Quality of Life and side effects in patients with Localized Prostate Cancer

Evaluation with self-assessment questionnaires

By
Per Fransson
ABSTRACT

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Localized prostate cancer (LPC) is predominantly a tumor among older men, and few patients will get symptoms from the disease. All methods to treat LPC with a curative intent have different types and degrees of side effects. It is therefore very important to evaluate the side effects thoroughly to make sure that treatment complications will not decrease the quality of life more than the disease would have done. In search for new and better treatments, complications has to be registered and evaluated in relation to quality of life (QOL) for the patients. Few validated self-assessment questionnaires for evaluation of external radiotherapy (EBRT) induced side effects has yet been developed. The present project focus on the development of the PC-specific questionnaire, QUFW94, and evaluation of symptoms in patients treated with EBRT and un-treated (watchful waiting) patients with a LPC. In the newly developed LPC-specific questionnaire a reliability and responsiveness test was performed. Both the inter-rater test and the test-retest show high correlation coefficients (ICC), above 0.60 for all scales. The internal reliability exceeded the lower acceptable limit (Cronbach α >0.70). The questionnaire was proven to be valid for the evaluations of EBRT side effects in LPC patients. Late side effects were evaluated 4 years after treatment in 181 LPC patients, treated with conventional large field EBRT, and compared with 141 age-matched PC disease free men. The most prominent urinary side effects were urgency and leakage which were doubled in the patient group. A ten fold increase was seen in comparison to controls at the most prominent intestinal problems, blood, mucus and leakage. The results support the use 3-D conformai therapy to decrease irradiation dose to the rectum and the bladder and thereby decreased side effects. A prospective additional evaluation 8 years after EBRT did not show any changes in urinary problems between 4 and 8-yr follow-up in the patients or the controls.

EBRT of LPC is also accompanied by disturbances in sexual function. These problems were therefore evaluated, 4 years after EBRT, in relation to the function in PC free men. Patients treated with EBRT indicated higher levels of sexual dysfunction than age-matched controls. No erection was reported from 12% of the control subjects, 56% of the patients who had only received radiotherapy (RT) and 87% of the RT+castration (RT+A) patients. The extended evaluation 8 years after EBRT show similar sexual function in all groups.

QOL and late side effects/symptoms were evaluated in the first and only randomized trial between RT and deferred treatment (DT) and compared to age-matched controls. QOL was evaluated with the general QOL formula, EORTC’s QLQ-C30 (+3), and LPC specific side effects with QUFW94 in 108 randomized patients with LPC 3 years after diagnosis. Social functioning was the only QOL scale where a significant difference was found between the two patient groups and in comparison with the control group. Multivariate regression analysis showed that hematuria, incontinence, mucus, and planning of the daily activities due to intestinal problems caused this decrease in QOL in the RT group. In conclusion, the LPC specific QUFW94 questionnaire was proven to be valid for evaluation of side effects and showed increased intestinal problems in the patients treated with conventional large field EBRT in comparison to untreated LPC patients. No difference in urinary and intestinal late side effects or sexual function was seen between a 4 year vs. 8 year follow-up.

Key words: prostate cancer, radiotherapy, complications, self assessment, questionnaires, validation, deferred treatment, quality of life
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Akademisk avhandling

Som med vederbörligt tillstånd av Rektorsämbetet vid Umeå Universitet för avläggande av medicine doktorsexamen offentligen kommer att försvaras I sal 244, by 7, Norrlands Universitetssjukhus, fredagen den 24 november 2000 kl 10.00

av

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by

Per Fransson
To my family

Sonja, Linda and Hanna
ABSTRACT

Localized prostate cancer (LPC) is predominantly a tumor among older men, and few patients will get symptoms from the disease. All methods to treat LPC with a curative intent have different types and degrees of side effects. It is therefore very important to evaluate the side effects thoroughly to make sure that treatment complications will not decrease the quality of life more than the disease would have done. In search for new and better treatments, complications have to be registered and evaluated in relation to quality of life (QOL) for the patients. Few validated self-assessment questionnaires for evaluation of external radiotherapy (EBRT) induced side effects has yet been developed. The present project focuses on the development of the PC-specific questionnaire, QUFW94, and evaluation of symptoms in patients treated with EBRT and un-treated (deferred treatment) patients with a LPC.

In the newly developed LPC-specific questionnaire a reliability and responsiveness test was performed. Both the inter-rater test and the test-retest show high correlation coefficients (ICC), above 0.60 for all scales. The internal reliability exceeded the lower acceptable limit (Cronbach α >0.70). The questionnaire was proven to be valid for the evaluations of EBRT side effects in LPC patients.

Late side effects were evaluated 4 years after treatment in 181 LPC patients, treated with conventional large field EBRT, and compared with 141 age-matched PC disease free men. The most prominent urinary side effects were urgency and leakage, which were doubled, in the patient group. A ten-fold increase was seen in comparison to the controls at the most prominent intestinal problems, blood, mucus, and leakage. The results support the use 3-D conformal therapy to decrease irradiation dose to the rectum and the bladder and thereby decreased side effects. A prospective additional evaluation 8 years after EBRT did not show any changes in urinary problems between 4 and 8-yr follow-up in the patients or the controls.

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QOL and late side effects/symptoms were evaluated in the first and only randomized trial between RT and deferred treatment (DT) and compared to age-matched controls. QOL was evaluated with the general QOL formula, EORTC's QLQ-C30 (+3), and LPC specific side effects with QUFW94 in 108 randomized patients with LPC, 3 years after diagnosis. Social functioning was the only QOL scale where a significant difference was found between the two patient groups and in comparison with the control group. Multivariate regression analysis showed that hematuria, incontinence, mucus, and planning of the daily activities due to intestinal problems caused this decrease in QOL in the RT group.

In conclusion, the LPC specific QUFW94 questionnaire was proven to be valid for evaluation of side effects and showed increased intestinal problems in the patients treated with conventional large field EBRT in comparison to untreated LPC patients. No change in urinary and intestinal late side effects or sexual function was seen between 4 year and 8-year follow-up.

Key words: prostate cancer, radiotherapy, complications, self assessment, questionnaires, validation, deferred treatment, quality of life
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBREVIATIONS</td>
<td>8</td>
</tr>
<tr>
<td>AIMS OF THE PRESENT STUDY</td>
<td>9</td>
</tr>
<tr>
<td>LIST OF PAPERS</td>
<td>10</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>11</td>
</tr>
<tr>
<td>INCIDENCE</td>
<td>11</td>
</tr>
<tr>
<td>DIAGNOSIS</td>
<td>12</td>
</tr>
<tr>
<td>Clinical staging</td>
<td>12</td>
</tr>
<tr>
<td>Histopathological grading</td>
<td>12</td>
</tr>
<tr>
<td>SURVIVAL</td>
<td>12</td>
</tr>
<tr>
<td>Localized prostate cancer</td>
<td>12</td>
</tr>
<tr>
<td>Locally advanced prostate cancer</td>
<td>13</td>
</tr>
<tr>
<td>TREATMENT FOR PROSTATE CANCER</td>
<td>13</td>
</tr>
<tr>
<td>Deferred treatment (DT)</td>
<td>14</td>
</tr>
<tr>
<td>Complications of deferred treatment</td>
<td>14</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>15</td>
</tr>
<tr>
<td>Complications of hormone therapy</td>
<td>15</td>
</tr>
<tr>
<td>Radical prostatectomy (RP)</td>
<td>16</td>
</tr>
<tr>
<td>Technical aspects of RP</td>
<td>16</td>
</tr>
<tr>
<td>Complications of RP</td>
<td>16</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>16</td>
</tr>
<tr>
<td>External beam radiation therapy (EBRT)</td>
<td>17</td>
</tr>
<tr>
<td>EBRT treatment techniques</td>
<td>17</td>
</tr>
<tr>
<td>Conventional box technique</td>
<td>17</td>
</tr>
<tr>
<td>3D- conformal technique</td>
<td>17</td>
</tr>
<tr>
<td>Intensity modulated radiotherapy technique</td>
<td>17</td>
</tr>
<tr>
<td>High precision conformal radiotherapy technique</td>
<td>18</td>
</tr>
<tr>
<td>Dose-escalation</td>
<td>18</td>
</tr>
<tr>
<td>Complications of EBRT</td>
<td>18</td>
</tr>
<tr>
<td>Acute side effects</td>
<td>18</td>
</tr>
<tr>
<td>Late side effects</td>
<td>18</td>
</tr>
<tr>
<td>Sexual function</td>
<td>19</td>
</tr>
<tr>
<td>Treatment technique development</td>
<td>19</td>
</tr>
<tr>
<td>Interstitial radiation therapy-brachytherapy</td>
<td>19</td>
</tr>
<tr>
<td>High dose brachytherapy</td>
<td>19</td>
</tr>
<tr>
<td>Low dose brachytherapy</td>
<td>20</td>
</tr>
<tr>
<td>Complications of brachytherapy</td>
<td>20</td>
</tr>
<tr>
<td>QUALITY OF LIFE (QOL)</td>
<td>20</td>
</tr>
<tr>
<td>SELF-ASSESSMENT QUESTIONNAIRES</td>
<td>21</td>
</tr>
<tr>
<td>METHODS</td>
<td>23</td>
</tr>
<tr>
<td>PATIENT AND CONTROL POPULATION</td>
<td>23</td>
</tr>
<tr>
<td>INSTRUMENTS</td>
<td>24</td>
</tr>
<tr>
<td>The QUFW94 questionnaire</td>
<td>24</td>
</tr>
<tr>
<td>Modification of the QUFW94 questionnaire</td>
<td>25</td>
</tr>
<tr>
<td>The EORTC QLQ-C30 questionnaire</td>
<td>26</td>
</tr>
<tr>
<td>TREATMENT TECHNIQUES</td>
<td>30</td>
</tr>
<tr>
<td>Conventional 4-field box technique</td>
<td>30</td>
</tr>
<tr>
<td>Conformal technique</td>
<td>30</td>
</tr>
</tbody>
</table>
ABBREVIATIONS

PC Prostate cancer
LPC Localized prostate cancer
RT Radiotherapy
EBRT External beam radiotherapy
Gy Gray, SI unit for absorbed dose
MV Megavolt
3D-CRT Three-dimensional conformal radiation therapy
DT Deferred treatment (watchful waiting)
PSA Prostate-specific antigen
LHRH Lutenising hormone releasing hormone
DRE Digital rectal examination
TRUS Transrectal ultrasonography
TUR-P Transurethral resection of the prostate
QOL Quality of life
RTOG Radiotherapy Oncology Group (in the USA)
EORTC European Organisation for Research and Treatment of Cancer
QUFW94 Side effect/symptom questionnaire developed by Fransson et Widmark (Appendix 1)
QLQ-C30 Quality of life questionnaire, developed by EORTC, including 30 items
BPH Benign prostatic hyperplasia
DSS Disease-specific survival
WHO World Health Organisation
AA Anti-androgen
TAB Total androgen blockade
IMRT Intensity modulated radiotherapy
CT Computerized tomography
HPCRT High precision conformal radiotherapy
HDR High dose radiotherapy (i.e. iridium-192)
LDR Low dose radiotherapy (i.e. Iodine-125 and Palladium-103)
CRE Cumulative radiation effect
ICC Intraclass correlation coefficient
VAS Visual analogue scale
RSSF Radiumhemmet Scale of Sexual Function questionnaire
IIEF International Index of Erectile Function questionnaire
AIMS OF THE PRESENT STUDIES

The aim of the present thesis was to investigate the symptoms in treated and un-treated patients with localized prostate cancer. The patients were also compared with an age-matched control population of prostate cancer disease free men.

The specific aims of the studies were:

1. **To** develop a prostate cancer-specific self-assessment questionnaire and perform a reliability and validity test of the questionnaire.

2. **To** study the patients own perception of late urinary-, intestinal side effects and sexual function after external beam radiotherapy of localized prostate cancer and to compare with an age-matched control population.

3. **To** evaluate and compare the patients quality of life and the urinary and intestinal symptoms in untreated patients with patients treated with external beam radiotherapy.
LIST OF PAPERS


INTRODUCTION

Prostate cancer (PC) is predominantly a tumor disease of older men, which frequently responds to treatment and may be cured when localized. The rate of tumor growth varies from very slow to rapid, and some patients may have prolonged survival with hormonal treatment even after the cancer has metastasized to distant sites, such as to bone. Since the median age at diagnosis is high (74 years), many patients, especially those with localized tumor, will die of other illnesses without symptoms or disability from their PC. The approach to treatment could be influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management.

This project focuses on the symptoms and side effects of patients treated with external beam radiotherapy (EBRT) and untreated (deferred treatment) patients with a localized PC (LPC).

INCIDENCE

PC is now the most common malignancy in males in Sweden (30% of all male cancer diagnosis). Sweden has among the highest incidence of PC in the world, reaching an age standard incidence of 142/100,000 new cases in 1998. More than 6600 new cases were diagnosed in Sweden during 1998. The average annual increase of PC in Sweden is 2.0%. The county of Västerbotten in the northern part of Sweden has the highest incidence, 198/100,000 new cases of PC in Sweden [1]. The incidence has increased during the last 30 years from about 40/100,000 in 1960 to 120/100,000 in 1995 in the northern part of Sweden [2] (Fig. 1). The main reason for this is increased diagnostic activity including the prostate specific antigen (PSA) blood test in patients often with a symptom free disease.

Figure 1. Age standardized incidence and mortality/100,000 in northern Sweden, 1959-95.
DIAGNOSIS

With increased age, many will often develop urinary problems with decreased urinary flow and increased urinary frequency. These symptoms are mostly due to benign prostatic hyperplasia (BPH) but could also be symptoms of a prostatic tumor, especially if the PSA value is increased. Patients are often referred for further investigation. Symptoms as an increased PSA often lead to a digital rectal examination (DRE) where sometimes a resistance (tumor) in the prostate could be diagnosed.

Clinical staging

Clinical staging of PC can be performed by using several different methods such as DRE, palpable tumor size, (T-stage), surgical lymph nodal evaluation (N-stage), and metastatic evaluation using bone scintigraphy (M-stage). Staging is the process of trying to describe and determine the extent of the tumor and relating it to prognosis. The cancer stage is a critical factor in selecting treatment options and predicting outcomes (likelihood of progression and survival). Histological evaluation is performed by needle biopsy, and transrectal ultrasound (TRUS).

Histopathological grading

The World Health Organisation (WHO) scale and the Gleason system and are the two most common used histopathological systems among the approximately 30 different systems for the histopathological grading of PC. The WHO system has three grades: grade 1 (high differentiation), grade 2 (medium-high differentiation), and grade 3 (low differentiation), which include both the degree of glandular differentiation and nuclear anaplasia. The Gleason system will also be used in Sweden in all patients from year 2000.

SURVIVAL

Localized PC

The extent of the tumor affects the prognosis of the disease [3]. Median survival of PC is largely dependent on stage at diagnosis and if the cancer is confined to the prostate gland. Localized disease, stages T0-T3, without evidence of metastasis is estimated to be found in about 50% of the patients [4] while only 20% of patients have metastasis at time of diagnosis. Since most patients are of advanced age and the tumors are often slow growing, many patients will die in intercurrent diseases. Results have shown that with deferred treatment (DT) 80% of these patients with small tumors (T0-T2) and well or moderately differentiated tumors will live 10 to 15 years after diagnosis [5], [6].

Table 1 shows recently reported overall and disease-specific survival (DSS) results from a pooled analysis of 1557 EBRT patients in four randomized Radiotherapy Oncology Group (RTOG) clinical trials [7].
The patient's age, other medical illnesses, together with PSA level at diagnosis, are also a prognostic factor in patients with PC that may be useful to consider when making therapeutic decisions \[8\], \[9\], \[10\], \[11\]. Patients with poorly differentiated tumors are more likely to have metastasized at diagnosis and are associated with a poorer prognosis.

Despite advances in early detection and treatment of PC, no clear impact on mortality has been seen although some American reports suggest decreased mortality in PC \[12\], \[13\], \[14\]. The mortality of PC in Sweden 1994 was 42 deaths/100.000 \[15\].

**Locally advanced PC**

Patients with locally advanced cancer are less curable. In the pooled RTOG studies \[7\] the 5-year, 10-year, and 15-year DSS in patients with T3Nx, Gleason score=8-10 were 64%, 34%, and 27%, respectively.

If the cancer has spread to distant organs (mostly bone), it will not be curable with available therapies. Median survival of metastatic PC is about 3 years \[16\].

**TREATMENT OF PROSTATE CANCER**

The choice of treatment for patients with LPC is complicated since good evidence based knowledge is lacking, the patient and his doctor must thoroughly discuss advantages and disadvantages of available treatment options (deferred treatment, hormonal treatment, radical prostatectomy (RP), EBRT, or brachytherapy). However, treatment of LPC is one of the most controversial topics in modern oncology.

No well conducted randomized trials have given any solid proof that the presently used curative treatment methods (such as EBRT or RP) can prolong survival as compared with symptomatic treatment (DT) in patients with LPC \[17\], \[18\], \[19\]. This means that after treatment, side effects have to be carefully monitored so that the treatment does not induce more problems than the disease itself.

Treatment of curative intent should be considered if the tumor is localized to the prostate gland and the patient has an expected survival more than 10 years.
Deferred treatment (DT)
An alternative to immediate active treatment in asymptomatic LPC patients, with low malignant (WHO grade 1 to 2) and early-stage tumors is careful observation (also named as watchful waiting, expectant or deferred treatment) [5], [11], [17], [20]. This option is more often used in patients with advanced age and with an expected survival of less than 10 years due to concomitant illness. In a Swedish study with 15 years of follow-up a survival rate of 81% without initial treatment in patients with LPC was reported, irrespective of age [6].

A population-based study of 94 patients with clinically LPC managed by a "watch and wait" (DT) strategy gave very similar results at 4 to 9 years of follow-up [21]. In the only published randomized follow-up (median follow-up 23 years) study between RP and deferred treatment, no statistically significant differences in survival could be demonstrated between the treatment groups [22]. The results are discussed considering the small sample size (n=111). La-Yao et al. [23] reported, in a large retrospective/population study of almost 60 000 men with LPC, no difference in DSS in patients treated with RP, EBRT or symptomatic treatment, although patients with aggressive (WHO grade 3) tumors seemed to do worse.

Deferred treatment is not a passive process. The physician closely monitor the progress of the PC by following the PSA value and by palpation to get information whether the cancer may be spreading outside the prostate and if the tumor size has increased the patient's discomfort.

Complications of deferred treatment
One risk with deferred treatment is the patient's cancer can progress beyond the chance for a cure. However, an adequate question is:

"Do we treat those who do not need to be treated and don't treat those who needs it".
Another negative and important factor is the fear of living with an “untreated” tumor and just waiting for the progression of the disease. In patients with untreated LPC, a high level of fear/worrying about the outcome of the disease was found in an interview study of seven men with untreated LPC (1 to 3 years after diagnosis). These patients described their situation as “a life in the shadow”. This suggests that living with untreated LPC is a burden, which also might explain the marginal difference in QOL between of treated and un-treated patients (unpublished data).

**Hormonal therapy**

Testosterone stimulates PC cells to grow. Castration therapy (Ablation, Luteinizing hormone-releasing hormone (LHRH) -agonists) abolishes testicular testosterone production and thereby decreases the PC cell proliferation and the cancer volume. Some cells will die due to apoptosis but hormonal therapy is not considered curative [24]. Castration therapy is also used as neoadjuvant or adjuvant hormonal therapy together with radiotherapy or surgery. Intermittent hormonal treatment means temporary castration therapy (3-9 months) followed by a period of no treatment than re-starting hormonal therapy again when PSA rises and stopping when PSA is lowered.

Hormone therapy can be delivered in different ways such as:

- **Orchiectomy** (surgical castration) is a surgical procedure to remove the testicles. It is called a hormone therapy because it takes away the body's main source of testosterone.
- **LHRH agonists** are drugs that by blocking the LH stimulation cease testicular testosterone (the body's main androgen) production. These drugs are injected periodically, mostly every 3 months.
- **Anti-androgens** (AA) are a relatively new form of drugs that act against PC by blocking testosterone receptors and thereby abolish the effect of testosterone. Sometimes they are used with orchiectomy or LHRH analogs in a combination called total androgen blockade (TAB).

In patients with symptomatic metastatic disease, hormonal therapy is an option to start at diagnosis. The timing of hormonal therapy in patients without symptoms is still controversial. A recent study from England on metastatic PC (M1) showed an advantage for primary hormonal treatment in patients with locally advanced PC in comparison to delayed treatment [25]. Decreased risk of severe complications was also found in the primary treatment group.

**Complications of hormone therapy**

Bilateral orchiectomy is cheap, and immediately lowers testosterone levels. Disadvantages are irreversibility, psychologic effects, loss of libido, impotence, hot flashes, decrease of muscle mass, and osteoporosis [26]. LHRH has the same side effects as orchiectomy but is reversible. Initial tumor flare reactions may occur but can be prevented by short-term AA. Estrogens will achieve castrate levels of testosterone, with some risk of cardiovascular side effects. Treatment with AA will not decrease testosterone levels and thereby causes fewer side effects. However, there is a high risk of developing gynecomastia and breast tenderness with AA-treatment. Gynecomastia may be prevented by single, low-dose irradiation to the breasts.
Radical prostatectomy (RP)

Radical prostatectomy (the surgical removal of the prostate) is usually reserved for patients with smaller tumors, good health, under the age of 70 years, and suitable for large surgical intervention [27], [28], [29]. These patients should have a negative bone scan and hopefully tumors confined to the prostate gland (T-stage 1 or 2).

Technical aspects of radical prostatectomy

The surgeon's first priority is to remove the cancerous tissue, secondarily to preserve as much of the patient's ability to maintain urinary control and to retain erection. The urethra, which carries urine out from the bladder, runs through the prostate, and has therefore to be re-implanted. There are nerves located close to the prostate that are essential for erection of the penis. Maintaining at least one of the nerve bundles can preserve the ability to have an erection after recovery from surgery.

Complications of radical prostatectomy

Complications can include urinary incontinence, urethral stricture, impotence, and the morbidity associated with general anesthesia and a major surgical procedure. An American national review of 10,600 radical prostatectomies determined that 30-day mortality was 2% and cardiovascular morbidity rates were 8% [30] although lower surgical mortality rates have more often been reported [31], [32]. Morbidity and mortality rates increase with age and were appreciably greater in those older than 75 years [30]. The most common form of incontinence is stress incontinence related to physical exertion. Approximately 1% to 3% of patients will have incontinence that requires the re-placement with an artificial sphincter (ring-like band to constrict the urethra and prevent the unwanted flow of urine) or other therapy for adequate control.

In one large study of men undergoing nerve-sparing RP technique, only about 6% required the use of pads for urinary incontinence, but an unknown additional proportion had occasional urinary dribbling. About 40% to 65% who were sexually potent before surgery retained potency adequate for vaginal penetration and sexual intercourse [33]. Preservation of potency with this technique is dependent on tumor stage and patient age, but the operation probably induces at least a partial deficit in nearly all patients [33]. If incontinence and impotence were evaluated with a self-assessment questionnaire the reported incontinence was 23% and about 60% of patients reported having no full or partial erections after surgery [34].

A cross-sectional survey of prostate cancer patients who had been treated in a managed care setting by either radical prostatectomy, radiation, or watchful waiting showed substantial sexual and urinary dysfunction in the prostatectomy group [35].

Radiotherapy

Today three different forms of radiotherapy are offered to the PC patients, EBRT, brachytherapy, or a combination of the both.
External Beam Radiation Therapy (EBRT)
External beam radiotherapy, introduced by Bagshaw in the 1950s [36], has been a cornerstone in the treatment of patients with PC. Radiotherapy with curative intent is commonly used to treat LPC.

Candidates for EBRT are the same patients who are candidates for radical prostatectomy plus many patients with locally advanced tumors that won’t be offered surgical treatment due to the high risk of incomplete resection. In addition, radiation is sometimes used post-operatively to surgery, in not radically operated patients.

Long-term results with radiation therapy, as with other treatment modalities, are dependent on tumor extent. A retrospective review of 999 patients treated with irradiation showed cause-specific survival rates at 10 years to be dependent of T-stage: T1 (79%), T2 (66%), T3 (55%), and T4 (22%) [37]. An initial serum prostate-specific antigen (PSA) level of greater than 15 nanogram per milliliter is a predictor of probable failure with conventional radiation therapy [38].

In a large population-based study of 60 000 patients with LPC treated by prostatectomy, radiotherapy, or conservative management, the long-term survival rates (10 years) were similar [23]. EBRT patients also avoid the risks associated with surgery and anesthesia [30].

**EBRT treatment techniques**

**Conventional box-technique**
Treatment techniques and treated volumes have changed considerably over the years. Historically only an 8 x 8 cm field size was used as a boost field after 50 Gy [36]. In the bulky prostate, this shrinked field size could miss up to 50% of the vesicles and 25% of the prostate as determined by computer tomography (CT) scans [39], [40]. This lead to larger field sizes with 4-field box techniques during the 70’s, but more normal tissue was unnecessarily irradiated with increased side effects. Bagshaw [36], who used large fields encompassing the pelvic lymph nodes up to 50 Gy and then decreased field size up to full dose, developed a combination of these techniques.

**3-D conformal technique (3D-CRT)**
Improved planning of external beam radiotherapy from the beginning of the 90’s has now rapidly emerged by using a CT-based three-dimensional (3-D) planning and conformal beam radiotherapy [39], [41]. This technique permits better sparing of the surrounding normal tissue and gives a better opportunity to increase tumor dose within a limited area.

**Intensity modulated radiotherapy technique (IMRT)**
IMRT with non-axial treatment fields and different kinds of sophisticated dose distributions is a further development of the 3D-CRT technique [42], [43]. Higher doses are warranted since studies have shown that a high percentage of patients (40-60%) have biopsy proven tumour like cells remaining in the prostate 2 years after conventional external beam dose-levels (<70 Gy) [44], [45], [46], [47], as well as after brachytherapy [48], [49].
High Precision Conformal Radio Therapy (HPCRT)
The stereotactic HPCRT technique (uses a special urethral catheter containing markers, BeamCath®) that help to visualise the prostatic urethra with portal imaging [50]. With this technique accurate localisation of the prostate can be achieved allowing doses up to 78 Gy to be given without increased complications compared to doses ≤ 70 Gy given with conventional or 3-D conformal techniques [51].

Dose escalation
Refined techniques have been used for dose-escalation in an attempt to completely eradicate all prostate tumour cells. Some centres of excellence in the USA are presently performing dose-escalation studies up to and above 80 Gy [52], [53], [54].

Complications of EBRT
All methods used to treat LPC with a curative intent have different types and degrees of side effects. The side effects of EBRT can be divided into acute and late effects.

- **Acute side effects**, occur during the treatment, are generally of minor to moderate severity, and resolve within 4 to 6 weeks following completion of the treatment. They are attributed to the effects of radiation on rapidly dividing cells, which for pelvic EBRT are the cells of the mucosal epithelium of the rectum, bladder, and prostatic urethra [55].

- **Late side effects**, are not generally manifested until several months after treatment and are more mediated by damage to the vasculoconnective tissue, resulting in hypovascularity, decreased perfusion, and fibrosis [55].

The possibility of chronic and debilitating morbidity from the late effects of EBRT must be taken into account when considering the use of this treatment modality, especially in a situation where there are other treatment options. Therefore it is very important to evaluate the side effects thoroughly hoping to improve treatments for minimizing complications, including a better QOL for the patients.

Acute side effects
Since parts of the bladder, rectum and the small intestine mostly are included in the prostate treatment volume, it is common for many patients to suffer of common acute side effects such as cystitis, proctitis, and sometimes enteritis [27], [56], [57]. However, these side effects have decreased with smaller treatment volumes [58] and are generally reversible [41], [59], [60], [61], [62].

Late side effects
Late effects are less common, about 15-20% of the patients describe mild to moderate urinary and gastrointestinal problems [63], [64]. These side effects may be chronic and of mild character and rarely require surgical intervention. To reduce the fairly high percentage of minor urinary and intestinal side effects presented during the 80’s, much effort has been put
into new treatment techniques with smaller treatment fields during the 90’s to reduce side effects\([39], [60], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74]\).

Another way to reduce the side effects would be to use protectors. Henriksson et al.\([75]\) showed in a prospective, controlled, randomized, double blind study that sucralfate (mucosal protector) decreased both the acute and late intestinal toxicity in patients treated with radiotherapy where the pelvic area was involved.

**Sexual function**

External beam radiotherapy also influences the sexual function in PC patients. Potency, in the short term, in previously potent patients is preserved with irradiation in the majority of cases, but may diminish over time. Studies report various frequencies of preserved potency (51-86%) in this patient group after EBRT\([76], [77], [78], [79], [80]\). Mantz et al.\([81]\) reported that 36 months after completion of EBRT for LPC, 66% of all patients were still potent; however, for patients younger than 70 years, the probability of impotence does not differ significantly from that for normal males.

Substantial sexual dysfunction in EBRT patients in comparison to those treated with either radical prostatectomy or watchful waiting was reported in a cross sectional study\([35]\).

**Treatment technique development**

Morbidity may also be reduced with the employment of sophisticated radiation techniques, such as the use of linear accelerators, careful simulation, and treatment planning\([52]\). The rapid development of new treatment techniques during the late eighties has improved precision and decreased the side effects. The better sparing of the surrounding normal tissue gives a better opportunity to increase tumor dose without increasing side effects.

Randomized comparison of radiation side effects of 3D-CRT vs. conventional radiation therapy using similar doses (total dose of 60-64 Gy) showed no difference in late morbidity\([64]\). Late side effects that were serious enough to require hospitalization were infrequent with both techniques. However, the cumulative incidence of mild or greater proctitis was lower in the conformal arm than in the standard therapy arm (37% vs. 56%, \(p=0.004\)). Urinary symptoms were similar in the two groups, as local tumor control and overall survival rates at 5-year follow-up. Koper et al.\([58]\) also showed that the reduction in gastrointestinal morbidity was mainly accounted for by reduced toxicity for anal symptoms using 3D-CRT. The study did not show a statistically significant reduction in acute rectum/sigmoid and bladder toxicity.

**Interstitial radiation therapy- brachytherapy**

**High dose interstitial brachytherapy (HDR; iridium-192)**

This brachytherapy technique has been employed in Sweden since late 80’s. A pre-planning transrectal ultrasound (TRUS) to view a picture of the prostate for completing the dose plan and a grid is used to the positioning of radioactive needles to deliver the radiotherapy.

Good local control has been reported with the combination of HDR plus EBRT\([82], [83]\).
Borghede et al. [83] reported that clinical and biopsy verified local control was achieved in 48 of the 50 (96%) patients; for stage T1-2 in 37 of 38 (97%) patients and for stage T3 in 11 of 12 (92%) patients.

**Low Dose Rate Interstitial brachytherapy (LDR; Iodine-125 and Palladium-103)**
In the USA, “seed” implant treatment is a new but commonly used brachytherapy technique. Results indicate that LDR is valid for treatment for patients with small localized tumors (T1-T3, PSA <10, Gleason 2-6) [84], [85].

**Complications of brachytherapy**
Morbidity after LDR was minimal if not prior TUR-P has been performed [86]. This treatment is relatively new, so some aspects of it are still controversial. In some cases, acute urinary symptoms (change in frequency, dysuria, irritation, etc.) and rectal problems like diarrhea may occur [86], [87]. Mantz et al. [88] reported preserved potency in 60-70% of the patients 5 years after treatment. However, in patients with failing potency prior to treatment only 40% preserved potency 5 years after treatment.

**QUALITY OF LIFE (QOL)**
Even if the patient is cured some psychosocial impairment may occur after treatment. The measurement of treated cancer patients quality of life (QOL) is difficult. There are four main categories of questions concerning the evaluation of the patients QOL during and after treatment that need to be answered:

- What is QOL?
- How should we measure QOL?
- Who should measure QOL?
- Why should we measure QOL?

During the first half of this century, treatment of cancer was only focused on mortality and morbidity. With newer and better treatments giving higher survival rates, more effort has been given to investigate the impact of the side effects on QOL. The WHO defined health in 1948 as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". The definition "quality of life" was defined by Ware 1978 [89] and could be described in three different areas: private, philosophical, or scholarly. It could also be measured in an objective or subjective way. Objective QOL could be: health (general), handicap, symptom control, family, relations, and economy. The objective QOL is probably easier to measure by the uninitiated (i.e. doctor or another nursing) than the subjective QOL, which is the individuals’ own perception of the life situation. Another problem with measurement of QOL is that it changes with time (both individually and globally) and might change with the patient’s ability to cope with his problems.
QOL is a very wide definition and contains many dimensions of the patients' perception of life during and after the treatment. A summary of these dimensions has been separated by researchers [90] into five domains such as:

- Physical functioning
- Role functioning
- Psychological functioning
- Social function
- Somatic complaints
- Well being

QOL should be measured by using a “standardized” disease-specific, multidimensional, and relatively short patient self-administrated QOL questionnaire with reliability, validity (cross-cultural as well as statistical), and responsiveness for the initiated patients.

The QOL should be measured because; making a treatment decision is a difficult and emotional task. The decision may permanently affect the QOL after therapy. When making a treatment decision there are four general areas that you have to consider.

- Information about the cancer such as where it may have spread
- Potential outcome and efficacy of treatment
- General health and lifestyle preferences.
- Tolerance to potential side effects on the QOL after treatment.

SELF ASSESSMENT QUESTIONNAIRES

During recent years there has been a growing interest in more systematic and detailed evaluations of side effects and quality of life (QOL) during and after cancer treatment. Assessments of complications after PC treatment are mostly based on medical records and treating physicians’ estimations of the side effects [65], [67], [68], [69], [72], [73], [74].

The European Organization for Research and Treatment of Cancer (EORTC, founded 1962) has developed a QOL core questionnaire, QLQ-C30, for general application on cancer patients and for use in cancer trials. The objective of the EORTC was to develop a cancer-specific, multidimensional, and relatively short patient self-administrated QOL questionnaire. This was used in clinical trials with reliability, validity (cross-cultural as well as statistical), and responsiveness for clinical trials [91], [92], [93]. The first core QLQ-C36 questionnaire was created 1987 and contained 36 items covering all cancer diagnoses. Further development of the formulas has been carried out and the currently used questionnaire QLQ-C30 (version 2) contains 30 items in 5 functioning scales:

1. Physical functioning
2. Role functioning
3. Emotional functioning
4. Cognitive functioning
5. Social functioning
The QLQ-C30 questionnaire also includes:

- A global health status/QOL scale.
- Three symptom scales:
  - nausea and vomiting
  - pain
  - fatigue
- Six single symptom items
  - constipation
  - diarrhea
  - loss of appetite
  - sleep disturbance
  - dyspnea
  - financial impact

One PC-specific module supplementing the QLQ-C30 questionnaire covering both localized and hormone refractory PC has recently been developed [94], [95]. The new QOL formula contained 19 questions regarding intestinal, urinary, and sexual function.

Until recent years, few studies were published which describe the PC patient’s own opinion of their side effects after pelvic radiation treatment using self-administered questionnaires [35], [94], [96], [97], [98], [99]. The rising interest in how patients live with the cancer on a daily basis has led many recent studies to include an evaluation of the PC patient’s perception of the QOL [35], [95], [99], [100], [101], [102].

A recent literature search at the Medline with “prostate cancer” and “QOL” as search criteria’s, shows the increase numbers of published manuscripts from 1975 to 2000 (Figure 2). However, none have so far compared symptoms and QOL using a patient population in a randomized trial of EBRT patients in comparison to patients with DT.

![Figure 2](image-url)

**Figure 2.** Numbers of published manuscripts, between 1975 and the 29 September 2000, containing the terms “prostate cancer” and “QOL” in the Medline database.
METHODS

PATIENT AND CONTROL POPULATION

Three different patient populations were used in the 5 studies. All patients received EBRT at the Department of Oncology, Radiotherapy unit, Umeå University Hospital, Sweden.

Paper I

The study included 31 patients with LPC who received external radiotherapy with curative intent during 1993.

All patients had a cytological or histologically verified LPC. The tumor stage at diagnosis is shown in table 2. The mean age of the patients was 67.2 years (range 52-77 years). One patient terminated radiotherapy by his own request at a total dose of 50 Gy, but he was included in the statistical analysis of the questionnaires.

Paper II and III

Paper II and III incorporated the same patient and control populations.

Between 1986 and the middle of 1989, 284 patients received EBRT to the pelvis with curative intention. From the primary group of patients, 89 patients were excluded who had:

- Died according to the Swedish population register (April 1, 1991)
- Distant metastases
- Received a total tumor dose of less than 60 Gy.

Out of the 195 questionnaires that were sent out, 181 (93%) were answered. These 181 patients were included in these two retrospective studies. All patients had a cytological or histological verified LPC. The tumor stage at diagnosis is shown in table 2.

Mean age at start of radiotherapy was 67.4 years (range 51 to 86 years).

The patient group was compared with an age-matched control group from the same region as the patients. Two hundred questionnaires were sent out to the control population and 141 (71%) were answered and returned.

Paper IV

In the prospective study the same patient (n=83) and control populations (n=95) were used as in the two studies (Paper II and III) except patients:

- Dead according to the Swedish population register (June 1, 1995)
- With a disease progression between the 4-year follow-up studies (Paper II and III) and this 8-year follow-up study.

The tumor stage at diagnosis is shown in table 2.
Between 1986 and 1996, 166 patients with LPC were included in the randomized trial (Umeå 1) comparing EBRT with DT. All patients had cytologically or histologically verified PC. The tumor stage at diagnosis is shown in Table 2.

From the primary group of 166 patients, 41 patients were excluded who had:

- Died according to the Swedish population register
- A follow-up less than 6 months
- Disease progression before the time of the questionnaire

The total number of patients included were: in the RT group n=59, and in the DT group n=49. The patient groups were also compared with an age-matched control group of LPC free men, recruited from the Swedish population register. One hundred and forty questionnaires were sent out to the controls, 68 questionnaires (49%) were returned.

The mean age at the time of questionnaire was 71.3 years (49.1-83.0 years) in the RT group, and 72.8 years (58.9-81.9 years, p=0.136) in the DT group.

The mean age in the control group was 72.2 years (58.9-81.9 years, p= 0.327).

**Table 2. T-stage (UICC 1992) at the time for diagnoses. *T-stage is changed from UICC 1978 to UICC 1992, were all T0 stages are changed to T1a.**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>16%</td>
<td>11%</td>
<td>11%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>T1b</td>
<td></td>
<td></td>
<td></td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>T1c</td>
<td></td>
<td></td>
<td></td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>T2</td>
<td>32%</td>
<td>52%</td>
<td>63%</td>
<td>75%</td>
<td>82%</td>
</tr>
<tr>
<td>T3</td>
<td>32%</td>
<td>33%</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>T4</td>
<td>19%</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**INSTRUMENTS**

**The QUFW94 questionnaire**

The newly developed PC-specific self-assessment questionnaire, QUFW94 (Appendix 1) was used in all five studies (Paper I to V). Some modifications to the questionnaire were instigated during the course of the research (see "Modifications of the QUFW94 questionnaire" page 25 and Table 3). The self-assessment questionnaire for evaluation of symptoms and side effects after pelvic radiotherapy in patients with LPC was designed in Swedish. The name of the questionnaire, QUFW94, comes from an abbreviation of Questionnaire Umeå Fransson Widmark 1994.
The development of the QUFW94 questionnaire process consists of 5 phases:

1. **Literature searches** of relevant issues of morbidity of EBRT. Performing a search of other questionnaires which evaluate side effects in PC patients [35], [94], [103]. Interviewing patients and doctors with great experience of patients treated with EBRT and evaluating side effects during radiotherapy [62], [75].

2. **Presentation** of the first questionnaire to relevant health care providers for feedback of the issues.

3. A **pilot study** of 10 patients with ongoing radiotherapy treatment for PC was also performed. The aim of the pilot study was to make sure that the patients understood the questions and to investigate whether they had any further questions or comments concerning the questionnaire.

4. **Validation**, reliability, and responsiveness testing (Paper I).

5. Using the questionnaire, a **field test** comparing urinary, intestinal, and sexual function in 181 PC patients, and 141 controls was also undertaken (Paper II [96], III [97] and IV [98].

The questionnaire was subdivided into four main categories:

1. General section (6 items)
2. Urinary problems (12 items)
3. Intestinal problems (14 items)
4. Sexual function (7 items)

The latest version of the QUFW94 questionnaire, used in Paper IV and V contained 39 questions. Twenty-seven questions had modified linear-analogue scales (L-A scale) containing values between 0 and 10, were 0=“no problem/very good function” and 10=“many problems/very bad function” (Appendix 1). Higher values mean more problems/worse function.

Seven questions contained only "yes" or "no" answer alternatives.

Three questions requested written answers (question no. 17, 31 and 38). These 3 questions have not been summarized and reported in these papers. Two questions (question no. 1 and 37) had other answer alternatives (Appendix 1).

The patients were encouraged to evaluate their general, urinary, intestinal symptoms, sexual function, and life situation during the previous week.

**Modification of the QUFW94 questionnaire (Table 3)**

Exactly the same questionnaire was used in the two 4-year follow-ups (Paper II and III). After the two first population studies (Paper II and III) modifications were made on the L-A scale such as: boxes were used instead of marking on a line.

After the validation of the questionnaire (Paper I) some changes to the questionnaire were made (Table 3).
The questions about existence (question no. 2), desire (question no. 34), erection (question no. 35), and life situation (question no. 39) were inverted so a value of 10 meant "many problems/very bad function" and 0 meant "no problems/very good function".

Six new questions were added:

1. Day urinary frequency (question no. 7): this was a sub-section of the question about "urination frequency during 24 hours" (E3) in the first version of the questionnaire
2. Night urinary frequency (question no. 8), see above
3. Pain during micturation (question no. 9)
4. Nausea (question no. 23)
5. Gases/bowel movements (question no. 24)
6. Erection quality (question no. 36)

Some questions were also excluded from this version of the questionnaire:

E1. The use of Eulexin (Flutamid®), This question was excluded from the next version of the questionnaire. This was due to difficulties many patients experienced in exactly defining the type of medication or surgical intervention that was used. It was much better/easier to obtain the relevant information from the patient records.
E2. Use of medication other than bowel medicines, see above
E3. Urinary frequency during 24 hours, see 1 above
E4. Operations in the urinary tract, see E1
E5. About colostomy, extremely rare problem, see also E1
E6. Sexual life, this question was almost the same question as question no. 32 and it was therefore excluded

**The EORTC QLQ-C30 (+3) questionnaire**

In Paper V QOL was evaluated with help of the QLQ-C30 (+3) questionnaire. The European Organization for Research and Treatment of Cancer group (EORTC) developed the QLQ-C30 (version 1) questionnaire which has been thoroughly validated and cross-culturally tested in cancer patients [19], [91], [92], [104], [105], [106]. The questionnaire used in this study, QLQ-C30 (+3), is an interim version, which contains questions from both the original version (version 1) and modified questions included in the latest version (version 2).
Table 3. Modifications of the QUFW94 questionnaire. The questionnaire used in the Paper IV and V are included in appendix 1. "X" marked questions are included in the version of the QUFW94 questionnaire.

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Which of the following statements do you think best describes your situation today?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2.</td>
<td>How would you describe your existence in general?</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>3.</td>
<td>Does your prostatic cancer disease limit your daily activities?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4.</td>
<td>Are you limited in your daily activity by some other diseases?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5.</td>
<td>Do you use any medicines for your bowel/stomach?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6.</td>
<td>Do you have urinary problems?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>7.</td>
<td>How many times do you urinate during the day?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>8.</td>
<td>How many times during the night do you have to go up to urinate?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>9.</td>
<td>Do you have pain when you urinate?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>10.</td>
<td>Do you have problems to start urination?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>11.</td>
<td>Do you have urinary leakage (incontinence)?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12.</td>
<td>Do you use diapers?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>13.</td>
<td>Do you have urgency?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>14.</td>
<td>Do you have blood in your urine?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>15.</td>
<td>Do you have a catheter?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>17.</td>
<td>If you have described some urinary problems, which problem(s) do you think is/are the worst?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>18.</td>
<td>Do you have stool problems?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>19.</td>
<td>How many stools/24 hours do you have?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>20.</td>
<td>How is the consistency on your stool?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>21.</td>
<td>Do you have fecal incontinence?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>22.</td>
<td>Do your stool problems make you plan your visits to the toilet?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>23.</td>
<td>Have you experienced nausea?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>24.</td>
<td>Do you have problems with excessive gas?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>25.</td>
<td>Do you use diaper?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>26.</td>
<td>Do you get cramps when you pass your stools?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>27.</td>
<td>Do you have mucus in your stools?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>28.</td>
<td>Do you have blood in your stools?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>29.</td>
<td>Do you have any special dietary habits because of your intestinal tract?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>30.</td>
<td>How much do your stool problems influence your daily activities?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>31.</td>
<td>If you have described some intestinal problems, which problem(s) do you think is/are the worst?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>32.</td>
<td>Do you have sexual problems?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>33.</td>
<td>Do you have a partner (wife, company)?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>34.</td>
<td>Do you feel desire for sexual activity?</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>35.</td>
<td>Can you have erection?</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>36.</td>
<td>If you have erection, is it enough to have intercourse?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>37.</td>
<td>Have you had intercourse/fondling during the last: week, month, year, not this last year</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>38.</td>
<td>If you have described some sexual problems, which problem(s) do you think is/are the worst?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>39.</td>
<td>How is your life situation in general?</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
</tbody>
</table>

Excluded questions from the latest version of QUFW94 (appendix 1).

E1. Do you use any medicine named Eulexin (Flutamide)?
E2. Do you use any other medicine?
E3. How many times do you urinate/24 hours?
E4. Have you been operated in your urinary tract?
E5. Do you have a colostomy?
E6. How is your sexual life?

Total no. of questions in the questionnaires: 43 35 35 39 39

* This question is transformed, in comparison to the questionnaire in Paper III and V, so the higher value, the more problems and the lower value the less/minor problems.
In the analysis of the data, only the questions included in version 2 are summarized and reported. The questionnaire contains 5 functioning scales: physical, role, emotional, cognitive and social functioning. It also includes a global health status/QOL scale. Higher mean scores on these scales reports better functioning and better QOL. Three symptom scales were also included concerning nausea and vomiting, pain, and fatigue. Six single symptom items measured the levels of constipation, diarrhea, loss of appetite, sleep disturbance, dyspnea, and the financial impact. Higher mean scores on the symptom and single items indicate more symptoms/problems.

**DISTRIBUTION OF QUESTIONNAIRES**

**Paper I**
The questionnaire (see “Modifications of the QUFW94 questionnaire” page 25 and Table 3) was administered consecutively during 1993 to all 31 patients who received EBRT with curative intent at the department. After a brief instruction from the research nurse, the patient filled out the questionnaire. The structured questionnaire was completed twice during the first treatment week and twice in the last treatment week (Fig. 3). On the first day of radiotherapy (questionnaire 1; untreated patients, only disease-induced symptoms), the patient was asked to grade his sexual function, urinary-, and intestinal symptoms during the previous week. The first 2 questionnaires were given to the patient on subsequent days. After returning the second questionnaire (questionnaire 2), a doctor, and an oncology nurse performed a structured interview of the patient. They had no prior knowledge of the patient’s answers in the previous questionnaire, and graded the patient’s symptoms and life situation (general, urinary, intestinal, and sexual) according to this description. The same procedure was repeated at the end of the radiotherapy (6 weeks later, questionnaire 3 and questionnaire 4) when patients often have radiotherapy-induced symptoms (Fig. 3).

**Paper II and III**
The self-administered questionnaire QUFW94 (see “Modifications of the QUFW94 questionnaire” page 25 and Table 3) was sent out to the patients during April 1991 and to the age-matched controls in November 1991. If no answer was received after one-month two letters of reminder were delivered to the recipient. After that a reminder phone call was made. The mean follow up time from the start of radiotherapy to the time of the questionnaire was 48 months (range 24 to 56 months).

**Paper IV**
The same patient and control population as in Paper II and III were re-evaluated 8-years after treatment. The questionnaire was sent out in May 1995 (see “Modifications of the QUFW94 questionnaire” page 25 and Table 3, Appendix 1). Patients and controls that had died according to the Swedish Population register (1 June 1995) or progressed within 6 months of receiving the questionnaire were excluded. If no answer was
received after one-month two letters of reminder were sent to the patient/subject. After that, a reminder phone call was made. The mean follow-up from the start of radiotherapy was 8 years (range 6-9 years).

**Paper V**

Two questionnaires were used. QOL was evaluated with EORTC QLQ-C30 (+3) formula. Urinary and intestinal problems were evaluated with the symptom specific self-assessment questionnaire, QUFW94 (Appendix 1). The questionnaires were mailed between 1991 and 1998 to all living patients included in the Trial 1 study (Umeå 1). Questionnaires were sent out in May 1995 to the age-matched controls. If no answer was received after one-month one letter of reminder was sent to the patient/subject. No reminding phone call was made. The median follow-up time from the randomization date to the time of the questionnaire was 40.6 months for the RT group, and 30.4 months for the DT group (p=0.055).

**Figure 3.** The procedure for administration, interviews, and the statistical tests of the QUFW94 questionnaire.
TREATMENT TECHNIQUES
All patients in Paper II, III, and IV were treated with the conventional 4-field box technique (see below). The patients in Paper I and 28 patients in Paper V (out of 59 patients) were treated with the conformal 3D-CRT technique (see below).

Conventional 4-field box technique (Fig. 4)
The conventional treatment schedule at that time was:

- Simple 3-slices CT-based conventional 4-field box-technique
- 2 Gy per fraction
- 5 fractions per week
- Cumulative radiation effect (CRE) value of 18.5, giving an average dose of 65.3 Gy
- A 2 to 3 week split course was given to some patients (Paper II and III; n=104).
- Large treatment volume was cranially extended to the sacral promontory, caudally to the ischial tuberosity, laterally to the medial walls of the pelvis, ventrally to the symphysis.
- Localized PC (T0-T2) received reduced treatment volume after 50 Gy, 9*9*9 cm field size (anterior-posterior-lateral).
- Locally advanced PC (N+ and or T3-T4) received full dose to the whole treatment volume.
- The treatment was given with 20.9-MV photons.

Conformal technique (Fig. 4)
The treatment was given with 20.9-MV or 50-MV photons. At the Umeå radiotherapy department at that time (1993 to 1996) the treatment schedule for this patient group was:

- CT-based conformal 4-field box technique
- 2 Gy per fraction
- 5 fractions per week
- Doses with curative intent up to 68 Gy
- Treatment volume including a 2-cm margin around the prostate
Figure 4. Example of a dose plan of conformal treatment technique (HPCRT) showing the target volume (dot-line). The straight-line shows a reconstruction of the target volume in the conventional 4-field box technique.

STATISTICAL METHODS

Paper I
The mean scores were calculated for all items and scales. For the analysis, the scale on the questions about existence, life situation, desire, erection function and sexual life were transformed/turned so that a high value always means much problems, and low values mean no/low problems. Wilcoxon’s matched-pairs signed ranks test was used to calculate the change between the two different time periods (start and end of the treatment). Inter-rater reliability was obtained by comparing the two interviewers (doctor and nurse) estimation of the patients’ symptoms both at the start and end of the treatment with Intraclass Correlation Coefficient (ICC) [107] statistics. Test-retest was obtained with ICC statistics, by comparing the patient’s first questionnaire with the second and the third questionnaire with the fourth (Fig. 1). The internal consistency reliability is a measure of the similarity of individual responses across several items, indicating the homogeneity of a scale. It was measured with Cronbach alpha coefficient (α) [108]. The reported values in the result section regarding start of the treatment refer to Questionnaire 2, while end of the treatment refers to Questionnaire 4 (Fig. 3). A p-value less than 0.05 were considered significant.
**Paper II and III**
For multiple comparisons [109] the T-test, chi-square test, and analyses of variance (ANOVA) were used. To study the correlation between the impacts of different sub questions, Pearson correlation coefficients were calculated. A p-value less than 0.05 were considered significant.

**Paper IV**
To evaluate differences between patient and control groups the non-parametric Wilcoxon´s rank-sum test was used. Correlation coefficients were calculated according to Pearson and considered significant when p < 0.05.

**Paper V**
Mean values were calculated for all items. Wilcoxon´s matched-pairs signed ranks test was used to calculate the change between the two different time periods (4-year and 8-year follow-up). To evaluate differences between patient and control groups, the non-parametric Mann-Whitney tests were used. A p-value < 0.05 was regarded as statistically significant. Multivariate linear regression analysis was used when trying to find the variable(s) best predicting the value of the different dependent variables. All calculations on the EORTC QLQ-C30 (+3) questionnaire were performed after the scores were linearly transformed to a 0 to 100 scale to facilitate presentation and interpretation of the data according to the EORTC recommendations.
RESULTS AND DISCUSSION

WHY MEASURE THE PATIENTS SIDE EFFECTS?

Historically, disease has been viewed in terms of a biomedical model, with the outcome of treatment measured in terms of death or inability to cure, with about 90% of published studies on the outcome of disease using biological data from diagnostic tests with endpoints such as operative mortality and complications [110]. The treatment outcome of cancer is no exception. In recent years, medical, social, and economic changes have made such measures of outcome insufficient. With newer, more effective and comparable treatment options (such as nerve-sparing surgery, conformal radiotherapy or perhaps watchful waiting in patients with LPC) providing high survival rates [23], measuring survival and tumor regress is no longer sufficient. In addition the patients' symptoms and side effects from the treatment and disease should be evaluated to judge the success of the treatment. Clinicians and scientists sometimes have difficulty accepting the measurement of subjective symptoms. There has been considerable skepticism as to whether self assessed side effects and QOL could be identified as an independent variable that can be objectively evaluated [111]. However, there is now increasing evidence that qualitative subjective feelings can be measured quantitatively, although debate still exists over the choice of instrument for such measurement [112]. Therefore, more effort has been given to systematically evaluate the side effects and QOL with validated self-assessment questionnaires. This will better describe the impact of the side effects on patients’ QOL and enable the following question to be answered:

"If we have treatment methods with comparable survival and tumor regress rates, which treatment is the most favorable for the patient regarding side effects and QOL”.

The increasing interest in measuring QOL is obvious. Since 1977 when QOL became a keyword in the “Medicine Medline Computer Research Program”, there has been a steady increase in the number of papers in the medical literature reporting QOL assessment with more than 400 articles per year since 1987. The PC-specific QOL published articles on “Medline” has also increased in the same degree (Fig. 2). Despite this acceleration of published papers, the definition of the term QOL remains ambiguous since QOL is highly subjective and complex. In studies of diseases and outcome, QOL is often described as a multi-dimensional concept and the dimensions can be grouped under the broad headings of physical, functional, psychosocial, and social health. Important concepts such as vitality (energy/fatigue), pain, anxiety/depression, and other cognitive functions are included within these broader categories [113].

METHODS FOR EVALUATION OF SIDE EFFECTS AND QOL

Evaluation of symptoms/side effects and QOL in patients with cancer has no standardized methods. It is not clear which method; quantitative or qualitative is preferable. In the field of clinical trials (often with many patients included), the quantitative method is usually preferable, since it is:
Qualitative methods with interviews are mostly used in psychological research, but are increasingly used in QOL in PC patients. An advantage of interviews is that patients can have some problems completing the questionnaire and therefore the question can be better understood from a trained interviewer and therefore reduces the errors of misunderstanding. Interviews or observations are of value in complementing the questionnaires enabling the researcher to get more adequate information. However, the patient may give answers that he thinks the interviewer wants to hear. This is most obvious when the data are collected directly by the operating surgeon or the treating radiotherapist, since the patients have a subconscious desire to produce responses that their physicians want to hear [114], [115], [116]. It is also a rather expensive method but does maximize the response rate and compliance.

In most cases, evaluation of side effects with self-assessment questionnaires is therefore the preferable method. The patient himself should complete the evaluation since the concordance between the doctor and patient has been shown to be less effective [117]. In a doctor-patient comparison, doctors underestimated the disturbance of sexual life in patients who had undergone androgen deprivation therapy but overestimated the impairment of QOL and psychosocial distress experienced by these patients [118]. Organizations like the EORTC, National Cancer Institute (NCI), and WHO suggest that QOL measurements should be:

- Quantitative
- Practical
- Multiple

There is now a consensus, except in uncommon circumstances, that questionnaires should be administered by individual self-assessment [119], [120], [121] and most instruments are now constructed to be completed in this way.

**MEASUREMENT OF SYMPTOMS WITH THE QUFW94 QUESTIONNAIRE**

The questionnaire is one of the first reliability-tested disease-specific self-assessment questionnaires for evaluation of EBRT side effects in patients with LPC. The advantage with this strategy is that it has improved patient compliance by including only relevant dimensions and is more sensitive to change in measured symptoms in the chosen population/condition. The QUFW94 questionnaire has been tested in both untreated (deferred treatment, Paper V), EBRT treated LPC patients (Paper I-IV), and compared to age-matched controls. It is therefore not just a treatment-specific formula.

The first attempt was to investigate which problem(s) the patients were most concerned about. At the beginning of the 90's, many studies were performed that measured the late side effects of EBRT. Most of these studies however were based on the evaluation of the patients major problems by the treating physician [65], [66], [67], [68], [69], [70], [73], [74]. The
assessments were often executed according to four graded scales (i.e. the RTOG/EORTC grading criteria for lower gastrointestinal and genitourinary acute and late toxicity). Spares studies were carried out using patient self-assessment questionnaires including the patients own perception of their problems following treatment with EBRT. Most of the reported studies with self-administrated questionnaires were focused on QOL following palliative treatment of hormone-refractory PC [122], [123], [124], [125]. However, at that time there were no known studies that had evaluated and compared the symptoms in a control population of PC disease free men at the same age with men treated with EBRT.

Due to the retrospective cross-sectional design of the Paper II and III studies, the patient reported levels of pre-treatment symptoms were not known. An additional comparison between treated patients and an age-matched control population was therefore performed. This would provide wider information about the magnitude of the EBRT side effects in comparison to an untreated PC free population.

It has been shown that pre-treatment information about symptoms could be difficult for the patients to remember. Litwin et al. [126] found that men undergoing RP for early-stage PC do not accurately recall their pretreatment QOL when asked 6 months to 3 years after surgery. Patients tended to remember their baseline QOL as being better than it actually was. Patients with worse post-treatment function overestimated their pre-treatment baseline function [127]. By collecting data before treatment and observing subjects longitudinally, investigators can ensure that QOL changes are analyzed in the context of any impairment that may have been present at baseline.

The differences between the patient's and the age-matched control's reported problems/symptoms were difficult to rank because the studies in the Papers II, III, and IV did not discriminate between the influence of the cancer itself and the side effects after treatment. To adequately answer the question regarding the treatment's side effects, a comparison between patients in the randomized study between EBRT vs. deferred treatment (Umeå Trial 1) was performed (Paper V).

With the knowledge of symptoms in all these groups:

- PC disease free – age-matched controls
- Untreated (watchful waiting) patients with LPC
- Treated (EBRT) patients with LPC

it is easier to adequately answer the question

"What is the impact of EBRT on acute and late side effects in LPC patients?"
HOW TO VALIDATE SELF-ASSESSMENT QUESTIONNAIRES?

The interpretation of data for therapeutic decision making requires an understanding of the methodology used to design and statistically evaluate the questionnaire. To be useful for research and clinical applications, a measure needs to be reliable, valid, and responsive.

Reliability

Reliability refers to the extent to which the measure consistently produces the same result, particularly when applied to the same subjects at different times. Therefore, it concerns the amount of error present in the assessment [128]. Measure of reproducibility could be achieved by testing the internal consistency; meaning that the questions in the questionnaire measuring the same scale function (i.e. urinary function) has a high correlation coefficient (Cronbach alpha >0.80). One way to measure the reproducibility quantitatively is to perform a test-retest. This was accomplished by delivering the same questionnaire twice (less than 1 week between the questionnaires) to the same patients [104], [129]. The correlation between the two questionnaires should be high (correlation coefficient > 0.80) if no treatment effect could influence the symptoms between the two measurements. In cancer patients this could sometimes be a problem, since sudden changes in the patients perception of symptoms/side effects could be seen. Reliability could also be evaluated with a qualitative method by interviewing the patient and assessing how his verbal descriptions of his symptoms/side effects are understood/interpreted by the staff. With this method the inter-rater-reliability can be measured, meaning that the results are the same even if two different people interview the same patient.

Validity

Validity is the degree to which the measure reflects what it is intended to measure rather than something else [130]. In other words "it measures what the researcher want to measure". The validity can be measured with multivariate methods. There are three types of validity:

- **Content validity** ("face validity"), the questions are relevant for the disease and treatment symptoms and are based on long experience (i.e. doctors with long experience of the symptoms of cancer treatment).

- **Criterion validity**, the questionnaire has high correlation to the "golden standard" of measuring the function (i.e. the Visual Analogue Scale (VAS) for measuring pain).

- **Construct validity or responsiveness**, of an instrument indicates its sensitivity to clinically significant change (i.e. changes over time, effect of a treatment, pre-treatment vs. post-treatment). Responsiveness to change is perhaps the most important criterion for the selection of a measure to evaluate patient outcomes.
THE VALIDATION OF THE QUFW94 QUESTIONNAIRE

The purpose of this study was to develop a reliable and valid questionnaire to assess the disease-specific dimensions of the urinary function, intestinal function, and sexual function domains of LPC patients treated with EBRT. Patients were given an eight-page questionnaire using modified LA-scale questions assessing four dimensions (general, urinary, intestinal and sexual function) during and after completing radiotherapy.

Inter-rater reliability test

The validation and reliability tests of the questionnaire were performed by using structured interviews with 31 patients. The inter-rater test was used to see if there was any clinical concordance between the physician, nurse, and patient regarding the symptom items in the formula. It was also used to assess whether the patient’s description of his symptoms were interpreted and graded similarly by all of the interviewers.

By calculating the Intra Class correlation coefficient (ICC) [131], a high inter-rater concordance between the two interviewers and the patients was measured. All four scales (general part, urinary-, intestinal problems and sexual function) showed ICC values above 0.6. These ICC values were high and are acceptable as reported by others [132]. Lower values (<0.7) were measured on the intestinal problem scale in some single items. These items were problems in which the patients reported “no” or very small values on the problems scale, especially at the start of the treatment. This was probably the main reason for the lower concordance.

When comparing the mean values on the different questions on the QUFW94 formula, a very good concordance between the interviewers and the patients was found (Fig. 5). The only significant difference was seen with the questions about the influence of the urinary and intestinal problems on the daily activity and the question about planning of the toilet visits because of the stool problem. Contrary to what other studies have shown, there was no significant difference between doctors, patients, and nurses in their assessment of problems in the domain of sexual function. Fosså et al. [118] showed that the doctor underestimated the disturbance of sexual life of hormonally treated patients. However, the comparison contained only 31 patients and the comparison was performed during the EBRT (week 1 and week 6-7). No change in the perception of sexual function would be expected at this time since the acute side effects of EBRT mostly are focused on urinary and intestinal problems.

Litwin et al. [116] also found that in men with early stage and advanced PC, physician’s ratings of patient symptoms did not correlate well with patients’ self-assessments of symptoms. In all domains (physical, sexual, urinary, and bowel function, fatigue and bone pain) the urologists underestimated the patients’ symptoms.
In an attempt to measure the reproducibility of the questionnaire, a test-retest was performed twice during the treatment period of about 6 to 7 weeks. By testing the questionnaire at two different times:

- At the start of the treatment (week 1, questionnaire 1 vs. questionnaire 2)
- At the end of the treatment (week 6, questionnaire 3 vs. questionnaire 4)

the test-retest reliability could be measured twice, first at the start and then at the end of the treatment. This was done to assess whether the QUFW94 could discriminate between when the patients were supposed to not have any problems (start) and when they were supposed to have the maximum degree of problems (end).

High ICC values (≥0.60 in all scales) were measured both when comparing the questionnaires at the start of the treatment and at the end of the treatment, indicating high reproducibility. These values are also comparable to values obtained in other test-retest evaluations [129], [133].

The QUFW94 questionnaire seems to yield high test-retest reliability in patients with LPC whose condition is not expected to change from one day to the next during pelvic treatment.

**Figure 5.** The concordance between the doctor, patient, and nurse. The figure shows the distribution of the mean values on four questions on the QUFW94 formula at the start and at the end of the EBRT. The higher value on the scale the more problems.
Internal consistency
The results of the present study confirm that the reliability of the multi-item scales is very high. All four scales have high α coefficient values, close to or exceeding 0.80, except on the sexual function scale at the end of the treatment. Similar levels of values were also reported by Borghede et al. [94] regarding bowel, urinary and sexual function and also by Litwin et al. [134]. A α coefficient, ≥0.70 is considered acceptable for internal group comparison [93], [94], [133], but a value of >0.80 is preferable [132].

In an attempt to better understand the single items influence in the four problem scales (i.e. urinary problems), a stepwise “deleting procedure” was performed. Each single item from the scale was deleted in order to measure if the alpha scale value had changed. If the total scale alpha value increased after the single item deletion, it was suggested that the item did not contribute to the explanation of the problem scale. Deleting of the sub-questions in the different groups of functioning scales showed that all included questions contributed well to the overall description of the studied problems.

Content validity
The content validity was performed in the initially phase of the development of the questionnaire by first performing a literature search of issues related to the morbidity of EBRT, then of questionnaires which evaluate side effects of PC patients [103]. Patient interviews and interviews with doctors (with great experience of patients treated with EBRT and evaluating of side effects during radiotherapy), were then carried out [62], [75]. After development of the questionnaire, the first version of the questionnaire was presented to relevant health care providers for feedback of the issues that arose. Thereafter, a pilot study including 10 patients with ongoing radiotherapy treatment of PC was performed. The aim of the pilot study was to make sure that the patients understood the questions and to investigate whether they had any further questions or comments concerning the questionnaire. With this knowledge about the sense (content validity) of the questions in the questionnaire, the questionnaire could be validated. It has been shown afterwards that questions from the QUFW94 questionnaire also are included in other questionnaires, which evaluate side effects of PC treatment [35], [94].

Criterion validity
In the validation of the questionnaire (Paper I) it was chosen not to report any comparison with another validated ”standard” questionnaire (i.e. QLQ-C30). Since the study was criticized because of the rather small sample of patients (n=31) we omitted the results of that comparison. However, in the first phase of the study, a comparison with the EORTC QLQ-C30 (version 1) QOL formula was performed. Unpublished results from that study did not show any change in QOL when evaluated with the QLQ-C30 (+3) formula. The QUFW94 formula however, detected an increase in acute side effects. Both were performed during the treatment period (6-7 weeks) in this patient population with LPC receiving conformal EBRT.

In Paper V, both the QUFW94 and QLQ-C30 (+3) questionnaires were used and the results of that study did not show any difference in QOL between treated, untreated or the age-matched controls, except on the social function scale. The “QOL” questions in the QUFW94 questionnaire; “limitation in the daily life caused by PC”, and “life situation” could however detect a difference between the treated and un-treated LPC patients. The EBRT patients
reported increased limitation in the daily life and worsened life situation in comparison with the patients who were un-treated (deferred treatment). The explanation for these findings may be the different type of scales used, 10-graded vs. 4-graded scales, or that the patients better understood the formulation of the questions in the QUFW94 formula. This needs to be further investigated.

However, the QUFW94 questionnaire detected a clear difference in urinary and intestinal problems between the patients and controls. Perhaps the QLQ-C 30 (+3) formula is not sensitive enough to detect QOL differences in this patient population. Litwin et al. showed that QOL in patients under observation, irradiation, and radical prostatectomy did not differ significantly [35]. Another explanation may be that 3-4 years after treatment, patients have adapted to live with their problems/symptoms (coping) and therefore they do not feel longer affected in their daily life (QOL) [135].

Further validation of the QUFW94 questionnaire was carried out by comparing the QUFW94 questionnaire with daily diary used in this study and also used by others [60], [62], [75]. This comparison (unpublished data) shows good concordance between the daily diary and the QUFW94 questionnaire when comparing reported values at the start of the EBRT (week 1) and the values at the end of the treatment (week 7, Fig. 6). However, the daily diary did not contain all items that are included in the QUFW94 questionnaire. The items that are comparable are questions regarding urinary and intestinal function (such as urinary and stool frequency, mucus, stool consistency, intestinal blood, intestinal cramp, starting problems when urinating, urgency, hematuria, and urinary pain when urinating). The daily diary also contained scales other than in the QUFW94 formula, these were graded verbally (4-graded) and on a simple no/yes scale. In this comparison, the scales in the QUFW94 questionnaire were converted in the same way as in Paper II (0-1= "No", 1.1-4.5= "A little", 4.6-7.5= "Quite a bit", and 7.6-10.0= "much" problems). In the questions where the scales in the diary contained two answer alternatives (yes/no), the questions in the QUFW94 were strictly converted to “yes” if the value was >1.0 on the scale (>1.0 to 10.0= "yes").

![QUFW94 vs Daily Diary](image)

**Figure 6.** Comparisons of mean values in 3 questions on the QUFW94 questionnaire and the daily diary at the end of the EBRT (week 7).
**Construct validity (Responsiveness)**

This study did not include information about the LPC patients’ symptoms prior to the EBRT treatment except in Paper I. In Paper I, the questionnaire could detect the expected increase in EBRT influenced acute urinary and intestinal side effects since prior information was available. The relatively small sample of patients (n=31) may make it inappropriate to state the level of pre-treatment side effects. It is therefore unfeasible to interpret the change of the symptoms over the time after the treatment. However, the urinary and intestinal symptoms, sexual function, and QOL in a population that didn’t receive EBRT (Paper V) and men without PC (age-matched controls) were evaluated. The difference in symptoms between treated and un-treated patients, and age-matched controls could therefore be compared. The study confirmed the expected increase in symptoms in the EBRT patients (Paper V).

Since 1992, all patients who have received EBRT using the conformal technique at our radiotherapy department in Umeå were given the QUFW94 and QLQ-C30 questionnaires prospectively. This is very valuable information for further analysis. Preliminary results of the reported overall urinary-, intestinal problems, and sexual function with a 5-year follow-up from that database, including almost 500 LPC patients undergone EBRT at the radiotherapy department in Umeå, are shown in figures 7a-c. These preliminary results showed improved urinary function (p=0.062) prior to treatment compared with 5-years post EBRT (Fig. 7a). The reported intestinal problems seem to increase during this follow-up (start vs. 5-year, p<0.001, fig. 7b). However, the level of the reported urinary, and intestinal problems are of mild nature (mean value <2.0 of maximum 10.0 on the scale), whereas the sexual problems rise from an already high level prior to treatment (mean=4.0) to a level of “quite a bit” to “many problems” (mean=6.0, Fig. 7c). A decline in bowel and bladder symptoms, 12 months after EBRT in comparison to 3 months after EBRT was reported in a patient self-reported study [99]. However, pretreatment bowel and bladder symptoms were uncommon. The reported sexual dysfunction after radiotherapy increased less but continually through 12 months, and it was suggested that observed treatment-related differences would decline with further follow-up. This suggestion is contrary to the preliminary results where the sexual problems increases during the follow-up from the start of EBRT up to 5-years afterward (Fig. 7c).

**ANSWER FREQUENCY**

The answer frequency among the patients in this survey was very high in all studies (over 85%). It is similar to other reported frequencies [104], [136], [137], [138].

In the control group the answer frequency was also high, above 70% of the controls answered the questionnaire (except in Paper V were 49% of the controls answered the questionnaire). The low frequency is however in the same magnitude or higher than reported in other studies [35], [102].

The technique with two letters of reminder and thereafter a reminding phone call if no answer was returned could be the reason for the high answer frequency among the patients. Paper V had lower answer frequency among the controls than in the other studies including age-matched controls (Paper II, III, and IV). This could be due to the reminder phone call being omitted and only one letter of reminder was sent out to the non-responders. There was no difference in mean age (71 years) between the recipients in Paper II or Paper V at the time of the questionnaire.

Further analysis of the answer frequency didn’t show any significant difference between the answer frequencies regarding the different categories of questions (general part, urinary, intestinal problems and sexual function, Paper I).
No significant difference in the answer frequency was seen when the patients and control subjects were divided into subgroups according to age (50-69, 70-74, >74 years).

Mean age at the time of answering the 8-yr follow-up questionnaire was 73 years (range 55-85 year) in both patient and control groups. The mean age of those not answering at the 8-year follow-up questionnaire was higher (77 yr, ns), in both groups (Paper III).

The high response rate among patients suggests that the questions were easy to answer but could also be due to that these men are especially interested in addressing both the general and disease-specific concerns that impact on their daily quality of life [134].

Figure 7a, 7b, and 7c. The mean values and 95% confidence interval (CI) of the prospective evaluation of urinary (7a), intestinal problems (7b), and sexual function (7c) with QUFW94 of the LPC patients with a follow-up from the start of EBRT and up to 5-years after treatment. The higher value on the scale the more problem.
SYMPTOM EVALUATION

The general part of the questionnaire
The patients' physical ability was very good despite the advanced age. More than 75% of the patients and 80% of the controls reported no problems with "moving freely indoors and outdoors". However, about 50% of the patients reported that their PC in some way limited their daily activity. A small difference was detected between the RT (mean=1.8) and DT (mean=0.7) patients regarding the "limitation in the daily life" caused by their PC (p=0.001, Paper V).

No difference was seen between the patients and controls regarding reported limits in their daily activity caused by other diseases. About 50% reported problems such as hip or other joint problems, hypertension, and angina. Comparing different medication, this was rather similar in patients and controls except that in the EBRT group, a much higher proportion of patients used medication for the prevention of diarrhea.

Sixty percent of the patients and 80% of the controls reported very good "life situation in general" at the first follow-up (Paper II and III). No change was seen in "life situation" in the patient group between the 4 year and 8 year follow-ups.

Other symptoms included in the QLQ-C 30 (+3) formula such as fatigue, nausea, and pain did not differ between the two patient groups with or without EBRT (Paper V) and was not reported as a problem. Fatigue for example was reported by Fosså et al. [118], using the same questionnaire QLQ-C 30 (+3), as a general problem in all four patient groups (DT, androgen deprivation, EBRT, and RP).

Urinary symptoms
Almost all patients in these studies received total tumor doses less than 70 Gy. The treatment technique used in most cases was the conventional 4-field box technique, including larger treatment volumes than treatment techniques used today. However, our department used 2 Gy per fraction while many centers use 1.8 Gy per fraction, suggesting that their side effects at least should not be worse. The reported late urinary problems in the patients treated with the conventional technique (Paper II) were fairly high. Fifty percent of the patients indicated some form of urinary problem, strictly defined as more than "one" on the L-A scale, to the question "Do you have problem with your urinary tract?". However, most of the problems were of mild character.

In the study 4-years after EBRT with conventional technique (Paper II), 33% and 9% of the patients reported problems with leakage and hematuria, respectively. Similar proportions of problems with leakage (33%) and hematuria (12%) were also seen with self-assessment questionnaires in a randomized dose-response study of conventional technique vs. 3DCRT technique [76]. The follow-up was more than 2 years. The group of conventionally treated patients received a field reduction (9x9 cm) after 46 Gy and a total tumor dose of 70 Gy. Dearnaley et al. [64] showed in a randomised study of conventional vs. conformal treatment that there were no differences between groups in bladder function >2 years after treatment (53 vs. 59% > or = grade 1, p=0.34; 20 vs. 23% > or = grade 2, p=0.61). Koper et al. [58] also reported the non-reduction in acute bladder toxicity between conventional and conformal technique.
The numbers needing protection for urinary incontinence (pads) was increased in our patients (19% in Paper I and 17% in Paper V) in comparison with about 0% to 11% which others have reported [76], [139], [140]. An explanation of the high proportion of patients using pads could be that the whole bladder was included in the target volume. Another clarification could be the straight and simple answer alternative (“No” or “Yes”) and that no question about frequency of using pads (i.e. numbers of pads per day) was missing in that version of the QUFW94 questionnaire. In comparison to surgery, where more than 30% of the patients used pads, the proportion of patients needing pads seems rather low [34], [99], [140], [141].

Potosky et al. [127] reported that more radical prostatectomy patients reported leaking urine (13.8% in RP vs. 2.3% in EBRT patients) and wearing pads to stay dry in a higher degree (28.1% in RP vs. 2.6% in EBRT patients). In the present study, no relation could be seen between urinary problems and the stage of the tumor. In a study of patients with deferred treatment an influence of the T-stage and the use of pads were found [139]. The patients with localized PC (stage T1a to T2b) were compared to patients with advanced disease (stage T3 and T4), and a significant higher numbers of patients with more advanced disease were using pads.

Jonler et al. [139] and Beard et al. [142] reported similar levels of urinary problems (about 30%), as in the patients treated with EBRT (Paper II). About 30% of the patients reported incontinence and it was reported as one of the most frequent urinary problems (Paper II and V). This is a higher level of incontinence than reported by others [143], but still not worse than patients who had undergone surgery [100]. Favorable incontinence morbidity results of brachytherapy have recently been shown by Benoit et al. [144] from the Medicare population. A diagnosis of urinary incontinence was seen in only 7% of the patients, but others have reported higher incontinence rates [145] especially after TUR-P [86], [87].

**Gastrointestinal symptoms**

Many patients in the population included in this study suffered from side effects of the gastrointestinal tract. Almost 60% of the patients receiving conventional treatment (Paper II) with doses up to 66 Gy reported intestinal problems. However, this high percentage was probably due to the high sensitivity of the questionnaire and the fact that problems were strictly defined problem as >1 on the scale. Among the 60% of the patients, 50% marked minor problems (1-4 on the scale). Fifty percent of the patients reported that these intestinal problems influenced their daily activities in some way (30% little, 10% quite a bit, 7% very much). The most frequently reported intestinal problems were intestinal blood, cramps, mucus, and leakage. Four patients (2%) had complications that were so serious that had to undergo surgery and received a stoma. The results show that the questionnaire detects late side effects after EBRT in patients with LPC and that these results are at the same level as reported by others [68], [69], [146].

In comparison with an age-matched control population, the patient group undoubtedly had more problems. Fifteen percent of the controls reported intestinal problems (>1 on the scale). There was a trend within the patients who were studied two years after EBRT to report a somewhat higher frequency of intestinal problems in comparison to 4 years after EBRT (unpublished data). This data is in accordance with Pilepich et al. [67] who also reported an increased incidence of problems during the second and third year after RT. Therefore further follow-ups were performed with the same patient population 8 years post EBRT (Paper IV). However, the reported late side effects (urinary, intestinal problems and sexual function) did not change significantly during this prolonged follow-up period.
The volume of the irradiated tissue and the influence of the grade on the side effects are often discussed. Many studies, as expected, report that a larger target volume correlates with more complications [73], [147], [148]. The present studies didn’t show any relationship between side effects and the treatment volume. This was despite the fact that 115 out of 181 patients received reduced treatment volumes after 50 Gy (Paper II and III).

This is probably due to the fact that this minor damage had already been induced at the dose of 50 Gy and it has already been shown by others that bowel complications increase after a dose of 45 Gy [149]. Dose-response induced complications in tumor doses <70 Gy were neither reported in the RTOG 75-06 [69] nor RTOG 77-06 studies [68].

In the rather small sample of patients receiving conventional (n=31) or 3D-CRT (n=28) treatment (Paper V) we did not detect any difference regarding bowel symptoms between the two different treatment techniques, conventional 4-field box vs. 3D-CRT technique. The reason for this is probably the small sample of patients and the relatively low dose <70 Gy. It was also described earlier that increased intestinal problems were reported within LPC patients treated with conventional 4-field box technique in comparison with those treated with 3D-CRT [60].

However, these patients received doses below 70 Gy and numerous articles show that doses over 70 Gy gives more serious complications [66], [69], [73], [147], [149], [150]. Many studies show that the conventional four-field box technique induces more side effects than the 3D-CRT technique [60], [64], [151].

Dea naley et al. [64] showed in a randomised study of conventional vs. 3D-CRT that significantly fewer men developed radiation-induced proctitis and bleeding in the conformal group than in the conventional group (37 vs. 56% > or = RTOG grade 1, p=0.004; 5 vs. 15% > or = RTOG grade 2, p=0.01).

Soffen et al. [41] showed in a retrospective comparison study that patients treated up to 68 Gy with conventional vs. 3D-CRT, the percentage of patients with acute urinary and rectal symptoms were similar, although fewer patients treated with 3D-CRT needed bowel medication. Symptom duration also showed a decreasing trend in the 3D-CRT group. All of this data favourably demonstrates decreased toxicity with conformal radiotherapy (small fields) in comparison to the conventional box-technique for PC (large fields).

It is now well known that EBRT induce more problems with bowel function than prostatectomy [99], [102], [140], [152], but these increased complications don’t seem to affect the patient’s QOL in relation to those with prostatectomy [35], [56], [100], [141].

**Sexual problems**

**Characteristics of patients and control subjects**

For the analysis of sexual problems (Paper III), the patient group was divided into two subgroups:

- **RT** - treatment with EBRT only (n=104)
- **RT+A** - treatment with EBRT plus castration (ablatio). Castration was performed by either orchectomy, Estramustin or GnRH (n=77).
At the time of the distribution of the questionnaires (Paper II and III, 1991), 36 patients (20%) had progressed to a more serious stage after primary radiotherapy. Twenty-seven out of the 36 patients primarily receiving radiotherapy had only received endocrine therapy at the time of the investigation and were therefore included in the RT+A group.

**Instruments**

Diseases of the prostate, prostatitis, prostatodynia, benign prostatic hyperplasia (BPH), and PC interfere with sexual function [153]. Since the American Urological Association (AUA) issued their position statement in 1990 stating that male sexual dysfunction is a recognized disease entity, many studies have examined the interrelation between sexuality and the prostate. This disorder attracted more interest and was included at least as one dimension of the more comprehensive assessment of QOL; either as a single item or as a sexual function-specific measurement [113]. O’Leary et al. [129] developed a brief 11 sexual function item inventory to capture the key areas of male sexuality as clearly and concisely as possible. However, men were recruited from a sexual dysfunction clinic and a general medicine practice and no total summary score could be measured. Helgason et al. [154] developed a more complex sexuality measurement instrument, the Radiumhemmet Scale of Sexual Function (RSSF).

The QUFW94 questionnaire contains 5 items about the sexual function (Table 3). Even if it is rather few questions they cover most of the dimension of the sexual dysfunction as in other more complex questionnaires such as the International Index of Erectile Function (IIEF) [155], RSSF [154].

The IIEF formula has been validated in many languages and addresses five relevant domains of male sexual function in 15 items. The IIEF is ready for future use and appears promising and may help to learn more about the impact of PC on sexual function [155]. A short version of this instrument, IIEF 5, [156] has been delivered prospectively to all patients receiving curative EBRT during this year (2000) in Umeå and is also included in the follow-ups. This might provide more information about the patients sexual function after EBRT treatment and will also be used for further validation of the sexual scale of the QUFW94 questionnaire.

**The influence of age on sexual function**

The RSSF formula has been used to evaluate sexual function in healthy aging men and in men with prostate diseases, with or without treatment [154]. The data showed that in men aged between 50 and 88 years old, 13% reported that sex was very important to them, 29% that sex was important, 41% that sex was a spice to life, and 17% that they could live without or never think of it. With this background information of aging Swedish men, 50 to 80 years old, it appears that studying sexual function and PC is of importance. However, this questionnaire is very complex and may not be useful in other populations [153].

The EBRT patients indicated higher levels of sexual problems than age-matched controls (Paper III). The younger (<70 years) hormonally treated patients (RT+A, median=8.5), reported almost doubled sexual problems in comparison to the older RT+A patients (70-74 years, median=4.8).

Paper III has shown that 60 % of the younger controls (<70 years), reported sexual activity during the last month. The sexual activities of the patients were decreased in comparison to
the controls while 42% and 14% in the RT and RT+A patient groups were sexual active, respectively.

For patients older than 74 years of age, decreased sexual function was not such a big problem despite abolished desire and erection. Decreased sexual activity is probably accepted or adapted by aging and treated LPC patients.

Regarding the sexual problems in general, no difference between the patients treated with or without hormonal treatment (RT or RT+A) could be detected. However, a clear decrease in desire and erection was reported in the hormonally treated patients (RT+A). This finding was also stated by van Andel et al. [157] who showed that patients receiving no hormonal therapy reported significantly better sexual function in all measurements over their counterparts being hormonally treated.

Beckendorf et al. [158] found that patients with stage A had better sexual function than those with stage D. This finding of stage influence of sexuality was not found in this patient population (Paper III).

**Sexual activity**

A strong factor predicting the preservation of the potency after EBRT seems to be the pretreatment level of sexual activity. If the frequency of intercourse is more than three times per month prior to treatment, the prognosis of maintaining potency remains good [78], [158]. The patient's age was also a factor for the frequency of intercourse reported in Paper III and by others [158] while younger were more sexually active.

These wise words by Bob Krane (erection function researcher) seem to be a good description.

"if you don’t use it, you lose it"

**Partner**

Most of the patients (86%) were living with a partner. However, no difference in sexual function could be detected between the patients living with or those without a partner (Paper II). One aspect when evaluating the sexual function is if there is any discrepancy in experience of the sexual life (function) between the patient and the sexual partner.

In a pilot survey of LPC patients following 3D-CRT, 61% of the partners agreed precisely with the level of sexual function reported by the patients prior to the treatment. The partner's responses more closely mirrored those of patients after the treatment, than before [77].

**THE INFLUENCE OF SEXUAL FUNCTION ON QOL**

During the last century, the influence of treatment for PC on sexual function has been studied worldwide. However, sexuality, sexual function, and sexual activity are complex to study since it also involves a relation (female) and is often associated with much “taboo”. One way
to study this domain is by using validated questionnaires, since only the patient himself can report on his sexuality. However, all aspects of sexuality might be difficult to discover with quantitative measurements and qualitative studies on this subject might highlight some of these difficulties with questionnaires.

Sexual function is an important part of QOL and if treatment is considered, the patient should be thoroughly informed about the eventually sexual dysfunction following the treatment. QOL is substantially diminished by erectile dysfunction regardless of the patient population predominantly in the domains physical role, emotional role, vitality, and social function when compared to age-adjusted standards. However, the patient selection was skewed because the patients were self-referred because of impotence and the patients who did not seek help because of their erectile impotency may not have an impaired.

The QOL in patients under observation, irradiation, and radical prostatectomy did not differ significantly [35]. The untreated patients reported a sexual function twice as good as those receiving surgery or being irradiated. They were also less concerned by the sexual impairment.

The lowest reduction of sexual life (as determined by the PAIS instrument [160]) occurred in the observation group in comparison to hormone, irradiation, or radical prostatectomy treatment [118]. Unfortunately, results from the randomized study (Paper V) cannot report the patient evaluated sexual function since the trial is recently closed. Information about patients that have progressed and received hormonal treatment would uncover the randomization.

Figure 8. The mean social function scale values on the QLQ-C30 (+3) formula divided into different age groups reported by the patients treated with EBRT (filled square) or deferred treatment (DT) and the age-matched controls. Higher score refers to better function.
GENERAL EFFECT OF AGE ON QOL
Complication rates in the treatment of LPC have decreased during the last 20 to 40 years. This decrease occurred despite that the average age of treated patients had increased during the same period [161].
The general effect of age on the patients' QOL was studied by Huguenin et al. [162] by using the QLQ-C30 formula. They found no significant difference in QOL five years after RT between the elderly patients (>74 years old) and the matched younger patients. Nor was there any difference in late toxicity between the two age groups. This was contrary to the results in Paper V where the RT patients >75 years old reported decreased social function in comparison to both the DT patients and the controls (Fig. 8).
Mameghan et al. [73] had earlier reported that older age at the time of radiotherapy was a significant patient-related risk factor for late radiation-induced bowel complications.

THE INFLUENCE OF COMORBIDITY ON SIDE EFFECTS/SYMPTOMS
Patients with a history of comorbidity have also been found to have an increased risk of EBRT reactions. Diabetes has been reported to be one factor that increases the urinary and gastrointestinal side effects [163], [164] as well as worsening the preservation of the erection function [88]. This increase in complications may be a reflection of increased vascular morbidity directly associated with diabetes or of the general poorer physical condition of these patients. No increase in urinary or gastrointestinal morbidity was observed in patients with known histories of hypertension, stroke, or heart disease [163].
We could not detect any significant influence of other illness on late urinary and intestinal side effects in this patient population (Paper II). This would perhaps be explained by the fact that the questionnaire contained only one question (No. 4, Appendix 1) about limitation in daily life caused by other illnesses. Experience has shown that patient reported illness should probably be verified from the medical records, this was not undertaken in this population. As a result, this study may have missed some patients with diabetes or other illness. This information has now been collected and an extended evaluation of the influence of other illness will soon be reported.
A history of current or past tobacco use significantly decreased the potency rate after treatment. None of the LPC patients who smoked at the time for the 3D-CRT treatment were potent 6 years later, as compared with 66% of the men who had never smoked [165]. Unfortunately, no information about the patients' smoking habits was available at the time of the present studies, but such data is currently being accumulated.
CONCLUSION

- A localized prostate cancer-specific self-assessment questionnaire (QUFW94) for evaluating urinary, intestinal symptoms and sexual function has been developed. The questionnaire has been proven to be valid and has high reproducibility for evaluations of symptoms in this patient population. QUFW94 could also detect a difference between patients treated with external beam radiotherapy and patients with deferred treatment. The questionnaire could also detect the difference between the patient groups and age-matched men without prostate cancer.

- Conventional EBRT in the late 80's induced a large number of minor late urinary and intestinal problems, especially compared to the age-matched controls. The most important urinary side effects were urgency and leakage. The most important intestinal side effects were blood, mucus, and leakage.

- In comparison to age-matched controls, the patients reported decreased sexual function although in patients younger than 70 years, their sexual activity was comparable. Addition of castration to radiotherapy increased the sexual problems, especially in patients younger than 70 years. For patients older than 74 years of age, decreased sexual function was not such a big problem despite abolished desire and erection.

- Evaluation of side effects of 4-year after treatment well predicts the level of very late side effects (8-years) of EBRT.

- Similar level of quality of life was seen, in patients treated with EBRT, in comparison to untreated patients (DT), except on social function. No difference in QOL was seen between the patients in comparison to PC disease free men. This could be due to coping of the symptoms or such a small magnitude of side effects that it not influences the QOL.
Randomized trials are under discussion to compare if there is any difference in survival between EBRT and prostatectomy, and also in comparison to deferred treatment in patients with LPC. Until these results are available and during the development of new treatment techniques, QOL and side effects should be compared by using the same instrument to better describe treatment symptoms with the different methods.

The following studies are in progress:

- Prospective evaluation of urinary and intestinal side effects (acute and late), sexual function, and QOL in a large series of LPC patients treated from 1992 onwards with different techniques (dose-escalation ≤80 Gy, HPCRT, and IMRT).

- Extended validation of the QUFW94 questionnaire with complementary items for patients undergoing surgery.

- Comparison of QOL and symptoms between EBRT and surgery.

- Evaluation of the influence of sexual function on QOL in the randomized trial between EBRT and deferred treatment.

- Evaluation of QOL and side effects in the randomized trial between the hormonal treatment, anti androgens with and without EBRT (SPCG-7/SFUO-3).

Prostatacancer (PC) är idag den vanligaste cancerformen bland män i Sverige och medelålder vid diagnos är 74 år. Hos 60-70 % av dessa patienter är sjukdomen lokaliserad till prostata utan spridning till andra organ. Vid tidig lokaliserad PC finns det inga säkra vetenskapliga resultat som talar för att dagens behandlingsmetoder, strålbehandling eller operation ger bättre överlevnad än exspektans. Det är viktigt att den behandling som erbjuds inte orsakar biverkningar och försämrar livskvaliteten mer än vad själva grundsjukdomen gör. Förekomsten av biverkningar och framför allt hur patienterna själva upplever dessa kan då få en avgörande betydelse för val av behandlingsform, vilket då gör det viktigt att studera detta problem.

Enkäten har skickats till patienter med PC som strålbehandlats samt till en åldersmatchad kontrollpopulation utan PC för att få information om urinvägs och avföringsproblem samt sexualfunktion. Patienterna har följts i upp till 8 år efter avslutad strålbehandling. Studien visar att de som fått strålbehandling i slutet av 80-talet hade mera urin- och avföringsbesvär i jämförelse med kontrollgruppen samt en försämrad sexualfunktion. Detta är mest uppenbart hos patienter som är under 70 år och som även fått hormonbehandling. Två tredjedelar hos kontrollgruppen under 70 år är sexuellt aktiva, vilket är jämförbart med de som endast strålbehandlats.

ACKNOWLEDGEMENTS

This study was performed at the Department of Radiation Sciences, Oncology, Umeå University. During my research, first as an oncology nurse and than as a doctoral student I have received much support from many persons.

I wish to express my sincere gratitude to:

Anders Widmark, my supervisor. For introducing me into the field of cancer research and for never stop pushing me forward when I sometime thought that I have reached the “blind alley” and there was no way out of it.

Lars Franzén, my assistant supervisor, Head of the Radiotherapy Department. For always supporting me in my work, both at the department of radiotherapy and as research nurse.

Roger Henriksson, Head of the Department of Radiation Sciences, Oncology. For nice discussions and giving me the opportunity to go further on with my research work at the Clinical Research Unit (KFE). “Alf” thanks you!

Bo Littbrand, earlier Head of the Department of Oncology. He has always giving me support in my work with interest and giving me the opportunity to work both at the Radiotherapy Department and as a research nurse at the department of oncology.

Björn Tavelin, my co-author, for all statistical support and nice discussions about everything (and sometimes about nothing).

Barbra Frankel, for correcting the English in several manuscripts.

James Turner, radiotherapist from England, for correcting the English in this dissertation.

Pia Granlund, and Monica Sandström, for skilful secretarial assistance with all the administrative work.

Jan-Erik Damber, earlier Head of the Department of Urology and co-author, for good cooperation and knowledge in the urological oncology.

Hans Modig, co-author, for good cooperation and knowledge in the urological oncology.

All colleagues at the Radiotherapy Department, for endless support during the years and always being helpfully. However, especially thanks for giving me technical assistance in my work has to be given to these colleagues at the Radiotherapy Department:

Barbro Widmark, head nurse, for always supporting me and giving me all possible assistance to have the opportunity to go on with my research.

Britt Lindström, for helping me to collect data and feeding the data in to the computer. Perhaps these words will give you pleasure “The daily diary era is soon over”.

53
Birgitta Bern, for helping me to collect patient data from the treatment planning system.

Eva Nyström and Karin Brännström, for helping me with the patient information and delivering of the questionnaires.

Lions’ Cancer Research foundation at Umeå University, the Swedish Cancer Society, The Swedish Association for Cancer and Traffic Victims (CTRF), Gunnar, Arvid, and Elisabeth Nilssons Cancer Foundation, Elsa and Folke Sahlbergs Foundation at Umeå University, JC Kempes Foundation at Umeå University, and The Swedish Foundation for Health Care and Allergy Research (Vårdalstiftelsen) for all financial support.

Finally but not least, my family Sonja, Linda, and Hanna, for the support and understanding during this period of the work with this dissertation (mostly in the office in the “garage”)

REFERENCES


Please, write date: ...........................

1. Which of the following statements do you think best describes your situation today?

   Mark an "X" in the square after the statement, which is the most appropriate for you.
   *Only one box should be marked in each section.*

I can get around without difficulty both indoors and outdoors, without wheel chair, crutches, or help from any person  

I can get myself around with some difficulty both indoors and outdoors, without wheel chair, crutches or help from any person.

I can get myself around both indoors and outdoors without anyone helping me, but I have to have support such as cane, wheel chair, crutches etc.

I can move by myself around indoors, but I need help from someone if I have to go outdoors.

Almost all of my time I must spend in a wheel chair.

I am forced to spend almost all of my time lying in bed.
Appendix 1

Answer these questions by marking an "X" in the appropriate box

2. How would you describe your existence in general?

<table>
<thead>
<tr>
<th>Very good</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very bad</th>
</tr>
</thead>
</table>

3. Does your prostatic cancer disease limit your daily activities?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

4. Are you limited in your daily activity by some other diseases?

No  ❑  Yes  ❑

If yes, what disease/diseases: ..............................................................

...........................................................................................................

5. Do you use any medicines for your bowel/stomach?

No  ❑  Yes  ❑

If yes, what medicine/medicines, strength, and number/day:

...........................................................................................................

6. Do you have urinary problems?

None  ❑  ❑  ❑  ❑  ❑  ❑  ❑  ❑  ❑  ❑  ❑  ❑  Very much

<table>
<thead>
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<th>None</th>
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<th>3</th>
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<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

Answer these questions by marking an "X" in the appropriate box

7. How many times do you urinate/24 hours?

8. How many times during the night do you have to go up to urinate?

9. Do you have pain when you urinate?

10. Do you have problems to start urination?

11. Do you have urinary leakage (incontinence)?

12. Do you use diapers?

No  □  Yes □  Numbers/day ................
Answer these questions by marking an "X" in the appropriate box

13. Do you have urgency?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

14. Do you have blood in your urine?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

15. Do you have a catheter?

No □

Yes □ Since when? ..............

16. How much do your urinary problems interfere with your daily activity?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

17. If you have described some urinary problems, which problem(s) do you think is/are the worst?

.............................................................................................................................................

.............................................................................................................................................
### Answer these questions by marking an "X" in the appropriate box

18. Do you have stool problems?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

19. How many stools/24 hours do you have?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | or more |

20. How is the consistency on your stool?

<table>
<thead>
<tr>
<th>Very loose</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very hard</th>
</tr>
</thead>
</table>

21. Do you have fecal incontinence?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

22. Do your stool problems make you plan your visits to the toilet?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>

23. Have you experienced nausea?

<table>
<thead>
<tr>
<th>None</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very much</th>
</tr>
</thead>
</table>
Answer these questions by marking an "X" in the appropriate box

24. Do you have problems with excessive gas?

None | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | Very much

25. Do you use diaper (because of stool leakage)?

No  |  ❑  | Yes | ❑  | Numbers/day ..........

26. Do you get cramps when you pass your stools?

None | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | Very much

27. Do you have mucus in your stools?

None | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | Very much

28. Do you have blood in your stools?

None | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | Very much

29. Do you have any special dietary habits because of your intestinal tract?

No  |  ❑  | Yes | ❑  

If yes,  low-fat diet | ❑  
high-fiber diet | ❑  
low-milk diet | ❑  
other | ❑  ..................
Answer these questions by marking an "X" in the appropriate box

30. How much do your stool problems influence your daily activities?

| None | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very much |

31. If you have described some intestinal problems, which problem(s) do you think is/are the worst?

32. Do you have sexual problems?

| None | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very much |

33. Do you have a partner (wife, company)?

No ☐ Yes ☐

34. Do you feel desire for sexual activity?

| Very much | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | None |

35. Can you have erection?

| Very much | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | None |
Answer this question by marking an "X" in the appropriate box

36. If you have erection, is it enough to have intercourse?
   No ☐       Yes ☐

37. Have you had intercourse/fondling during the last:
   week ☐    month ☐   year ☐     not during the last year ☐

38. If you have described some sexual problems, which problem(s) do you think is/are the worst?
   ........................................................................................................
   ........................................................................................................

39. How is your life situation in general?
   Very good 0 1 2 3 4 5 6 7 8 9 10 Very bad

THANKS FOR YOUR COOPERATION!