shifted:

> One can adapt more than one thinks. The first time you hear about it, you get a terrible shock, but you keep on adapting. Things you consider terrible at first don't seem so terrible later on. Why does it work this way? Maybe because the mind is compliant and maybe also because you're just happy to be alive. [….] In the beginning you don't put up with many complaints. That changes tremendously in time.

> When answering the questions I consider the side-effects I experience since prostate cancer treatment a little bit, but they don't mean much to me. No. It's very little. They can be overcome. I can live with them. And I think, yes, if they had not intervened, that operation; maybe I wouldn't have been here anymore.

Insensitivity of generic QoL measures

Additional to the presence of acceptance a consistent finding in our interview data was that respondents tended not to consider urinary, bowel and especially sexual dysfunction as aspects of health. These respondents did not exclude such dysfunction because they had forgotten about it (they reported urinary, bowel and sexual problems without hesitation when asked specifically about them), but consciously excluded it from considerations regarding general health questions because they deemed it irrelevant to their 'health'. The following citations illustrate this phenomenon. Respondent 7, 67 years of age and having some bowel problems since treatment, indicated that bowel problems had nothing to do with health:

> At a certain moment you accept your symptoms. And then you carry on living… Actually without restrictions. Yes, you just have to take account of it. I mean, I urinate in the morning as well. As soon as I get out of bed in the morning, I have to run to the toilet otherwise I will lose it. Well, then we go for a swim, because we've got such a daily rhythm. When I get home after swimming, then I'll have to go again, but then I'm OK for the rest of the day. So, yes, you know it and you accept it and you just carry on. [….] Treatment of prostate cancer hasn't affected my health as such. Yes, some complaints have remained. Primarily those bowel problems in my case. And like I said, you learn to live with them and I don't think that has anything to do with health.

Respondent 8, 68 years of age, declared himself healthy in spite of urinary leakage and erectile dysfunction since treatment:

> Well, yes, actually I feel well, healthy. I don't have any restrictions. Sometimes I urinate blood. To be honest I think that's really nasty. But apart from that I'm healthy.

Respondent 9, 64 years of age and having some urinary leakage and erectile dysfunction since treatment, did not consider these dysfunctions as real health problems:

> I think, slight urinary leakage, or hardly being able to get an erection, are things you can live with, if you're healthy. That's my opinion about it. […] I don't consider urinary leakage a health problem.

Respondent 10, 67 years of age and experiencing some bowel problems and no erectile function since treatment, said that erectile problems belong to an area different from health:

> When answering the questions I don't think about the consequences of the treatment at all. No. Not at all, because …. I didn't think of those things at all. […] When I'm asked about my health I don't consider the fact that I cannot have erections anymore, because that's another area. [laughs] That's another area.

And finally respondent 11, 67 years of age, reporting some urinary leakage and erectile dysfunction since treatment, who needs to go to the bathroom 3 or 4 or even 20 times a night, stated that his health was not influenced by prostate cancer treatment:

> The fact that I was treated for prostate cancer actually didn't have any consequences for my health. Ac-tu-ally not. No, that I was confronted with some small inconveniences, that's true, but to say 'my health deteriorated', I don't think so.

In conclusion of the results

These findings can be summarized as follows. We found evidence of adaptation in respondents who accepted their shortcomings and adapted to them. However, such adaptation could not be observed in all patients, and we also found a counter-example in which an initial adaptation was reversed. We conclude that these patients adapted to their new situation, but that it could not be the sole explanation of the discrepancy between urinary and bowel side-effects on the one hand and generic QoL scores on the other.

The numerous and consistent instances of insensitivity of generic measures in our interview data suggest that insensitivity is the main reason for the discrepancy between specific and generic QoL measures in patients treated for prostate cancer. If urinary, bowel and/or sexual dysfunctions are not considered by patients as being related to health, assessments by health measures such as the SF-36 and EQ-5D can never reveal the true influence of such dysfunction on health.

Discussion

In this qualitative interview study, we found that prostate cancer patients might consider sexual, urinary and bowel dysfunctions as problems, but not as problems of *health*. Furthermore, patients accepted side-effects as the inevitable consequence of treatment of

prostate cancer - a condition they perceived as life-threatening. Finally, they trivialized sexual dysfunctions referring to old age. The last finding was confirmed in interviews with elderly men without prostate cancer. It may also be the case in other old-aged, whether or not they are prostate cancer patients and regardless of sex.

Recently, interviews among prostate cancer patients in Australia revealed that many patients premised their willingness to accept impotence on their advanced age (Oliffe, 2005).

We found that people have different opinions on what constitutes health. This confirms earlier findings in other populations. Krause and Jay, for example, asked 158 respondents in an in-depth interview study to rate their overall health as excellent, good, fair, or poor. They revealed that some respondents considered specific health problems when asked to rate their health, whereas others thought in terms of either general physical functioning or health behaviours (Krause & Jay, 1994). Mallinson observed that elderly completing the SF-36 excluded some types of health problems. Chronic health conditions were discounted because interviewees thought 'ill' referred to more acute everyday health problems such as coughs and colds. Mallinson concluded that if some people include health problems while others exclude them, collected data will be inconsistent with an uncertain meaning (Mallinson, 2002).

In our study many patients accepted side-effects after treatment of prostate cancer because a feeling of relief prevailed. They were so happy to have survived a condition they perceived as life-threatening that side effects were of minor importance to them. The experience of being diagnosed with and treated for a life-threatening disease apparently led to a change in the concept of 'health': at first both duration and quality of life were considered important, but when duration was threatened (e.g. by disease), people accepted a lower quality of life to preserve lifetime. This mechanism of adaptation complicates the assessment of the importance of agrological side-effects to prostate cancer patients. Using discrete choice experimentation might be a more suitable method, whereby patients choose from several options, each of which details a series of health characteristics (e.g. diarrhoea or ability to maintain an erection), at different levels, for example absent, mild, moderate. Changing the levels of the characteristics and asking patients to make their choice again can assess the relative importance of characteristics to patients and the trade-offs made between them. First findings of this method in health care research are encouraging (Sculpher, Bryan, 2004).

To conclude, for a number of reasons we do not support the claim by Krahn et al. that the impact on QoL of sexual, urinary and/or bowel dysfunctions after prostate cancer treatment may be overstated (Krahn, Ritvo, 2003). First, if patients do not consider sexual, urinary and/or bowel dysfunctions as related to health, assessment by generic measures which refer to

health, like the SF-36, the EQ-5D, and the EORTC QLQ-C30, can never reveal the impact of these side-effects on QoL. Besides, the fact that men adapted to dysfunction after treatment of a – in their opinion - life-threatening disease does not imply that others can judge these side-effects as irrelevant. Furthermore, many men will accept side-effects of treatment, but not all - as illustrated in our study by Respondent 1. We have presented convincing evidence that high generic scores of prostate cancer patients cannot be interpreted as 'these men are doing just fine'. We agree with McColl et al who showed in patients with ulcerative colitis that disease specific and generic measures are complementary rather than interchangeable (McColl, Han, 2004).

Introduction of a population-based screening program for prostate cancer with prostate specific antigen tests offered to asymptomatic men will lead to an increasing number of small tumours being detected and of men being treated. Not all of these men would have died of prostate cancer or even have experienced prostate cancer complaints in the absence of a screening program, implying that inevitably overtreatment will occur (Draisma, Boer, 2003). For the individual man who considers prostate cancer testing this means that he runs the risk of being diagnosed with and treated for a disease, and subsequently experience side-effects of treatmen while having no benefit of this process. We argue that overtreatment should be included in the evaluation of population-based prostate cancer-screening programmes, for instance by discrete choice experiments (Sculpher, Bryan, 2004).

Acknowledgements

The authors thank all patients for participating in the study, thank Rianne Frenken for performing the interviews in sample A and the Dutch Cancer Society for funding this study (EUR 2000-2329).

CHAPTER 7

Side effects of prostate cancer treatment: comparison of valuations by patients and healthy men

Korfage IJ, de Koning HJ, Habbema JDF, Essink-Bot ML, submitted 2005.

Abstract

Reason for the study Prostate cancer is increasingly being detected and treated early, and more men are facing the long-term consequences of primary treatment, including urinary, bowel and sexual dysfunction. To explore the impact of such dysfunctions we compared valuations of 5 health states associated with prostate cancer treatment by men with (n=54) and without prostate cancer (n=53). Visual Analog Scale (VAS) and (an impersonal version of) Time Trade-Off (TTO) We hypothesized that patients would value these health states as better than men without prostate cancer, because they may have adapted to their changed health. To allow interactive interviewing we developed a computer-based questionnaire.

Main findings Valuations in both groups resulted in a similar ranking order by both methods, except for 1 health state. Patients' valuations did not differ from those of men without prostate cancer except for one valuation by VAS. Average TTO values of patients and healthy men were higher than average VAS values.

Principal Conclusions When applying an impersonal version of TTO which does not include an aspect of 'self', patients and healthy men agreed on which health state was worse than others.

Clinical Implications Our results suggest that there is no objection to the use of population-based utilities in economic evaluations of primary prostate cancer therapy.

Background

Prostate cancer is increasingly being detected early in many countries, especially due to prostate-specific antigen testing of asymptomatic men. As a consequence more men receive treatment for localized prostate cancer and subsequently face the long-term consequences including urinary and sexual dysfunction after prostatectomy, and bowel and sexual dysfunction after radiotherapy (Potosky, Legler et al. 2000; Bacon, Giovannucci et al. 2001; Madalinska, Essink-Bot et al. 2001; Talcott, Manola et al. 2003; Korfage, Essink-Bot et al. 2005). Despite these side effects, prostate cancer patients typically report high generic QoL scores (Talcott, Rieker et al. 1998; Clark, Rieker et al. 1999; Lepore and Eton 2000; Potosky, Legler et al. 2000; Galbraith, Ramirez et al. 2001; Lee, Hall et al. 2001; Schapira, Lawrence et al. 2001; Staff, Salner et al. 2003; Korfage, Essink-Bot et al. 2005) when completing e.g. the Short Form 36 (SF-36, (Ware and Kosinski 2001), and the EuroQol (EQ-5D, (Dolan 1997). Generic QoL-scores in patients were sometimes even better than those of healthy population norms (Korfage, Essink-Bot et al. 2005).

The discrepancy between high generic scores and the high prevalence of dysfunction after treatment makes one wonder what side effects mean to patients. It seems implausible that side effects do not matter at all. Several explanations for the discrepancy have been put forward, including the short length of follow-up so that studied patients still expect their side effects to be temporary, unresponsiveness of generic QoL instruments to changes in health states after prostate cancer treatment as perceived by patients (Clark, Rieker et al. 1999) and 'response shift' (Madalinska, Essink-Bot et al. 2001), which denotes adaptation to changing health (Schwartz and Sprangers 2000). The real valuation of health states that are associated with prostate cancer treatment is important in the evaluation of screening. Randomised trials are ongoing in the U.S.A. and Europe to assess if screening can reduce prostate-cancer specific mortality (PLCO (Andriole, Levin et al. 2005), ERSPC (de Koning, Auvinen et al. 2002)). For the economic evaluation of screening, valuations of health states are needed to enable a judgment on which health states are more preferable than others. Opinions vary as to who should valuate these health states. Some argue that only patients can validly value health states since they experienced impairments and know the impact that dysfunction can have on QoL (i.e. the patient perspective). However, patients might have become accustomed to disease-specific dysfunction, in this case urinary, bowel and/or sexual problems. Assessing the 'true' impact of impairments might be unfeasible for them because they have adapted to their changed health, i.e. they have experienced response shift (Schwartz and Sprangers 2000). Furthermore, valuation by patients leads to mutually incomparable results: a prostate cancer patient who values health states associated with prostate cancer treatment will apply his own internal scale which will probably differ from a colon cancer patient who values colostomy-specific health states, and from a psoriasis patient valuing psoriasis-specific health states, etc. Others argue that aggregated values of people who do not have any particular interest in specific health states are most appropriate to use in economic analyses (i.e. the societal perspective) (De Wit, Busschbach et al. 2000). We asked both prostate cancer patients and men without prostate cancer to value health states. We hypothesized that patients would value the health states associated with prostate cancer treatment as being better than men without prostate cancer, because patients adapted to their changed health.

Participants and Methods

Ethics approval and informed consent

The ethics review committee of the Erasmus MC, the University Medical Center Rotterdam, the Netherlands, approved the research protocol. All participating men gave written informed consent.

Participants

We selected participants from a cohort of prostate cancer patients who were followed from pre-treatment till 5 years later. Subjects were eligible for an inter-active interview if 1) they experienced dysfunctional health state since – but not before - treatment of prostate cancer, including urinary, bowel and/or sexual dysfunction; and 2) their life-expectancy was at least 10 years, in order to warrant a useful completion of the Time Trade-Off session. For the Dutch situation this amounted to a maximum age of 74 years.

Participants without prostate cancer, designated here as 'healthy men', were included through an epidemiological survey assessing the prevalence of benign hyperplasia (Blanker, Driessen et al. 2002) and were therefore known *not* to have benign hyperplasia or prostate cancer. The healthy men were eligible for participation in an inter-active interview if they were 74 years of age or younger. We assessed if differences in judgment were present (the Have-Not have discrepancy) (Baron, Asch et al. 2003) and if so, of what size.

Selecting health states associated with prostate cancer treatment

Longitudinal data on 5 years of follow-up in 314 prostate cancer patients were analysed to compose 5 descriptions of health states that are associated with localized prostate cancer treatment. The health-state descriptions included items on prostate cancer-specific problems (i.e. urinary, bowel and sexual dysfunction). The format of the EQ-5D classification (Dolan 1997) was used as a framework for the descriptions. The health states differed in their values on 7 variables (mobility; self-care; usual activities; urinary leakage; bowel problems; erectile function and anxiety/depression) and by 3 levels of severity (no, some or extreme problems), see Appendix 7.1 for a complete list of descriptions. To encourage the valuation of health states purely on the descriptions no names or disease labels were added.

Questionnaire

We developed a computer-based questionnaire to enable inter-active interviewing. The tool, named VIA© (Valuations Inter-Active) could be applied through the internet as well as stand-

alone and was divided in four parts: Part 1) items on respondent's own functioning; Part 2) ranking of 5 generic and 5 health states associated with prostate cancer treatment; Part 3) valuation of 5 health states associated with prostate cancer treatment by a Visual Analog Scale (VAS); Part 4) valuation of the same 5 health states associated with prostate cancer treatment by Time Trade-Off (TTO).

Part 1 contained items on respondent's own generic and disease specific functioning including an evaluation of own health using a VAS. A vertical thermometer was depicted on the computer screen anchored at the lower end (0) by 'worst possible health state' and at the upper end (100) by 'best possible health state'. Ticks at 25, 50 and 75 were marked with numbers. Participants were asked to indicate the level of their current health by positioning an indicator bar on the thermometer or by registering the preferred number in a box. The software allowed responses in increments of 1 on a 0-100 scale. In part 2, respondents were asked to rank 2 sets of 5 descriptions of health states from best to worst. The first set served as a 'warm up' for the following parts and consisted of generic health states ranging from extremely well to extremely bad. The second set consisted of the health states associated with prostate cancer treatment, referred to hereafter as 'health states'. In part 3 the health states were valued using a VAS. Participants could indicate the level of the health states above by positioning an indicator bar or by registering the preferred number in a box. Part 4 consisted of the valuation of the health states through an impersonal version of TTO. This version was developed to elicit a relatively common sense judgment about which of 2 people is better off, without forcing subjects to make a (hypothetical) treatment decision (Chapman, Elstein et al. 1998). We presented 2 hypothetical persons (one with a life expectancy of 10 years experiencing urinary, bowel and/or sexual dysfunctions, the other with a life expectancy of 5 years in perfect health) and asked respondents to indicate which man they would rather be. Depending on the choice that interviewees made, a new choice was offered. If, for example, a respondent preferred 5 years in perfect health to 10 years with specific side effects, the 10-years health state was subsequently to be compared with 9 years in perfect health. The number of healthy years offered was systematically varied using a ping-pong procedure. The software allowed choices in increments of 6 months, the equivalent of 5 on a 0-100 scale. The utility was equivalent to the ratio between final choice of disease-free time and 10 years.

Interactive interviews took place at the participant's home or at the university. An interviewer was present to assist with questions but otherwise remained unobtrusive.

Statistical analysis

Between-group differences in background characteristics and descriptive statistics on generic and prostate cancer-specific items were calculated using the statistical package 'SPSS for Windows', release 10.0.7. Chi-square tests were used for categorical variables, Mann Whitney U tests for continuous ones.

Among the health states were 2 'dominant pairs' identified, i.e. if levels of severity in one state are better than or equal to the levels in the other state regarding all variables (Man 1 > Man 4 and Man 3 > Man 4, see Appendix 7.1). We assessed logical inconsistencies by identifying violations of dominant pairs, i.e. if the dominant state of a pair is valued lower than its counterpart (Essink-Bot, Bonsel et al. 1990).

All VAS and TTO data were converted to scores between 0 and 1. Rank, mean scores and standard deviations were calculated per respondent group, per health state and per method. Statistical significance of differences between groups in valuations per health state was determined using Mann Whitney U tests (p <0.01). Power analysis showed that differences of 0.08 points on a scale of 0-1 between average group scores could be detected as significant with $\alpha = 5\%$, $(1-\beta) = 80\%$. Cohen's effect sizes of differences between groups were assessed, with effect sizes designated 'small' if larger than 0.2 but smaller than 0.5 (Cohen 1977). The correlation between the patients' and the healthy men's VAS and TTO valuations was calculated (Pearson Correlation and the Intraclass Correlation Coefficient).

Results

In the present study, 53 out of 63 eligible prostate cancer patients completed an interactive interview. Nine men were not included because of having passed away (n=1), refusal after initial consent (n=1), having moved house (n=1), being out of reach (n=1) and saturation of samples (n=5). One interview had to be ended prematurely because of the participant's memory problems. Out of 56 eligible healthy men 52 completed an interactive interview. Three men were not included because of saturation of the sample (n=2), and unknown reasons (n=1). One interview ended prematurely because the participant considered choosing between lifetimes inappropriate. The use of the computer-based questionnaire 'VIA©' ascertained completeness of data.

On average healthy men were younger than prostate cancer patients (63 vs. 67 years, p <0.001), reported significantly better urinary, bowel and sexual function, and rated their own health better (86 vs. 74, p <0.001, Table 7.1).

Table 7.1 Characteristics of prostate cancer (PC) patients and healthy men

	PC Patients (n=53) **Number (Percentage)**	**Healthy Men** (n=52) **Number (Percentage)**	***P*-value**[1)]
Urinary Leakage			<0.001
no	22 (41)	47 (90)	
some	28 (53)	5 (10)	
serious	3 (6)	-	
Bowel Problems			0.001
no	35 (66)	49 (94)	
some	17 (32)	3 (6)	
serious	1 (2)	-	
Sexually Active			<0.001
yes	23 (43)	42 (81)	
no	30 (57)	10 (19)	
Erectile Dysfunction			<0.001
yes	42 (79)	11 (21)	
no	11 (21)	41 (79)	
	Mean (SD)	**Mean (SD)**	
AGE in years	67.1 (4.3)	62.7 (4.3)	<0.001
EuroQol-utility (0-100)	83 (28)	92 (11)	0.105
EuroQol Assessment of Own Health (0-100)	74 (17)	86 (10)	<0.001

[1)] Chi-square tests were used for categorical variables; the Mann Whitney U test for continuous ones.

At least 1 of the dominant pairs was violated by 7 respondents (7%, 3 patients and 4 healthy men) when completing the VAS valuations and by 7 others (7%, 4 patients and 3 healthy men) when completing the TTO. We conclude that the majority of respondents provided consistent valuations. The data of all respondents were included in further analyses.

Average TTO values were higher than average VAS values, with differences between methods per health state ranging from 0.10 to 0.27 on a scale of 0 to 1. Six patients and 5 healthy men (10% of participants) were reluctant to trade in TTO; they never scarified lifetime to gain perfect health.

Valuations in both groups and by each method resulted in the same order except for Man 3: both groups rated him best when they applied TTO, but third (patients) or second (healthy men) based on the VAS-valuation.

Table 7.2 Visual Analog Scale (VAS) and Time Trade-Off (TTO) valuations of prostate cancer-specific health states by prostate cancer (PC) patients and healthy men, 0 = worst imaginable health state and 1 = best imaginable health state

	PC patients (n=53)			**Healthy men** (n=52)				
VAS	**Rank**	**Mean**	**SD**[1)]	**Rank**	**Mean**	**SD**	***P*-value**[2)]	**Effect size**[3)]
Man 1 severe impotence[4)]	1	0.74	0.16	1	0.72	0.12	.08	0.17
Man 2 some incontinence some impotence moderately anxious	2	0.65	0.15	3	0.60	0.13	.03	0.33
Man 3 some bowel problems, some impotence	3	0.62	0.14	2	0.62	0.11	.95	-0.05
Man 4 severe incontinence	4	0.56	0.15	4	0.56	0.14	.87	0.00
Man 5 severe bowel problems severe impotence	5	0.47	0.16	5	0.46	0.14	.65	0.03
TTO								
Man 1	2	0.84	0.26	2	0.84	0.20	.37	0.01
Man 2	3	0.76	0.29	3	0.79	0.21	.93	-0.12
Man 3	1	0.86	0.23	1	0.89	0.13	.71	-0.15
Man 4	4	0.69	0.33	4	0.70	0.27	.58	-0.05
Man 5	5	0.61	0.32	5	0.66	0.27	.48	-0.18

[1)] SD = Standard Deviation
[2)] Mann Whitney U tests were used for continuous variables.
[3)] Effect size: >.2= small effect; >.5= medium effect; >.8= large effect.
[4)] See Appendix 7.1 for descriptions of health states.

Average prostate cancer patients' valuations did not differ from those of healthy men except for the VAS valuation of Man 2 (0.65 vs. 0.60, p =0.03, Table 7.2). Effect sizes of differences per health state valuations between groups were smaller than 0.2, except for the VAS valuation of Man 2 (Figure 7.1). Standard deviations were on average 28% larger in prostate cancer patients than in healthy men. The Pearson Correlations between the patients and the healthy men were 0.98 for the 5 VAS valuations, and 0.99 for the 5 TTO valuations. The Intraclass Correlation Coefficients were 0.98 for VAS and for TTO.

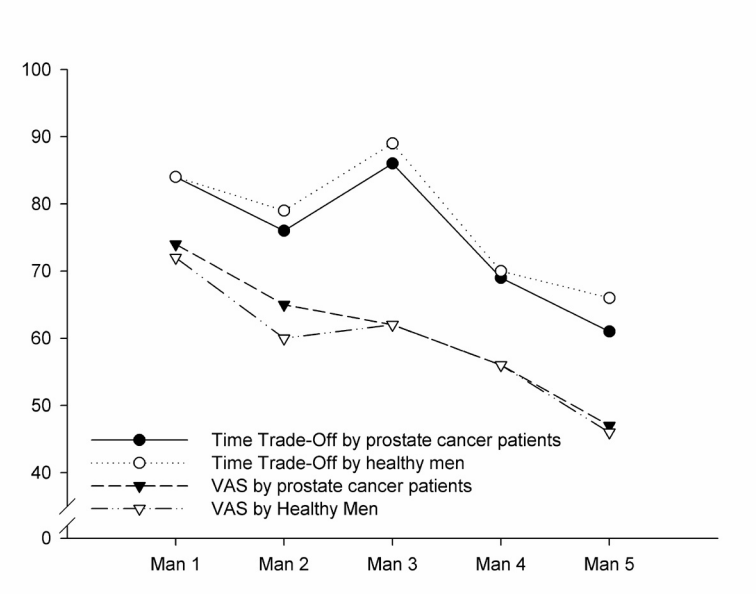


Figure 7.1 Visual Analog Scale (VAS) and Time Trade-Off (TTO) Valuations with Standard Errors by Prostate Cancer Patients and Healthy Men

Discussion

At group level few to no differences were found between men with and without prostate cancer in the valuation of prostate cancer specific health states. Effect sizes of the differences in 9 out of 10 valuations were 'smaller than small'. As expected, the healthy men reported significantly better prostate cancer-specific function than patients. Since the healthy men were on average younger (63 vs. 67 years), age may have played a role. However, differences between groups in, for instance, erectile dysfunction were that large (80% in patients vs. 20% in healthy men) that age does not seem to be a sufficient explanation.

In both groups average TTO values were higher than average VAS values. Trade-off techniques such as TTO share conceptual advantages over rating scale techniques, because they require people to hypothetically sacrifice one valuable commodity (e.g. life expectancy in TTO) in order to gain another valuable commodity (e.g. quality of life), such that they are indifferent between the 2 states (Dolan and Sutton 1997). Although valuations by VAS are easier for the respondents, because they do not contain an element of 'trade-off' they are commonly regarded as theoretically inferior (Dolan and Sutton 1997). VAS valuations for health states do not have any (hypothetical) consequences for the respondents, such as less life years to be lived. We are not the first to observe that VAS thus generates lower average valuations than TTO (Krabbe, Essink-Bot et al. 1997). However, Dolan *et al* found that the relationship between VAS and TTO scores depended on the severity of the state: TTO valuations were higher than VAS responses for mild states and lower for more severe states

(Dolan and Sutton 1997). The disease-specific health states to be valued in the present study can be considered as comparatively mild. Our findings are thus in line with Dolan's.

Remarkably, in both respondent groups the valuation methods led to different preferences concerning Man 3. This suggests a method effect; i.e. outcome of health state preferences did not depend solely on the descriptions, but also on the method that was applied. Such a result has been reported before (Krabbe, Essink-Bot et al. 1997).

Opinions vary as to whose values should count when health states are evaluated. We asked both patients and healthy men to evaluate health states associated with prostate cancer treatment and found only small differences at group level, as well as high correlations between groups (Pearsons and Intra Class Correlations were close to 1). In their study, Krahn *et al.* included 141 prostate cancer patients and obtained both patient's and community's utilities from them; patients' directly elicited utilities for their own health were higher than community-derived utilities obtained from administration of the Health Utility Index and the Quality of Well-Being scale to the same patients (Krahn, Ritvo et al. 2003). Chapman *et al.* studied prostate cancer patients' utilities by comparing a personal version of TTO with an impersonal one; patients' willingness to trade time for quality of life was greater when using the impersonal version (Chapman, Elstein et al. 1998). These studies have as a common result that patients' valuations of health states changed when the aspect of 'self' was removed.

In previous studies patients with a certain disorder typically reported better ratings for health states describing such a disorder than those without that disorder (Elstein, Chapman et al. 2004) - the Have-Not have discrepancy (Baron, Asch et al. 2003). Often cited examples include the study by Sackett *et al.* where patients valued a dialysis-specific health state at 0.56 vs. 0.39 in the general public (Sackett and Torrance 1978), and the study by Boyd *et al.* where the patients' average estimate of a colostomy-specific health state was 0.92 vs. 0.80 in the general public (Boyd, Sutherland et al. 1990). Additionally, a review study on the differences in valuation for hypothetical and actual health states between patients and other raters showed that in a majority of 38 studies patients' values were higher than other groups' values (De Wit, Busschbach et al. 2000). Ubel *et al.* explored several factors that may contribute to discrepancies between patients and the general public, e.g. incomplete health state descriptions whereby subjects fill in the blanks according to their own experiences or stereotypes, and the focusing illusion whereby subjects are made to focus on those activities affected by the disease, while ignoring activities unaffected by it (Ubel, Loewenstein et al. 2003). According to Gilbert *et al.* people tend to underestimate the duration of their affective reactions to negative events (Gilbert, Pinel et al. 1998). These factors, if indeed present, all

contribute to healthy persons evaluating health states as worse than patients would do. This is in line with our a priori hypothesis that prostate cancer patients would value disease-specific health states as better than healthy men. We found that valuations barely differed at group level: no differences between respondent groups were found in 9 out of 10 valuations.

We examined the possibility of a different result had the number of respondents been larger. We found that had the number of respondents been 4 times larger, 8 out of 10 valuations had been identical. Hence we consider the number of participants sufficient to conclude that at group level few to no differences existed between healthy men and prostate cancer patients experiencing urinary, bowel and/or sexual side effects, regarding the valuation of permanent dysfunctional health states after prostate cancer treatment. This suggests that there is no objection to the use of population-based utilities in economic valuations of costs and health effects of primary prostate cancer therapy.

Acknowledgements

The authors thank all patients for participating in the study, E. Neeleman for the friendly cooperation in the development of the computer-based questionnaire, Dr. F. Groeneveld of the Department of General Practice for the recruitment of men without prostate cancer, R. Frenken for conducting part of the interview sessions, and the Dutch Cancer Society for funding this study (EUR 2000-2329).

Appendix 7.1 Description of health states associated with prostate cancer treatment as they were offered to respondents (i.e. without disease labels)

MAN 1
- no problems in walking about
- no problems with washing or dressing self
- no problems with performing daily activities
- no urinary leakage
- no bowel problems
- (almost) never an erection if wished for
- not anxious or depressed

MAN 2
- no problems in walking about
- no problems with washing or dressing self
- no problems with performing daily activities
- some urinary leakage
- no bowel problems
- sometimes an erection if wished for, sometimes not
- moderately anxious or depressed

MAN 3
- no problems in walking about
- no problems with washing or dressing self
- no problems with performing daily activities
- no urinary leakage
- some bowel problems
- sometimes an erection if wished for, sometimes not
- not anxious or depressed

MAN 4
- no problems in walking about
- no problems with washing or dressing self
- some problems with performing daily activities
- serious urinary leakage
- no bowel problems
- (almost) always an erection if wished for
- not anxious or depressed

MAN 5
- no problems in walking about
- no problems with washing or dressing self
- some problems with performing daily activities
- no urinary leakage
- serious bowel problems
- (almost) never an erection if wished for
- moderately anxious or depressed

CHAPTER 8

Receiving a prostate cancer diagnosis: the impact on patients' mental health

Korfage IJ, Essink-Bot ML, Roobol M, Schröder FH, de Koning HJ, submitted 2005.

Abstract

Introduction Especially since the introduction of PSA-testing the incidence of prostate cancer has increased. The impact of prostate cancer diagnosis on patients' mental health is unknown.

Patients and methods Participants to a prostate cancer screening trial (ERSPC) completed a questionnaire on health (SF-36 Mental Health and Vitality, EQ-5D VAS for self-rated overall health) before screening, and, if diagnosed with prostate cancer at 2 additional time points.

Results Before screening 3,800 men (response 88%) completed the questionnaire on health. Of 82 men subsequently diagnosed with prostate cancer, 52 completed 2 additional assessments (response 63%). Gleason scores were below or equal to 7 or smaller in 96% of men. Mental and self-rated overall health worsened significantly after having received the prostate cancer diagnosis ($p \leq 0.04$). After initiation of treatment, mental and self-rated health improved and did not differ significantly from the diagnosis anymore. Non-response does not seem to have affected these results.

Discussion This paper is the first to have obtained a pre-diagnosis assessment of quality of life in prostate cancer patients-to-be. We concluded that prostate cancer diagnosis after PSA-testing had a significant negative impact on men's mental and self-rated overall health. The clinical implication of this finding is the recommendation for clinicians to share their knowledge on the generally favourable prognosis with newly diagnosed patients. The methodological implication is that considering an assessment of health-related quality of life after prostate cancer diagnosis may lead to an underestimation of the patients' mental and self-rated overall health.

Introduction

Prostate cancer is highly prevalent in elderly men and the most frequent cause of cancer death after lung cancer in most Western countries. Prostate cancer can be detected early by testing for prostate-specific antigen (PSA), a biologic tumour marker. Since its introduction in the 1980s a substantially higher proportion of prostate cancers has been diagnosed in earlier stages than before (Cancer Statistics, 2004) (Etzioni, Penson et al. 2002). Prostate cancer screening through regular PSA-testing, for example once every four years, is estimated to advance diagnosis with on average 11 years (Draisma, Boer et al. 2003). Whether early detection followed by appropriate treatment will reduce prostate cancer-specific mortality is currently being assessed in two large randomised trials; the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the USA (Andriole, Levin et al. 2005) , and the European Randomized Screening for Prostate Cancer (ERSPC) trial in Europe(de Koning, Auvinen et al. 2002). The

outcomes on life years gained are not expected before 2007 (de Koning, Liem et al. 2002). Information on side effects of primary prostate cancer treatment is currently available from longitudinal observational studies that typically report mainly erectile and urinary dysfunction after radical prostatectomy, and erectile and bowel dysfunction after external radiotherapy (Madalinska, Essink-Bot et al. 2001; Schapira, Lawrence et al. 2001; Penson, Feng et al. 2003; Potosky, Davis et al. 2004; Korfage, Essink-Bot et al. 2005).

In its early stage, prostate cancer does not cause pain or other dysfunction. The average man who is diagnosed through PSA-screening may have regarded himself healthy before he is being diagnosed with prostate cancer, a disease often perceived as life-threatening (Korfage, Hak et al. 2005). The impact on mental health of being diagnosed with prostate cancer after screening is so far unknown. Studies on health-related quality of life in prostate cancer patients included patients before the initiation of treatment (Madalinska, Essink-Bot et al. 2001; Schapira, Lawrence et al. 2001), (Lee, Hall et al. 2001; Litwin, Melmed et al. 2001) or shortly thereafter (Potosky, Davis et al. 2004), but never before diagnosis. In a previous longitudinal study on primary prostate cancer patients treated by radical prostatectomy or external radiotherapy, we found a striking improvement in reported mental health after primary treatment compared to pre-treatment (Korfage, Essink-Bot et al. 2005). We hypothesized that low mental health before treatment might have been caused by the preceding diagnosis of prostate cancer. To truly assess the impact of diagnosis – in this case of prostate cancer – on mental health a baseline assessment before diagnosis is required. Such an assessment is usually not feasible, since it is unknown who will develop cancer and when, so that the inclusion of a very large cohort would be required. The unique context of the ERSPC, however, enabled the inclusion of a male cohort before screening and thus before diagnosis.

We conducted a prospective study to assess the impact of being diagnosed with prostate cancer in a screening program on mental and self-rated health in men who did not experience any pain or other prostate cancer symptoms.

Patients and methods

Ethics approval and informed consent

The ethics review committee of the Erasmus MC, University Medical Center Rotterdam, the Netherlands, approved the research protocol. All participating men gave written informed consent to be interviewed for the study.

ERSPC

The inclusion of ERSPC participants was initiated in the region of Rotterdam in 1994, and continued until 1999. All male inhabitants of the Rotterdam region between 55 and 74 years of age were identified through the population registry and invited to participate in the trial. Men who gave informed consent (49.2%) were randomly assigned to the study (n=21,210) or the control (i.e. unscreened) arm (n=21,166). Participating in the study arm entails a PSA-test once every four years and, if indicated, a biopsy of the prostate. Details on inclusion have been reported before (Roobol, Kirkels et al. 2003) .

Participants

Between January 2003 and May 2004 screen participants who were due for the second (n=2,798) or the third screening round (n=2,024) received a short baseline questionnaire on health (see below) by mail, attached to the invitation for screening. If men 1) completed the baseline questionnaire before the PSA-test in their second or third screening round; and 2) were subsequently diagnosed with prostate cancer, they were asked to complete the questionnaire on health two additional times through a telephone interview: before initiation of primary treatment and six months afterwards, resulting in three assessments per 'respondent'.

The men who were diagnosed with prostate cancer through screening but refused to complete further assessments will be referred to as 'non-respondents'. Their baseline (i.e. before diagnosis) assessments will be used to analyse non-response. The men who completed the questionnaire on health before screening and who were found not to have prostate cancer will be referred to as 'screen negative men.' Their baseline assessment will be used to assess comparability of respondents versus screen negative men.

Questionnaire

The questionnaire on health consisted of 1) the SF-36 scales on Mental Health and Vitality and 2) the EQ Valuation of Own Health.

1. The complete SF-36 (Short-Form 36) consists of 8 scales on physical and mental domains of health. Because the present study focused on mental health and we wanted to reduce the questionnaire burden for screen participants, we used the 2 scales on Mental health (5 items on being nervous, down, peaceful, depressed and happy) and Vitality (4 items on being full of life, having a lot of energy, being worn out and tired), and excluded the other SF-36 scales. Scales were transformed to ranges of 0 to 100

with higher scores indicating better Mental health and Vitality (Ware and Kosinski 2001). Differences of at least 7.9 points are considered clinically meaningful (Norman, Sridhar et al. 2001).

2. The EQ (EuroQol) 5D Valuation of Own Health assesses self-rating of own overall health, which we expected to be influenced by the receipt of prostate cancer diagnosis. The 'EQ-5D Valuation of Own Health' is a vertical Visual Analog Scale (a thermometer), anchored at the lower end (0) by 'worst imaginable health state' and at the upper end (100) by 'best imaginable health state'. Participants were asked to indicate on the thermometer how good or bad they perceived their current health to be (Brooks 1996).

Additionally, information on age, screening history and Gleason score was obtained through the screening office.

Statistical analysis

Paired t-tests were used to test for statistical significance of the within subject differences in outcomes from baseline to 7 months post-diagnosis. Cohen's effect sizes (d) were used to assess the magnitude of the differences between the assessments, and interpreted as follows: $0.2 < d < 0.5$ indicates a small, $0.5 \leq d < 0.8$ a moderate and $d \geq 0.8$ a large effect size (Cohen 1977).

Unpaired t-tests were used to analyse non-response bias by testing differences between the respondents and the non-respondents and to test the statistical differences between respondents and screen negative men at baseline, which was 2 months before diagnosis.

Results

Respondents

Of the men who were invited for screening, 4,193 participated (2,599 second screenings and 1,594 third screenings). Reasons not to participate were for example having moved home, a bad health, or not being motivated anymore. Of the screen participants, 3,800 (response 88%) completed the mailed questionnaire before screening. Of this group, 82 men were subsequently diagnosed with prostate cancer. Fifty-two (response 63%) gave informed consent for 2 additional assessments. Another two men, who gave informed consent only after the initiation of their therapy were excluded from the interview study and included in the group of non-respondents. The average age of respondents at baseline was 67.3 years (SD 4.4), ranging from 60 to 74. All respondents completed the first telephone assessment before

Tabel 8.1 Gleason scores and treatment modality of cohort members (n=52)

	Gleason score < 7, n=42	**Gleason score 7,** n=8	**Gleason score > 7**, n=2	**Total,** n=52
Radical prostatectomy	18	6	1	25
External Radiotherapy	1	2		3
Brachytherapy	13			13
Watchful Waiting	9			9
Hormonal Treatment			1	1
Undecided	1			1

treatment was initiated, at a median time of 31 days after diagnosis. One respondent refused the second telephone assessment.

Data on screening history showed that 40 respondents were diagnosed with prostate cancer in their second screening round. Of these men, 24 had not been referred for a prostate biopsy before and 16 had had a negative biopsy in the first screening round. Twelve respondents were diagnosed with prostate cancer in their third screening round. Of these men, 9 had not been referred for a biopsy before and 3 had had a negative biopsy in their second screening round. The Gleason score was below or equal to 7 in the majority of patients (Table 8.1). Between 1 and 7 months after diagnosis primary prostate cancer treatment was initiated in the majority of men, consisting of radical prostatectomy (n=24), brachytherapy (n=12), external radiotherapy (n=4), or hormonal treatment (n=1). Ten men opted for watchful waiting and one man had not decided yet (Table 8.1).

Mental and self-rating of overall health

Compared to pre-diagnosis, the average Mental health and Self-rating of own overall health scores decreased significantly 1 month after diagnosis. Effect sizes were medium (Table 8.2, Figure 8.1), indicating that mental and self-rated health worsened after being notified of the diagnosis of prostate cancer. After the initiation of treatment the average scores of mental and self-rated health improved. Although they did not return completely to the original level, scores did not differ significantly from the scores preceding the diagnosis anymore. The average Vitality score decreased non-significantly throughout follow-up, ranging from 75.3 before diagnosis to 73.0 at 7 months post-diagnosis.

We repeated the above-described analysis including the men who opted for ‘active treatment’ (n=42) and excluding those who opted for watchful waiting or had not decided yet on

Table 8.2 Average scores (SD) of screendetected prostate cancer patients (n=52)

Scales (0-100)	2 Months before diagnosis	1 Month after diagnosis	7 Months after diagnosis	*p*-value*)	Effect size 1)*)	*p*-value **)	Effect size **)	*p*-value ***)	Effect size ***)
SF-36 Mental health	83.2 (12)	75.8 (17)	80.0 (14)	0.001	0.64	0.07	0.25	0.10	0.28
SF-36 Vitality	75.3 (16)	74.8 (14)	72.8 (18)	0.77	0.04	0.23	0.13	0.28	0.16
EQ Valuation of own health	80.2 (12)	74.5 (15)	77.4 (14)	0.01	0.49	0.18	0.19	0.20	0.24

1) Cohen's effect size: >.2= small effect; >.5= medium effect; >.8= large effect
*) regarding differences between 2 months before diagnosis and 1 month after diagnosis
**) regarding differences between 1 and 7 months after diagnosis
***) regarding differences between 2 months before diagnosis and 7 months after diagnosis

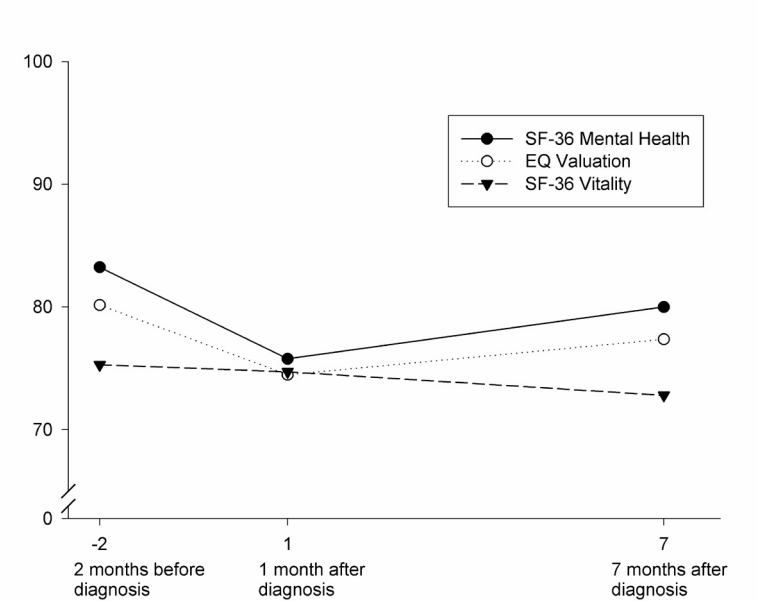


Figure 8.1 Average scores of prostate cancer patients (n=52) before and after diagnosis.

treatment choice. Results considering *p*-values and effect sizes were similar to those of the entire cohort.

Non-response analysis

The baseline average age in the non-responding prostate cancer diagnosed men (n=30) was 66.7 (SD 4.3, range 59 to 73). The non-respondents did not differ significantly from the respondents on age or other health measures (Table 8.3).

Table 8.3 Baseline (i.e. 2 months before diangosis) average scores (SD) of screen-detected prostate cancer patients, both respondents-to-be (n=52) and non-respondents-to-be (n=30)

Scales (0-100)	Screen detected respondents-to-be, *n*=52	Screen positive non-respondents-to-be, *n*=30	*p*-value
SF-36 Mental health	83 (12)	84 (11)	0.77
SF-36 Vitality	75 (16)	79 (15)	0.26
EQ Valuation of own health	80 (12)	83 (12)	0.39

Table 8.4 Baseline (i.e. 2 months before diagnosis) average scores (SD) of screen-detected respondents-to-be and screen negative-to-be men

Scales (0-100)	Screen detected respondents-to-be, *n*=52	Screen negative-to-be men, n=2066	*p*-value
SF-36 Mental health	83 (12)	82 (14)	0.59
SF-36 Vitality	75 (16)	75 (17)	0.86
EQ Valuation of own health	80 (12)	81 (20)	0.81

Comparability of respondents versus screen negative men

With a baseline average age of 68.1 (SD 4.2, range 60 to 77), screen negative men (n=2,066) were on average slightly older than the respondents. Average mental health and self-rated health scores of screen negative men and respondents were similar (Table 8.4).

Discussion

We found that despite its favourable prognosis, being notified of prostate cancer diagnosis after PSA-testing had a significantly negative impact on men's mental and self-rated overall health. This negative impact showed that a first assessment before treatment but after diagnosis is not a true baseline assessment in the sense of representing the situation without prostate cancer.

Our study had several strengths and limitations. We consider the design of the study as one of its strengths; the unique context of the ERSPC enabled the inclusion of patients before anyone knew he would be diagnosed with cancer, which is usually unfeasible. This study is the first to have obtained a pre-diagnosis assessment of quality of life, and can thus describe the impact of the diagnosis itself on mental and self-rated health. Additional qualities are the large proportion of screen participants that completed the baseline assessment (88%) and the fact that it is unlikely that non-response influenced the results of the study. The limited number of respondents can be explained by the low detection rate in the group of 3,800 men who completed the baseline questionnaire. Furthermore, we acknowledge that offering questionnaires in 2 different modes - self-administered questionnaires before diagnosis vs.

telephone interviews afterwards - was sub optimal. Feasibility considerations prompted this design, because assessments by telephone in 3,800 screen participants were deemed not possible, nor were self-administered questionnaires after diagnosis since we had to be sure of completion of the questionnaire before the initiation of treatment.

To our best knowledge an identical design has not been reported before for prostate cancer or other types of cancer. We are aware of one study on knowledge of cancer diagnosis and quality of life. In this study, average scores did not differ between lung cancer patients who knew their diagnosis (n=30) and patients who had not yet heard that they had lung cancer (n=99). The authors concluded that 'a baseline assessment of quality of life in cancer patients with knowledge of their diagnosis can be considered valid' (Montazeri, Hole et al. 2004). We agree that such an assessment can be considered a 'valid baseline assessment' if, for example, the effects on quality of life of two different therapies are compared. However, we do not consider such an assessment after diagnosis 'valid' to represent the quality of life of someone without cancer, for example in burden-of-disease studies. An important distinction between the study on lung cancer patients and ours was, that the lung cancer patients experienced symptoms and were in a process of being diagnosed; the diagnosis might have confirmed what they already feared. The screen participants, on the other hand, typically did not experience any symptoms. Although their health did not change after diagnosis in the sense of dysfunction or pain, their self-rated overall health decreased significantly. Norm data of men without prostate cancer can be an alternative source of 'baseline' scores, for instance as reported by Litwin (Litwin 1999b).

The significant negative impact of diagnosis after screening on mental and self-rated overall health as we reported may be an underestimation of this impact since the respondents in this study were participants in a screening trial. They knew they could be diagnosed with prostate cancer, contrary to men who undergo a routine health check-up and may not even be aware this includes a PSA-test. In what they claim to be the first longitudinal study on psychological and decision-related adjustment after prostate cancer treatment, Steginga et al. followed a cohort of 111 men with localized prostate cancer till 12 months afterwards. They found that psychological and decision-related distress decreased with time, independent of treatment modality (Steginga, Occhipinti et al. 2004). This corresponds with our finding that seven months after diagnosis, when treatment had been initiated for most men, mental and self-rated overall health scores did not differ significantly from baseline anymore, indicating that the majority of men felt better again.

Men who were diagnosed with prostate cancer after PSA-testing generally have a favourable prognosis. The American Cancer Society reported a relative 5-year survival rate in prostate cancer patients of 98% (Cancer statistics, 2004), and among patients who were diagnosed with well or moderately differentiated localized/regional prostate cancers even 5- and 10-year relative survival rates of over 100% have been recorded (indicating the lack of any excess mortality) (Brenner and Arndt 2005). Clinicians, who are aware of the favourable prognosis of early detected prostate cancer, may not always realize the magnitude of the impact that receiving a prostate cancer diagnosis nonetheless has. We recommend clinicians to share their knowledge on prognoses with newly diagnosed prostate cancer patients. We do not consider our results as a recommendation for or against the uptake of screening, but as useful information for men who consider PSA-testing and for doctors or others who inform such men on screening and its possible implications.

We found that in spite of its favourable prognosis, receiving a prostate cancer diagnosis after PSA-testing had a significant negative impact on men's mental and self-rated overall health. This may have clinical implications for counselling. Furthermore, we conclude that 'baseline' Mental health scores from prostate cancer patients prior to treatment as usually reported, are in fact lower than baseline, because the diagnosis itself is associated with mental distress. This may well be true for other screen-detected or clinically diagnosed cancers as well.

ACKNOWLEDGEMENTS

We are grateful to the patients for participating in the study. We thank the urology screening office of the Erasmus University Medical Center Rotterdam for their friendly cooperation. We gratefully acknowledge the Dutch Cancer Society for funding our study (EUR 2000-2329). We thank L. Burdorf and A. Oenema for useful comments on an earlier version of the manuscript.

CHAPTER 9

Including the quality of life effects in the evaluation of prostate cancer screening: expert opinions revisited?

Essink-Bot ML, Korfage IJ, de Koning HJ, BJU Int 2003;92 Suppl 2:101-5.

Abstract

Objective To apply the general empirical framework for estimating utilities for use in cost-utility analysis (CUA) of population-based prostate cancer screening, including an assessment of empirical health status with a classifying measure (e.g. the EQ-5D) and linking these descriptions to utility estimates using the standard preference-based algorithm; combining them with the appropriate durations into QALYs; and sensitivity analysis.

Material and methods Empirical studies to describe and value the health status effects of prostate cancer screening have been ongoing within the Rotterdam centre of the European Randomised study on Screening for Prostate Cancer since 1995. The results of these studies, including the screening itself, the primary treatment phase and advanced disease will be used in estimating utilities for cost-utility analysis.

Results Estimation of cost-utility of population based prostate cancer screening with the results of the 3 empirical health status studies yielded partly counterintuitive results, underestimating the unfavourable health status effects that are inevitably associated with prostate cancer screening. This may be caused by other than health effects of the screening itself ('process effects') and adaptive changes in perception of their situation in patients after curative primary treatment ('response shift'), among other elements.

Conclusion These results prompted us to reconsider the suitability of the general framework of CUA for screening programmes. Possible directions for solutions are indicated.

Introduction

Two large-scale screening trials, the European Randomised study on Screening for Prostate Cancer (ERSPC) and the Prostate Lung Colon and Ovary (PLCO) trial are on-going to evaluate population-based PSA-driven screening for prostate cancer, with prostate cancer mortality as the primary outcome measure (Gohagan, Prorok et al. 2000; de Koning, Auvinen et al. 2002). The first results of the ERSPC relating to the main endpoint may become available between 2005 and 2010. If there is a substantial decrease in prostate cancer mortality one question is whether that benefit is worth the total financial costs incurred by screening. Additional to costs (certain) and survival effects (as yet, not proven) prostate cancer screening has favourable and unfavourable side effects on health-related quality of life (QoL). Theoretically these can be taken into account in the ultimate cost-effectiveness analysis by using quality-adjusted life-years (QALYs) as the measure of effect and hence establishing a cost-utility analysis.

QoL (i.e. health status) relates to functioning in the physical, mental and social domains and is as such the complement of survival time in outcome research. At the societal level, unfavourable health status effects of prostate cancer screening, if compared to the situation of 'no screening available' can result from the screening procedures and from additional primary treatments incurred by the screening program. Being invited and screened may be associated with increased anxiety and distress. Screening tests and diagnostic follow-up, especially TRUS and prostate biopsy, are to some extent bothersome. Additional primary treatments may cause an increase in life-years lived by the patients with the side effects of radical prostatectomy, external beam radiotherapy, and alternative primary treatment options, including watchful waiting. However, provided there is a decrease in prostate cancer mortality as a result from prostate cancer screening, favourable health status effects occur from the associated decrease in incidence of end-stage prostate cancer (Miller, Madalinska et al. 2001). Empirical studies on health status to enable an estimation of the effects of PSA screening have been included in the Dutch part of the ERSPC from the beginning. The present paper addresses the issue of the inclusion of their results in the evaluation of prostate cancer screening. To this end, we describe the framework used for these studies, and briefly describe the results (extensive reports of separate studies have been and will be published elsewhere) (Essink-Bot, de Koning et al. 1998; Madalinska, Essink-Bot et al. 2001). Subsequently we uncover the problems met with the application of the results in the cost-effectiveness analysis, and provide explanations and suggestions for possible solutions. We end by outlining how we plan to proceed with the cost-utility analysis (CUA) within the ERSPC.

Methods and results

In addition to the cost per life-year gained (the common metric of cost-effectiveness analysis), the outcomes of CUA are expressed per QALY gained. Health status effects are included in the CUA by combining data on duration (life-years) with a quality weight ('utility') into QALYs. The common empirical approach to utility estimates of health status effects includes the following steps:

- Empirical description of health status effects, by patients completing the EuroQoL EQ-5D self-classifier of health (Brooks and Group 1996) or a similar measure;
- Linking of the descriptions obtained to preference-based utility scores that are standard and available for EQ-5D (Dolan 1997);
- Estimating the associated duration and frequency of the relevant health states;

- Combining utility scores and durations into QALYs;
- Sensitivity analysis.

Health status descriptions are to be obtained from patients (or subjects) themselves, by repeated self-assessment of health status. Health status measures such as the EQ-5D provide a standard scoring algorithm (based on previous preference studies) to summarise the resulting descriptions in a single utility estimate.

To illustrate the complete procedure, the estimation of QALYs for a (hypothetical) randomised prostate cancer screening trial with 6 participants is described in Appendix 9.1.

The study by De Haes *et al*. provided a realistic and scientifically justified attempt to estimate QALYs for the Dutch breast cancer screening programme (de Haes, de Koning et al. 1991). After identifying relevant phases in screening and the course of breast cancer, health status descriptions for each of these phases were obtained on the basis of published empirical studies. The descriptions were valued by a convenience sample of 31 researchers. The resulting values were inserted into the MISCAN computer simulation programme to estimate the incidence and duration of each of the phases with and without a breast cancer-screening programme. Finally, sensitivity analysis was performed. This resulted in an estimated 8% decrease in effectiveness of the Dutch breast cancer screening programme when using QALYs instead of life-years gained as the outcome measure.

Cost-utility analysis of prostate cancer screening in the ERSPC – general approach

The effect of population-based PSA-driven screening on prostate cancer mortality needs to be evaluated by intention-to-treat analysis of large-scale randomised controlled screening trials. It is not considered feasible and is unnecessary to assess the health status effects only among participants in the screening trials. For example, empirical assessment of the health status effects in the phases of primary treatment and advanced disease within the trial framework would take many years of follow-up of an immense cohort of screening participants and controls. Instead, the unfavourable effects from primary therapies induced by screening and the favourable effects of preventing advanced prostate cancer can be estimated in samples of non-trial patients(Miller, Madalinska et al. 2001).

As the relevant phases for estimating health status effects of prostate cancer screening, we identified the process of screening, the phase of primary therapy, and the advanced disease phase. Three empirical health status studies were initiated, one for each phase, using a combination of measures to allow for estimating and interpreting of utility scores. In all 3 studies we used the EQ-5D to obtain descriptions of health status in each phase and the SF-36

as a multi-dimensional generic descriptive measure. Measures to capture specific health status effects for each phase were added (see below).

The Rotterdam QoL studies

Health status effects of screening and diagnostic follow-up (Essink-Bot, de Koning et al. 1998)

We conducted a longitudinal follow-up study of 626 attendees (age range, 55-69 years) to the Rotterdam screening programme and a survey of 500 men who refused to participate. Among attendees, health status was assessed 3 weeks before the visit to the screening centre, in the waiting room for screening (at that time PSA, digital rectal examination (DRE) and trans-rectal ultra sound (TRUS)) and, if the results were not suspicious, one week after being informed (381 men). Among the 160 men with initially positive screening results and who subsequently had a prostate biopsy, health status was also assessed during the period waiting for the biopsy result, and, if prostate cancer was not confirmed, one week after being informed (116 men). We used the EQ-5D and SF-36, the State-trait Anxiety Inventory and items on pain and discomfort experienced during and after the screening tests. Results included physical discomfort during TRUS and DRE in 29% to 37% of men, and during prostate biopsy in 55%. At the group level there were no significant changes in anxiety levels, but there was tendency for average anxiety levels to decrease below the population norm after obtaining the message that prostate cancer was not found. This can possibly be interpreted as reassurance. Among the men with initially false-positive screening results, 89% reported ‘a lot of experienced benefit’; 91% intended to participate again in the next screening round.

Primary therapy study (Madalinska, Essink-Bot et al. 2001; Korfage, Essink-Bot et al. 2002)

The ongoing primary treatment study started in 1996 and aims to provide a detailed description of the health status effects of primary treatments for localised prostate cancer. In all 314 (of 344) prostate cancer patients, diagnosed within the ERSPC or outside the trial, who were treated at Erasmus MC (University Hospital Rotterdam) or one of 3 general Rotterdam hospitals by radical prostatectomy or external beam radiotherapy in 1996 – 98 were included. Health status was assessed with EQ-5D, SF-36 and the UCLA Prostate Cancer Index (Korfage, Essink-Bot et al. accepted for publication) to estimate the frequency and impact of side effects such as urinary, bowel and sexual dysfunction. Assessments were timed to before the start of treatment, and 6 months, 1 year and 4 years later. The results from the study until 1 year after diagnosis (the series of 4-years assessments was completed only

recently), covariance analysis with adjustment for differences in baseline characteristics showed no significant differences in EQ-5D utility scores between treatment groups. Moreover, utility estimates at 1 year after diagnosis were in the range of age- and sex specific general population norms. The men who underwent prostatectomy reported significant decreases in urinary and erectile function. The men who underwent primary radiotherapy reported significant changes in bowel and sexual function.

Advanced disease (J.B. Madalinska, personal communication).
In a cross-sectional study, 82 patients with prostate cancer from a sample of 132 (response rate 62%) with confirmed distant metastases (M1 disease) completed a questionnaire at a median time after diagnosis of M1 of 27 months. Two years later, 28 % of respondents had shown further progression, whereas 31% had already died. The data showed significant detriments in health status with advanced prostate cancer, both at the generic and symptom-specific level.

Discussion

The 'problem'

From the screening study we concluded that men were able to cope with screening-associated distress. If screening had any effect on general anxiety levels, there was an indication of a reduction of anxiety levels to lower than observed in the general population. Even in men with initially false-positive screening tests the positive evaluations of the screening predominated. These men had no clear health benefit from the screening, because they had no prostate cancer to start with, they had no prostate cancer afterwards, and in-between they were subjected to PSA, DRE, TRUS and prostate biopsy and had to see the urologist several times at the out-patient clinic. We hypothesise that the benefit of screening for most of these men is in reducing uncertainty. After screening they were as sure as possible that they did not have detectable prostate cancer. The results are also in accordance with coping models, e.g. (Folkman and Moskowitz 2000), published by Folkman, that help to explain the positive appraisal of enduring stress followed by a 'good' outcome.
The results of the primary treatment study were similarly remarkable. Several possible explanations for the finding that changes in generic health status over time appeared to be small despite significant physical symptoms and discomfort are currently subjects of our research. We expect that 'response shift', i.e. the adaptation of subjectively reported health status to a contextual change (a cancer diagnosis puts side-effects of treatment into a different

perspective) will prove to be a major factor (Schwartz and Sprangers 1999). Men may have adapted to their situation, probably dependent on their perception of benefit of the relatively early detection of their prostate cancer. They may regard side effects of treatment as 'all in the bargain', as the price paid for the treatment they underwent to get rid of their prostate cancer and to improve their chances of survival. The finding that mental function improves after primary treatment supports this idea.

A second type of explanatory factor may be an insensitivity of the health status classifiers and generic descriptive measures of health status used for the specific consequences of primary treatment for prostate cancer. First results from an on-going qualitative study indicate that men do not consider their sexual function when asked to provide a judgement of their own health (Korfage, in preparation).

Both studies were undertaken to enable a value to be placed on the populations' utility losses that were expected to result from prostate screening itself (small but large-scale negative effects caused by distress and physical discomfort) and from 'excess' primary treatments resulting from screening. Both were well-conducted studies (Ganz and Litwin 2001), but use of the empirical results so far would result, contrary to a priori expectations and somehow counterintuitively, in a zero or almost zero utility loss attributable to screening. What went wrong - if anything?

'Solutions'

Problems with CUA of screening programmes include the distribution of health effects and the exclusive focus of CUA on health effects. Cancer screening programmes show a specific distribution of health effects. All participants in the screening experience a transient relatively minor decrement in health status caused by the screening procedure (the 'burden of screening'). The subjects in whom cancer diagnosis is advanced and prognosis improved experience a large health gain at the individual level. All other participants either experience no health gain or even a loss of health. The presence of prostate cancer is not confirmed in most men who participate in prostate cancer screening, and hence their benefits *in terms of health* are negligible. However, they perceive the benefit of screening, in terms of reduced uncertainty, participation in what is generally perceived as 'good health behaviour', and other so-called 'process effects' (Donaldson and Shackley 1997; Drummond, O'Brien et al. 1997; Birnie, Bossuyt et al. 2000). If and how to take burden of screening (or more generally, very short episodes of impaired health) into account in CUA is open to debate. The same holds about whether to include other than health effects in CUA of health interventions, and if so,

how. The relevance of both burden and non-health effects should be discussed within the scientific community, among health policy makers, and the general public (including patients). As to the burden of screening, empirical assessment of the acceptability of burden of screening relative to the expected health gains may be a first step (is PSA-driven screening of 100 men resulting in 10 life-years gained in one of them acceptable? And what if we need to screen 500 men to reach the same result?).

Second, we tentatively conclude that empirical descriptive health status data of men diagnosed with and under treatment for localised prostate cancer are valuable for our understanding, but that their usefulness in providing the appropriate utility estimates to account for additional primary treatments induced by the screening programme is limited. Men who undergo primary treatment are not in the position to evaluate their treatment as if it was 'extra'. They underwent treatment to be cured from prostate cancer. Given our understanding of the natural history of prostate cancer we know that some of them were cured, whereas others would have lived with no treatment, but neither doctors nor patients know who's who in advance at the individual level. Assessing the health status effects of primary treatment in a screening trial with a control arm with no screening invitation would not help; all men treated for prostate cancer, detected by screening or not, will perceive their treatment as potentially curative for a life-threatening disease.

An easy conclusion from this discussion could be that there is no place for empirical health status assessments in research evaluating healthscreening programmes. Such a conclusion is obviously unwarranted. For example, studies by us and others (Essink-Bot, Korfage et al. accepted for publication) have given important insights into the prevalence of side effects of primary treatment for prostate cancer, and in the quality of life as perceived by patients after successful primary treatment. We do not regard response shift as undesirable 'bias'. Our studies have shown that men are generally able to live well with the side-effects of primary treatment for localised prostate cancer, and underline that a continued search for methods to optimise patient selection for invasive primary therapy is warranted.

However useful for descriptive purposes, we may need others than the patients with prostate cancer for estimating the utility loss caused by these side effects resulting from 'excess' primary treatments after screening. An approach using experts or other outsiders to judge vignettes with empirically based descriptions of patients, as e.g. used in the study by De Haes *et al* (de Haes, de Koning et al. 1991) and in the Dutch Disability Weights study (Stouthard, Essink-Bot et al. 2000), may prove to be useful in this respect

As for the CUA linked to the ERSPC we plan to estimate utilities by combining the empirical studies described above with available literature and the Dutch Disability Weights study (including subsequent similar studies). Following the example of the study by De Haes *et al.* (de Haes, de Koning et al. 1991) these estimates will be imputed in the MISCAN simulation model, followed by sensitivity analysis. Methodological studies on, e.g. response shift, will continue; you will be hearing from us soon!

Appendix 9.1

As an illustration of the procedure of estimating QALYs from a screening trial, QALYs are described for a hypothetical randomised prostate cancer screening trial with 6 healthy participants (3 controls and 3 screenees) aged 70 years at randomisation, and with a complete follow-up until death of all participants.

Control group

- C1 and C2 were healthy men who lived their normal life span of 12 years in optimal health (utility = 1.0), until their instantaneous deaths from other causes. For each of them this outcome can be quantified as 12 x 1 = 12 QALYs.
- C3 lived 3 years in optimal health (3 x 1 = 3 QALYs), was diagnosed with localised prostate cancer and underwent primary treatment (for 1 year; hypothetical utility estimate 0.5; 0.5 x 1 = 0.5 QALYs); lived 4 years with the side effects of primary treatment, estimated utility 0.75 (4 x 0.75 = 3 QALYs); developed advanced disease and died after one year with an estimated utility of 0.25 (1 x 0.25 = 0.25 QALYs) from prostate cancer. Total QALYs of C3 after randomisation: 3 + 0.5 + 3.0 + 0.25 = 6.75 QALYs

Screening group

- S1 underwent PSA, DRE, TRUS screening with no further diagnostic procedures 3 times (QALYs per screening period: 1 week = 0.02 year with u = 0.98), and lived his normal life span of 12 years: Total QALYs = (0.06 x 0.98) + (11.94 x 1.0) = 11.99.
- S2 underwent PSA, DRE, TRUS with an initially false-positive result and a negative biopsy (total duration 6 weeks = 0.12 years, estimated u = 0.9); uneventful re-screening (0.02 x 0.98) at 1 year, 5 years and 9 years. Total QALYs: (0.12 x 0.9)+(0.06 x 0.98)+(11.82 x 1) = 0.108 + 0.0588 + 11.82 = 11.987.
- S3 underwent screening including a biopsy procedure (0.12 years * 0.9), resulting in the detection of localised prostate cancer followed by primary treatment (0.5 x 1.0

year), and a normal life span of 10.88 years lived with the side effects of primary treatment (u = 0.75). Total QALYs = (0.12 x 0.9) + (1 x 0.5) + (10.88 x 0.75) = 8.87.

Thus the total QALYs of the control arm = 12 + 12 +6.75 = 30.75; and of the screening arm = 11.999 + 11.987 + 8.87 = 32.856.

Phase	Estimated duration, years	Estimated utility	QALYs
Screening	0.02	0.98	0.0196
Screening + biopsy	0.12	0.90	0.1080
Primary therapy	1.00	0.50	0.5000
1 year with lasting side effects of primary therapy	1.00	0.75	0.7500
1 year with advanced disease	1.00	0.25	0.2500

CHAPTER 10

Discussion

In the first part of this chapter we will answer the research questions as listed in the general introduction. In the second part we will provide overall conclusions followed by recommendations for clinical and screening practice and for further health-related quality of life (QoL) research.

Part 1 Answers to the research questions

Q 1. What is the burden of long-term sexual, urinary and bowel dysfunctions after radical prostatectomy and external radiotherapy in men with localized prostate cancer for the population?

Four to five years after radical prostatectomy, 88% of men reported erectile dysfunction and 31% experienced urinary leakage at least several times weekly. After external radiotherapy, erectile dysfunction was reported by 64% and bowel problems by 11% of patients. Our longitudinal study showed that although urinary problems may improve in some patients between 1 and 4 to 5 years after treatment, the vast majority of urinary, bowel and erectile dysfunctions at 1-year follow-up will be permanent. In both treatment groups generic QoL scores were equal to or higher than in the general male age-related population.

The 2 treatment groups in our observational study differed, with prostatectomy patients being on average 6 years younger than radiotherapy patients and having less co-morbidity. Disease-specific and generic QoL data were therefore presented in graphs with the average age per treatment group on the x-axes so the age difference between treatment groups was clear. At 5-year follow-up, the effects of ageing and the treatment could not be disentangled. A comparison with healthy controls may be helpful in untwining them.

Our results reflect common practice with the typical man treated by prostatectomy being younger and healthier than the typical man receiving radiotherapy. These results cannot support conclusions about one therapy being superior to another. The percentages of long-term dysfunction as reported in our longitudinal study may lead patients to reconsider their treatment choice (if possible) to avoid side effects they perceive as more bothersome.

Q 2. How anxious and depressed are men in the years following diagnosis and treatment of localized prostate cancer?

Shortly after prostate cancer diagnosis roughly one in every four respondents reported high levels of anxiety and symptoms of depression. At 6-months follow-up, when primary therapy had been initiated, these levels had decreased towards less anxiety and depression. We suggest that a prolonged delay between prostate cancer diagnosis and its treatment is

undesirable and should be prevented. We examined if baseline anxiety scores were predictive for anxiety and symptoms of depression at 12-months follow-up and found that 71% of high-anxiety and 60% of symptoms of depression could be detected. This prediction might be improved by, for instance, including disease characteristics as the Gleason score in the prediction.

Information on the generally favourable prognosis of early-detected prostate cancer might help to reduce fear. Such information, however, cannot take away anxiety caused by the foresight of treatment including pain, hospital visits and other inconveniences it will entail. Referral to psychosocial support or self-help groups might be helpful for selected patients.

Q 3. When asking patients, how important are side effects after primary prostate cancer treatment for them?

In our qualitative study we found that men with side effects after primary prostate cancer therapy are aware of their sexual, urinary, and bowel dysfunctions, but they did not call them health problems. The impact of these dysfunctions can thus hardly ever be revealed by generic QoL measures referring to *health.* This cause of insensitivity of generic measures was disclosed by combining quantitative and qualitative research methods, which is common practice in psychological research. We consider quantitative and qualitative methods as complementary rather than as interchangeable and recommend using them both in epidemiological and public health research. A common application is, for instance, the qualitative testing of questionnaires before applying them on a larger scale in quantitative research, but we plead to combine quantitative and qualitative methods more often.

Another finding in the qualitative study was that many patients accepted side effects after prostate cancer treatment because of a prevailing feeling of relief. Having survived a condition that was perceived as potentially life threatening reduced the importance of side effects. This adaptation to changed health indicated the presence of response shift.

It seems to be a common opinion that the significance of sexual activity diminishes with the increase of age. In our interview study, elderly men with and without prostate cancer tended to trivialize sexual problems by referring to their age. Men with erectile dysfunction since treatment observed for example ‘Treatment of prostate cancer does have consequences for the sexual life. But I will be 75 years old now, so, of course that’s not a major theme anymore.’ and ‘I mean, you’ve got your age as well. I will be 70 years old. It might be different when you’re young, but …. no. I’m happy that I was treated in time.’ On the other hand, a number

of respondents indicated explicitly that they regretted to have lost their erectile function. The commercial attention is big: men are recommended by TV-spots to visit their physician in case of no erections, indicating that such an absence is supposed to be a problem. In an often-used prostate cancer specific questionnaire men are asked to rate their level of sexual desire on a scale from 'very poor' to 'very good' (Wei, Dunn et al. 2000), suggesting that one should have at least a certain level of sexual desire. Opinions on the significance of erectile dysfunction thus vary widely. However, the patient himself is the one to judge whether his erectile (dys)function is a problem and whether he wishes to act on it. We should not presume that sexual function is unimportant to elderly patients.

Q 4. What mental impact does early prostate cancer diagnosis through screening have on symptomless men?

A prostate cancer diagnosis through PSA-screening had a significant unfavourable impact on patients' mental and self-rated overall health. Clinicians may not always realize this. We recommend clinicians to share their knowledge about the generally favourable prognosis with newly screen-detected patients. At 6-months follow-up, when primary treatment had been initiated in most patients, mental and self-rated overall health improved and did not significantly differ from pre-diagnosis scores anymore. The impact of prostate cancer diagnosis through screening is an event of short duration but it occurs frequently and thus still has an impact at population level, even more so because in prostate cancer screening inevitably overdiagnosis will occur.

Part 2 General discussion

Our study aimed on the effects of prostate cancer diagnosis and primary treatment on QoL in a screening context. Screening programmes in general lead to treatments, whether or not with side effects. The selection of participants for screening influences thus who will be treated as a consequence. Our study results have mainly implications for treatment of localized prostate cancer, but because of the context they may have implications for screening as well.

Four to five years after primary prostate cancer therapy a considerable number of our respondents experienced side effects. Survival rates, on the other hand, are favourable. Five- and 10-year relative survival rates of over 100% - indicating the lack of any excess mortality - have been recorded among patients who were diagnosed with well or moderately differentiated localized/regional prostate cancers (Brenner and Arndt 2005). Recent data of Albertsen *et al*. on 20-year survival of men who were diagnosed with clinically localized

prostate cancer and treated with observation or androgen withdrawal therapy alone showed that men with low-grade prostate cancers (Gleason scores of 2-4) also had a minimal risk of dying of prostate cancer during 20 years of follow-up, i.e. 6 deaths per 1,000 person-years (Albertsen, Hanley et al. 2005). Thus, a favourable life expectancy can in some cases be achieved without treatment and its inevitable side effects. Ideally treatment should be restricted to those newly diagnosed prostate cancer patients who are expected to benefit from it. Future research is needed to improve the selection of men whose tumours that need to be treated, e.g. by identifying prognostic factors or developing prognostic models.

Another way to reduce the burden of treatment is to search for new, less invasive treatment modalities for early-diagnosed prostate cancer patients that entail a minimum of side effects. Brachytherapy was intended to be such a treatment. An interesting development is active surveillance (also called monitoring or watchful waiting) for men with well-differentiated tumours; a comparatively new approach, for which a Dutch protocol is currently being developed. It is not yet known how men will appreciate the periodical checks of their PSA-level in the long-term while active treatment is not forthcoming. Women with early stages of cervical cancer, for instance, sometimes prefer active treatment above repeated check-ups. However, contrary to prostate cancer the treatment of pre-invasive stages of cervical cancer (e.g. CIN) has limited side effects.

Prostate cancer screening through regular PSA-testing, for example once every four years, is known to cause overdetection at the population level (Etzioni, Penson et al. 2002). At the individual level overdetection can be interpreted as a chance that treatment will not lead to benefit. Uncertain benefit may influence the preferences for cancer screening programmes. Discrete choice experiments can be used to assess the impact of the uncertain benefit on preferences for cancer screening programmes. In such experiments respondents are offered descriptions of alternative screening set-ups containing attributes such as number of screening tests, risk of dying of the disease, risk of no benefit, costs etc, and asked to make a choice (Gyrd-Hansen and Sogaard 2001).

Methodological implications of our study results mainly concern the interpretation of QoL study results. We will discuss 2 of them.

Generic QoL instruments are intended to cover all aspects of life relating to disease and/or treatment. Considering the high generic QoL scores of prostate cancer patients side effects of treatment were not detected. The specific nature of prostate cancer and treatment-related dysfunctions such as urinary, bowel, and sexual problems may have played a role. Patients are

generally well, but experience dysfunctions in specific domains. Oesophageal carcinoma patients, for example, typically experience 'generic' dysfunctions such as pain and fatigue and in their case generic QoL scales were more responsive than disease-specific QoL scales (Homs, Essink-Bot et al. 2004). We agree with amongst others McColl *et al*. and Essink-Bot who concluded that disease specific and generic measures are complementary rather than interchangeable (Essink-Bot 1995; McColl, Han et al. 2004) and recommend using both.
We included a cohort of possible prostate cancer patients-to-be 2 months before their diagnosis. The negative mental impact of prostate cancer diagnosis appeared to be significant. The methodological implication is that considering a QoL assessment after prostate cancer diagnosis as 'baseline' may lead to an underestimation of the patients' mental and self-rated overall health. We are currently developing norm scores of age-related patterns of sexual, urinary and bowel function in over 3,000 men without prostate cancer to facilitate the interpretation of outcomes after localized prostate cancer diagnosis or treatment.

Early detection of disease always has pros and cons. The pros usually seem to be clear at first sight. People expect early detection to lead to early treatment and thus to a reduced chance of death from the disease. The cons are more difficult to grasp. Consequences such as having to live 'extra' years as a cancer patient and the chance of receiving treatment without having benefit of it, do not intuitively come to mind on individuals considering early detection. In general it is thus necessary to provide people with adequate information about pros and cons of screening to enable an informed choice on participation. An informed choice has been defined in the screening context as consistent with preferences and values (Marteau, Dormandy et al. 2001). In the case of prostate cancer, however, no evidence is yet available that screening leads to reduced prostate cancer mortality. People should be aware of this to prevent regret after testing. A qualitative study of Chapple *et al.* showed that some men only realized what PSA-testing can entail after a positive PSA-test, concluding for instance 'Basically I wish I hadn't known. I would have happily lived on in ignorance' (Chapple, Ziebland et al. 2002).

Pros and cons of screening also need considering at the population level. Two randomised controlled trials on prostate cancer screening are currently in progress. Although the results on mortality reduction are not expected before 2007, opportunistic screening is increasing in the Netherlands, possibly indicating that some people expect to benefit from it. On the other hand it is argued that carrying out a trial is unethical, because no benefit is to be expected for

participants, let alone introducing a population-based screening programme (Adami, Baron et al. 1994).

These opposite signals indicate the importance of using the forthcoming results of randomised trials in deciding on the introduction of a screening programme. Thanks to carefully carried out trials the association between PSA-screening and prostate-cancer specific mortality will hopefully be known within a few years. Subsequently the cost-effectiveness of prostate cancer screening can be estimated and evidence-based decisions on the introduction of population-based screening programmes can be made. A randomised controlled treatment trial in the UK is currently comparing survival and QoL after radical prostatectomy, external beam radiotherapy and monitoring (Donovan, Mills et al. 2002). In the mean time screening by general practitioners and other clinicians is not justified. While commercial organisations promote PSA-testing, at least unbiased information on possible consequences of early detection and treatment of prostate cancer should be made available for men who consider PSA-testing. Such information should state that currently no evidence exists for reduced prostate cancer mortality after PSA-testing. Unregulated screening is a growing problem in other areas as well. As the British Medical Association stated: 'Patients may be putting themselves at unnecessary risk—with very little benefit to their health—by opting to undergo scans and genetic tests that are offered to them as part of a screening programme by private sector healthcare organisations' (Eaton 2005). Someone has to take the responsibility to supply unbiased information, for example the Ministry of Health, physicians, patients, or the public health community. In cooperation with the Dutch Cancer Society we made a start by developing an information leaflet on PSA-testing.

We conclude, that quality of life studies are important for the selection of cancer screening programs that can supply benefit at population and individual level, and for the protection of people against bad screening tests and commercial exploitation.

FINAL RECOMMENDATIONS

1. Men who consider PSA-testing should be provided with unbiased information on possible consequences of early detection and treatment of prostate cancer;
2. Newly diagnosed prostate cancer patients should be provided with adequate information on prognosis of early detected prostate cancer and on prevalence of sexual, urinary and bowel dysfunctions after different treatment modalities before making a treatment choice;

3. Further research is needed to assess the impact of uncertain benefit in prostate cancer screening on preferences for cancer screening programmes, for e.g. by discrete choice experiments.
4. Our results confirm previous findings that disease-specific and generic measures are complementary rather than interchangeable. We recommend using both. The same applies for qualitative and quantitative techniques in assessing quality of life;
5. Patients were very much willing to discuss the subject of sexual, urinary and/or bowel dysfunctions. We recommend clinicians not to avoid these topics.

Summary

In Western countries prostate cancer is the most prevalent malignancy in males. In its early stage prostate cancer usually does not cause any pain or other symptoms. It can be detected early by testing for prostate-specific antigen (PSA). Since the 1980s the PSA-test has been applied at a large scale, resulting in an increased prevalence of prostate cancer. Overdiagnosis, defined as the detection and subsequent treatment of prostate cancer through PSA-testing that otherwise would not have been diagnosed within the patients' lifetime, is considered a major potential drawback of PSA-testing.

The increase in the number of men being diagnosed with prostate cancer – especially in its early stage – and subsequently receiving primary treatment is associated with a proportional rise in the prevalence of side effects. Side-effects mainly concern erectile and urinary dysfunction after radical prostatectomy, and erectile and bowel dysfunction after external radiotherapy.

This thesis focuses on the effects of prostate cancer diagnosis and primary treatment on quality of life of patients. 'Quality of life' (QoL) will be restricted to 'health-related quality of life' or 'health status', defined as quality of life relating to disease and/or treatment.

The following research questions were addressed:

Q 1. What is the burden of long-term sexual, urinary and bowel dysfunction after radical prostatectomy and external radiotherapy in men with localized prostate cancer for the population?

Q 2. How anxious and depressed are men in the years following diagnosis and treatment of localized prostate cancer?

Q 3. When asking patients, how important are side effects after primary prostate cancer treatment for them?

Q 4. What mental impact does early prostate cancer diagnosis through screening have on symptomless men?

Chapter 2 presents a review of prospective cohort studies on QoL in patients with localised prostate cancer treated with radical prostatectomy or external beam radiotherapy. We identified 5 cohort studies with a pre-treatment assessment and one population-based study.
The cohort studies confirmed findings from previous cross-sectional studies with respect to the side effects of prostatectomy and radiotherapy on urinary, bowel and sexual function. After adjustment for baseline characteristics most studies did not show differences in generic QoL at 12 months post-diagnosis between men treated by prostatectomy versus those treated by radiotherapy. In both treatment groups generic QoL scores at 12-months follow-up showed small changes, if any, if compared to pre-treatment scores.
After completion of the review in 2003 an update on the population-based study with similar findings was published in 2004.

In **Chapter 3** we describe the development and testing of a Dutch QoL measure for localized prostate cancer patients. Scales from the UCLA Prostate Cancer Index (PCI) on urinary and bowel function and bother underwent formal linguistic and cultural translation. PCI scales on sexual function and bother were replaced by Dutch single items on sexual activity. After qualitative pilot testing, 389 patients with localized prostate cancer completed the measure before and at 2 time points after primary treatment. We concluded, that the Dutch PCI performed well psychometrically (feasibility, score distribution, reliability, construct validity and responsiveness to change) in men treated for early stage prostate cancer. The items on sexual activity were useful in identifying men experiencing erectile dysfunction.

The increased early detection of prostate cancer leads to more men facing the long-term consequences of primary treatment. To measure these consequences we conducted a prospective, longitudinal study among 300 men with newly diagnosed localised prostate cancer from 4 Rotterdam hospitals. Men completed 4 questionnaires: once before primary treatment (radical prostatectomy or external beam radiotherapy) and again at 6-months, 12-months and 5-year follow-up. To study QoL over time repeated-measures models were applied that allowed for the use of all available data including incomplete records. **Chapter 4** reports on the prevalence of side effects and the bother they cause in the years following localized prostate cancer treatment (assessed by the UCLA-PCI) and on generic QoL (SF-36,

EQ-5D). Pre-treatment, 12% of prostatectomy patients experienced urinary leakage at least several times weekly, at 5-year follow-up this was the case for 31%. At 5-year follow-up, 11% of the radiotherapy group considered their bowel habits as a big or moderate problem compared to 1% of the prostatectomy group. Erectile dysfunction was defined as regularly or often having problems in achieving or maintaining an erection if wished to, or not being sexually active because of erectile problems. At 5-year follow-up 88% of prostatectomy patients and 64% of radiotherapy patients reported erectile dysfunction. Before treatment these percentages had been 31% and 40%, respectively. Our longitudinal study showed that although urinary problems may improve in some patients between 1 and 4 to 5 years after treatment, the vast majority of urinary and bowel dysfunctions at 12-months follow-up will be permanent.

Men treated by prostatectomy were on average 6 years younger and had less co-morbid conditions before treatment than men treated by radiotherapy. Furthermore, they reported better generic functioning (e.g. physical activities such as walking and bathing, mental health and social functioning), both pre- and post-treatment. Physical functioning over time improved slightly in prostatectomy patients, but declined in radiotherapy patients. The decrease in physical functioning with ageing was generally steeper for older subjects than for younger ones. The physical decline in radiotherapy patients at 5-year follow-up resulted at least partly from ageing, although treatment effects cannot be excluded. Because effects of ageing and treatment could not be disentangled, we decided to present the QoL scores in graphs with the average age of the treatment groups depicted on the x-axes. In this way the difference in average age between treatment groups is clear, and misinterpretation because of non-recognition of age differences is prevented. We suggest that innovative graphs describing disease-specific and generic functions after treatment can help patients and physicians in their treatment choices.

SF-36 scores were both before and after treatment equal to or higher than Dutch and US age and sex-adjusted norms. The better generic pre-treatment scores may have to do with a higher socio-economic status (SES) among patients, since SES is positively associated with screening attendance and with prostate cancer incidence.

Chapter 5 concerns the same cohort of newly diagnosed prostate cancer patients as described in chapter 4. We assessed anxiety (STAI-State) and symptoms of depression (CES-D) after diagnosis but before treatment till 5-year follow-up. Furthermore, we examined if anxiety scores at inclusion were predictive for anxiety and symptoms of depression at 12-months

follow-up. Respondents were subdivided according to therapy (prostatectomy versus radiotherapy) and anxiety (high-anxiety versus low-anxiety). Pre-treatment 28% of all respondents were classified as 'high-anxiety'. High-anxiety scores decreased significantly post-treatment, i.e. towards less anxiety. One year after diagnosis 27% of men treated by radiotherapy reported clinical significant levels of depression while 20% is expected in a general population. Anxiety scores at inclusion predicted 71% of high-anxiety at 12-months follow-up and 60% of symptoms of depression. The performance might be improved by including disease characteristics as the Gleason score in the prediction, or by applying other measures.
Because being diagnosed with prostate cancer may have a considerable impact on patients' mental health, we recommend clinicians to attempt early detection of patients who are at risk of high levels of anxiety and symptoms of depression in the year following prostate cancer diagnosis, and offer them mental support.

Although primary prostate cancer treatment often results in sub optimal urinary, bowel and/or sexual function, patients typically report high generic QoL scores. This discrepancy between disease-specific and generic results brings up the question how important prostate cancer diagnosis and side effects are to patients. We examined this issue through qualitative interviews (chapter 6), a valuation study (chapter 7) and a cohort study on the mental impact of prostate cancer diagnosis on symptomless men (chapter 8).

Chapter 6 describes a qualitative study in which we explored 2 mechanisms that may explain the discrepancy: an insensitivity of generic QoL-measures to sexual, urinary, and bowel symptoms and/or adaptation to changed health (response shift). We conducted semi-structured interviews with 33 prostate cancer patients experiencing sexual, urinary or bowel dysfunction since treatment. Eighteen of them were asked for their opinions regarding their own health, their QoL and associations with prostate cancer treatment. Fifteen others completed a questionnaire while we observed their behaviour, for example expressions of confusion and non-understanding. Comments on the questionnaire and its items were solicited. We found that patients trivialized sexual (dys) function referring to old age, remarking for example 'All of my life I was a very active sexual human being, but now I've reached an age that I realise it's not the only thing in the world'. We found that interviewees are aware of their sexual, urinary, and/or bowel dysfunctions, but that they nonetheless did not take them into account when completing QoL measures, because they did not view these

dysfunctions as aspects of health. We concluded that generic QoL measures referring to *health* can thus not disclose the impact of sexual, urinary and bowel dysfunctions on patients. This finding revealed a cause of the insensitivity of generic measures. Furthermore, response shift appeared to be present: many patients accepted the side effects as inevitable consequences of having been treated for prostate cancer, a condition they perceived as potentially life threatening.

In **chapter 7** we assessed if patients value urinary, bowel and sexual dysfunction after prostate cancer treatment differently than men without prostate cancer. We compared valuations of men with (n=54) and age-related men without prostate cancer (n=53) of 5 health states that are associated with prostate cancer treatment. We hypothesized that patients might have adapted to their changed health and would value the health states higher than men without prostate cancer. The valuations through Visual Analog Scales (VAS) and an impersonal version of Time Trade-Off (TTO) were completed using a computer-based tool. Both methods resulted in both groups in the same ranking, except for one health state. Average valuations were similar in both groups except for one valuation by VAS. Average TTO values were higher than average VAS values, as has been observed before. Using an impersonal version of TTO, patients and healthy men agreed on which health state was worse than others. Our results suggest that there is no objection to the use of population-based utilities in economic evaluations of primary prostate cancer therapy.

In **chapter 8** we describe the mental impact of prostate cancer diagnosis through PSA-testing. Before screening, 3,800 participants of the ERSPC prostate cancer screening trial completed a questionnaire (SF-36 Mental Health and Vitality, EQ-5D VAS for self-rated overall health). Of 82 men who were subsequently screen-detected with prostate cancer, 52 agreed with completing 2 additional assessments. After prostate cancer diagnosis, the average rating of own overall health decreased from 80 to 75 on a 0-100 scale, while no pain or other prostate cancer symptoms were experienced. Mental health also worsened significantly. Six months later, when treatment had been initiated in the majority of diagnosed men, mental and self-rated overall health improved and did not significantly differ from pre-diagnosis anymore. Non-response does not seem to have affected these results. We concluded that prostate cancer diagnosis after PSA-testing had a significant negative impact on men's mental and self-rated overall health. The clinical implication of this finding is the recommendation for clinicians to share their knowledge on the generally favourable prognosis with newly diagnosed patients.

The methodological implication is that considering an assessment of quality of life after prostate cancer diagnosis as ‘baseline’ may lead to an underestimation of the patients’ mental and self-rated overall health.

The results of empirical studies on QoL, including those on the phases of screening, primary treatment and advanced disease, are to be employed in estimating utilities. In **chapter 9** we showed that applying the general framework to estimate cost-utility of population based prostate cancer screening with the results of the 3 empirical studies will lead to an underestimation of the unfavourable health status effects that are inevitably associated with prostate cancer screening. This may be caused by non-health effects of the screening itself (‘process effects’) and adaptive changes in perception of their own situation in patients after curative primary treatment (‘response shift’), among other elements. These results prompt us to reconsider the suitability of parts of the common methodology of prevention assessment with regard to screening evaluation. Possible directions for solutions are indicated, such as using experts to judge vignettes with empirically based descriptions of patients.

In **chapter 10** the research questions as posed in the general introduction are answered. Implications that our study results may have for treatment and screening are described. Our longitudinal study confirms earlier findings of cross-sectional studies that primary prostate cancer treatment results in urinary, bowel and sexual dysfunction in a considerable portion of treated men. At the same time it is uncertain whether treatment will result in benefit for the individual. The impact of the uncertain benefit on preferences for cancer screening programmes in the general public should be assessed, for instance by so-called discrete choice experiments. Ideally treatment should be restricted to men who are expected to benefit from it. Future research is needed to improve the selection of these men, e.g. by identifying prognostic factors. Another way to reduce the burden of treatment is to search for new, less invasive treatment modalities for early-diagnosed prostate cancer patients that entail a minimum of side effects.
A methodological implication of our study results is that considering a QoL assessment after prostate cancer diagnosis as ‘baseline’ may lead to an underestimation of the patients’ mental and self-rated overall health. Furthermore, our results confirm earlier findings that disease specific and generic measures are complementary rather than interchangeable. We recommend using both.

Finally, we state that screening by general practitioners and other clinicians is not justified while early detection followed by appropriate treatment has not yet shown to reduce prostate cancer-specific mortality. While commercial organisations promote PSA-testing, at least unbiased information on possible consequences of early detection and treatment of prostate cancer should be made available for men who consider PSA-testing.

Samenvatting

In westerse landen is prostaatkanker de meest prevalente maligniteit (vorm van kanker) onder mannen. In een vroeg stadium veroorzaakt prostaatkanker normaal gesproken geen pijn of enig ander symptoom. Het kan vroeg ontdekt worden door te testen op prostaat-specifiek antigeen (PSA). Sinds de jaren tachtig van de vorige eeuw wordt de PSA-test op grote schaal toegepast, hetgeen resulteerde in een toegenomen prevalentie van prostaatkanker. Overdiagnose, gedefinieerd als de ontdekking en daaropvolgende behandeling van prostaatkanker middels de PSA-test die anders niet gediagnosticeerd zou zijn tijdens het leven van de patiënt, wordt als een belangrijk potentieel nadeel van de PSA-test beschouwd.

De toename in het aantal mannen dat in een vroeg stadium van prostaatkanker wordt gediagnosticeerd en vervolgens primarie behandeling ondergaat, gaat gepaard aan een toename in de prevalentie van bijeffecten van die behandeling. Bijeffecten betreffen met name erectiestoornissen en plasklachten na radicale prostatectomie (operatie), en erectiestoornissen en darmproblemen na externe radiotherapie.

Dit proefschrift richt zich op de effecten van prostaatkankerdiagnose en primaire behandeling op de kwaliteit van leven van patiënten. In dit proefschrift beperkt ‘kwaliteit van leven’ (KvL) zich tot ‘gezondheidsgerelateerde kwaliteit van leven’ oftewel ‘gezondheidstoestand’, gedefinieerd als kwaliteit van leven in relatie tot ziekte en/of behandeling.

De volgende onderzoeksvragen worden behandeld:

V 1. Wat is op lange termijn de belasting voor de populatie van erectie-, plas- en darmklachten na behandeling van gelokaliseerde prostaatkanker middels radicale prostatectomie of externe radiotherapie?

V 2. Hoe angstig en depressief zijn mannen in de jaren die volgen op diagnose en behandeling van gelokaliseerde prostaatkanker?

V 3. Indien het aan patiënten gevraagd wordt, hoe belangrijk zijn bijeffecten na primaire prostaatkanker behandeling dan?

V 4. Wat voor impact heeft prostaatkankerdiagnose door screening op de psychische gezondheid van mannen?

In **hoofdstuk 2** wordt een overzicht gegeven van prospectieve cohort studies naar de KvL van patiënten met gelokaliseerde prostaatkanker die behandeld zijn middels radicale prostatectomie of uitwendige radiotherapie. We vonden 5 cohort studies met een eerste meting voor behandeling en 1 studie gebaseerd op de nationale bevolking.
De cohort studies bevestigden bevindingen van eerdere cross-sectionele studies wat betreft de bijeffecten van prostatectomie en radiotherapie op plas-, darm- en erectiele functies. Na aanpassing voor kenmerken bij inclusie rapporteerden de meeste studies 12 maanden na diagnose geen verschil in generieke KvL tussen geopereerde en bestraalde mannen. In beide behandelingsgroepen vertoonden de generieke KvL scores bij 12 maanden follow-up weinig tot geen veranderingen ten opzichte van de scores voorafgaand aan de behandeling.
Na afronding van het literatuuronderzoek in 2003 verscheen in 2004 een update van de op de bevolking gebaseerde studie. De resultaten van deze studie bevestigden eerdere bevindingen.

In **hoofdstuk 3** beschrijven we de ontwikkeling en het testen van een Nederlands KvL meetinstrument voor mannen met gelokaliseerde prostaatkanker. Schalen van de UCLA Prostaatkanker Index (PCI), die plas- en darmfunctie en -klachten meten, ondergingen een formele linguïstische en culturele vertaling. De PCI-schalen over seksuele functie en klachten werden vervangen door Nederlandse losse items over seksuele activiteit. Na een kwalitatieve testfase vulden 389 patiënten met gelokaliseerde prostaatkanker het meetinstrument in vóór primaire behandeling en op 2 tijdstippen erna. Wij concludeerden, dat de Nederlandse PCI op psychometrische aspecten (toepasbaarheid, scoreverdeling, betrouwbaarheid, construct validiteit en sensitiviteit voor veranderingen) goed functioneerde bij mannen die behandeld waren voor gelokaliseerde prostaatkanker. De items over seksuele activiteit waren nuttig bij het identificeren van mannen met erectiele dysfunctie.

Door vroege ontdekking van prostaatkanker worden meer mannen geconfronteerd met de lange termijn gevolgen van primaire behandeling. Om deze gevolgen te meten voerden we een prospectieve, longitudinale studie uit onder 300 recent met gelokaliseerde prostaatkanker gediagnosticeerde mannen uit 4 Rotterdamse ziekenhuizen. Deelnemers vulden vier keer een

vragenlijst in: de eerste vóór primaire behandeling (radicale prostatectomie of uitwendige radiotherapie) en vervolgens 6 maanden, 12 maanden en 5 jaar daarna nogmaals. Om de KvL door de tijd heen te kunnen bestuderen werden zgn. 'repeated-measures' modellen toegepast die het gebruik van alle beschikbare data mogelijk maken, ook van mannen die minder dan 4 keer een vragenlijst invulden. **Hoofdstuk 4** gaat over de prevalentie van bijeffecten en de last die zij veroorzaken in de jaren die volgen op behandeling van gelokaliseerde prostaatkanker (zoals gemeten met de UCLA-PCI) en over generieke KvL (SF-36, EQ-5D).

Voor behandeling ondervond 12% van de geopereerde patiënten minimaal enige keren per week ongewenst urineverlies, 5 jaar later was dit het geval bij 31%. Vijf jaar na behandeling vond 11% van de bestraalde mannen hun stoelgang een matig tot ernstig probleem t.o.v. 1% van de geopereerde mannen. Erectiele dysfunctie werd gedefinieerd als het regelmatig of vaak ervaren van problemen bij het krijgen of behouden van een gewenste erectie, of het niet seksueel actief zijn vanwege erectieproblemen. Vijf jaar na behandeling rapporteerden 88% van de geopereerde en 64% van de bestraalde mannen erectieproblemen. Voor behandeling waren deze percentages 31% respectievelijk 40%. Onze longitudinale studie toonde aan dat, hoewel plasproblemen in sommige patiënten kunnen verminderen tussen 1 en 4 à 5 jaar na behandeling, verreweg de meeste plas-, darm- en erectieproblemen bij 12-maanden follow-up blijvend zullen zijn.

Geopereerde mannen waren gemiddeld 6 jaar jonger en hadden voor de behandeling minder co-morbiditeit dan bestraalde mannen. Daarbij rapporteerden zij zowel voor als na de behandeling een beter generiek functioneren, d.w.z. fysieke activiteiten als lopen en baden, psychische gezondheid en sociaal functioneren. Door de jaren heen verbeterde het fysieke functioneren van geopereerde mannen licht, maar het verslechterde in de bestraalde mannen. De verslechtering met het ouder worden van met name het fysieke functioneren verliep steiler in oudere mannen dan in jongere mannen. Het niveau van fysiek functioneren van bestraalde mannen hield bij 5-jaar follow-up in ieder geval gedeeltelijk verband met het ouder worden, hoewel behandelingseffecten niet uitgesloten kunnen worden. Omdat leeftijdseffecten niet onderscheiden konden worden van het behandelingseffect besloten wij de KvL-scores te presenteren in grafieken met de gemiddelde leeftijd per behandelingsgroep weergegeven op de X-as. Zo is het leeftijdsverschil tussen de behandelingsgroepen duidelijk en wordt misinterpretatie door het niet onderkennen van het leeftijdsverschil voorkomen. De innovatieve grafieken die ziekte-specifiek en generiek functioneren na behandeling weergeven kunnen patiënten en artsen helpen bij het maken van hun behandelingskeuzes.

Zowel voor als na de behandeling waren SF-36 scores gelijk aan of hoger dan Nederlandse en Amerikaanse, voor leeftijd en sekse aangepaste, normscores. De betere scores voor behandeling kunnen het gevolg zijn van een hoge sociaal-economische status (SES) van de patiënten, aangezien SES positief geassocieerd is met deelname aan screening en met de incidentie van prostaatkanker.

Hoofdstuk 5 gaat over hetzelfde cohort van mannen met gelokaliseerde prostaatkanker dat reeds beschreven werd in hoofdstuk 4. We maten angst (STAI-State) en symptomen van depressie (CES-D) na diagnose, maar voor behandeling tot 5-jaar follow-up. Verder gingen we na of angstscores bij inclusie voorspellend waren voor angst en symptomen van depressie bij 1 jaar follow-up. Respondenten werden onderverdeeld naar behandeling (prostatectomie versus radiotherapie) en angstniveau (hoog versus laag angstniveau). Voor behandeling werd 28% van de patiënten geclassificeerd als 'hoog angstniveau'. De gemiddelde angstscores in de groepen met hoog angstniveau daalden significant na behandeling in de richting van minder angst. Een jaar na behandeling rapporteerde 27% van de geopereerde mannen een klinisch niveau van depressie tegen 20% in de algemene populatie. De angstscores bij inclusie voorspelden 71% van het hoge angstniveau bij 1 jaar follow-up en 60% van de klinische niveaus van depressie. Wij raden verder onderzoek aan om tot een betere voorspelling te kunnen komen, bijv. door ziektekenmerken zoals de Gleason-score mee te wegen of door andere meetinstrumenten te gebruiken.
Omdat het gediagnosticeerd worden met prostaatkanker een grote impact kan hebben op de psychische gezondheid van patiënten, raden wij clinici aan om vroege ontdekking te betrachten van patiënten die het risico lopen langdurig angst en gevoelens van depressie te ervaren en om hen mentale steun te kunnen bieden.

Hoewel behandeling van primaire prostaatkanker vaak resulteert in suboptimale plas-, darm- en/of erectiele functies, rapporteren patiënten opvallend genoeg hoge generieke KvL scores. Deze discrepantie tussen ziekte-specifieke en generieke resultaten roept de vraag op welke betekenis patiënten hechten aan de diagnose van prostaatkanker en de bijeffecten die zij na behandeling ervaren. Wij onderzochten dit fenomeen middels kwalitatieve interviews (hoofdstuk 6), een waarderingsstudie (hoofdstuk 7) en een cohort studie naar de impact van prostaatkanker diagnose op de psychische gezondheid van betreffende mannen (hoofdstuk 8).

Hoofdstuk 6 beschrijft een kwalitatieve studie waarin we 2 mechanismen onderzocht hebben die mogelijk de discrepantie tussen ziekte-specifieke en generieke resultaten kunnen verklaren: generieke KvL-maten zijn ongevoelig voor erectie-, plas- en darmklachten of patiënten hebben hun veranderde gezondheid geaccepteerd ('response shift'). Wij voerden semi-gestructureerde interviews uit met 33 prostaatkankerpatiënten, die sinds hun behandeling erectie-, plas- en/of darmklachten ervaren. Wij vroegen 18 mannen naar hun mening over hun gezondheid, hun KvL en de relatie met prostaatkankerbehandeling. De overige 15 mannen vroegen wij een vragenlijst in te vullen en onderwijl hardop te praten. Wij observeerden hun gedrag, bijv. uitdrukkingen van onbegrip of verwarring, en vroegen hen om commentaar bij de vragenlijst en de items. We bemerkten dat patiënten ertoe neigen hun seksuele (dys)functioneren te trivialiseren onder verwijzing naar hun leeftijd. Zij doen uitspraken als 'Ik was mijn hele leven een erg actief seksueel mens, maar nu heb ik zo'n leeftijd bereikt dat ik me realiseer dat het niet het enige is in de wereld'. We constateerden dat geïnterviewden zich bewust zijn van hun erectie-, plas- en darmklachten, maar dat zij ze desondanks niet in overweging namen bij het invullen van KvL-maten, omdat zij hun klachten niet beschouwden als aspecten van gezondheid. Wij concludeerden dat generieke KvL-maten die naar 'gezondheid' verwijzen zodoende de impact van erectie-, plas- en darmklachten niet kunnen weergeven. Deze bevinding legde een oorzaak van de ongevoeligheid van generieke maten bloot. Verder bleek 'response shift' aanwezig te zijn: veel patiënten accepteerden de bijeffecten na behandeling als een onvermijdelijke consequentie van het behandeld zijn voor prostaatkanker, een aandoening die zij als potentieel levensbedreigend beschouwen. Patiënten hebben de bijeffecten op de koop toegenomen.

In **Hoofdstuk 7** onderzochten we of mannen na prostaatkankerbehandeling erectie-, plas- en darmklachten anders beoordelen dan mannen zonder prostaatkanker. We vergeleken hoe mannen met (n=54) en even oude mannen zonder prostaatkanker (n=53) 5 gezondheidstoestanden waardeerden, die vaak voorkomen na prostaatkankerbehandeling. Onze hypothese was dat patiënten zich wellicht hadden aangepast aan hun veranderde gezondheid en zij daardoor de gezondheidstoestanden hoger zouden waarderen dan mannen zonder prostaatkanker.

De waarderingen werden gemeten door middel van een computerinstrument. We pasten Visueel Analoge Schalen (VAS) toe en een onpersoonlijke versie van Time Trade-Off (TTO). De waarderingen leidden in beide groepen en volgens beide methodes tot een identieke rangorde met uitzondering van 1 gezondheidstoestand. De gemiddelde waarderingen van

mannen met en zonder prostaatkanker kwamen overeen behalve bij één VAS waardering. Gemiddeld waren de TTO waarderingen hoger dan de VAS waarderingen, hetgeen eerdere bevindingen van anderen bevestigt. Bij toepassing van een onpersoonlijke versie van TTO waren patiënten en gezonde mannen het eens over welke gezondheidstoestand beter was dan een andere. Onze resultaten suggereren dat er geen bezwaar bestaat tegen het gebruik van 'population-based' utiliteiten in de economische evaluatie van behandeling van primaire prostaatkanker.

Hoofdstuk 8 beschrijft de psychische gevolgen van prostaatkanker diagnose na de PSA-test. Voor de screening vulden 3.800 deelnemers aan de ERSPC prostaatkankerscreening studie een vragenlijst in. Van de 82 mannen die vervolgens met prostaatkanker gediagnosticeerd werden gingen 52 akkoord met het invullen van nog 2 vragenlijsten. Na de diagnose daalde bij hen de gemiddelde waardering van de eigen gezondheid van 80 naar 75 op een schaal van 0-100, terwijl deze mannen geen pijn of ander symptoom van prostaatkanker ervaarden. Ook de psychische gezondheid verslechterde significant. Zes maanden later, toen in een meerderheid van de mannen behandeling was ingezet, verbeterden de psychische en zelf-gerapporteerde algemene gezondheid en verschilden niet meer significant van de scores voor diagnose. Non-respons lijkt deze resultaten niet te hebben beïnvloed. Dit is de eerste studie met een meting van KvL in prostaatkankerpatiënten voor diagnose. We concludeerden dat de diagnose van prostaatkanker na een PSA-test een significant negatieve impact had op de psychische en zelf-gerapporteerde algemene gezondheid. De klinische implicatie hiervan is het advies aan clinici om hun kennis over de algemeen gunstige prognose te delen met gediagnosticeerde mannen. De methodologische implicatie is dat het beschouwen van een KvL-meting na prostaatkankerdiagnose als 'baseline' beschouwen, kan leiden tot een onderschatting van de psychische en zelf-gerapporteerde algemene gezondheid.

De resultaten van eerder beschreven studies, namelijk betreffende KvL in de fases van screening, van primaire behandeling en van gevorderde ziekte, dienen onder andere voor het schatten van utiliteiten voor de kosten-utiliteiten analyse. In **hoofdstuk 9** toonden we aan dat toepassen van het algemene model om de kosten-utiliteiten van bevolkingsonderzoek naar prostaatkanker te schatten in combinatie met de resultaten van de 3 empirische gezondheidstoestanden zal leiden tot onderschatting van de ongunstige gezondheidseffecten, die onvermijdelijk aan prostaatkanker screening verbonden zijn. Dit kan bijv. veroorzaakt zijn door niet-gezondheidseffecten van de screening op zichzelf ('proces effecten') en door

aanpassingen in de perceptie van de eigen situatie door patiënten die curatieve primaire therapie ondergaan hebben ('response shift'). Deze resultaten dwingen ons om de toepasbaarheid van gedeeltes van de gangbare methodologie van het meten van voorkeuren te heroverwegen wat betreft de evaluatie van screening. Mogelijke richtingen voor oplossingen worden aangegeven, zoals het gebruik maken van experts of andere buitenstaanders om vignetten te beoordelen die gebaseerd zijn op empirische beschrijvingen van patiënten.

In **hoofdstuk 10** worden de in de introductie gestelde onderzoeksvragen beantwoord. Mogelijke implicaties van onze studie resultaten voor behandeling en screening worden beschreven. Onze longitudinale studie bevestigt eerdere bevindingen van of cross-sectionele studies: primaire prostaat kanker behandeling leidt tot plas-, darm- en erectieklachten in een aanzienlijk deel van de behandelde mannen. Tegelijkertijd is het onzeker of de betreffende man baat zal hebben bij de behandeling. De invloed van de onzekere baten op voorkeuren voor screeningsprogramma's op kanker zou onderzocht moeten worden, bijv. door zgn. 'discrete choice' experimenten. In het ideale geval wordt behandeling beperkt tot diegenen die er waarschijnlijk belang bij zullen hebben. Toekomstig onderzoek is nodig om de selectie van die mannen te verbeteren, bijv. door het vaststellen van prognostische kenmerken. Een andere manier om de last van behandeling te verminderen is door te zoeken naar nieuwe, minder invasieve behandelingen voor vroeg gediagnosticeerde mannen, die weinig bijwerkingen met zich meebrengen.

Een methodologische implicatie van onze studie resultaten is het beschouwen van een KvL meting na prostaatkanker diagnose als 'baseline' tot een onderschatting kan leiden van de psychische en zelf gerapporteerde gezondheid van patiënten. Verder bevestigen onze resultaten de constatering dat ziekte-specifieke en generieke maten niet zozeer verwisselbaar zijn maar complementair. Wij raden aan ze beiden te gebruiken.

Tenslotte stellen we vast dat het toepassen van screening door huisartsen en andere artsen niet geoorloofd is zolang niet vast staat dat vroege opsporing gevolgd door adequate behandeling leidt tot daling van prostaatspecifieke mortaliteit. Terwijl de commercie de PSA-test aanraadt, zou er op zijn minst onbevooroordeelde informatie over mogelijke gevolgen van vroege opsporing en behandeling beschikbaar moeten zijn voor mannen die de PSA-test overwegen.

References

Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. (1998) Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 51(11): 1055-68.

Adami HO, Baron JA, Rothman KJ (1994) Ethics of a prostate cancer screening trial. Lancet 343(8903): 958-60.

Albertsen PC, Hanley JA, Fine J (2005) 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 293(17): 2095-101.

Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D, et al. (2005) Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 97(6): 433-8.

Bacon CG, Giovannucci E, Testa M, Kawachi I (2001) The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. J Urol 166(5): 1804-10.

Bacon CG, Giovannucci E, et al. (2002) The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. Cancer 94(3): 862-71.

Balderson N, Towell T (2003) The prevalence and predictors of psychological distress in men with prostate cancer who are seeking support. Br J Health Psychol 8(Pt 2): 125-34.

Baron J, Asch DA, Fagerlin A, Jepson C, Loewenstein G, Riis J, et al. (2003) Effect of assessment method on the discrepancy between judgments of health disorders people have and do not have: a web study. Med Decis Making 23(5): 422-34.

van der Bij AK, de Weerd S, Cikot RJ, Steegers EA, Braspenning JC (2003) Validation of the dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes. Community Genet 6(2): 84-7.

Birnie E, Bossuyt PMM, Bonsel GJ. (2000) Towards a framework for evaluation of non-health outcomes. Measurement and implications for cost-effectiveness analysis. Fetal monitoring at home in high-risk pregnancy (chapter in thesis). W. Monincx and E. Birnie. Amsterdam, University of Amsterdam.

Blanker MH, Driessen LF, Bosch JL, Bohnen AM, Thomas S, Prins A, et al. (2002) Health status and its correlates among Dutch community-dwelling older men with and without lower urogenital tract dysfunction. Eur Urol 41(6): 602-7.

Bouma J, Ranchor AV, Sanderman R, van Sonderen E. (1995). Het meten van symptomen van depressie met de CES-D [Measuring symptoms of depression using the CES-D]. Groningen, Rijksuniversiteit Groningen, Noordelijk Centrum voor Gezondheidsvraagstukken.

Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. (1990) Whose utilities for decision analysis? Med Decis Making 10(1): 58-67.

Brenner H, Arndt V (2005) Long-term survival rates of patients with prostate cancer in the prostate-specific antigen screening era: population-based estimates for the year 2000 by period analysis. J Clin Oncol 23(3): 441-7.

Brooks R. (1996) EuroQol: the current state of play. Health Policy;37(1):53-72.

Cancer statistics, a presentation from the American Cancer Society. (2004). http://www.cancer.org/downloads/PRO/Cancer%20Statistics%202004.ppt

Carlson LE, Angen M, Cullum J, Goodey E, Koopmans J, Lamont L, et al. (2004) High levels of untreated distress and fatigue in cancer patients. Br J Cancer 90(12): 2297-304.

Chapman GB, Elstein AS, Kuzel TM, Sharifi R, Nadler RB, Andrews A, et al. (1998) Prostate cancer patients' utilities for health states: how it looks depends on where you stand. Med Decis Making 18(3): 278-86.

Chapple A, Ziebland S, Shepperd S, Miller R, Herxheimer A, McPherson A. (2002) Why men with prostate cancer want wider access to prostate specific antigen testing: qualitative study. BMJ 325(7367): 737.

Clark JA, Rieker P, Propert KJ, Talcott JA. (1999) Changes in quality of life following treatment for early prostate cancer. Urology 53(1): 161-8.

Cohen J (1977) Statistical power analysis for the behavioral sciences.New York, Academic Press.

de Haes JC, de Koning HJ, van Oortmarssen GJ, van Agt HM, de Bruyn AE, van Der Maas PJ. (1991) The impact of a breast cancer screening programme on quality-adjusted life-years. Int J Cancer 49(4): 538-44.

de Koning HJ, Liem MK, Baan CA, Boer R, Schroder FH, Alexander FE (2002) Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPC) trial. Int J Cancer 2002;98(2):268-73.

de Koning HJ, Auvinen A, Berenguer Sanchez A, Calais da Silva F, Ciatto S, Denis L, et al. (2002) Large-scale randomized prostate cancer screening trials: Program performances in the European randomized screening for prostate cancer trial and the prostate, lung, colorectal and ovary cancer trial. Int J Cancer 97(2): 237-44.

De Wit GA, Busschbach JJ, De Charro FT (2000) Sensitivity and perspective in the valuation of health status: whose values count? Health Econ 9(2): 109-26.

Dolan P (1997) Modeling valuations for EuroQol health states. Med Care 35(11): 1095-108.

Dolan P, Sutton M. (1997) Mapping visual analogue scale health state valuations onto standard gamble and time trade-off values. Soc Sci Med 44(10): 1519-30.

Donaldson C, Shackley P. (1997) Does "process utility" exist? A case study of willingness to pay for laparoscopic cholecystectomy. Soc Sci Med 44(5): 699-707.

Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. (2002) Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. BMJ 325(7367): 766-70.

Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, et al. (2003) Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 95(12): 868-78.

Drummond MF, O'Brien B, Stoddart GL, Torrance GW (1997) Methods for the Economic evaluation of Health Care Programmes. Oxford, Oxford University Press.

Elstein AS, Chapman GB, Chmiel JS, Knight SJ, Chan C, Nadler RB, et al. (2004) Agreement between prostate cancer patients and their clinicians about utilities and attribute importance. Health Expect 7(2): 115-25.

Essink-Bot ML, Bonsel GJ, van der Maas PJ (1990) Valuation of health states by the general public: feasibility of a standardized measurement procedure. Soc Sci Med 31(11): 1201-6.

Essink-Bot ML (1995) Health status as a measure of outcome of disease and treatment. PhD thesis. Department of public health. Rotterdam, Erasmus University of Rotterdam.

Essink-Bot ML, de Koning HJ, Nijs HG, Kirkels WJ, van der Maas PJ, Schroder FH.(1998). Short-term effects of population-based screening for prostate cancer on health-related quality of life. J Natl Cancer Inst 90(12): 925-31.

Essink-Bot ML, Korfage IJ, de Koning HJ (2003) The impact of radical prostatectomy and primary radiotherapy for localised prostate cancer on quality of life. (pp. 14-21) In : Proceedings of the PACIOU VII Symposium. D. Newling and C. Bangma. Lancaster LA1 4XF, UK, Parthenon Publishing.

Etzioni R, Penson DF, Legler JM, di Tommaso D, Boer R, Gann PH, et al. (2002) Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 94(13): 981-90.

Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. (2002) Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care 2002;40(2):113-28.

Folkman S, Moskowitz JT. (2000). Positive affect and the other side of coping. Am Psychol 55(6): 647-54.

Fowler FJ, Jr., Barry MJ, Lu-Yao G, Wasson JH, Bin L. (1996) Outcomes of external-beam radiation therapy for prostate cancer: a study of Medicare beneficiaries in three surveillance, epidemiology, and end results areas. J Clin Oncol 14(8): 2258-2265.

Galbraith ME, Ramirez JM, Pedro LW (2001) Quality of life, health outcomes, and identity for patients with prostate cancer in five different treatment groups. Oncol Nurs Forum 28(3): 551-60.

Ganz PA, Litwin MS (2001) Prostate cancer: the price of early detection. J Clin Oncol 19(6): 1587-8.

Gilbert DT, Pinel EC, Wilson TD, Blumberg SJ, Wheatley TP (1998) Immune neglect: a source of durability bias in affective forecasting. J Pers Soc Psychol 75(3): 617-38.

Gohagan JK, Prorok PC, Hayes RB, Kramer BS (2000) The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 21(6 Suppl): 251S-272S.

Gold M. (1996) Cost-effectiveness in health and medicine. New York, N.Y.: Oxford University Press.

Gyrd-Hansen D, Sogaard J (2001). Analysing public preferences for cancer screening programmes. Health Econ 10(7): 617-34.

Hak T, Van der Veer K, Jansen H (2004) The Three-Step Test-Interview (TSTI): An observational instrument for pretesting self-completion questionnaires. ERIM Report ERS-2004-029-ORG. Rotterdam, Erasmus Research Institute of Management.

Hamilton AS, Stanford JL, Gilliland FD, Albertsen PC, Stephenson RA, Hoffman RM, et al. (2001) Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. J Clin Oncol 19(9): 2517-26.

Hermanek P, Sobin LH (1992) TNM Classification of Malignant Tumours. UICC International Union Against Cancers. Berlin, Springer-Verlag.

Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. (2002) A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 347(11): 781-9.

Homs MY, Essink-Bot ML, Borsboom GJ, Steyerberg EW, Siersema PD (2004) Quality of life after palliative treatment for oesophageal carcinoma -- a prospective comparison between stent placement and single dose brachytherapy. Eur J Cancer 40(12): 1862-71.

Incrocci L, Madalinska JB, Essink-Bot ML, Van Putten WL, Koper PC, Schroder FH (2001) Sexual functioning in patients with localized prostate cancer awaiting treatment. J Sex Marital Ther 27(4): 353-63.

Jorm AF (2000) Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. Psychol Med 30(1): 11-22.

Joung IM, van de Mheen H, Stronks K, van Poppel FW, Mackenbach JP (1994) Differences in self-reported morbidity by marital status and by living arrangement. Int J Epidemiol 23(1): 91-7.

Korfage IJ, Essink-Bot ML, Kirkels WJ, de Koning HJ, Schröder FH (2002) Long-term health-related quality of life in localized prostate cancer. Qual Life Res 11(7): 623 (Abstract).

Korfage IJ, Essink-Bot ML, Madalinska JB, Kirkels WJ, Litwin MS, de Koning HJ (2003) Measuring disease specific quality of life in localized prostate cancer: the Dutch experience. Qual Life Res, 12(4), 459-464.

Korfage IJ, Essink-Bot ML, Borsboom GJJM, Madalinska JB, Kirkels WJ, Habbema JDF, et al. (2005) Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 116(2): 291-6.

Korfage IJ, Hak T, de Koning HJ, Essink-Bot ML (2005) Patients' perceptions of the side-effects of prostate cancer treatment - a qualitative interview study. submitted.

Krabbe PF, Essink-Bot ML, Bonsel GJ (1997) The comparability and reliability of five health-state valuation methods. Soc Sci Med 45(11): 1641-52.

Krahn M, Ritvo P, Irvine J, Tomlinson G, Bremner KE, Bezjak A, et al. (2003) Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. Med Care 41(1): 153-64.

Krause N, Jay K (1994) What do global self-rated health items measure? Med Care 32(9): 930-42.

Lee WR, Hall MC, McQuellon RP, Case LD, McCullough DL (2001) A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy. Int J Radiat Oncol Biol Phys 51(3): 614-23.

Lepore SJ, Eton DT (2000) Response shifts in prostate cancer patients: an evaluation of suppressor and buffer models. Adaptation to changing health, response shift in quality-of-life research. C. E. Schwartz and M. A. G. Sprangers. Washington D.C.

Lintz K, Moynihan C, Steginga S, Norman A, Eeles R, Huddart R, et al. (2003) Prostate cancer patients' support and psychological care needs: Survey from a non-surgical oncology clinic. Psychooncology 12(8): 769-83.

Litwin MS, Lubeck DP, Spitalny GM, Henning JM, Carroll PR (2002) Mental health in men treated for early stage prostate carcinoma: a posttreatment, longitudinal quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. Cancer 95(1): 54-60.

Litwin MS, Melmed GY, Nakazon T (2001) Life after radical prostatectomy: a longitudinal study. J Urol 166(2): 587-92.

Litwin MS, Pasta DJ, Yu J, Stoddard ML, Flanders SC (2000) Urinary function and bother after radical prostatectomy or radiation for prostate cancer: a longitudinal, multivariate quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. J Urol 164(6): 1973-7.

Litwin MS, Flanders SC, Pasta DJ, Stoddard ML, Lubeck DP, Henning JM (1999) Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 54(3): 503-8.

Litwin MS (1999a) Examining health-related quality of life in men treated for prostate cancer. World J Urol 17(4): 205-10.

Litwin MS (1999b) Health related quality of life in older men without prostate cancer. J Urol 161(4): 1180-4.

Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH (1998) The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure.

Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Leach GE, et al. (1995) Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 273(2): 129-135.

Liu L, Cozen W, Bernstein L, Ross RK, Deapen D (2001) Changing relationship between socioeconomic status and prostate cancer incidence. J Natl Cancer Inst 93(9): 705-9.

Lubeck DP, Litwin MS, Henning JM, Stoddard ML, Flanders SC, Carroll PR (1999) Changes in health-related quality of life in the first year after treatment for prostate cancer: results from CaPSURE. Urology 53(1): 180-6.

Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH (2001a). Health-related quality of life in patients with screen-detected versus clinically diagnosed prostate cancer preceding primary treatment. Prostate 46(2): 87-97.

Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH (2001b) Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. J Clin Oncol 19(6): 1619-28.

Mallinson S (2002) Listening to respondents: a qualitative assessment of the Short-Form 36 Health Status Questionnaire. Soc Sci Med 54(1): 11-21.

Marteau TM, Dormandy E, Michie S (2001) A measure of informed choice. Health Expect 4(2): 99-108.

McColl E, Han SW, Barton JR, Welfare MR (2004) A comparison of the discriminatory power of the Inflammatory Bowel Disease Questionnaire and the SF-36 in people with ulcerative colitis. Qual Life Res(13): 805-811.

Millar K, Jelicic M, Bonke B, Asbury AJ (1995) Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. Br J Anaesth 74(2): 180-3.

Miller AB, Madalinska JB, Church T, Crawford D, Essink-Bot ML, Goel V, et al. (2001) Health-related quality of life and cost-effectiveness studies in the European randomised study of screening for prostate cancer and the US Prostate, Lung, Colon and Ovary trial. Eur J Cancer 37(17): 2154-60.

Montazeri A, Hole DJ, Milroy R, McEwen J, Gillis CR (2004) Does knowledge of cancer diagnosis affect quality of life? A methodological challenge. BMC Cancer 4(1): 21.

Nordin K, Berglund G, Glimelius B, Sjoden PO (2001) Predicting anxiety and depression among cancer patients: a clinical model. Eur J Cancer 37(3): 376-84.

Norman GR, Sridhar FG, Guyatt GH, Walter SD (2001) Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. Med Care 39(10): 1039-47.

Oliffe J (2005) Constructions of masculinity following prostatectomy-induced impotence. Soc Sci Med, 60(10), 2249-2259.

Parkin DM, Bray FI, Devesa SS (2001) Cancer burden in the year 2000. The global picture. Eur J Cancer 37 Suppl 8: S4-66.

Penson DF, Litwin MS, Aaronson NK (2003) Health related quality of life in men with prostate cancer. J Urol 169(5): 1653-61.

Penson D, Feng Z, Kuniyuki A, McClarren D, Albertsen PC, Deapen D, et al. (2003) General quality of life 2 years following treatment for prostate cancer: what influences outcomes? Results from the prostate cancer outcomes study. J Clin Oncol 21(6): 1147-54.

Pietrow PK, Parekh DJ, Smith JA, Jr., Shyr Y, Cookson MS (2001) Health related quality of life assessment after radical prostatectomy in men with prostate specific antigen only recurrence. J Urol 166(6): 2286-90.

van der Ploeg HM, Defares PB, Spielberger CD (1980) Validation of the state-traite anxiety inventory (Handleiding bij de zelfbeoordelingsvragenlijst) (in Dutch). Ned T Psychologie 35: 243-9.

Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. (2004) Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 96(18): 1358-67.

Potosky AL, Legler J, Albertsen PC, Stanford JL, Gilliland FD, Hamilton AS, et al. (2000) Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst 92(19): 1582-92.

Radloff LS (1977) The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1(3): 385-401.

Roobol MJ, Kirkels WJ, Schroder FH (2003) Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). BJU Int 92 Suppl 2: 48-54.

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49(6): 822-30.

Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al. (2003) The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with with prostate cancer. Cancer 97(11): 2910-8.

Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC (1998) Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 82(10): 1904-8.

Sackett DL, Torrance GW (1978) The utility of different health states as perceived by the general public. J Chronic Dis 31(11): 697-704.

Schapira MM, Lawrence WF, Katz DA, McAuliffe TL (2001) Effect of treatment on quality of life among men with clinically localized prostate cancer. Med Care 39(3): 243-53.

Schwartz CE, Sprangers MAG (2000) Adaptation to changing health : response shift in quality-of-life research. Washington, DC, American Psychological Association.

Schwartz CE, Sprangers MA (1999) Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 48(11): 1531-48.

Sculpher M, Bryan S, Fry P, de Winter P, Payne H, Emberton M (2004) Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. BMJ 328(7436): 382.

Sesti A (2000) State Trait Anxiety Inventory (STAI) in Medication Clinical Trials. Quality of Life Newsletter 25: 16-7.

Siston AK, Knight SJ, Slimack NP, Chmiel JS, Nadler RB, Lyons TM, et al. (2003) Quality of life after a diagnosis of prostate cancer among men of lower socioeconomic status: results from the Veterans Affairs Cancer of the Prostate Outcomes Study. Urology 61(1): 172-8.

Slob AK, Blom JH, van der Werff ten Bosch JJ (1990) Erection problems in medical practice: differential diagnosis with relatively simple method. J Urol 143(1): 46-50.

Spielberger CD, Vagg PR (1984) Psychometric properties of the STAI: a reply to Ramanaiah, Franzen, and Schill. J Pers Assess 48(1): 95-7.

Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48(11): 1507-15.

Staff I, Salner A, Bohannon R, Panatieri P, Maljanian R (2003) Disease-specific symptoms and general quality of life of patients with prostate carcinoma before and after primary three-dimensional conformal radiotherapy. Cancer 98(11): 2335-43.

Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. (2000) Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 283(3): 354-60.

Staquet MJ, Hays RD, Fayers PM (1998) Quality of Life Assessment in Clinical Trials, Methods and Practice, Oxford University Press.

Steginga SK, Occhipinti S, Gardiner RA, Yaxley J, Heathcote P (2004) Prospective study of men's psychological and decision-related adjustment after treatment for localized prostate cancer. Urology 63(4): 751-6.

Steginga SK, Occhipinti S, Gardiner RA, Yaxley J, Heathcote P (2002) Making decisions about treatment for localized prostate cancer. BJU Int 89(3): 255-60.

Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, De Haes HJ (1996) The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? Int J Technol Assess Health Care 12(2): 291-8.

Stouthard M, Essink-Bot ML, Bonsel GJ (2000) Methodology. Disability weights for diseases: a modified protocol and results for a Western European region. Eur J Public Health 10: 24-30.

Talcott JA, Manola J, Clark JA, Kaplan I, Beard CJ, Mitchell SP, et al. (2003) Time course and predictors of symptoms after primary prostate cancer therapy. J Clin Oncol 21(21): 3979-86.

Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, et al. (1998) Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. J Clin Oncol 16(1): 275-83.

Ubel PA, Loewenstein G, Jepson C (2003) Whose quality of life? A commentary exploring discrepancies between health state evaluations of patients and the general public. Qual Life Res 12(6): 599-607.

Ware JE, Kosinski M (2001) Interpreting SF-36 summary health measures: a response. Qual Life Res 10(5): 405-13; discussion 415-20.

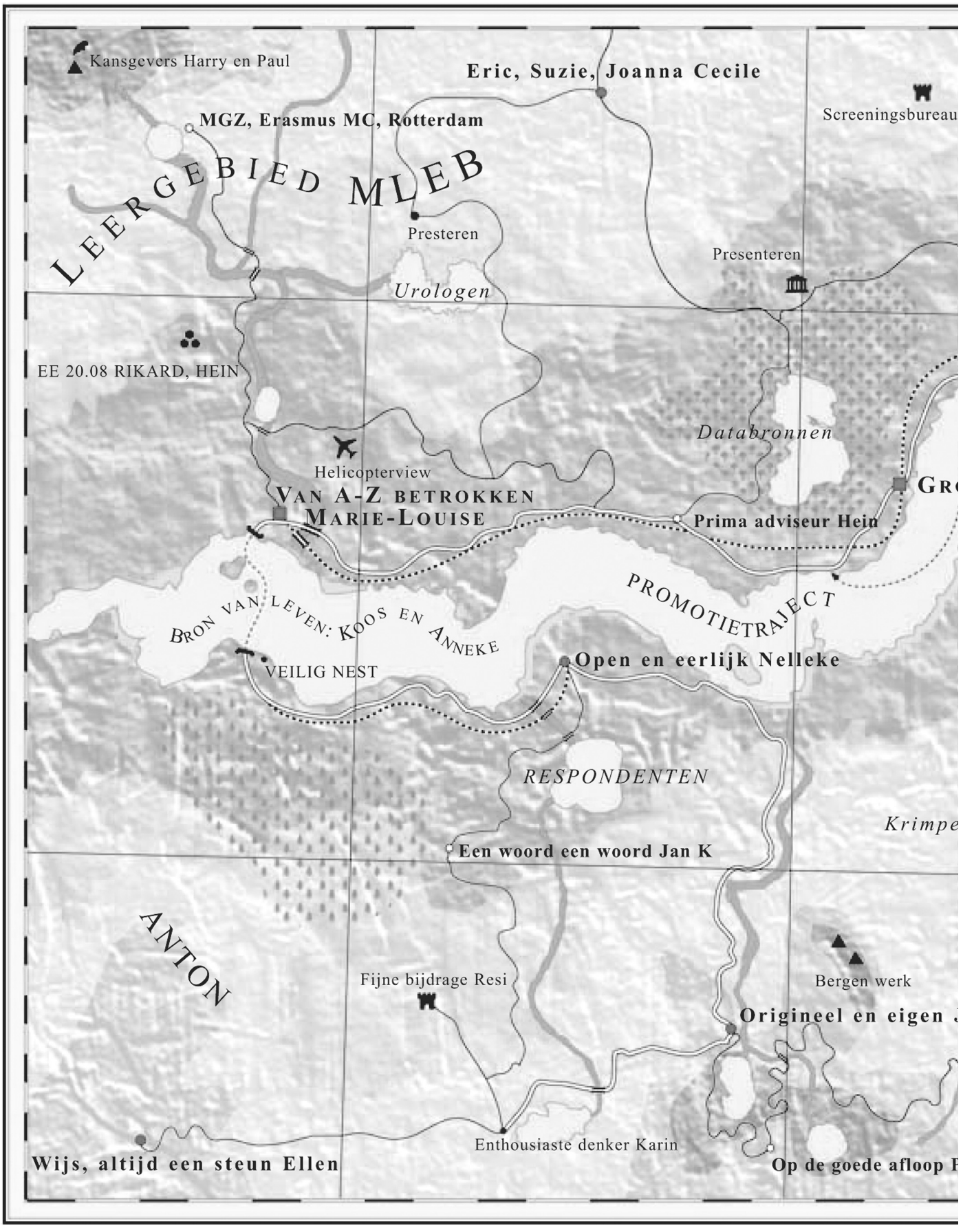
Ware JEJ, Snow KK, Kosinski M, Gandek BG (1993) SF-36 health survey: manual and interpretation guide, Boston, MA : The Health Institute, New England Medical Center.

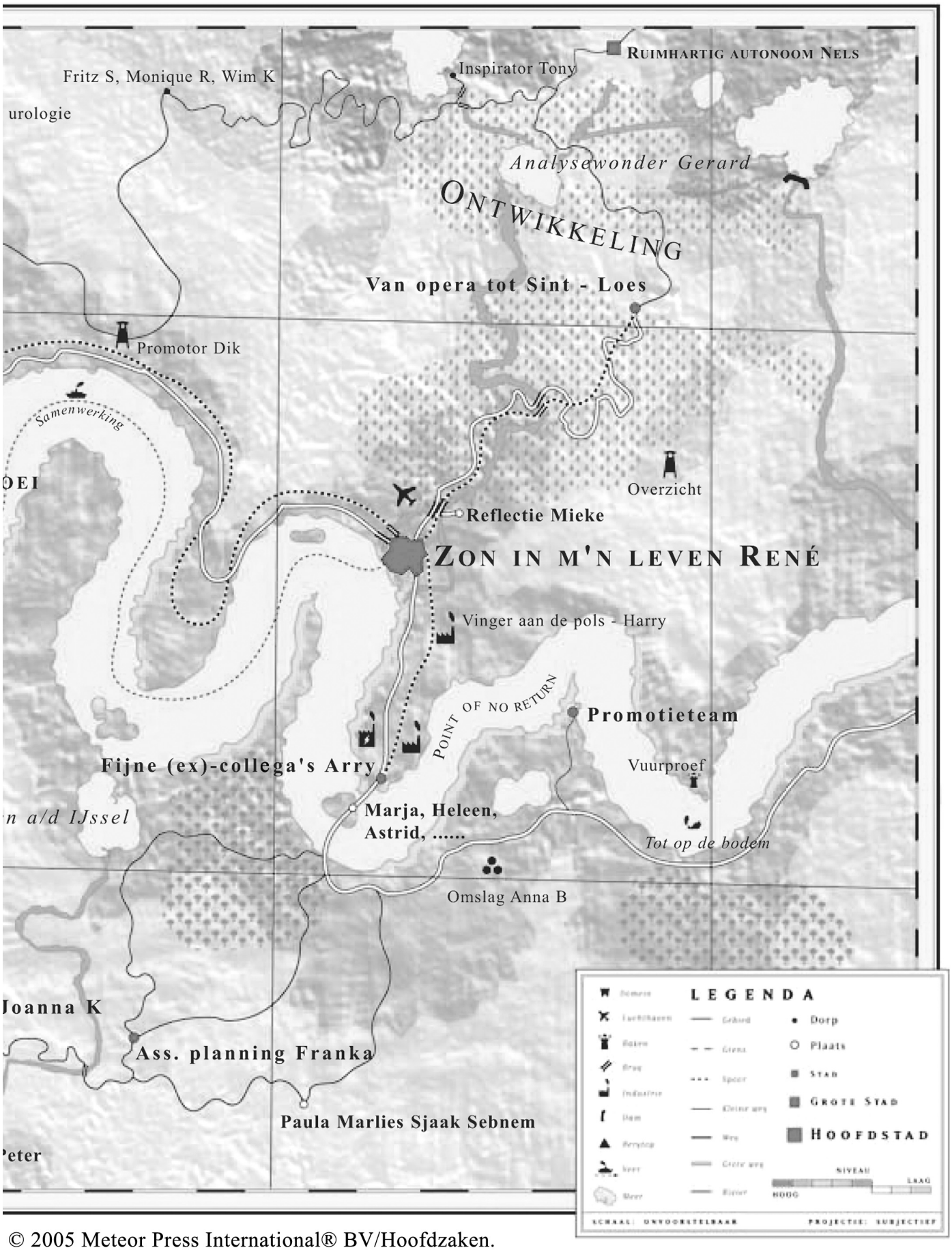
Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG (2000) Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 56(6): 899-905.

Weinstein MC, Stason WB. (1977) Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 296(13):716-21.

Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 67: 361-370.

Dankwoord





Curriculum vitae

Ida Korfage werd geboren op 11 oktober 1963 in Pijnacker. Ze behaalde in 1982 haar VWO diploma aan het Sint Janscollege in Den Haag. Na het afronden van de HBO-Verpleegkunde te Leiden werkte zij gedurende 13 jaar als verpleegkundige, o.a. als wijkverpleegkundige in Den Haag. In 1994 behaalde zij haar doctoraal bul algemene economie aan de faculteit van de economische wetenschappen van de Erasmus Universiteit te Rotterdam. Sinds 1997 werkt zij op de afdeling Maatschappelijke Gezondheidszorg van ErasmusMC, Universitair Medisch Centrum Rotterdam. De eerste jaren werkte zij aan kosten-effectiviteitsanalyses, later voerde ze een studie naar screening op scoliose uit en was ze betrokken bij de evaluatie van de Wet op het Bevolkingsonderzoek (WBO). In 2002 rondde zij de post-doctorale opleiding epidemiologie af aan het Netherlands Institute for Health Sciences van het ErasmusMC. In 2000 startte Ida haar werkzaamheden aan het onderzoek dat is beschreven in dit proefschrift: kwaliteit van leven bij prostaatkanker. Sinds 1 juli 2005 voert zij op de afdeling Maatschappelijke Gezondheidszorg een studie uit naar kwaliteit van leven effecten van screening op baarmoederhalskanker.