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Late urinary morbidity and quality of life after radical prostatectomy and salvage radiotherapy for prostate cancer*

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ABSTRACT

Objective: There is a paucity of knowledge of long-term urinary morbidity in patients treated for prostate cancer (PCa) with radical prostatectomy (RP) and salvage radiotherapy (SRT). Improved long-term survival calls for heightened awareness of late effects from radiotherapy after RP. The purpose of this study was to assess late urinary morbidity and its potential impact on quality of life (QoL) in patients treated with RP plus SRT compared with patients treated with RP alone.

Materials and methods: Long-term morbidity and QoL were evaluated using a cross-sectional design with validated questionnaires in urinary morbidity (Danish Prostatic Symptom Score (DAN-PSS)) and QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)). Included were a total of 227 patients treated with SRT and 192 treated with RP in the periods 2006–2010 and 2005–2007, respectively.

Results: Weak stream, straining, frequency and nocturia were significantly more prevalent in patients treated with RP + SRT than in patients treated with RP alone. Patients treated with RP + SRT generally suffered from more severe urinary symptoms. The QoL scores of the two treatment groups were not statistically significantly different, but a high level of urinary morbidity was significantly related to decreased QoL (p = 0.000).

Conclusions: Patients treated with SRT have a higher rate of urinary morbidity than do patients treated with RP alone. Severe urinary morbidity was significantly related to decreased QoL, but did not differ between the two treatment groups.

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Introduction

Lower urinary tract symptoms (LUTS) are prevalent in patients treated for prostate cancer (PCa) with either radical prostatectomy (RP), radiotherapy or a combination of RP and salvage radiotherapy (SRT), and LUTS can have a major impact on the patients' quality of life (QoL).

As a high number of patients undergo curative treatment for PCa, it is necessary to consider the severity of LUTS and their potential impact on QoL [1].

RP is often the treatment of choice for patients with clinically localized PCa. Approximately 15–25% of patients who undergo RP for clinically localized PCa will experience biochemical failure [2]. If the patient is considered to be at high risk based on examination of the operation specimen, he is offered adjuvant radiotherapy (ART) right away; if the failure is diagnosed later as a rise in prostate-specific antigen (PSA), SRT is the generally accepted and potentially curative treatment option [3–6].

There is little knowledge of long-term urinary morbidity in patients treated for localized PCa with a combination of RP + SRT. When considering SRT as a treatment option for patients after surgery, one has to be aware of potential side-effects. The improved long-term survival in patients treated for PCa makes the questions of late morbidity and QoL even more important.

The purpose of this study was to evaluate retrospectively late urinary morbidity and its impact on QoL in patients treated with RP + SRT compared with patients treated with RP alone.

A comparison of LUTS and QoL in the two treatment groups provides relevant and important aspects for consideration in relation to optimally managing patients with biochemical failure after RP.

Materials and methods

Study population

This cross-sectional survey investigated late urinary morbidity and QoL after treatment for localized PCa. The study...
population consists of two different cohorts of PCa patients: a national cohort of 270 patients including all the patients treated with SRT in Denmark in the period from 2006 to 2010 because of biochemical failure after RP, and a cohort of 247 patients treated with RP alone (Figure 1). The guidelines for treatment were in keeping with the Danish Prostate Cancer Group (DAPROCA) and the European Association of Urology (EAU) guidelines for PCa [7,8].

Before RP, all of the patients were diagnosed with clinically localized PCa and were staged by digital rectal examination and transrectal ultrasonography. The diagnosis was confirmed by six to 12 prostate biopsies. RP was performed in the period from 1999 to 2009 either by an open procedure or by a robot-assisted laparoscopic procedure. Before 2005, all of the patients had a pelvic lymphadenectomy in the fossa obturatorii. After this date, only patients with intermediate or high risk according to the D’Amico risk score had pelvic lymphadenectomy [9].

**SRT cohort**

SRT has been defined as the administration of radiotherapy to the prostatic bed in patients with biochemical failure after RP and no evidence of distant metastatic disease.

The patients were treated with a median dose of 69 Gy (range 66–74 Gy) in 2 Gy daily fractions to the prostatic bed and the location of the seminal vesicles if there was a high risk of invasion of the vesicles. Treatment was performed according to the Radiation Therapy Oncology Group (RTOG) guidelines [10]. Over the years, the SRT technique has changed, and SRT was given either as three- to four-field conformal, intensity-modulated radiotherapy or as volumetric arc therapy. Pelvic lymph nodes were not included in the target volume. A total of 102 patients received neoadjuvant androgen deprivation therapy (ADT) for a median of 14.8 months (range 1.2–98 months). The physician initiated ADT based on clinical assessment and without using standardized criteria.

In total, 267 patients treated with RP + SRT in Denmark during the period 2006–2010 were invited to participate in the survey [11].

**RP cohort**

The RP cohort is a subset of a larger group of patients who had already completed a questionnaire survey for another study that compared long-term morbidity after external beam radiotherapy or RP for PCa [12]. The RP cohort consists of 247 patients treated with RP at the Department of Urology, Aarhus University Hospital, Denmark, in the period from 2005 to 2007.

**Assessment of lower urinary morbidity and its relation to QoL**

Patient- and treatment-related factors were retrieved from the patients’ medical charts at the Department of Oncology and Urology. Late morbidity after treatment in the RP and SRT cohort was defined as morbidity persisting beyond day 90 or developing later than day 90 after treatment.

**Questionnaires**

The Danish Prostatic Symptom Score (DAN-PSS) questionnaire was used to evaluate late urinary morbidity [13]. QoL was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0) [14].

The DAN-PSS questionnaire was developed and validated for patients suffering from LUTS due to infravesical prostate obstruction [13], and the EORTC QLQ-C30 provides a reliable and valid measurement of QoL in cancer patients [14].

The RP cohort received the questionnaire in the period from April to June 2010, and the RP + SRT cohort from October to November 2011. The DAN-PSS questionnaire
consists of 12 questions concerning LUTS. Questions 1–4 relate to obstructive symptoms, questions 5–8 to irritative symptoms and questions 9–12 to miscellaneous symptoms. Each of these 12 questions is divided into a part A, concerning the frequency and severity of the symptom during the past 2 weeks, and a part B, addressing the bother of the symptom. In each question, the degree of severity and bother is scored from 0 to 3. The symptoms were dichotomized into no clinical symptoms (0) and clinically severe symptoms (2–3). Bother scores were similarly dichotomized into no bother (0–1) and substantial bother (2–3). The total DAN-PSS index was calculated by multiplying the symptom score by the corresponding bother score and then adding the results. The prevalence and bother of each symptom were calculated as the percentage of patients having a score above 1 of the total number of answers to the question.

The EORTC QLQ-C30 (version 3.0) is a 30-item questionnaire, incorporating nine multi-item scales: five functional scales, three symptom scales and a global health and QoL scale.

Analyses from the QLQ-C30 were performed after linear transformation of the scores on scales from 0 to 100, according to the questionnaire manual. A high score on the global health/QoL scale and functional scales represents a high level of QoL. A difference in mean score of 5–10 between the two treatment groups was considered a minor difference. A difference >10 was considered clinically significant, according to the questionnaire manual [15].

**Statistical analysis**

Comparison of patient characteristics and differences in symptoms between treatment groups was performed with a chi-squared test for categorical data and Wilcoxon rank test for continuous variables. The Spearman rank correlation coefficient was used to test for correlations between the global QoL scale and the total DAN-PSS index. A stratified test, using the Wilcoxon rank sum test, by stratification for age, was performed to test the difference in global QoL between the two treatment groups and to test for the influence of ADT and concurrent comorbidity.

The monotonic association between the global QoL and the DAN-PSS index was tested with an age-adjusted Spearman correlation. A value of $p < 0.05$ was considered statistically significant. Data were analysed with STATA version 12.0 (Stata, College Station, TX, USA).

**Results**

The patient and tumour characteristics are shown in Table 1. The response rate to the questionnaire survey was 86.1% for the SRT cohort and 88.3% for the RP cohort (Figure 1). The median time from treatment to answering the questionnaire was 23.1 for the RP + SRT cohort and 41.7 for the RP cohort.

**LUTS**

All of the patients, except for one, had experienced at least one symptom during the previous 2 weeks. Among those who experienced one or more symptoms, 67 patients (16.0%) reported that they were not bothered by their symptoms.

**Table 1.** Clinicopathological, biochemical and treatment characteristics of salvage radiotherapy (SRT) and radical prostatectomy (RP) patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SRT ($n = 227$)</th>
<th>RP ($n = 192$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RP PSA level (ng/ml)</td>
<td>15.8 (3.2–91)</td>
<td>11.6 (1.5–61)</td>
</tr>
<tr>
<td>Pre-SRT PSA level (ng/ml)</td>
<td>0.5 (0.1–31)</td>
<td>–</td>
</tr>
<tr>
<td>Pathological Gleason score</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&lt;7</td>
<td>43 (18.9)</td>
<td>85 (44.3)</td>
</tr>
<tr>
<td>7</td>
<td>124 (54.6)</td>
<td>92 (47.9)</td>
</tr>
<tr>
<td>8–10</td>
<td>52 (22.9)</td>
<td>9 (4.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (3.5)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>Pathological T stage</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PT1–PT2</td>
<td>52 (23.0)</td>
<td>16 (8.3)</td>
</tr>
<tr>
<td>PT3–PT4</td>
<td>152 (67.0)</td>
<td>169 (88.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (10.1)</td>
<td>7 (3.6)</td>
</tr>
<tr>
<td>Surgical margin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive</td>
<td>143 (63.0)</td>
<td>45 (23.4)</td>
</tr>
<tr>
<td>Negative</td>
<td>71 (31.3)</td>
<td>141 (73.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (5.7)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>SRT dose (Gy)</td>
<td>68.8 (66–74)</td>
<td>–</td>
</tr>
<tr>
<td>Androgen deprivation therapy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>102</td>
<td>–</td>
</tr>
<tr>
<td>No</td>
<td>118</td>
<td>–</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Age at survey (years)</td>
<td>67.7 (54.5–80.8)</td>
<td>67.7 (49.8–79.8)</td>
</tr>
<tr>
<td>Time from RP to SRT (months)</td>
<td>29.0 (2.1–106)</td>
<td>–</td>
</tr>
<tr>
<td>Time from treatment to survey (months)</td>
<td>23.3 (3.2–62.1)</td>
<td>41.7 (28.7–66.7)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td>94 (41)</td>
<td>133 (59)</td>
</tr>
</tbody>
</table>

Data are shown as median (range) or n (%).

PSA: prostate-specific antigen.

**Table 2.** Prevalence of urinary symptoms and the corresponding bother among 227 patients treated with radical prostatectomy and salvage radiotherapy (SRT group) and 192 patients treated with radical prostatectomy/primary radiotherapy (RP group) for prostate cancer.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>SRT ($n = 227$)</th>
<th>RP ($n = 192$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td>B/S</td>
<td>Prevalence (%)</td>
</tr>
<tr>
<td>Voiding symptoms</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>5.43</td>
<td>66.70</td>
</tr>
<tr>
<td>Weak stream</td>
<td>14.40</td>
<td>65.60</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>8.36</td>
<td>79.00</td>
</tr>
<tr>
<td>Straining</td>
<td>13.10</td>
<td>38.00</td>
</tr>
<tr>
<td>Storage symptoms</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Frequency</td>
<td>16.60</td>
<td>62.20</td>
</tr>
<tr>
<td>Nocturia</td>
<td>18.20</td>
<td>57.50</td>
</tr>
<tr>
<td>Urgency</td>
<td>40.00</td>
<td>66.20</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>13.00</td>
<td>90.00</td>
</tr>
<tr>
<td>Miscellaneous symptoms</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dysuria</td>
<td>4.52</td>
<td>60.00</td>
</tr>
<tr>
<td>Dribbling</td>
<td>42.80</td>
<td>53.70</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>30.40</td>
<td>84.00</td>
</tr>
<tr>
<td>Other incontinence</td>
<td>22.40</td>
<td>84.00</td>
</tr>
</tbody>
</table>

B/S: percentage of subjects being bothered among those having the symptom.

*Significant difference ($\chi^2$ test).
In Figure 2, the DAN-PSS index was divided into three grades: mild (<19), moderate [8–15,16–18] and severe (>19) [19]. When dichotomizing the DAN-PSS index into mild/moderate (<19) and severe (>19), we found that 324 patients had a mild-to-moderate DAN-PSS index score, while 93 patients had a severe score, and that patients treated with both RP and SRT suffered significantly more from severe morbidity than the RP cohort (p < 0.017). More than half of the patients (63%) with a severe DAN-PSS index score had been treated with both RP and SRT. Regarding patients treated with RP + SRT, none of the following treatment-related factors was statistically significantly associated with severe DAN-PSS index, GS, locally advanced disease, age at the time of treatment, early SRT or concomitant treatment with ADT.

**QoL**

QoL scores on the functional and symptom scales in the RP + SRT and RP groups are shown in Table 3. No difference was observed in the distribution of scores between the two treatment groups. A stratified test, corrected for age, found no statistical differences between the two groups for the QoL scores on the functional and symptom scales in the three age groups. The patients were divided into three age groups: 50–59, 60–69 and 70–79 years, and mean global health and quality of life (global QoL) scores among salvage radiotherapy (SRT) and radical prostatectomy (RP) patients: functional and symptom scales. For both treatment groups, an increasing degree of LUTS (DAN-PSS index) was significantly related with decreasing global QoL (p < 0.000).

**Correlation between QoL and urinary morbidity**

Figure 3 shows the relation between global QoL and the DAN-PSS index divided into the three grades: mild (grade 1), moderate (grade 2) and severe (grade 3), for both treatment groups. The figure illustrates that there is a relation between global QoL and the DAN-PSS index in both treatment groups and for all age groups. An age-adjusted analysis was performed to test whether there were any correlations between the global QoL and the total DAN-PSS index. For both treatment groups, an increasing degree of LUTS (DAN-PSS index) was significantly related with decreasing global QoL (p < 0.000).

**Discussion**

This cross-sectional study evaluated patient-reported outcomes on LUTS and QoL in patients treated with RP alone and with a combination of RP and SRT.

All except for one patient reported LUTS in the questionnaire. The results indicate that patients treated with RP + SRT had a higher prevalence of LUTS in all aspects covered by the DAN-PSS questionnaire, except for urinary dribbling. Both voiding and storage symptoms, including weak stream, straining, nocturia and frequency, were significantly more prevalent in patients treated with RP + SRT. When evaluating the DAN-PSS index divided into mild/moderate (<19) and severe (>19), patients treated with RP + SRT were found to suffer significantly more from severe morbidity that patients who were treated with RP alone. No treatment-related factors were found to be statistically significantly related to severe LUTS, including time from RP to SRT.

Urinary incontinence (UI) is a well-documented treatment-related morbidity in patients treated with RP [16]. In the present study, UI was more prevalent in the group of patients treated with RP + SRT than in patients treated with RP alone, although the difference was not statistically significant. Stress incontinence was the most prevalent type of UI in both
treatment groups, represented by 30.4% and 22.0% of the patients treated with RP + SRT and RP, respectively.

In general, the high rate of LUTS was related to a high rate of bother, with 84% of the patients being substantially bothered by their LUTS. With such a high percentage of patients being bothered by LUTS, the evaluation of the potential influence of LUTS on QoL becomes highly important. When analysing QoL in all nine QoL scores, no significant difference in QoL were found between the two cohorts; this may be because of the relatively small number of patients. When analysing global QoL, there was a tendency towards decreasing global QoL in patients treated with RP + SRT in the age group 50–59 years, and the difference was clinically significant. It seemed that younger patients had lower QoL scores owing to symptoms arising after RP + SRT, which was not the case for the older patient groups and patients treated with RP only. This study also demonstrates that the grade of LUTS had a significant influence on global QoL in both treatment groups. Although several factors could potentially influence QoL, the results, surprisingly, showed that ADT had no influence on QoL, whereas patients with concurrent comorbidity experienced decreased global QoL compared to patients without any concurrent diseases.

UI is a prevalent and distressing problem for many PCA patients. In patients treated with RP, the addition of radiotherapy may aggravate the severity of UI. It is well known that sphincter weakness is the most frequent reason for UI in patients treated with RP [16]. To prevent further UI, it is important to leave enough time for the urinary sphincter to recover before initiation of radiotherapy; a period between 12 and 16 weeks is most often recommended [17]. Only a few studies address the association between UI and post-prostatectomy radiotherapy, and they present a blurred picture [18,20–22]. A study with 361 patients demonstrated a significant effect of ART on urinary recovery; at the 3 year follow-up, the urinary recovery rate was 59% for patients treated with ART versus 87% for patients in the observation group [23].

Results from the randomized trial by Thompson et al. confirmed the results, with a higher rate of UI in patients treated with ART (6.5%) than in the control group (2.8%) [5]. Van Cangh et al., representing the principal centre of the EORTC trial, found that ART did not affect UI [20]. Unfortunately, the RTOG and EORTC grading systems do not grade UI, making it difficult to draw conclusions on UI from these studies. UI is considered one of the most bothersome LUTS symptoms, which is also demonstrated in the current results, where considerable bother was scored with all types of UI (Table 2). A low rate of severe late toxicity is shown by the results from other reports evaluating ART or SRT [20,24,25]. The results of the present study generally show a larger number of LUTS in patients treated with RP + SRT, which could be related to inflammatory changes and fibrosis in the bladder neck and the part of the bladder that was exposed to radiation [26]. When evaluating fibrosis-induced changes, a long follow-up period is important. In the present study, the questionnaire was completed within 23 months after SRT, but an even longer follow-up time is warranted.

Only a few studies have examined health-related quality of life (HRQoL) after post-RP radiotherapy. Results from the SWOG trial showed that global HRQoL was initially worse in patients treated with ART than in the observation group, but that QoL improved over time [27]. The improvement of QoL over time could be related either to the potentially decreasing symptom burden during follow-up or to adaptation to and acceptance of the symptoms. A study evaluating HRQoL found only minor changes in patients treated with radiotherapy in the postprostatectomy setting [19]. In the National Prostate Cancer Register of Sweden, one of the secondary endpoints was HRQoL, and sexual, bowel and urinary functions were associated with decreased HRQoL in patients treated for PCA compared with controls [28]. Another study that evaluated HRQoL in patients treated with RP + SRT
compared with patients treated with RP found that several domains of HRQoL were poorer in patients treated with RP + SRT [29].

In the present study, a significant influence of the grade of LUTS on global QoL was found in both treatment groups, together with a tendency towards decreasing levels of global QoL in the youngest patients in the RP + SRT cohort. The influence on global QoL could be due to reasons such as the PCA diagnosis together with the potential influence of disease failure and living a life with long-term morbidity. Concurrent comorbidity was related to decreased global QoL. Furthermore, the RP cohort had a higher prevalence of comorbidity than the SRT cohort.

A Danish study demonstrated an age-dependent decrease in QoL using the EORTC QLQ-C30 questionnaire [30]. Considering age-related influence, age is related not only to QoL, but also to an increasing frequency of LUTS [31]. The median age in the present study was 67.7 years in both treatment groups, which makes the cohorts comparable. However, given the age-related influence on LUTS and QoL, it would be relevant to include an age-matched control group in future prospective studies. This study found a decreased QoL in younger patients treated with a combination of RP and SRT. One explanation for decreased QoL in younger patients may be that elderly men are more likely to accept LUTS, because they are a well-known health problem for their age group. Younger men are more affected by the grade of LUTS and thus report decreasing QoL.

The three randomized controlled trials of ART to the prostate bed – the EORTC 22911, the SWOG 8794 and the ARO 96-02 – all showed benefits of ART [4,6,32]. The SWOG 8794 documented a statistically significant overall survival, while the two other studies documented a reduced risk of PSA failure after ART. However, these studies do not prove that ART is superior to SRT given early when an increase in PSA is observed, and studies comparing morbidity after ART and SRT are warranted. The forthcoming results of the two ongoing randomized controlled trials – Radiotherapy and Androgen Deprivation In Combination After Surgery (NCT00541047, clinicalTrials.gov) and Radiotherapy Adjuvant Versus Early Salvage (NCT00860652, ClinicalTrials.gov) – will answer these important questions [33,34]. In the prospective setting of such studies, assessment of patient-reported outcome measures (PROMs) is a very important aspect to consider in the management of individual patients. A study by Adam et al., which investigated functional outcomes and QoL in patients treated with RP alone versus patients treated with a combination of RP, radiotherapy and hormonal therapy, used PROMs to evaluate urinary function, erectile function and QoL. Their results are comparable to the results of this study, indicating that patients treated with RP, radiotherapy and ADT had a higher rate of UI than patients treated with RP alone. Furthermore, the addition of radiotherapy and/or ADT to patients treated with RP was associated with lower QoL [22]. The present study confirms that patients treated with SRT have a higher rate of UI than patients treated with RP alone, but we did not find that ADT increased the incidence of UI, nor did we find a difference in QoL between the two cohorts, or any influence of ADT on QoL.

In the analysis of PROMs, it is important to remember that the pathophysiology of the lower urinary tract is very complex and that better understanding of the specific symptoms reported by patients should be verified with a urodynamic examination. A correlation between symptoms and urodynamic findings would help to improve understanding of the mechanisms behind the development of radiotherapy-related LUTS.

This study has its strengths and limitations. One limitation is the cross-sectional design and the lack of baseline data. A prospective setting evaluating acute and late morbidity before, during and after SRT may provide better information on the development of symptoms and better understanding of specific mechanisms behind the development of long-term morbidity after SRT. Further limitations are the lack of a pad-weight test to evaluate UI and the evaluation of erectile and bowel function. In a future study, it would also be of interest to include more precise data on comorbidity, e.g. using the Charlson Comorbidity Index.

Despite the limitations of this study, a considerable strength is the national study set-up, which included all patients treated with SRT in Denmark during the 5 year period from 2006 to 2010.

In conclusion, patients in this study treated with RP and SRT have a higher rate of severe LUTS than do patients treated with RP alone. Severe LUTS were significantly related to decreasing global QoL in both treatment groups. The results confirm that late morbidity and HRQoL are among important considerations in the decision process for patients with biochemical failure after RP. Further studies using a prospective set-up are required for a more specific evaluation of the side-effects related to SRT.

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