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CLINICAL INVESTIGATION

10-YEAR SURVIVAL AND QUALITY OF LIFE IN PATIENTS WITH HIGH-RISK $_pN_0$ PROSTATE CANCER FOLLOWING DEFINITIVE RADIOTHERAPY

ARNE BERG, M.D.,* WOLFGANG LILLEBY, M.D., PH.D.,† ØYVIND SVERRE BRULAND, M.D., PH.D.,*† AND SOPHIE DOROTHEA FOSSÅ, M.D., PH.D.*†

*Faculty of Medicine, University of Oslo, Oslo, Norway; and †Department of Oncology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway

Purpose: To evaluate long-term overall survival (OS), cancer-specific survival (CSS), clinical progression–free survival (cPFS), and health-related quality of life (HRQoL) following definitive radiotherapy (RT) given to $T_{1\text{-}4p}N_0M_0$ prostate cancer patients provided by a single institution between 1989 and 1996.

Methods and Materials: We assessed outcome among 203 patients who had completed three-dimensional conformal RT (66 Gy) without hormone treatment and in whom staging by lymphadenectomy had been performed. OS was compared with an age-matched control group from the general population. A cross-sectional, self-report survey of HRQoL was performed among surviving patients.

Results: Median observation time was 10 years (range, 1–16 years). Eighty-one percent had high-risk tumors defined as $T_{3\text{-}4}$ or Gleason score (GS) ≥7B (4+3). Among these, 10-year OS, CSS, and cPFS rates were 52%, 66%, and 39%, respectively. The corresponding fractions in low-risk patients ($T_{1\text{–}2}$ and GS ≤7A [3+4]) were 79%, 95%, and 73%, respectively. Both CSS and cPFS were predicted by GS and T-classification; OS was associated with GS only. High-risk, but not low-risk, patients had reduced OS compared with the general population ($p < 0.0005$). When pelvis-related side effects were included in multivariate analyzes together with physical function and pain, sexual, urinary, and bowel function were not independently associated with self-reported global quality of life.

Conclusions: Despite surgically proven $_pN_0$, RT with dosage <70 Gy as monotherapy does not give satisfactory CSS rates after 10 years in patients with $T_{3\text{-}4}$ or GS ≥7B.

Adverse effects, Lymphadenectomy, Prostate cancer, Quality of life, Radiotherapy.

INTRODUCTION

Curatively intended definitive radiotherapy (RT) for nonmetastatic prostate cancer (PC) was introduced at our institution in 1989. Initially this was primarily a treatment modality for patients who were regarded unsuitable for radical prostatectomy due to extracapsular extension of tumor ($T_{3\text{-}4}$) or other concerns such as comorbidity, age, or obesity. To improve staging and to avoid treatment of patients less likely to be cured, such therapy was only offered to those who had proven lymph node negative stage ($_pN_0$).

In the late 1980s and early 1990s, many institutions such as ours considered a target dose of 65–70 Gy to provide a reasonable chance of cure without unacceptable risk of pelvis-related adverse effects in patients with locally advanced tumors. Today a target dose of >70 Gy and adjuvant hormone treatment (HT) are recommended to these patients (1, 2).

The natural course of PC is slow, and most prospective studies therefore evaluate biochemical relapse (prostate specific antigen [PSA]) as a surrogate-marker for clinical progression and death. However, the impact of PSA-defined progression on clinical progression and mortality is not fully understood, and many patients might experience PSA changes without any subsequent clinical symptoms during their lifetime (3). Therefore, long-term studies with robust clinical endpoints that address health-related quality of life (HRQoL) are urgently needed, even though this covers treatment strategies applied 1 to 2 decades ago that do not always fulfill today's requirements of optimal RT-techniques and adjuvant treatment.

In 2003, we published our early experience on clinical outcome in patients receiving RT as monotherapy between 1989 and 1996 (4). We now present mature 10-year survival rates from the same cohort just described. We have also performed

Reprint requests to Arne Berg, M.D., University of Oslo, Faculty Division, Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway. Tel: (+47) 22934000; Fax: (+47) 22509199; E-mail: arne.berg@radiumhospitalet.no

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a self-report survey on HRQoL among patients who were still alive at the end of the observation period.

METHODS AND MATERIALS

Patients

The cohort contains all patients who were treated by definitive RT between 1989 and February 1996 at the Norwegian Radium Hospital (now called the Rikshospitalet-Radiumhospitalet Medical Center). Clinical staging included digital rectal examination, bone scan, and bilateral pelvic lymphadenectomy with resection of the obturatory lymph nodes, the latter preferably done at local hospitals before referral to our center.

All prostate tumor biopsies except four were centrally revised according to Gleason's recommendations (Gleason score [GS]) and further dichotomized into GS ≤7A (3+4) vs. ≥7B (4+3) (5). The four biopsies that were not available were originally graded according to the World Health Organization system (6). Those that were described as well or poorly differentiated were lumped to GS 4–6 or 8–10, respectively. One biopsy was described as moderately differentiated and categorized as GS ≤7A for the purpose of this study. The patients were allocated to a low-risk group ($T_{1\text{-}2}$ and GS ≤7A) or a high-risk group ($T_{3\text{–}4}$ or GS ≥7B) on the basis of the first report in which initial PSA (iPSA) did not show any prognostic impact.

Control group

To compare 10-year overall survival (OS) in PC patients with that of men from the general population, Statistics Norway constructed a control cohort: three age-matched men for each nonemigrating patient were randomly identified. Eligible control subjects had to be alive the year RT was started in the corresponding case. The years of birth and death for each anonymous control subject was made available to the first author.

Radiotherapy

The primary treatment has been previously described in detail (4, 7). Briefly, RT was applied with a four-field box technique (opposing anterior–posterior fields and two opposing lateral fields). During the first years, multiple customized shielding was used. In August 1994, a modification was introduced by using a multileaf collimator. The gross target volume (GTV) was defined by a three-dimensional CT planning system (Helax, Uppsala, Sweden) and covered the prostate and the seminal vesicles. For tumors that did not involve the seminal vesicles, GTV encompassed the prostate only after 50 Gy. All patients received megavolt photon energy, 15 MV, with daily fractions of 2 Gy, 5 days per week. The target dose was 66 Gy in 196 patients, 64 Gy in 3, 68 Gy in 1, and 70 Gy in three patients.

Follow-up after radiotherapy

All patients were seen at the Norwegian Radium Hospital outpatient department 3 months after RT. Thereafter, they were followed up at their urologist's discretion. Many patients were rereferred to the hospital during the observation time for reevaluation or because of disease progression. Each patient's survival status on the cutoff date of the study (December 31, 2005) was retrieved from the Central Population Registry based on the national 11-digit personal identification number. The cause of death was retrospectively determined by reviewing the hospital records and contact with the responsible local clinicians. These sources also provided information on eventual date and type of progression.

Clinical endpoints

Death of any cause was evaluated for OS. The endpoint of cancer-specific survival (CSS) was death due to PC, to complications from PC treatment, from unknown causes in patients who had been proven to suffer from progressive PC, excluding unexpected deaths suggestive of cardiovascular events in patients with stable PC. The critical event for clinical progression-free survival (cPFS) was the first proof of clinical progression: locoregional progression was defined as symptomatic and clinically detectable growth of the prostate tumor or regional lymph nodes. Distant progression was defined as radiographic evidence of metastases. PSA progression alone was not considered to be an endpoint, because serum PSA was not routinely determined during follow-up of PC early in the 1990s in Norway.

Long-term health-related quality of life

Patients who were still alive on December 31, 2005, were included in a self-report survey. By mail, they received the Brief Male Sexual Function Inventory (BSFI) (8), questions regarding urinary and bowel function/bother from the University of California at Los Angeles Prostate Cancer Index (PCI) (9) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Instrument, version 3.0 (QLQ-C30) (10, 11). Two ad hoc questions regarding fecal control and the use of pads were added to cover this potentially important side effect from RT.

The results were compared with published, age-adjusted normative data from population studies (12–15). Furthermore, some important single items regarding pelvis-related morbidity were considered. In the QLQ-C30, self-rating of global health status and quality of life is assessed by two separate items scored by 7-point Likert scales ranging from *very poor* to *excellent*. The scores are combined in a global health status/quality of life domain (GlobQL). We have studied the impact of other, more specific cancer-related domains and pelvic morbidities on this general domain.

Statistics

All analyses were performed by the Statistical Package for Social Science (SPSS for Windows 12.0, SPSS, Chicago, IL) using descriptive parametric or nonparametric tests, as appropriate. The Kaplan–Meier method was used to evaluate OS, CSS, and cPFS. The observation time started at the first day of RT and ended at the date of the specific endpoint, death, emigration, or cutoff date, whichever occurred first. When OS was compared with the control group from the general population, the time-interval started the year RT was commenced in the patients and ended at the year of death or in 2005 for living men. The predictive impact of pretreatment variables was assessed by log-rank tests for univariate comparisons and by backward conditional Cox regression for multivariate analyzes.

The questionnaires were scored according to published recommendations (9, 10, 15). Missing values were substituted by the respective items' mean value if the patient had responded to at least 50% of the single items in a domain. Otherwise the individual domain was excluded from further analysis. Domains constructed of more than one item were analyzed for correlation with GlobQL by Spearman's rho. Scores from important single-item domains were dichotomized, and differences of GlobQL between groups were tested by the Mann–Whitney test. Domains that had statistically significant impact on GlobQL in univarite comparisons were included in a logistical regression backward conditional analysis with GlobQL-score split by 75 on the 0 to 100 scale being the dependent

variable. Domains with strong intercorrelation (Spearman's rho >0.7) were represented by the domain that correlated most strongly with GlobQL in the univariate analysis.

Tests were two-sided, and a p value <0.05 was considered to be statistically significant.

Because of low sample-size in our cohort, statistical comparisons between scores from the questionnaire with normative data were not considered reliable and therefore not performed. A difference of at least 10 points on a 0 to 100 scale in the QLQ-C30 was, however, regarded as clinically relevant (16).

RESULTS

Survival outcomes

Demographics and clinical outcome. A total of 165 men (81%) had high-risk tumors before treatment (Table 1). Minimum observation time was 10 years for surviving patients, except for two men who were lost to follow-up after 1 and 5 years because of emigration. Clinical progression was reported in 109 patients (54%). Of these, the first appearance was local growth of the prostate gland in 40 patients (37% of those who progressed), growth of regional lymph nodes in 2 (2%), distant metastases in 59 (54%), and combined locoregional and distant progression in 8 patients (7%). Overall, locoregional progression was reported in 53 patients (26% of all patients) and distant metastases in 82 (40%). The 10-year cumulative probabilities of OS, CSS, and cPFS were 57%, 72%, and 45% respectively (Fig. 1A). The overall death rate remained relatively constant for 15 years after therapy, whereas the risk of clinical progression tended to decline after 10 years. For low-risk patients, the 10-year cumulative probabilities of OS, CSS, and cPFS were 79%, 95%, and 73%, respectively, the comparable fractions in high-risk patients being 52%, 66%, and 39% (Fig. 2). High-risk patients had significantly inferior OS compared with the general population, whereas no difference appeared for those with low-risk tumors (Fig. 3).

Predictive impact of pretreatment factors. GS ≥7B compared with GS≤7A was significantly associated with reduced OS (p = 0.02), CSS (p = 0.002), and cPFS (p < 0.0001) in univariate analyzes (Fig. 1B). Compared with $T_{1–2}$, $T_{3–4}$ was associated with reduced CSS (p = 0.002) and cPFS (p = 0.0002) (Fig. 1C). No association was observed between iPSA and any of the endpoints (Fig. 1D). Neither did treatment delay nor age at treatment start have a significant impact on outcome when dichotomized by the median (data not shown). The number of resected lymph nodes also had no impact on any of the endpoints, either when dichotomized by the median (8) or when using a cutoff number of 15.

In multivariate analyzes, including all factors from Table 1, GS and T-classification remained independently associated with cPFS and CSS (Table 2). Only GS had independent influence on OS.

Self-report survey on health-related quality of life

Demographics. Of 90 patients who were alive on December 31, 2005, 64 (71%) returned the questionnaire. Nonresponders and responders were well balanced by clinical progression (data not shown). At the time of participation, median age was 78 years (range, 63–87 years) and only 3 men (5%) were aged <70 years. The questionnaire was completed 10 to 16 years after treatment (median, 11 years). Twenty of the responders (31%) had progressed clinically at the time of response; eight with locoregional progression only, eight with distant metastases only, and four with both. Twenty-eight patients (44%) were on HT at the time of the survey. Of these, nine used a nonsteroid antiandrogen only, 16 used a gonadotropin-releasing hormone (GNRH) analogue only, two were on total androgen blockade (antiandrogen and GNRH-analogue), and one had been surgically castrated. Eleven of the 28 patients on HT had not progressed clinically and therefore were assumed to be treated because of PSA progression.

Sexuality. Patients scored lower on sexual function domains and overall sexual satisfaction but similar on sexual problem assessment compared with age-adjusted Norwegian men from the general population (Fig. 4A). Patients who had progressed clinically, were on HT at the time of response, or both generally reported poorer sexual function compared with patients who were free of progression. Eighty-seven percent had not experienced firm enough erections for sexual intercourse during the previous 4 weeks compared with 49%

Table 1. Demographics of 203 pN_0M_0 patients treated by definitive radiotherapy for prostate cancer, 1989–1996

Variable	Distribution
T-classification	
T1-2	66 (33%)
T3-4	137 (67%)
Gleason score	
≤7A (3+4)	97 (48%)
≥7B (4+3)	106 (52%)
PSA (ng/ml)	
≤10	52 (26%)
11–20	49 (24%)
>20	102 (50%)
Risk stratification	
Low risk*	38 (19%)
High risk†	165 (81%)
Age at start of treatment, years	66 (48–81), 66 ± 5.5‡
Lymphadenectomy treatment, days	55 (17–301), 59 ± 28.8‡
No of removed lymph nodes	8 (0–29), 9 ± 5.4‡
Observation time, years	10 (1–16), 9 ± 3.6‡
Status on last observation	
Alive	90 (44%)
Emigrated	2 (1%)
Dead	111 (55%)
Cause of death	
Prostate cancer	64 (58%)
Other causes	43 (39%)
Unknown	4 (4%)

* Gleason score ≤3+4 and $T_{1–2}$.
† Gleason score ≥4+3 or $T_{3–4}$.
‡ Median (range), mean ± SD.

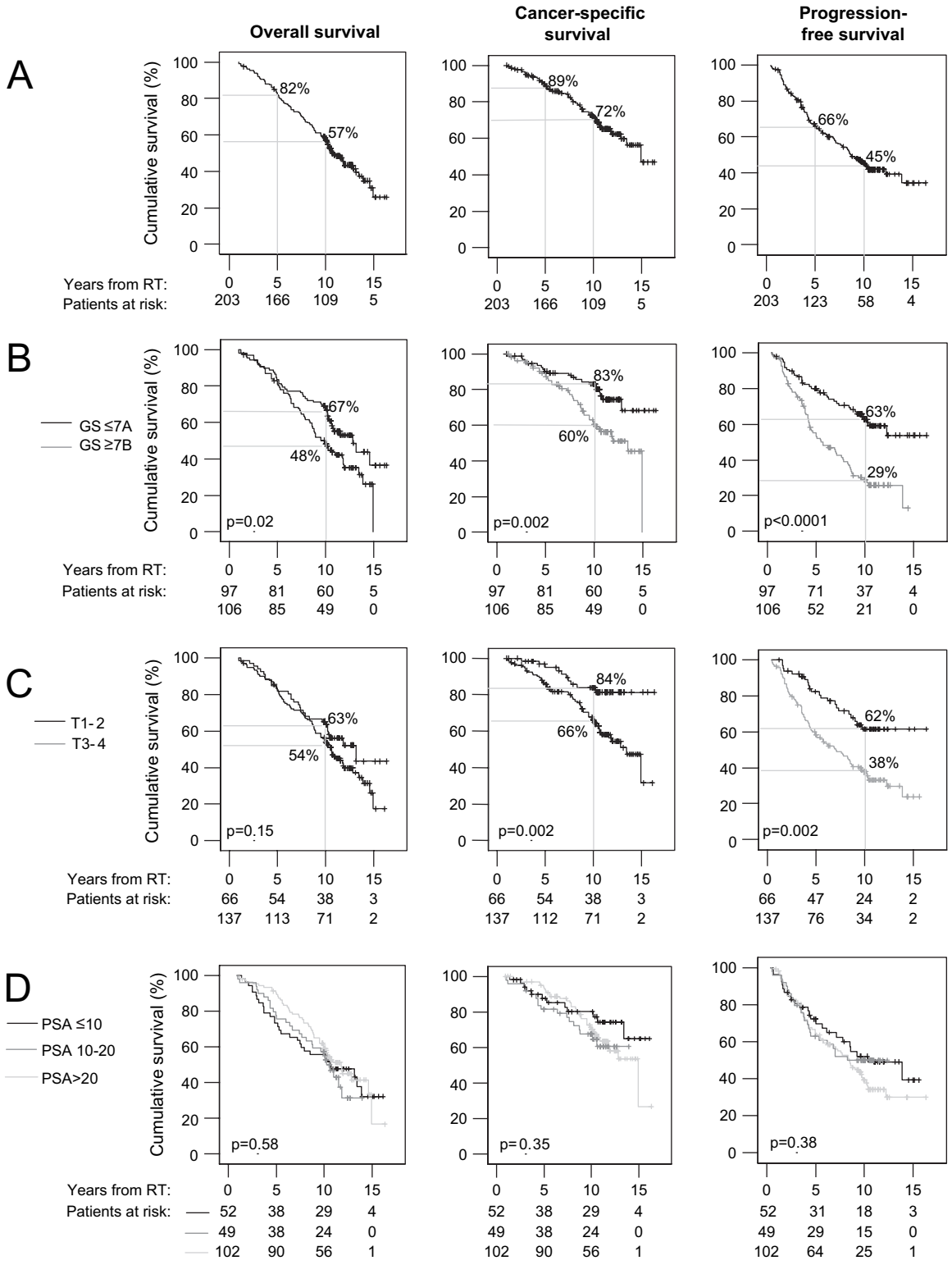

Fig. 1. Clinical outcome among 203 $T_{1\text{-}4}pN_0M_0$ prostate cancer patients following definitive radiotherapy (RT). (A) All patients. (B–D) Patients categorized by Gleason score, T-classification, and prostate specific antigen.

among American men >70 years as reported by O'Leary et al (15). Despite this, only 39% of the patients and 32% of the general population considered their inability to get and keep erections as a medium or big problem. Furthermore, 63% of the patients reported that they had felt no sexual drive the last 4 weeks, in contrast to 26% in O'Leary's study.

Urinary and bowel function. According to the PCI, patients scored lower on urinary function, urinary bother, and bowel bother compared with age-adjusted men from the general population in the United States (Fig. 4B). The mean score on bowel function was similar, however. Compared with patients who had no clinical progression or HT, patients who

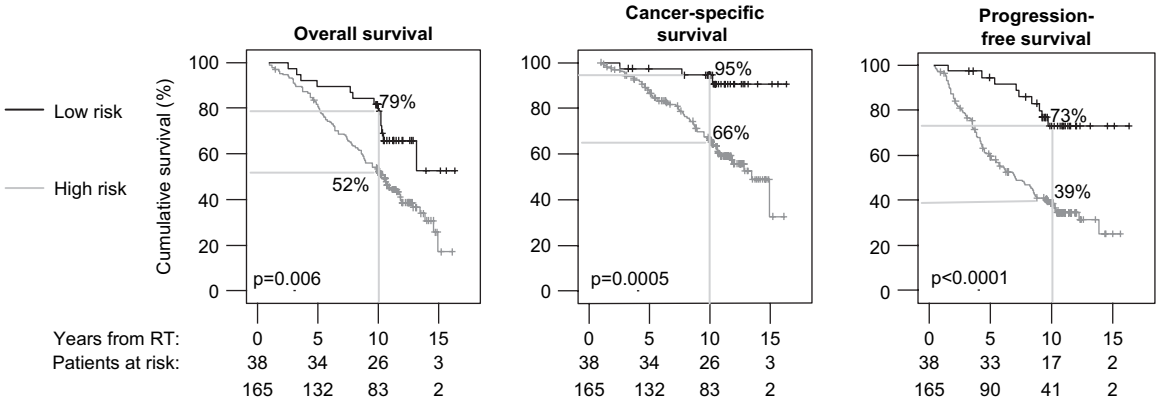

Fig. 2. Clinical outcome in 203 $T_{1\text{-}4}pN_0M_0$ patients treated by definitive radiotherapy (RT), comparing low-risk ($T_{1\text{-}2}$ and Gleason score ≤7A) with high-risk tumors ($T_{3\text{-}4}$ or Gleason score ≥7B).

had progressed or used HT had slightly lower mean score on urinary function but scored similar in urinary bother, bowel function, and bowel bother (Fig. 4B). Some degree of urinary leakage was reported by 46% of the patients (Table 3). In addition, two patients who did not answer the questions regarding urinary function stated that they had a permanent urethral catheter. Among elderly American men without PC, 30% reported some degree of urinary leakage on the same questionnaire (13). In our study, 44% reported some degree of fecal leakage (Table 3), in contrast to 1% to 11% reported in general-population-based studies applying different definitions of fecal leakage (17, 18).

EORTC QLQ-C30. In the 15 domains within the QLQ-C30, patient scores were similar to Norwegian normative data, except that patients overall reported more diarrhea and that those who had progressed clinically, used HT, or both reported poorer social function and sleeping problems (Table 4). Fifty-five of the 64 responders had been included in a similar cross-sectional survey approximately 2 years after RT when the QLQ-30 questionnaire, version 1.0, was used (7). At that time, 54 of these patients had no evidence of clinical progression. In this subpopulation, the answers from both surveys could be compared with each other in a longitudinal fashion. In the second survey, the mean outcomes were worse for most domains (Fig. 5A). Furthermore, the differences between mean scores tended to be larger among patients who had progressed clinically, were on HT, or both at the time of the second survey. These findings corresponded to larger reduction in GlobQL and function domains and more aggravation of symptoms compared with patients who remained free of progression (Fig. 5B).

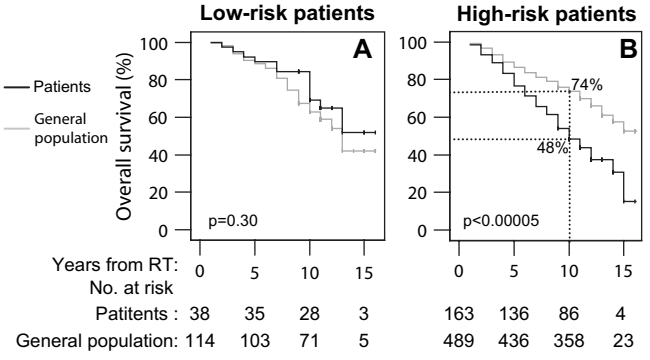

Fig. 3. Overall survival in 201 nonemigrating $T_{1\text{-}4}pN_0M_0$ prostate cancer patients following definitive radiotherapy (RT) compared with age-matched control subjects from the general population. The observation time commenced the year RT was started for patients and their corresponding control subjects. Survivors were censured in 2005. (A) Low risk patients ($T_{1\text{-}2}$ and Gleason score ≤7A). (B) High risk patients ($T_{3\text{-}4}$ or Gleason score ≥7B).

Interdomain correlations—prediction of Global Health Status/Quality of Life. In univariate analyzes, GlobQL correlated statistically significantly with physical function, role function, emotion function, cognitive function, social function, fatigue, pain, erection, ejaculation, urinary function, and bowel function (Spearman's rho). The difference in GlobQL were not statistically significant according to the Mann–Whitney test in patients when they were dichotomized by bowel bother ($p = 0.07$), urinary bother ($p = 0.49$), sexual satisfaction ($p = 0.74$), or clinical progression status (no progression vs. clinical progression and/or HT, $p = 0.82$). In a multivariate analysis of GlobQL, physical function was included at expense of role function and fatigue because of strong intercorrelation (Spearman's rho >0.7). For the same reason, erection was included at the expense of ejaculation. Thus, physical function, emotional function, cognitive function, social function, pain, erection, urinary function, and bowel function were included for logistical regression analyzes. Physical function (RR = 1.09 [95% confidence interval [CI]: 1.03–1.15], $p = 0.003$), and pain (RR = 0.94 [CI: 0.87–1.00], $p = 0.06$) remained in the final model independently associated with GlobQL.

DISCUSSION

This study represents one of the largest published RT series with $_pN_0$ category in hormone-naive patients with PC, the overwhelming majority being in a high-risk group. We found a steady decline in OS, CSS, and cPFS the first 10 years after definitive RT. CSS and cPFS were associated with GS and T-classification, whereas OS only was predicted

Table 2. Pretreatment factors with independently predictive impact on survival endpoints in patients with pN_0M_0 prostate cancer treated by definitive radiotherapy (Cox backward conditional regression)

	Overall survival			Cancer-specific survival			Progression-free survival		
Factor	RR	CI	*p*	RR	CI	*p*	RR	CI	*p*
Gleason score*	1.6	1.1-2.3	0.02	1.9	1.2-3.3	0.02	2.3	1.5-3.5	<0.0005
T-classification†		‡		2.3	1.2-4.7	0.02	2.0	1.2-3.2	0.004

Abbreviations: RR, relative risk; CI, confidence interval (95%).
* Gleason score ≤3+4 vs. ≥4+3.
† T_{1-2} vs. T_{3-4}.
‡ T-classification was excluded from the final model of factors with independent impact on overall survival.

by GS. Initial PSA did not predict outcome. Overall survival was significantly lower among high-risk patients than in a control group from the general population. Ten years after RT, surviving patients had increased risk of pelvis-related morbidity compared with normative data, however, with similar scores on GlobQL.

Despite negative CT scan, 13% to 52% of $T_{2-3}M_0$ PC-patients are expected to have regional lymph node metastases (19), which are associated with poor prognosis and by many considered to be a sign of systemic disease (20). Magnetic resonance imaging after administration of lymphotropic superparamagnetic nanoparticles might be a noninvasive alternative to surgical staging in the future (21). At present, however, pelvic lymphadenectomy is the gold standard for locoregional staging and may have several therapeutic benefits: patients with $_pN_0$ can, for example, avoid RT of pelvic lymph nodes and possibly adjuvant HT. Furthermore, patients with $_pN_+$ may be considered for specific treatment of lymph-node metastases or less mutilating palliative therapy if the chance of cure seems small.

The evaluation of various staging and treatment strategies in nonmetastatic PC is hampered by lack of large prospective, randomized trials. Outcomes from our study are compared with other $_pN_0$-series and selected series of non-lymphadenectomized patients in Table 5, although the validity of such comparison is limited by differences in patient characteristics, treatment strategies, stratification according to prognostic factors, and endpoint definitions. Taking these reservations into account, our results compare well with published 10-year OS (22), CSS (23), and cPFS (24, 25) rates in $_pN_x$ patients. Clinical and anatomic studies have shown that

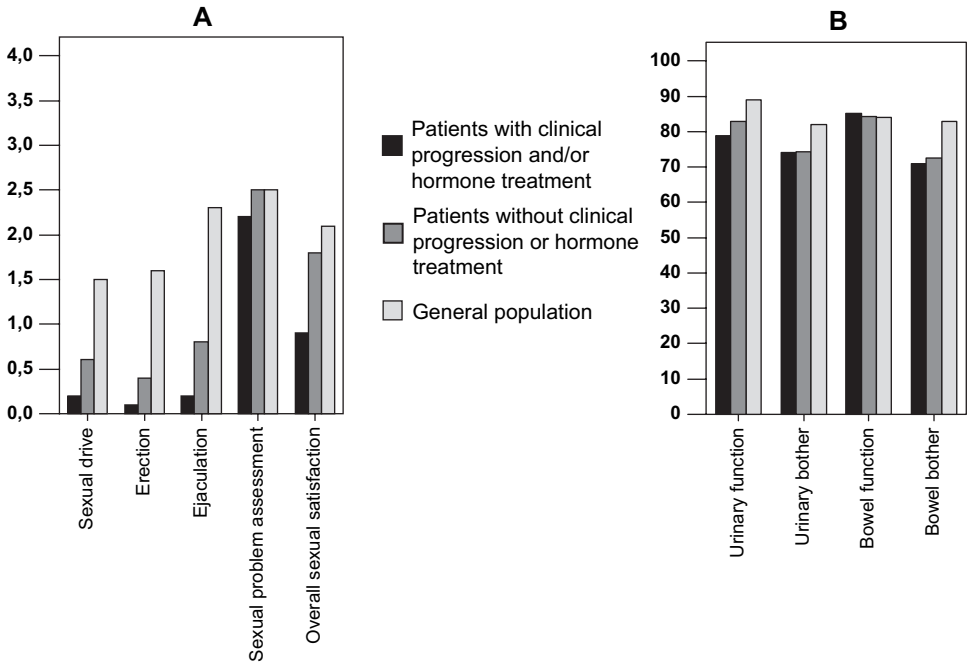

Fig. 4. (A) Mean scores from the Brief Male Sexual Function Inventory 10 to 16 years after definitive radiotherapy (RT) for prostate cancer compared to age-adjusted men from the Norwegian general population (15). The domains are constructed of 1 to 4 items scored by Likert scales ranging from 0 to 4. Higher score reflects better function, fewer problems, and higher degree of satisfaction. (B) Mean scores from the University of California at Los Angeles Prostate Cancer Index in patients 10 to 16 years after definitive radiotherapy and in American age-adjusted men without prostate cancer (13). Scores are linearly transformed to 0 to 100 based on raw scores from 3- to 6-point Likert scales. The function domains are constructed of 4 to 5 items and the bother domains of one item. Higher score reflects better function and less bother.

Table 3. Urinary and fecal leakage at least 10 years after definitive radiotherapy for prostate cancer

During the last 4 weeks:	
How often have you leaked urine?*	*n* = 61
Not at all	33 (54%)
Less than 1/wk	14 (23%)
About 1/wk	4 (7%)
Every day	10 (16%)
How many pads or adult diapers per day did you usually use to control urinary leakage?*	*n* = 62
None	47 (76%)
1–2	12 (20%)
3 or more/day	3 (5%)
How often have you had involuntarily leakage of feces?†	*n* = 61
Not at all	34 (55%)
Less than 1/wk	20 (33%)
About 1/wk	7 (11%)
Every day	0
How many pads or adult diapers per day did you usually use to control leakage of feces?†	*n* = 63
None	54 (86%)
1–2	8 (13%)
3 or more/day	1 (2%)

* Single items from the University of California at Los Angeles Prostate Cancer Index.

† Ad hoc questions.

extended dissection with removal of at least 20 pelvic lymph nodes are required for optimal staging (19, 26), although this requirement is somewhat controversial (27, 28). Most of our patients were staged by a limited dissection with a median of only eight removed nodes. We therefore suspect a certain degree of understaging in our material, possibly affecting the results. Nonetheless, the number of removed nodes did not affect outcome among our patients. We conclude that it is still an open question whether pre-RT lymphadenectomy improves outcome in high-risk patients.

Increasing GS is associated with increased prevalence of occult, disseminated tumor cells in bone marrow at diagnosis of high-risk PC (29). Consequently, unrecognized systemic disease might partly explain why GS is such a strong predictor of unfavorable outcome in these patients who only received locally targeted therapy. Although iPSA in general is considered to be an important predictive and prognostic factor (30), in our study, this pretreatment parameter was not significantly associated with outcome. Our results are in agreement with a patterns of care study from 1989 in which iPSA was an independent risk factor for PSA progression but not for clinical failure and death when GS was included in multivariate analyzes (31).

Consistent with previous findings (22), our data clearly demonstrate that irradiated patients with high-risk PC have unfavorable overall survival rates compared with the general population, even though the inclusion criteria for RT selected men without major comorbidities. This confirms the necessity of more effective treatment strategies for these patients, such as the application of dose escalation and adjuvant HT.

Although we confirm the well-recognized risk of sexual, urinary, and bowel morbidity after RT (32), this might be caused by age-related comorbidity, disease progression, HT, toxicity from RT, or a combination of these. Therefore, randomized trials with baseline data in which RT is compared with conservative treatment are necessary to estimate the proportion of the morbidity that directly is caused by RT. To our knowledge, such studies have currently not been published. Surprisingly, the mean score in the bowel function domain of the PCI was similar to normative data. The lower scores on bowel bother and more diarrhea compared with normative data clearly suggest, however, that a substantial proportion of our patients have bowel side effects from irradiation. The PCI does not cover typical side effects from RT such as proctitis and fecal leakage, and we therefore question the validity of the PCI bowel function domain in evaluating outcome after RT.

General health measures such as physical function and pain were more important predictors of GlobQL than specific pelvis-related morbidities in multivariate analyzes. The patients' mean score on GlobQL was also similar to Norwegian normative data. The findings might reflect a response shift (33); patients with malignancies adapt well to their organ-specific morbidities and accept them as inevitable side effects from treatment. Others have previously pointed out that the impact of treatment-related side effects on quality of life in PC patients might be overestimated (34, 35), consistent with our findings. However, it can be argued that general questions about subjective health and well-being might be insensitive for changes induced by treatment, possibly limiting their value in evaluating treatment outcome.

In a longitudinal analysis of two surveys applying QLQ-C30 in the same patients approximately 2 and 10 years after RT, there was a decline in GlobQL and function scores along with increased symptom scores. Some of these changes were expected because of aging (12), but the functional impairment and increase of symptoms were particularly pronounced in patients who had progressed clinically or who were put on HT between the surveys compared with progression-free and hormone-naive patients. We take this in account for that the QLQ-C30 to a certain degree is sensitive for changes due to disease progression.

There is substantial level 1 evidence that survival outcomes in patients with high-risk PC improve with combined therapy: RT with HT or by RT dose escalation alone (2, 36). We are aware that our low target dose is a shortcoming in this study. With appropriate attendance to volume constrains and neo-adjuvant application of HT (37), higher dosages can likely be applied with modern RT techniques without increase of side effects to the rectum.

In our study, we were not able to assess biochemical progression-free survival (bPFS), which in contemporary studies allows shorter follow-up time compared with studies that apply clinical progression and death as endpoints. The limitations of bPFS as an endpoint lie in uncertainties about clinical relevance and possible overreporting because of

Table 4. Mean scores from the European Organization for Research and Treatment of Cancer QoL questionnaire 10–16 years after definitive radiotherapy for prostate cancer compared with normative data

Domain/item*	Patients with clinical progression and/or HT (n = 33)	Patients without clinical progression or HT (n = 31)	General population >70 years (12) (n = 134)
Global health status/QoL	68.3	70.2	71.4
Physical functioning†	76.5	79.4	77.7
Role functioning	73.7	69.4	73.3
Emotional functioning	87.4	84.0	87.7
Cognitive functioning	78.5	81.8	77.6
Social functioning	70.6‡	79.6	81.6
Fatigue	34.4	28.0	28.5
Nausea and vomiting	5.4	2.1	3.3
Pain	16.1	19.2	22.5
Dyspnea	24.4	23.2	26.0
Insomnia	29.0‡	17.2	17.3
Appetite loss	6.5	4.0	8.6
Constipation	22.2	25.0	17.7
Diarrhea	21.5‡	24.7‡	9.9
Financial difficulties	5.6	2.1	4.7

Abbreviations: HT, hormone treatment; QoL, quality of life.

* Raw scores from Likert scales were linearly transformed into scales ranging from 0 to 100. Higher scores in global health status/QoL and the functioning domains reflect better function. Higher scores in the symptom domains reflect more symptoms.

† The items in the physical function domain were scored by 2-point scales in the population study (EORTC-QLQ-C30 version 2.0) and 4-point scales in the current study (version 3.0).

‡ Clinically relevantly different from general population (mean score at least 10 points different).

PSA-bouncing after RT {Hanlon, 2001 (38)}. Although the long-term follow-up in our study allowed more robust clinical endpoints, there are uncertainties related to cPFS and CSS because they were retrospectively assessed. Clinical progression might have been underreported in patients who were put on HT because of PSA elevation, possibly masking symptoms that would have led to search for recurrent disease. OS is, however, extremely reliable because of our updated official death registry and the fact that only two patients were lost to follow-up.

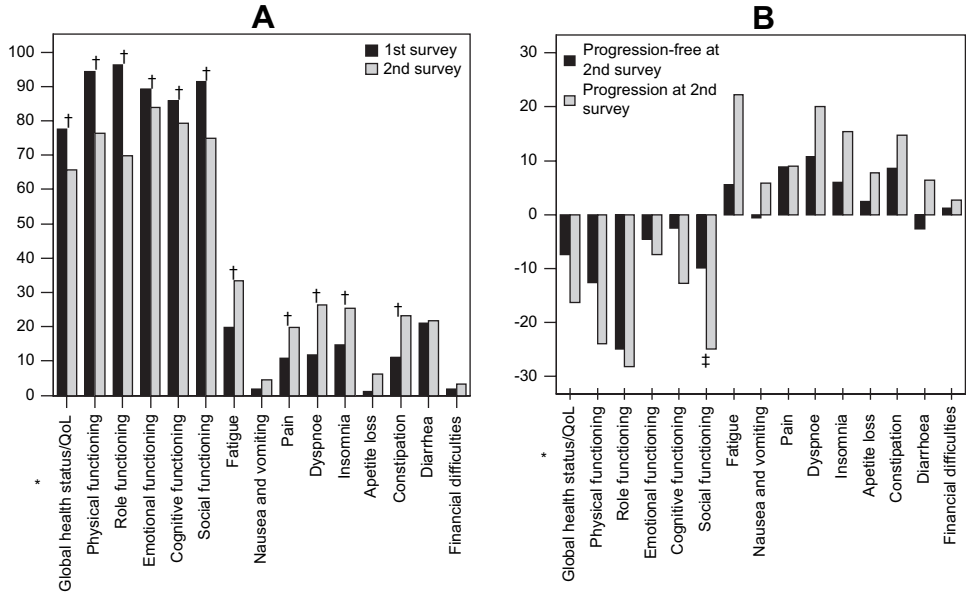

Fig. 5. Longitudinal results from two surveys applying European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Instrument (QLQ-C30) in 54 prostate cancer patients approximately 2 and 10 years after definitive radiotherapy. * The physical function and role function domains were constructed by items scored by 2-point scales in the first survey (version 1.0 of QLQ-C30. and changed to 4-point scales in the second survey (version 3.0). (A) Mean scores of all patients at the first and second survey. † $p < 0.05$ (Wilcoxon matched pairs signed rank sum test). (B) Differences between means (second minus first survey) in patients stratified by clinical status at the time of the second survey (progression defined as clinical progression and/or hormone treatment). ‡ $p < 0.05$ (Mann–Whitney test).

Table 5. Comparison of outcome in patients with nonmetastatic prostate cancer

Reference	Risk group	No. of patients	5-year OS	10-year OS	10-year CSS	10-year cPFS	10-year alive and free of progression
		pN_0 patients, radiotherapy only					
Present series	T_{1-2}/GS ≤7A	38	89%	79%	95%	73%	NA
	T_{3-4} and/or GS ≥7B	165	81%	52%	66%	39%	NA
	T_{1-2}	66	82%	63%	84%	62%	NA
	T_{3-4}	137	83%	54%	66%	38%	NA
Gray *et al.* (39)	T_{1-3}*	129	NA	63%	75%	NA	NA
Asbell *et al.* (40)	T_{1-2}	117	95%	64%	86%	NA	50%
Gervasi *et al.* (20)	T_{1-3}†	359	90%	62%	83%	57%	NA
		pN_0 patients, radical prostatectomy					
Bill-Axelson *et al.* (41)	T_{1-2}	347	92%	73%	90%	NA	NA
		pNx patients, radiotherapy only					
Chuba *et al.* (31)	T_1	71	79%	NA	NA	NA	NA
	T_2	203	81%	NA	NA	NA	NA
	T_{3-4}	100	63%	NA	NA	NA	NA
Perez *et al.* (24)	$T_{1b,c}$	112	NA	NA	NA	69%	NA
	T_2	373	NA	NA	NA	57%	NA
	T_3	434	NA	NA	NA	41%	NA
Roach *et al.* (23)	T_{1-2} and GS <7	363	85%	59%	86%	NA	NA
	T_3/GS <7 or T1-2/GS = 7	443	82%	50%	75%	NA	NA
	T_3/GS = 7 or T_{1-2}/GS = 8–10	338	68%	32%	62%	NA	NA
	T_3/GS8-10	324	52%	19%	34%	NA	NA
Zietman *et al.* (25)	T_{1-2}	504	NA	NA	NA	65%	NA
Zagars *et al.* (22)	T_{3-4}	551	72%	47%	NA	NA	30%
Bolla *et al.* (1)	T_{1-4}‡	198	62%	NA	NA	NA	NA
		pNx patients, radiotherapy + adjuvant androgen deprivation					
Bolla *et al.* (1)	T_{1-4}‡	207	78%	NA	NA	NA	NA
		pNx patients, watchful waiting					
Bill-Axelson *et al.* (41)	T_{1-2}	340	90%	68%	85%	NA	NA

Abbreviations: OS, overall survival; CSS, cancer-specific survival; cPFS, clinical progression-free survival; GS, Gleason score; NA, not available.

* 89%T_{1-2}.

† 56%T_3.

‡ 91%T_{3-4}.

Although the translated versions of the QLQ-C30 and BSFI have been validated in large Norwegian surveys, the translated version of the PCI was piloted only in a small group of patients before its application here (not published). Furthermore, the normative data from PCI are retrieved from a U.S. population, which might differ significantly from our Norwegian sample. Finally, lack of baseline data and our small sample size must be taken into consideration when the results from the questionnaire survey are interpreted.

The strengths in our study include follow-up of at least 10 years in survivors, with only two patients lost to follow-up (because of emigration), clinically relevant endpoints, and a control group from the general population. Furthermore, we have presented longitudinal HRQoL measures and their changes.

We conclude that patients with high-risk $_pN_0$ prostate cancer steadily progress clinically and die due to PC during the first 10 years after insufficient definitive radiotherapy <70 Gy without adjuvant HT. Such therapy might still, however, be regarded as an option in selected elderly patients with T_{1-2} and GS ≤7A. Prospective, randomized studies are necessary to evaluate further the role of pre-RT lymphadenectomy.

REFERENCES

1. Bolla M, Collette L, Blank L, *et al.* Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet* 2002;13(360): 103–106.
2. Ganswindt U, Paulsen F, Anastasiadis AG, *et al.* 70 Gy or more: Which dose for which prostate cancer? *J Cancer Res Clin Oncol* 2005;131:407–419.
3. Kupelian PA, Buchsbaum JC, Patel C, *et al.* Impact of biochemical failure on overall survival after radiation therapy for

localized prostate cancer in the PSA era. *Int J Radiat Oncol Biol Phys* 2002;52(3):704–711.
4. Fossa SD, Lilleby W, Waehre H, *et al*. Definitive radiotherapy of prostate cancer: The possible role of staging lymphadenectomy. *Int J Radiat Oncol Biol Phys* 2003;57:33–41.
5. Lilleby W, Torlakovic G, Torlakovic E, *et al*. Prognostic significance of histologic grading in patients with prostate carcinoma who are assessed by the Gleason and World Health Organization grading systems in needle biopsies obtained prior to radiotherapy. *Cancer* 2001;92:311–319.
6. Mostofi FK, Davis CJ Jr., Sesterhenn IA. Pathology of carcinoma of the prostate. *Cancer* 1992;70(Suppl. 1):235–253.
7. Lilleby W, Fossa SD, Waehre HR, Olsen DR. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. *Int J Radiat Oncol Biol Phys* 1999;43:735–743.
8. O'Leary MP, Fowler FJ, Lenderking WR, *et al*. A brief male sexual function inventory for urology. *Urology* 1995;46: 697–706.
9. Litwin MS, Hays RD, Fink A, *et al*. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. *Med Care* 1998;36:1002–1012.
10. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–376.
11. Bjordal K, de GA, Fayers PM, *et al*. A 12 country field study of the EORTC QLQ-C30 (version 3.0. and the head and neck cancer specific module (EORTC QLQ-H&N35. in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000; 36(14):1796–1807.
12. Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). *J Clin Oncol* 1998;16:1188–1196.
13. Litwin MS. Health related quality of life in older men without prostate cancer. *J Urol* 1999;161:1180–1184.
14. Mykletun A, Dahl AA, O'Leary MP, Fossa SD. Assessment of male sexual function by the Brief Sexual Function Inventory. *BJU Int* 2006;97:316–323.
15. O'Leary MP, Rhodes T, Girman CJ, *et al*. Distribution of the Brief Male Sexual Inventory in community men. *Int J Impot Res* 2003;15:185–191.
16. Osoba D, Rodrigues G, Myles J, *et al*. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–144.
17. Edwards NI, Jones D. The prevalence of faecal incontinence in older people living at home. *Age Ageing* 2001;30:503–507.
18. Goode PS, Burgio KL, Halli AD, *et al*. Prevalence and correlates of fecal incontinence in community-dwelling older adults. *J Am Geriatr Soc* 2005;53:629–635.
19. Bader P, Burkhard FC, Markwalder R, Studer UE. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? *J Urol* 2002;168:514–518.
20. Gervasi LA, Mata J, Easley JD, *et al*. Prognostic significance of lymph nodal metastases in prostate cancer. *J Urol* 1989; 142(2 Pt 1):332–336.
21. Harisinghani MG, Barentsz J, Hahn PF, *et al*. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003;348(25):2491–2499.
22. Zagars GK, von Eschenbach AC, Johnson DE, Oswald MJ. Stage C adenocarcinoma of the prostate. An analysis of 551 patients treated with external beam radiation. *Cancer* 1987; 60:1489–1499.
23. Roach M, Lu J, Pilepich MV, *et al*. Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. *Int J Radiat Oncol Biol Phys* 2000;47:609–615.
24. Perez CA, Michalski J, Lockett MA. Radiation therapy in the treatment of localized prostate cancer: An alternative to an emerging consensus. *Mo Med* 1995;92(11):696–704.
25. Zietman AL, Coen JJ, Dallow KC, Shipley WU. The treatment of prostate cancer by conventional radiation therapy: An analysis of long-term outcome. *Int J Radiat Oncol Biol Phys* 1995;32: 287–292.
26. Weingartner K, Ramaswamy A, Bittinger A, *et al*. Anatomical basis for pelvic lymphadenectomy in prostate cancer: Results of an autopsy study and implications for the clinic. *J Urol* 1996; 156:1969–1971.
27. DiMarco DS, Zincke H, Sebo TJ, *et al*. The extent of lymphadenectomy for pTXNO prostate cancer does not affect prostate cancer outcome in the prostate specific antigen era. *J Urol* 2005; 173:1121–1125.
28. Stone NN, Stock RG, Unger P. Laparoscopic pelvic lymph node dissection for prostate cancer: comparison of the extended and modified techniques. *J Urol* 1997;158:1891–1894.
29. Berg A, Berner A, Lilleby W, *et al*. Impact of disseminated tumor cells in bone marrow at diagnosis in patients with nonmetastatic prostate cancer treated by definitive radiotherapy. *Int J Cancer* 2007;120:1603–1609.
30. Bostwick DG, Foster CS. Predictive factors in prostate cancer: Current concepts from the 1999 College of American Pathologists Conference on Solid Tumor Prognostic Factors and the 1999 World Health Organization Second International Consultation on Prostate Cancer. *Semin Urol Oncol* 1999;17:222–272.
31. Chuba PJ, Moughan J, Forman JD, *et al*. The 1989 patterns of care study for prostate cancer: five-year outcomes. *Int J Radiat Oncol Biol Phys* 2001;50:325–334.
32. Bhatnagar V, Stewart ST, Huynh V, *et al*. Estimating the risk of long-term erectile, urinary and bowel symptoms resulting from prostate cancer treatment. *Prostate Cancer Prostatic Dis* 2006; 9:136–146.
33. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* 1999;48(11):1507–1515.
34. Korfage IJ, Essink-Bot ML, Borsboom GJ, *et al*. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. *Int J Cancer* 2005;116:291–296.
35. Krahn M, Ritvo P, Irvine J, *et al*. Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. *Med Care* 2003;41:153–164.
36. Kumar S, Shelley M, Harrison C, *et al*. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev* 2006;4:CD006019.
37. Lilleby W, Fossa SD, Knutsen BH, *et al*. Computed tomography/magnetic resonance based volume changes of the primary tumour in patients with prostate cancer with or without androgen deprivation. *Radiother Oncol* 2000;57:195–200.
38. Hanlon AL, Pinover VH, Horwitz EM, Hanks GE. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Biol Phys* 2001;50:845–849.
39. Gray CL, Powell CR, Riffenburgh RH, Johnstone PA. 20-year outcome of patients with T1-3N0 surgically staged prostate cancer treated with external beam radiation therapy. *J Urol* 2001; 166:116–118.
40. Asbell SO, Martz KL, Shin KH, *et al*. Impact of surgical staging in evaluating the radiotherapeutic outcome in RTOG #77-06, a phase III study for T1BN0M0 (A2. and T2N0M0 (B. prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1998;40: 769–782.
41. Bill-Axelson A, Holmberg L, Ruutu M, *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005 May 12;352(19):1977–1984.