

## Late Effects to the Rectum and Anus in Prostate Cancer Patients Randomized to Hormonal Therapy Versus Hormonal Therapy Plus Radiotherapy

Jo-Åsmund Lund, Arne Wibe, Anders Widmark, Arne Solberg, Stein Kaasa

Jo-Åsmund Lund, Arne Solberg, Stein Kaasa, Department of Medical Oncology and Radiotherapy, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Jo-Åsmund Lund, Arne Wibe, Stein Kaasa, Department of Cancer and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Arne Wibe, Department of Surgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Anders Widmark, Department of Radiation Sciences, Umeå University Hospital, Umeå, Sweden

Correspondence to: Jo-Åsmund Lund, Department of Medical Oncology and Radiotherapy, St. Olavs Hospital, N-7006 Trondheim, Norway. [jo-asmund.lund@stolav.no](mailto:jo-asmund.lund@stolav.no)

Telephone: +47-72-82-54-90

Fax: +47-72-82-54-49

Received: July 9, 2013

Revised: August 23, 2013

Accepted: August 30, 2013

Published online: October 21, 2013

### ABSTRACT

**AIM:** The aims of this study were to evaluate patient reported outcomes, physician assessed toxicity and physiological measurements in patients randomized to hormonal treatment versus hormonal treatment plus radiotherapy for locally advanced prostate cancer.

**METHODS:** The Scandinavian Prostate Cancer Group SPCG-7/SFUO-3 study included 880 patients from 47 centres in Scandinavia. One hundred and sixty-one patients randomized at St. Olavs Hospital were approached for inclusion in the study. The patients were evaluated by two patient reported symptom scores (EORTC QLQ-C30 and QUFW94), physician assessed toxicity score (LENT/SOMA) and physiological measurements (anorectal manometry and endoanal ultrasound).

**RESULTS:** Five years after cancer treatment, there were significantly higher symptom burdens in several QUFW94 single items in the group of patients treated by radiotherapy. Mean LENT/SOMA score was 0.15 for patients with hormonal therapy plus radiotherapy, compared to 0.03 for patients treated by hormonal therapy alone ( $p < 0.001$ ). Patients treated by radiotherapy had reduced rectal compliance compared to patients treated by hormonal therapy alone (43 mL vs 64 mL,  $p < 0.001$ ).

**CONCLUSION:** This trial provides evidence that addition of

radiotherapy to hormonal therapy for locally advanced prostate cancer implies deterioration of anorectal function.

© 2013 ACT. All rights reserved.

**Key words:** Prospective; Radiotherapy; Randomized; prostate; Cancer; Side-effects

Lund JÅ, Wibe A, Widmark A, Solberg A, Kaasa S. Late Effects to the Rectum and Anus in Prostate Cancer Patients Randomized to Hormonal Therapy Versus Hormonal Therapy Plus Radiotherapy. *Journal of Gastroenterology and Hepatology Research* 2013; 2(10): 827-832 Available from: URL: <http://www.ghrnet.org/index./joghr/>

### INTRODUCTION

Patients with locally advanced prostate cancer can be offered curative treatment options with surgery or radiotherapy combined with hormonal therapy. The patients often have a long life expectancy regardless of treatment.

Previous randomized trials as well as a meta-analysis have shown that hormonal treatment (HT) plus radiotherapy (RT) increase survival compared to RT alone<sup>[1-4]</sup>. Furthermore, a RT dose-escalation study have indicated that 78 Gy is superior to 70 Gy in achieving freedom from progression<sup>[5]</sup>.

The Scandinavian Prostate Cancer Group 7/Swedish Society for Urological Oncology 3 (SPCG-7/SFUO-3) study was initiated in 1995 and closed in 2002. The SPCG-7/SFUO-3 study demonstrated that RT in addition to HT reduced 10-year cancer specific mortality from 23% to 11%<sup>[2]</sup>.

External beam radiotherapy can induce late side effects in a number of cancer diagnoses. Accurate knowledge of late side effects is important with regards to international recommendations and for decision making for individual patients. Hence, a trade-off between treatment efficacy and late side effects has to be made.

Modern RT techniques such as intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT) and volumetric modulated arc therapy (VMAT) can reduce rectoanal side effects in prostate cancer patients. Although many pre-clinical and prospective clinical trials support this, randomised controlled trials comparing

conventional RT to IMRT, IGRT and/or VMAT are lacking<sup>[6]</sup>.

Late side effects to the rectum and anus after radiotherapy for prostate cancer have been reported in numerous reports<sup>[7-13]</sup>. A variety of instruments has been applied; patient reported health-related quality of life (HRQOL) questionnaires; professional health care provider administered toxicity grading systems; and physiological measurements. More recent reports have advocated combination of measures as standard for reporting adverse effects in RT<sup>[14,15]</sup>. To our knowledge, no prior publication has reported on comprehensive evaluation of patient reported outcomes (PROs), physiological methods and physician assessment combined in any randomized trial comparing high dose RT to no RT.

The present study was based upon the following hypothesis: The number and magnitude of late anorectal side effects are more pronounced in the RT+HT group of patients as compared to the group of patients treated by HT alone.

## METHODS

### Patients and setting

The SPCG-7/SFUO-3 study recruited 880 patients during 1995 to 2002. Patients with prostate cancer stages T1G3/T2G2-G3/T3G1-G3 N0M0 were randomized to either HT alone or HT plus RT. The HT was identical in both treatment groups and consisted of three months of a gonadotropin-releasing hormone analogue (leuporelin) combined with an anti-androgen (flutamide) followed by flutamide alone. The study was designed in 1995 and the choice of anti-androgen was based on preliminary reports on outcome comparable to that after castration.

External beam radiotherapy was started after three months of total androgen blockage (TAB). Study protocol instructed that RT was delivered by 6-18 megavolt (MV) linear accelerator, 2 Grays (Gy) per fraction, 5 fractions per week to a total dose of at least 70 Gy. The radiotherapy should be conformal, based on a 3-D computerized tomography (CT) plan. The gross tumor volume 1 (GTV1) should consist of the prostate alone, while the GTV2 should include both the prostate and the seminal vesicles. The planning target volumes (PTV) included the GTVs plus a safety margin of 2 cm, except for the posterior margin which was 1.5 cm. The outer contour of the rectum with content was delineated within and below the treatment field. The rectal volume was recommended shielded so that no more than half the rectal circumference was given 50 Gy or more in any CT section, regardless of consequences for the dose to the posterior edge of the PTVs. However, the GTVs plus a safety margin of 0.5 cm for microscopic spreading should receive the prescribed dose. For the patients with malignant infiltration of the seminal vesicles (T3b), both the prostate and the seminal vesicles were recommended treated to 70 Gy. For the other patients, the seminal vesicles should be treated to 50 Gy and the prostate to 70 Gy or higher.

Of the 880 patients included in SPCG-7/SFUO-3, 178 patients were randomized at St. Olavs Hospital with this hospital as separate strata (Figure 1). After an observation time of at least three years from randomization we observed that 17 patients had died. The remaining 161 patients were invited by mail to the present study, which had been approved by the regional ethical committee. One hundred and three patients accepted inclusion by completing a written and oral consent when attending the out-patient clinic at the Department of medical oncology and radiotherapy.

Forty-eight of the participating patients were randomized to HT plus RT, while 55 patients were randomized to HT alone. However, two of the patients randomized to HT alone received RT as salvage treatment in the time-span between randomization and inclusion

in the study; hence 53 patients were included in the non-irradiated group, while 50 patients were included in the irradiated group.

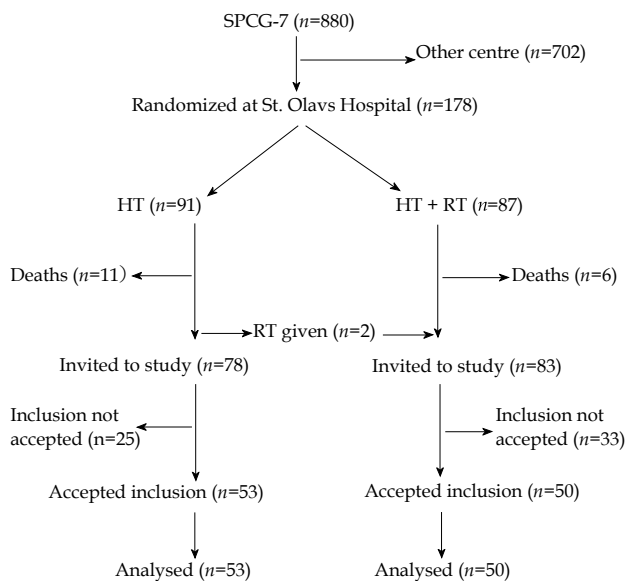


Figure 1 Consort diagram.

### Outcome measures

Three types of outcomes were applied (Figure 2):

(1) PROs were measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 and by the intestinal part of the QUFW-94. The EORTC QLQ-C30 is a patient reported 30 item HRQOL questionnaire measuring six functional scales; physical, role, cognitive, social and emotional function, as well as global quality of life (QOL)<sup>[16]</sup>. The QLQ-C30 is often supplemented by a disease specific questionnaire such as the QUFW94<sup>[11]</sup>. This questionnaire's responsiveness, reliability and content have been validated<sup>[17]</sup>. The QUFW94 measures organ specific symptoms from the sexual, urinary and gastrointestinal organ systems by self-reported answers on 39 single items. The intestinal part of this questionnaire contains 13 questions. Three of these are dichotomous or descriptive; the remaining 10 are answered in a 0-10 numerical rating scale. Both questionnaires were given to patients upon attendance to the out-patient clinic. The HRQOL data were collected for the purpose of the present trial and have not been reported previously.

(2) Physician's grading of anorectal symptoms was measured by the Late Effects Normal Tissue/Subjective Objective Management Analytic (LENT/SOMA) score<sup>[18-20]</sup>. In the present trial, a LENT/SOMA score was achieved by a semi-structured interview and a rectoscopy performed by J.Å.L. For the first patients included in the study, the analytic domain of the LENT/SOMA score was not

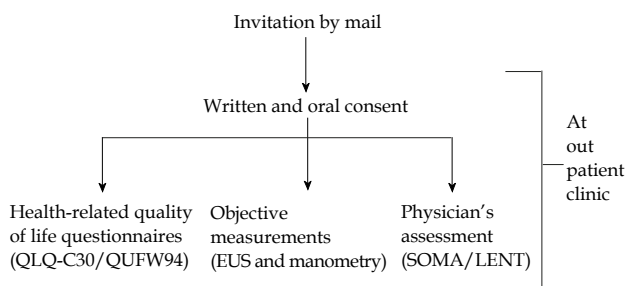


Figure 2 Measures and inclusion for 103 patients diagnosed with locally advanced prostate cancer evaluated for late anorectal side effects.

included. However, after noting pronounced mucosal changes at rectoscopy in several patients, the analytic domain was included as grading of mucosal findings ( $n=54$ )<sup>[21]</sup>.

(3) Anorectal physiology and anal anatomy were measured by manometry and endoanal ultrasound (EUS). One of two involved surgically trained nurses performed anorectal manometry. These measurements were compiled using a two-channel PC Polygraf HR (Synectics Medical, Stockholm, Sweden), registering pressures in mmHg. The manometry catheter was withdrawn 25 mm per second. One of five involved surgeons performed EUS, recording thickness of internal and external sphincter at rest and at maximum squeeze. These measurements were made in the anterior part of the sphincters, and thus, closest to the GTV for the group having RT. The EUS was performed by utilizing a Bruel and Kjaer Leopard 2001 seven MHz ultrasound device (B & K Medicals, Naerum, Denmark).

### Statistics

All EORTC QLQ-C30 data were transformed linearly into a 0-100 scale as recommended by the EORTC scoring manual<sup>[22]</sup>. The QUFW94 data were scored as previously done by Fransson *et al.*<sup>[7]</sup>, thus only the 10 single items answered by a 0-10 numerical rating scale were analysed. Furthermore, a function/bother scale was analysed, composed of the mean of five single items (intestinal problems in general, stool frequency in 24 hours, stool leakage, excessive gas and limitation in daily activity caused by intestinal problems), as proposed by a previous report from our group<sup>[17]</sup>.

For evaluation of differences between treatment groups, mean scores with 95% confidence intervals (CI) were calculated, and statistical significance was evaluated by the Mann-Whitney U tests for non parametric samples (two tailed significance levels). Differences greater than 10 in the linearly transformed QLQ-C30 scores were considered clinically significant, whereas for QUFW94 scores a difference of 1.0 or more was considered clinically significant<sup>[7,23]</sup>.

The LENT/SOMA scores were calculated in two manners. First, the highest single item score was defined as the total LENT/SOMA score. Second, a mean LENT/SOMA score was calculated by adding all the single item scores and divide the sum by the number of items. Differences in means between treatment groups were tested by *t*-test for independent samples, using two-tailed significance levels.

The means of anorectal manometry and EUS data with CI's were calculated. Rectal compliance was calculated by subtracting the volume needed to give the patients a first feel of pressure from the volume needed to incite an urge to defecate. Mean scores with 95% CI's are presented, as well as statistical significance as evaluated by *t*-test for independent samples.

Overall and prostate cancer specific survival rates at seven years were calculated by the same approach as presented by Widmark *et al.*<sup>[2]</sup>, in order to ensure the validity of the sub sample results presented here.

Prior to analysis of all data the randomization data were checked against the internal radiotherapy registry in order to control for any treatment cross over.

All data handling was performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Illinois, USA).

## RESULTS

Baseline characteristics were similar in both groups of patients (Table 1). Of the irradiated patients, 49 received 70 Gy, one patient received 76 Gy. Only three patients were given 70 Gy to both the prostate and the seminal vesicles. Treatment time for radiotherapy varied from 44 to 57 days.

**Table 1** Baseline characteristics for 103 prostate cancer patients treated by HT<sup>1</sup>+RT<sup>2</sup> versus HT alone.

	HT+RT	HT
Mean age, years (95% CI)	69 (68-71)	71 (70-73)
T1 ( <i>n</i> )	1	0
T2 ( <i>n</i> )	0	4
T3 ( <i>n</i> )	49	49
Present hormonal treatment	24	34
Months from treatment, mean (95% CI)	60 (56-64)	58 (56-61)
Previous ano-rectal surgery	4	3
Previous ano-rectal trauma	0	2

<sup>1</sup> Hormonal therapy; <sup>2</sup> Radiotherapy.

The results of the HRQOL analyses are given in table 2. The answering rate for the HRQOL questionnaires was 90 % in the irradiated group of patients and 96% amongst the patients treated by HT alone (ns). For single item diarrhoea, the irradiated patients displayed higher mean score of 22 as compared to the non-irradiated group of 14, although the difference did not reach statistical significance ( $p=0.18$ ).

The irradiated patients reported more symptoms from their rectum and anus assessed by the QUFW94, in that statistical and clinical significant differences between groups were found (Table 2).

**Table 2** Mean scores (95% CI) of HRQOL<sup>1</sup> in 94 patients with prostate cancer treated by HT<sup>2</sup> vs HT plus RT<sup>3</sup>.

	HT+RT	HT	<i>p</i>
<b>EORTC-QIQC30</b>			
Global QOL	78 (72-84)	70 (69-80)	0.50
Functioning scales			
Physical	91 (87-95)	88 (84-93)	0.26
Role	87 (80-93)	82 (74-89)	0.31
Emotional	89 (84-95)	89 (84-93)	0.84
Cognitive	83 (75-90)	81 (76-87)	0.57
Social	83 (77-90)	81 (75-87)	0.74
Symptom scales			
Fatigue	22 (15-29)	24 (18-29)	0.91
Nausea and vomiting	5 (1-10)	3 (1-5)	0.29
Pain	9 (4-13)	11 (5-17)	0.82
Single items			
Dyspnoe	21 (13-29)	21 (14-28)	0.84
Insomnia	18 (9-26)	12 (5-18)	0.31
Loss of appetite	4 (-1-10)	2 (-1-5)	0.51
Constipation	16 (9-23)	14 (7-22)	0.91
Diarrhoea	22 (13-30)	14 (8-20)	0.19
Financial impact	3 (0-7)	4 (1-8)	0.63
<b>QUFW94</b>			
Intestinal problems in general <sup>4</sup>	1.8 (1.02-2.48)	0.9 (0.34-1.42)	0.04
Stool frequency / 24 hrs <sup>4</sup>	2.9 (2.34-3.52)	1.6 (1.34-1.90)	<0.001
Stool consistency	4.8 (4.21-5.34)	5.3 (4.85-5.72)	0.11
Stool leakage <sup>4</sup>	0.4 (0.20-0.62)	0.2 (0.01-0.46)	0.02
Planning of toilet visits	1.4 (0.75-2.07)	0.4 (0.07-0.74)	<0.01
Excessive gas <sup>4</sup>	3.0 (2.25-3.79)	3.0 (2.14-3.86)	0.67
Pain at defecation	0.4 (0.12-0.65)	0.6 (0.02-1.08)	0.73
Mucus	1.2 (0.54-1.78)	0.4 (0.05-0.76)	0.02
Blood	0.6 (0.19-0.95)	0.2 (-0.09-0.42)	0.03
Limitation in daily activity*	1.1 (0.69-1.58)	0.3 (0.05-0.52)	0.001
Function/bother scale	1.5 (1.14-1.91)	0.7 (0.49-0.90)	<0.001

<sup>1</sup> Health-related quality of life; <sup>2</sup> Hormonal therapy; <sup>3</sup> Radiotherapy; <sup>4</sup> Single items composing Function/bother scale.

LENT/SOMA score was achieved in all patients. Grading of the rectal mucosa was achieved in 24 of the irradiated patients and 30 of the patients treated by HT alone. Significant differences between groups were demonstrated (Table 3).

The manometry results are given in table 4. The rectal compliance and the volumes needed to give the patients a first feel of pressure and urge to defecate differed significantly between the two treatment groups.

The thickness of the external and the internal anal sphincters remained unchanged during squeeze as evaluated by EUS. There were no detectable differences in sphincters' thicknesses between treat-

ment groups (Table 5).

At seven years follow up, prostate cancer specific mortality rates were 4 % in the group of patients treated by RT + HT and 7 % amongst the patients treated by HT alone. Overall mortality rates were 5 % and 10 %, respectively.

**Table 3** SOMA/LENT score in 103 prostate cancer patients treated by HT<sup>1</sup>+RT<sup>2</sup> or HT alone.

SOMA grade	HT+RT (n)	HT (n)	p
0	4	38	
1	20	11	
2	15	4	
3	5	0	
4	6	0	
Mean (95% CI)	0.15 (0.12 - 0.18)	0.03 (0.02 - 0.04)	<0.001

<sup>1</sup> Hormonal therapy; <sup>2</sup> Radiotherapy.

**Table 4** Recto-anal manometry in 100 prostate cancer patients treated by HT<sup>1</sup> + RT<sup>2</sup> or HT alone.

	HT+RT mean (95% CI)	HT mean (95% CI)	p
Resting pressure (mm Hg)	69 (61.89-75.64)	72 (64.67-78.69)	ns
Squeeze pressure (mm Hg)	109 (96.13-122.09)	116 (101.99-130.24)	ns
Length of anal canal (mm)	51 (48.67-53.24)	53 (49.39-56.12)	ns
First feel of press (mL)	53 (44.52-60.56)	75 (62.91-86.14)	0.003
Urge to defecate (mL)	96 (85.64-105.42)	138 (122.87-153.36)	<0.001
Rectal compliance (mL)	43 (36.20-48.80)	64 (54.73-72.44)	<0.001

<sup>1</sup> Hormonal therapy; <sup>2</sup> Radiotherapy.

**Table 5** Endoanal ultrasound in 100 prostate cancer patients treated by HT<sup>1</sup> alone or HT plus RT<sup>2</sup>.

	HT+RT mean (95% CI)	HT mean (95% CI)	p
External - rest (mm)	6.8 (5.7-8.1)	6.3 (5.5-7.1)	ns
External - squeeze (mm)	7.1 (5.6-8.6)	6.3 (5.3-7.3)	ns
Internal - rest (mm)	2.1 (1.7-2.4)	2.4 (1.8-2.9)	ns
Internal - squeeze (mm)	2.0 (1.7-2.3)	2.3 (1.6-3.1)	ns

<sup>1</sup> Hormonal therapy; <sup>2</sup> Radiotherapy.

## DISCUSSION

This trial provides evidence that patients with locally advanced prostate cancer had significantly increased recto anal late side effects when treated by RT+HT compared to HT alone. The irradiated patients had more recto anal symptoms evaluated by self-administered questionnaires; higher toxicity grades measured by LENT/SOMA and impaired physiological rectal function measured by manometry as compared to the patients treated by HT alone.

The study protocol for this trial was designed in 1995. RT planning and delivery was consequently not directly comparable to modern RT (IMRT, IGRT, VMAT). Furthermore, recent dose limits recommended to reduce the risk of anorectal side effects<sup>[24]</sup> were obviously not taken into consideration when treating the patients included here. The results need to be interpreted in this context.

Only one of the reports on late rectal toxicity after radiotherapy for prostate cancer compared patients treated by RT to patients not treated by RT in a randomized design<sup>[7]</sup>. Fransson *et al* reported only on PROs, not on physicians' evaluation or physiological measurements. Hence, the present study offer the most comprehensive insight to late radiotherapy induced rectal toxicity.

The physiological results of this trial offer a biological explanation to the symptoms reported by the patients in our study as well as in the previous randomized trial by Fransson *et al*<sup>[7]</sup>. Most likely radiotherapy induces rectal fibrosis and consequently a less flexible rectal wall, reducing the patients' ability to store stools. RT may affect the rectal nerves and the rectoanal inhibitory reflex in different

ways. Radiation nerve damage may reduce rectal sensations, thus making the patients less aware of rectal filling. In this scenario the level of rectal volume needed to defecate may increase. In contrast, if the nerves are not damaged, they may be more stimulated by the radiation induced proctitis, which may reduce the rectal volume needed to empty the bowel. As rectal pressures were not measured, we cannot draw any conclusions on this issue.

Some may argue that the withdrawal technique for measuring anal sphincter pressures is a limitation of this study. However, due to the randomised design of this trial, and the fact that both groups of patients were measured by the same technique, any technical bias is unlikely.

Although the irradiated patients reported significantly higher anorectal symptom burdens in the present study, they reported overall HRQOL that was similar to what was found in the patients treated by HT alone as well as by previously reported normal populations<sup>[7,25]</sup>. Other trials on HRQOL in long term prostate cancer survivors have demonstrated that younger (age<75 years) prostate cancer patients report HRQOL comparable to that of a normal population<sup>[26]</sup>. Hence, psychological coping mechanisms such as benefit finding and posttraumatic growth might have contributed to the seemingly contradiction between increased organ specific symptoms and unchanged overall HRQOL in the irradiated patients in this trial<sup>[27]</sup>. Another explanation might be that the magnitude of side-effects is not of such importance that they would induce a difference between treatment groups when measuring HRQOL by EORTC QLQ-C30.

The baseline characteristics of the patients indicate that the treatment arms were well balanced, also after treatment cross-over of two patients. The differences between groups in 7 and 10 year cancer specific and overall survival rates were similar in the present trial as compared to the results of the SPCG-7 trial, supporting the validity of the present sub group study.

The thickness of the anal sphincters did not differ between treatment groups, as evaluated by endoanal ultrasound. One might conclude that the increased stool leakage reflected the decrease in rectal compliance rather than a diminished sphincter function. This view is supported by the anal manometry results, as neither resting pressure nor squeeze pressure were affected by radiotherapy.

The LENT/SOMA scoring of the two treatment groups differed significantly. Our results represent a higher level of symptoms than in some previous reports. Livsey *et al* reported on 101 patients with prostate cancer having received radiotherapy at least three years previously<sup>[9]</sup>. Of these, 22 (22%) had rectal LENT/SOMA score higher than 1. However, those patients received only 50 Gy which could explain the difference to the present results. Kuban *et al* reported LENT/SOMA toxicity score in 149 patients treated with radiotherapy to a total dose of 70 Gy in a randomised dose-escalation study<sup>[5]</sup>. Seventeen of these patients (11%) had LENT/SOMA score higher than 1, but the margins from the prostate to the field shielding were smaller than in the present report and this could explain the difference. Furthermore, both Kuban *et al* and Livsey *et al* applied a modified LENT/SOMA score in their studies, which might also have contributed to the differences observed.

The results of the SPCG-7/SFUO-3 trial demonstrated reduction in cumulative overall mortality from 39% to 30% at ten years and moderate increase in ano rectal symptoms when adding RT to HT<sup>[2,28]</sup>. The reduction in mortality and the patient reported symptoms were similar in the SPCG-7 trial and the present study. However, the present study adds to the information offered by the SPCG-7 trial, as doctor's evaluation of anorectal symptoms and anorectal manometry have been added as outcomes. These added outcomes demonstrated



larger differences between patient groups than the patient reported symptoms presented previously<sup>[2,28]</sup>. This underlines the importance of including several outcomes when evaluating side-effects in clinical trials on radiotherapy. Furthermore, the anorectal manometry results presented here are a matter of concern; might the 50% reduction in rectal compliance indicate a potential severe increase in anorectal symptoms as time from treatment increases? Maybe an increase in side effects as time passes might challenge the overall benefit to the patients from a survival benefit as demonstrated by the SPCG-7 study?

These questions can only be answered by studies on very late rectal toxicity after radiotherapy for prostate cancer.

In conclusion, the present study provides evidence that addition of 3-D CT based radiotherapy to a total dose of 70 Gy to hormonal therapy for locally advanced prostate cancer implies deterioration of anorectal function. There is a need for longer follow up to fully evaluate the balance between a survival benefit and the negative effects of radiotherapy related side effects.

## ACKNOWLEDGMENTS

The authors thank professor H.E.Myrvold for his initial support in planning the study, and the following for data sampling: H. Wasmuth, A. Rydning, B. Endreseth, M. Svinsås, I. H. Bodsberg and J. Ingdal. The support of the SPCG-7/SFUO-3 study board and K Tulluan is appreciated. The study was supported by The Norwegian Cancer Society and The Norwegian Medical Association. None of the sponsors participated in the study design, nor in data collection, analysis and interpretation, nor in preparation of manuscript.

## REFERENCES

- Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Mattelaer J, Lopez Torecilla J, Pfeffer JR, Lino Cutajar C, Zurlo A, Pierart M. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002; **360**: 103-106
- Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, Lund JA, Tasdemir I, Hoyer M, Wiklund F, Fosså SD; Scandinavian Prostate Cancer Group Study 7; Swedish Association for Urological Oncology 3. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009; **373**: 301-308
- D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004; **292**: 821-827
- See WA, Tyrrell CJ. The addition of bicalutamide 150 mg to radiotherapy significantly improves overall survival in men with locally advanced prostate cancer. *J Cancer Res Clin Oncol* 2006; **132 Suppl 1**: S7-16
- Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, Lee AK, Pollack A. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 67-74
- Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010; **22**: 643-657
- Fransson P, Damber JE, Tomic R, Modig H, Nyberg G, Widmark A. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. *Cancer* 2001; **92**: 3111-3119
- Lilleby W, Fossa SD, Waehre HR, Olsen DR. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. *Int J Radiat Oncol Biol Phys* 1999; **43**: 735-743
- Livsey JE, Routledge J, Burns M, Swindell R, Davidson SE, Cowan RA, Logue JP, Wylie JP. Scoring of treatment-related late effects in prostate cancer. *Radiother Oncol* 2002; **65**: 109-121
- Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW, Lebesque JV, Koper PC. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 1019-1034
- Widmark A, Fransson P, Tavelin B. Self-assessment questionnaire for evaluating urinary and intestinal late side effects after pelvic radiotherapy in patients with prostate cancer compared with an age-matched control population. *Cancer* 1994; **74**: 2520-2532
- Yeoh EE, Holloway RH, Fraser RJ, Botten RJ, Di Matteo AC, Moore JW, Schoeman MN, Bartholomeusz FD. Anorectal dysfunction increases with time following radiation therapy for carcinoma of the prostate. *Am J Gastroenterol* 2004; **99**: 361-369
- Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, Wiegel T. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012; **61**: 112-127
- Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK, Yorke ED. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76**: S3-9
- Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *J Natl Cancer Inst* 2011; **103**: 1808-1810
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Fibilerti A, Flechtner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-376
- Reidunsdatter RJ, Lund JA, Fransson P, Widmark A, Fosså SD, Kaasa S. Validation of the intestinal part of the prostate cancer questionnaire "QFW94": psychometric properties, responsiveness, and content validity. *Int J Radiat Oncol Biol Phys* 77: 793-804
- Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot JC, Bolla M, Bartelink H. EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol* 1995; **35**: 11-15
- Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH. RTOG Late Effects Working Group. Overview. Late Effects of Normal Tissues (LENT) scoring system. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1041-1042.
- Lund JÅ, Kaasa S, Wibe A, Widmark A, Fransson P. Late radiation effects to the rectum and anus after treatment for prostate cancer; validity of the LENT/SOMA score. *Acta Oncol* 2013; **52**: 727-735
- Feldman M, Friedman Lawrence S, Sleisinger Marvin H. Sleisinger & Fordtran's gastrointestinal an liver disease; patophysiology, diagnosis, management. Saunders 2003
- Fayers PM, Aaronson NK, Bjordal K, Sullivan M. EORTC QLQ-C30. *Scoring Manual In* 1995; 1 -49.

- 23 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139-144
- 24 Alsadius D, Hedelin M, Lundstedt D, Pettersson N, Wilderäng U, Steineck G. Mean absorbed dose to the anal-sphincter region and fecal leakage among irradiated prostate cancer survivors. *Int J Radiat Oncol Biol Phys* 2012; **84**: e181-185
- 25 Hjerstad MJ, Fayers PM, Bjordal K, Kaasa S. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). *J Clin Oncol* 1998; **16**: 1188-1196
- 26 Mols F, van de Poll-Franse LV, Vingerhoets AJ, Hendriks A, Aaronson NK, Housterman S, Coebergh JW, Essink-Bot ML. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. *Cancer* 2006; **107**: 2186-2196
- 27 Helgeson VS, Reynolds KA, Tomich PL. A meta-analytic review of benefit finding and growth. *J Consult Clin Psychol* 2006; **74**: 797-816
- 28 Fransson P, Lund JA, Damber JE, Klepp O, Wiklund F, Fosså S, Widmark A; Scandinavian Prostate Cancer Group Study 7; Swedish Association for Urological Oncology 3. Quality of life in patients with locally advanced prostate cancer given endocrine treatment with or without radiotherapy: 4-year follow-up of SPCG-7/SFUO-3, an open-label, randomised, phase III trial. *Lancet Oncol* 2009; **10**: 370-380

**Peer reviewers:** Gokulakrishna Subhas, Department of general surgery, Providence hospital and medical centres, 16001 W. 9 mile road, Southfield, Michigan, the United States; Emad H Aly MBBCh, MS, MD, FRCS, MEd, Consultant Colorectal & General Surgeon, Laparoscopic Colorectal Surgery & Training Unit - Aberdeen Royal Infirmary, Honorary Senior Lecturer - University of Aberdeen, ASGBI Director for Surgical Education, Aberdeen Royal Infirmary, Ward 34, Foresterhill, Aberdeen, AB25 2ZN, the United Kingdom.