Second cancers in patients with locally advanced prostate cancer randomized to lifelong endocrine treatment with or without radical radiotherapy. Long term follow- up of the Scandinavian Prostate Cancer Group-7 trial.

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Contributors

BYA, JÅL, OK and AS designed the study. BYA, TÅM and ES planned the statistical analysis. BYA and TÅM were responsible for the statistical analysis. BYA, JÅL and AS drafted the manuscript. AW was

the PI of the original study SPCG-7. All authors were involved in revision and have approved the final manuscript. BYA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Summary

Background

Curative radiotherapy (RT) constitute a cornerstone in prostate cancer (PC) treatment. We present long-term follow-up estimates for second cancer (SC) risk and overall survival (OS) in patients randomized to endocrine therapy (ET) alone or combined with 70Gy prostatic radiotherapy (RT) in the Scandinavian Prostate Cancer Group -7 study (SPCG-7). We explored the effect of salvage RT (≥60Gy to ET-group) and report causes of death.

Methods

The SPCG-7 study (1996-2002) was a randomized controlled trial that included 875 men with locally advanced non-metastatic PC. In this analysis including data from the Norwegian and Swedish Cancer- and Cause of Death registries for 651 Norwegian and 209 Swedish study patients, we estimated hazard ratios (HRs) for SC and death, and cumulative incidences of SC.

Findings

Median follow-up of the 860 (431 ET and 429) ET+RT patients was 12.2 years for SC risk analysis and 12.6 years for the OS analysis. Eighty-three of the Norwegian ET patients received salvage RT, median time to salvage RT was 5.9 years We found 125 and 168 SCs in the ET and ET+RT patients, respectively. With ET alone as reference, ET+RT patients had a HR of 1.19 (95%CI 0.92-1.54) for all SCs and 2.54 (95 % CI 1.14-5.69) for urinary bladder cancer (UBC). The total number of UBC was 31 (23 in ET+RT/ 8 in ET), and the vast majority (85 %) were superficial. The HR for SC in salvage RT patients was 0.48 (95% CI 0.24-0.94). Median OS was 12.8 (95 % CI 11.8-13.8) and 15.3 (95% CI 14.3-16.4) years in the ET and ET+RT groups, respectively. Compared to ET alone, the risk of death was reduced in ET+RT patients (HR 0.73, 95% CI 0.62-0.86), and in ET patients receiving salvage RT (HR 0.44, 95% CI 0.30-0.65).

Interpretation.

Although the risk of UBC was increased in PC patients who received RT in addition to ET, this disadvantage is by far outweighed by the OS benefit of RT confirmed in our study. The risk of SC, and especially UBC, should be discussed with patients and be reflected in follow-up programs.

Introduction

Second primary cancer (SC) is an increasing health problem world- wide due to increased survival of patients after the first cancer and a longer life expectancy in general.[1,2] SCs are associated with several risk factors such as genetic predisposition, life style factors, and previous treatment.[3,4]

Radiotherapy (RT) can cause SC.[5-9] The magnitude of the excess risk for different therapeutic RT schedules is however, debated. All studies regarding SC after prostate cancer (PC) treatment are to our knowledge registry-based.[7,10-14] Consequently, the comparison of groups may be biased.

During 1996-2002, The Scandinavian Prostate Cancer Group (SPCG) performed a randomized controlled trial (RCT), the SPCG-7 trial. The primary objective was to compare prostate cancer specific mortality in patients with locally advanced or aggressive PC, randomized to either endocrine therapy (ET) alone or endocrine therapy plus radical radiotherapy (ET+RT).[15] The SPCG-7 trial showed that the addition of radiotherapy to ET halved the PC specific mortality rate at 15 years and prolonged median overall survival (OS) with 2·4 years.[16]

To our knowledge, no previous RCT has reported on the long-term risk of SC in patients treated with or without radical RT for PC. Herein, we present estimates of SC risks and OS in the two SPCG-7 trial arms, with a median follow-up of more than 17 years in surviving patients. Additionally, we report causes of death of the study participants, and SC risk and OS following radical RT to the prostate after primary ET (salvage RT).

Methods

Study design and participants

Details of the SPCG-7 study protocol and participants have been published previously [15,17]. After informed consent, eligible patients were included at 47 centres in Norway, Sweden, and Denmark. The included patients had a histologically verified locally advanced or aggressive PC with no evident lymph node- or distant metastases, were younger than 76 years, had a life expectancy of ≥ 10 years, and a World Health Organization (WHO) performance status 0-2. Moreover, eligible patients either had clinical tumour (cT) stage T1 and a WHO tumour grade (G) 3, a T2 G 2-3 tumour, or a T3 G 1-3 tumour, and a serum-PSA < 70 ng/ml. Patients with a PSA >10 ng/ml underwent bilateral lymph node dissection of the obturatory nodes, and only node-negative patients were included. Patients with previous malignancies other than basal cell carcinoma of the skin, were not included. In the study period 1996-2002, 875 patients were included and randomized to receive either endocrine therapy

alone (Arm 1, n=439) or endocrine treatment plus radical radiotherapy (Arm 2, n=436). Randomization was stratified according to study centre, cT-stage, and tumour grade.

Six hundred and fifty-one included patients were from Norway, 212 were from Sweden and 12 patients were from Denmark. After randomization, all patients received androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone (LHRH) agonist (leuprorelin) and an oral anti-androgen (flutamide 250mg three times a day). The LHRH agonist was discontinued after three months in both arms. Antiandrogen treatment was continued in all patients, and the patients in arm 2 were treated with standard 3D conformal external beam radiotherapy (EBRT) to the prostate and seminal vesicles with a dose of at least 70 Gy (2 Gy pr. fraction). Although the SPCG-7 protocol originally recommended castration in case of progression, salvage radiotherapy to the prostate was allowed for patients in arm 1.

We have collected updated information on the patients from Norway and Sweden included in the SPCG-7 trial (n=863) from the Cancer Registry of Norway and the Swedish Cancer Registry. Patients were followed from the date of randomization to the event of interest (second cancer or death) or to date of censoring, whichever came first. For the patients from Sweden follow-up was complete until 31 Dec 2016, while for the patients from Norway follow up was complete until 31 Dec 2017. Three patients from Sweden were not registered with a PC diagnosis in the Swedish cancer registry and were not included in the present analysis. We did not have access to follow-up data on the 12 SPCG-7 patients from Denmark. All SC and all deaths after the date of randomization in the SPCG-7 trial were registered. Causes of death were registered by linking data to the Norwegian and Swedish Cause of Death registries. We categorized causes of death in three groups; death from prostate cancer, death from other cancers, and death from other causes.

Since 1997, the Cancer Registry of Norway has recorded treatment data from all RT units in Norway, and we collected RT data on all Norwegian patients. Salvage RT was defined as RT to the prostate with a total dose of at least 60 Gy, given to patients randomized to ET alone. We did not have access

to salvage RT data on the Swedish patients in arm 1. For analyses regarding salvage RT, the patients from Norway were categorized in three groups; salvage RT (Arm 1 patients who received salvage RT), ET only (Arm 1 patients not given salvage RT), and ET+RT (Arm 2 patients).

The SPCG-7 study was registered as an International Standard Randomised Controlled Trial, (number ISRCTN01534787), and the present study was approved by the Regional Committee for Medical and Health Research Ethics of South East Norway (Ref. 2011/2344-26).

Statistical analyses

The aims of this paper were twofold, and required two different statistical methods. In order to quantify the causal impact of RT on the SC risk we estimated cause specific hazard ratios (HRs) with 95 % confidence intervals (Cis) using standard Cox proportional hazard regression with censoring for competing events, as this is the preferred and recommended method for causal inference. [18,19] To quantify the probability of SC and death due to PC, SC, and other causes we applied the Aalen-Johansen estimator and treated the outcomes not of primary interest as competing risks. [20] To avoid immortal time bias in analyses regarding salvage RT in Norwegian patients, we treated salvage RT as a time- varying covariate.To prevent confusion, we use the terms “risk” and “relative risk” for cause specific hazard ratios from Cox-regressions, and the terms “cumulative incidence” and “probability” for estimates from competing risks analyses. We provided point estimates of SC probability and OS at 5, 10, 15, and 20 years after randomization. A p-value <0·05 was considered statistically significant. All analyses were done using the software package STATA IC, version 15 (StataCorp ©).

Results

The analyses included a total of 860 patients, 651 (75·7%) Norwegian and 209 (24·3%) Swedish patients included in the SPCG-7 study. Of these, 431 had been randomized to ET alone (Arm 1) and 429 to ET+RT (Arm 2). Of the 329 Norwegian patients randomized to endocrine treatment, 83 patients (25·2 %) had received salvage radiotherapy (exclusively EBRT) to the prostate. No Norwegian patients were treated with curative RT for cancers other than PC.

With a median follow up of 12·2 years for all patients, we found a total of 293 second cancers, 125 cases in the ET group and 168 cases in the ET+RT group (Figure 1). The most common second cancer was colon cancer (n=47) followed by lung cancer (n=43). There were 31 cases of urinary bladder cancer and 19 cases of rectal cancer (Supplementary Table 1, available online). The 31 urinary bladder cancers comprised 27 Norwegian cases of which the vast majority were superficial (, 85 %). One patient was diagnosed with sarcoma in our study. The relative risk of any second cancer in patients treated with ET+RT was 1·19 (95 % CI 0·92-1·54) as compared to patients treated with ET alone (Table 1). As illustrated in Figure 1, the difference in SC risk between the groups increases after 10 years of follow-up. Supplementary table 2, available online, shows the cumulative incidence of SC after 5, 10, 15, and 20 years after randomization. We also estimated the cumulative incidence of second urinary bladder cancer, lung cancer, colon cancer, and rectum cancer (Figure 2), and calculated the relative risks in the irradiated patients with the ET patients as reference (Table 1). We found a HR for urinary bladder cancer of 2·54 (95% CI 1·14-5·69) in patients treated with ET+RT (Table 1).

When analysing the Norwegian cohort only we found that patients treated with ET and later salvage RT had a HR of 0·48 (95% CI 0·24-0·94) for SC compared with ET patients that did not receive salvage RT (Table 1). Figure 3 shows the cumulative incidence of SC in the Norwegian cohort. In the Norwegian patients, median time to salvage RT was 5·9 years (Supplementary figure 1, available online).

After a median follow up of 12·6 years, 557 (65%) of 860 patients had died, including 69·8 % (301/431) of patients in the ET group and 59·7% (256/429) of patients in the ET+RT group (Table 2). Prostate cancer was the most common cause of death (n=244, Table 2). Estimated OS was highest in the ET+RT group (Supplementary Table 2, available online). Median overall survival was 12·8 (95 % CI 11.8-13.8) years in the ET group and 15.3 (95% CI 14.3-16.4) years in the ET+ RT group. Patients in the ET+RT group had a significantly lower risk of death from any cause compared to patients in the

ET group, HR= 0.73 (95 % CI 0.62-0.86, Table 1, Figure 4). The risk of death from SC was 1.42 (95 % CI 0.96-2.08) for ET+RT patients compared to the ET group (Table 1, Figure 5). Of patients who died from second cancer, 14 patients died of colon cancer, 35 of lung cancer, 5 of urinary bladder cancer and 5 of rectal cancer (Supplementary table 1, available online). Figure 5 shows the stacked cumulative incidence of causes of death according to treatment groups. Patients who received salvage RT to the prostate had a 56 % relative risk reduction of death from any cause compared to patients that received ET only (Table 1, Figure 6), $p < 0.001$.

Discussion

Patients with locally advanced PC randomized to radiotherapy in addition to endocrine therapy in the SPCG-7 trial experienced numerically more second cancers than patients treated with endocrine therapy alone. Although the cause specific HR for all SC was 1·19 (95 % CI 0·92-1·54), and the risk not statistically significantly increased at the 5% level, we did find a statistically significant and more than doubled risk of urinary bladder cancer in the irradiated patients.

The SPCG-7 study and subsequent RCTs have established radical radiotherapy as a cornerstone in locally advanced PC therapy. [15,21,22] Our study confirms that the survival benefit (median 2·5 years) from radiotherapy previously shown in the SPCG-7 study prevails with increasing follow-up. [15,16]

The reports from previous studies on SC risk after RT for PC are inconsistent. Several studies have not shown an increased SC risk after RT for PC [23-25] however; two large, systematic reviews both concluded that radiotherapy increases the SC risk in PC patients. Murray et al.[26] found a general increased SC- risk as well as specifically for rectal-, and urinary bladder cancer, whereas Wallis et al. [27] reported an increased risk of colon-, rectal-, and urinary bladder cancer in patients treated with RT. Moschini et al. found an increased risk of urinary bladder cancer in RT treated patients vs. patients treated with prostatectomy (RP), even after adjusting for smoking status.[14] In our previously reported registry-based study on SC risk in radically treated PC patients,[13] we found an increased risk of all SCs both in patients who received primary RT and RT after RP. In addition, we found a near doubled

urinary bladder cancer risk following primary and salvage RT, and a fifty percent increased risk of rectal cancer in primary RT patients. Consistently, Hegemann et al. [10] reported increased risk of all SCs, rectal-, and urinary bladder cancer in primary irradiated PC patients. However, since this study was not able to demonstrate increased SC risk in patients treated with radical RT after RP, the authors concluded that the higher SC rate in the RT patients reflected differences in life style habits and comorbidities rather than increased risk caused by RT. Given the randomized SPCG-7 study design, it is unlikely that confounders like smoking and comorbidity have biased our results. We believe that our findings strongly supports an increased risk of urinary bladder cancer after pelvic RT. Still, diagnostic bias from increased diagnostic awareness caused by hematuria in RT treated patients, could have led to earlier diagnosis of urinary bladder cancer and may have influenced our estimates. Furthermore, an increased SC-risk solely due to superior survival in irradiated patients cannot be ruled out. However, given the undoubted benefit from radical RT in locally advanced PC, a moderately increased SC risk must be accepted.

Unlike several registry-based studies, the present study did not demonstrate an increased risk of rectal cancer following RT. This might be explained by a generally low number of second rectal cancers and lack of statistical power in our study. In our opinion, clinicians should be aware of the possible increased second rectal cancer risk in irradiated PC patients.

Whether scattered radiation from RT to the pelvis leads to an increased lung cancer risk is controversial. Several studies have shown higher lung cancer risk after RT to the prostate and pelvis. [7,28-30] However, many of these studies are probably biased by differences in smoking habits. In our study, smokers are presumably evenly distributed in the two study arms by randomization. Although not statistically significant at the 5% level, the cause specific HR of 1·82 (95%CI 0·96-3·47) for the irradiated patients does not entirely rule out a higher lung cancer risk for RT patients. Nevertheless, it is possible that the lower lung cancer risk, and SC risk in general, partly is caused by a selection of healthy, non-smokers as long-term survivors in the ET group.

In the Norwegian cohort we found a lower SC risk and a superior OS in patients treated with ET and later salvage RT compared to patients treated with ET alone as well as ET+ primary RT. Most likely, patients who received salvage RT were a highly selected group with lower comorbidity and mortality risk than the general SPCG-7 study population. We were not able to collect salvage RT data from the Swedish patients, leading to a reduced sample size (209 patients) available for analysis of salvage RT data. Nevertheless, both the estimates for SC risk and OS were statistically significant, and we believe that less SC risk factors (e.g. smoking) in this generally healthy subgroup outweighs any increased SC risk from RT. Since the median time to salvage RT was 5·9 years, several of these patients also have relatively short follow-up time as RT treated patients, further contributing to lower SC risk. The relatively long time to salvage RT and the superior OS for this group of patients, indicates that salvage RT to the prostate should be considered as a treatment option for selected patients many years after the primary diagnosis.

The SPCG-7 study patients did not receive RT to the pelvic lymph nodes. Contemporary patients with a high risk of lymph node metastases are usually offered pelvic lymph node irradiation,[31,32] and might have a higher SC risk than patients in the SPCG-7 study population as a result of a larger irradiated volume. The patients given RT in the SPCG-7 study were all treated with a 3D conventional box technique. At present, intensity modulated radiotherapy (IMRT)/volumetric modulated arch therapy (VMAT) is widely used in prostate cancer treatment. There are studies indicating an increased SC risk after treatment with these novel techniques.[33,34] On the other hand, proton irradiation with potentially less risk of SC may offer an alternative to photon- beam therapy in the future. Also, with improved cancer survival and even longer life expectancy, we must prepare for an increased number of patients with second cancers in coming years.[1,2]

To avoid anti-androgen induced gynecomastia, the SPCG-7 study protocol recommended prophylactic RT (PRT) to the breast buds in all patients. Even though data regarding SC risk after PRT are limited, there is evidence that PRT is not associated with male breast cancer [35] and we do not

believe that PRT to the breast buds has influenced on our results. Moreover, we believe that palliative RT given to patients with progression contributed negligibly to SC development, due to the short life expectancy of patients needing such treatment.

A limitation of our study is that the SPCG-7 study was not originally designed for analysis of SC risk. The numbers of second cancers were relatively low. Some of the confidence intervals of our estimates were wide, and a larger sample size would have strengthened the accuracy of our results. Other limitations comprise lack of follow-up data on the 12 Danish patients as well as lack of salvage RT data in the 209 Swedish patients. Although inclusion of these patients in the salvage RT analysis would have increased statistical power, we believe that this has not influenced on the general conclusions.

In our study we collected data from the Norwegian and Swedish Cancer registries, in addition to the Norwegian and Swedish cause of death registries. This is mainly a strength to our study, since these registries are known to be valid and near complete for the variables applied in our study. [36-39]Misattribution in the Cause of death registries could, however, be a limitation. In a study by Löffeler et al. 33 % of PC deaths in a county of Norway was regarded as over-reported.[40] The major strength of our study is that the analysis of data from a well-balanced RCT most likely is unbiased by comorbidity and life-style factors.

Conclusion

In this analysis of follow-up data from a randomized controlled trial, we have found an increased risk of urinary bladder cancer in patients who received radical prostatic irradiation combined with endocrine therapy for prostate cancer. Although an increased risk of second cancer in general caused by radical RT cannot be ruled out on the basis of this study, these disadvantages are by far outweighed by the overall survival benefit of RT confirmed in this analysis. In our opinion, the present study results give no reason to warn against RT for prostate cancer, especially since the majority of the second bladder cancers were superficial. However, the risk of SC, and especially

bladder cancer, should be taken into account when discussing treatment options and designing follow-up guidelines.

Declaration of interests

We declare no conflict of interests.

Disclosure

This study used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended or should be inferred.

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Figure 1. Probability of all second cancer, all patients (n=860).

Abbreviations: ET= Endocrine therapy, RT= Radiotherapy

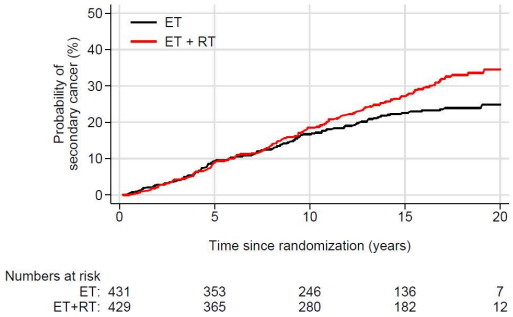

Figure 2. Probability of second urinary bladder cancer, lung cancer, colon cancer, and rectal cancer, all patients (n=860).

Abbreviations: ET= Endocrine therapy, RT= Radiotherapy

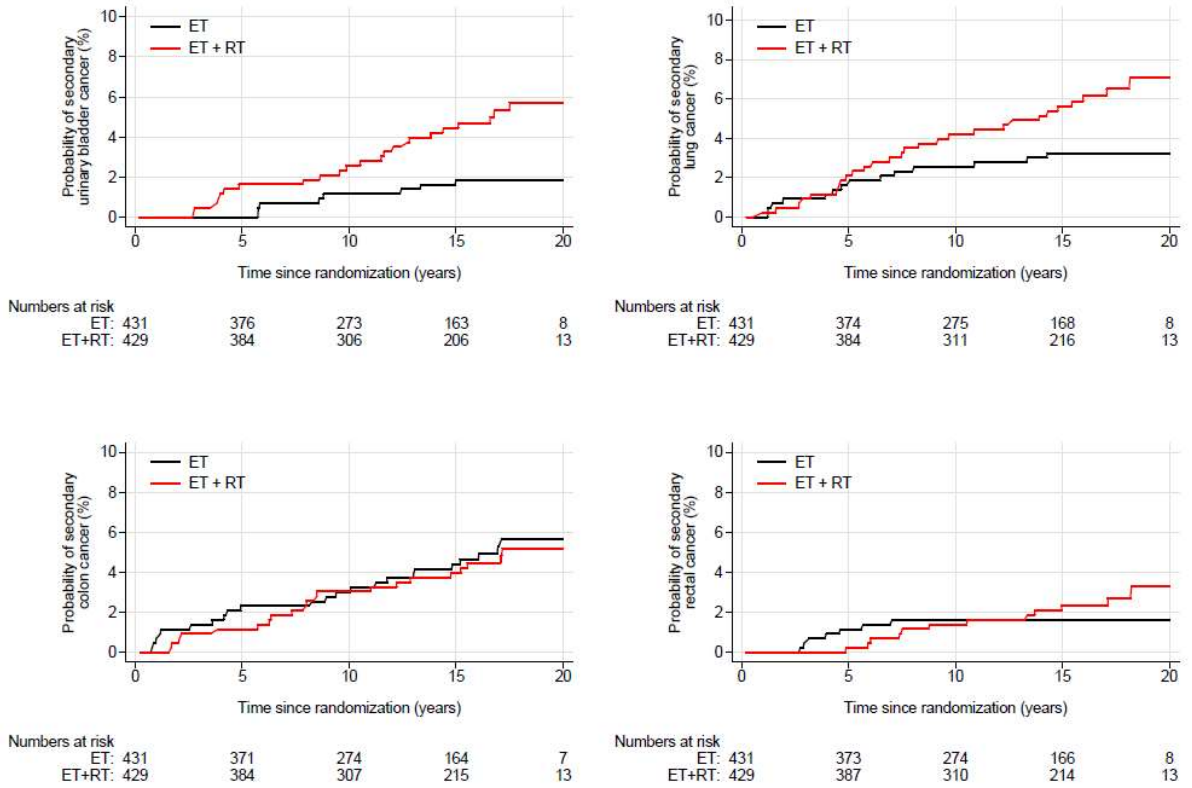

Figure 3. Probability of second cancer in the Norwegian cohort of patients (n=651).

Abbreviations: n=number, ET= Endocrine therapy, RT= Radiotherapy

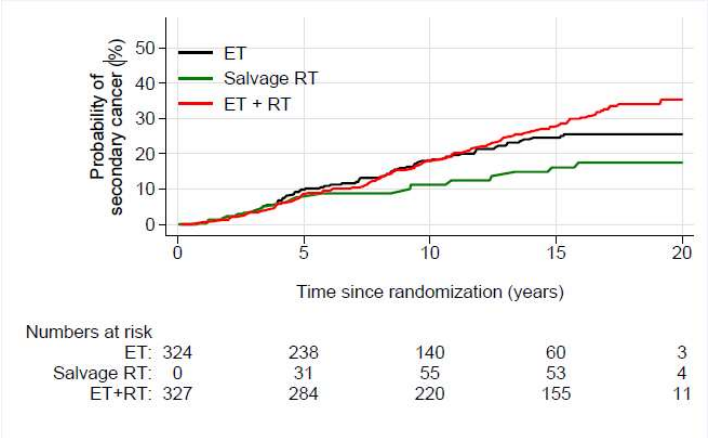

Figure 4. Overall survival, all patients (n=860).

Abbreviations: ET= Endocrine therapy, RT= Radiotherapy

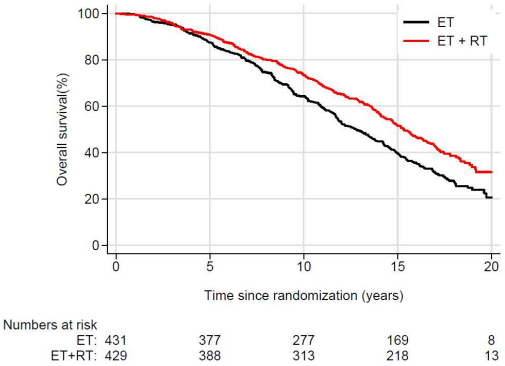

Figure 5. Stacked cumulative incidence of causes of death according to treatment groups.

Abbreviations: PC= Prostate cancer.

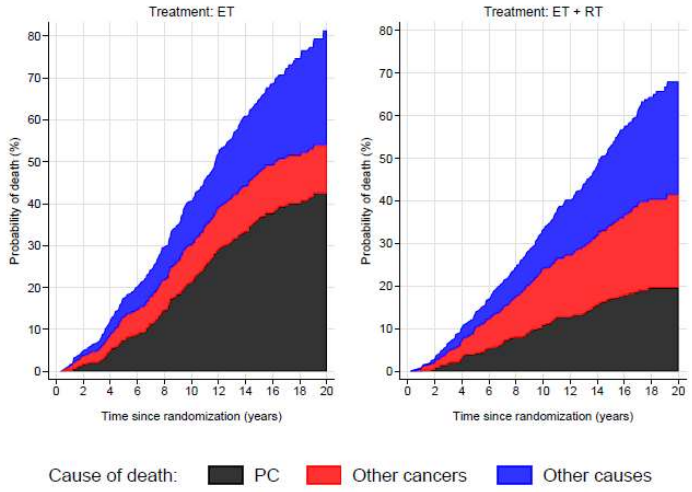

Figure 6. Overall survival, Norwegian cohort of patients (n=651).

Abbreviations: ET= Endocrine therapy, RT= Radiotherapy

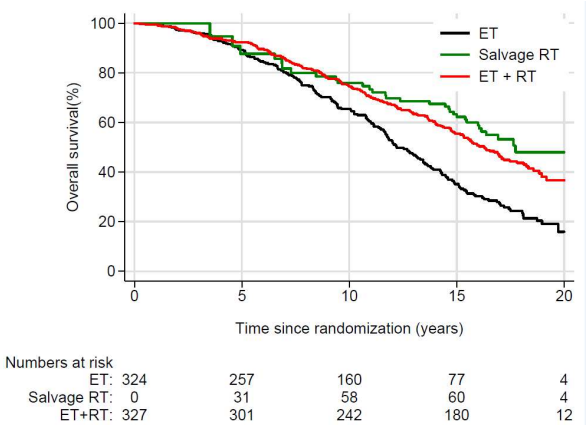

Table 1 Relative risk of main endpoints with corresponding *P* values and 95% confidence intervals

	HR	*P* value	95 %CI
Second cancer risk, total cohort (n = 860)			
Second cancer risk	—	—	—
ET	1	NA	NA
ET + RT	1.19	.181	0.92-1.54
Second urinary bladder cancer risk	—	—	—
ET	1	NA	NA
ET + RT	2.54	.023	1.14-5.69
Second lung cancer risk	—	—	—
ET	1	NA	NA
ET + RT	1.82	.067	0.96-3.47
Second colon cancer risk	—	—	—
ET	1	NA	NA
ET + RT	0.81	.482	0.45-1.46
Second rectal cancer risk	—	—	—
ET	1	NA	NA
ET + RT	1.54	.363	0.61-3.92
Second cancer risk, Norwegian cohort (n = 651)*			
ET	1	NA	NA
ET + RT	1.06	.709	0.78-1.44
Salvage RT	0.48	.032	0.24-0.94
All-cause mortality risk, total cohort (n = 860)			
ET	1	NA	NA
ET + RT	0.73	<.001	0.62-0.86
All-cause mortality risk, Norwegian cohort (n = 651)*			
ET	1	NA	NA
ET + RT	0.59	<.001	0.48-0.73
Salvage RT	0.44	<.001	0.30-0.65
Risk of death from second cancer			
Total cohort (n = 860)			
ET	1	NA	NA
ET + RT	1.42	.078	0.96-2.08

Abbreviations: CI = confidence interval; ET = hormone therapy; HR = hazard ratio; NA = not applicable; RT = radiation therapy.

* ET group consists of patients randomized to ET except patients who received salvage RT.

Table 2 Causes of death in 557 patients.

Cause of Death	1 ET	2 ET + RT	Total
PC	166 (55.2%)	78 (30.5%)	244 (43.8%)
Other cancers	49 (16.2%)	84 (32.8%)	133 (23.9%)
Other causes	86 (28.6 %)	94 (36.7%)	180 (32.3%)
Deaths in total	301	256	557

Abbreviatons: ET = hormone therapy; RT = radiation therapy; PC = prostate cancer.

Supplementary table 1. Second cancers and death from second cancers in 860 patients in the SPCG-7 study.

		SC cancers			Death from SC		
Site	**ICD 10 code**	**ET**	**ET+RT**	**N of cancers (%)**	**ET**	**ET+RT**	**N of deaths (%)**
Colon	C18,C19	25	22	47(16)	8	7	15 (11·3)
Lung	C34	15	28	43(14·7)	13	25	38 (28·5)
Non melanoma skin	C44	19	20	39(13·3)	0	0	0
Hematologic	C81-C96	12	20	32(10·9)	5	8	13 (9·8)
Urinary bladder	C67, C68	8	23	31(10·6)	2	5	7 (5·3)
Rectum	C20	7	12	19(6·5)	2	3	5 (3·6)
Gastric	C16	4	12	16(5·5)	3	8	11 (8·3)
Melanoma	C43	9	6	15(5·1)	0	2	2 (1·5)
Kidney	C64	11	3	14(4·8)	5	2	7 (5·3)
Breast	C50	0	1 (bilateral)	1(0·3)	0	1	1 (0·8)
Other	NA	15	21	36(12·3)	11	23	34 (25·6)
Total	NA	**125(42·7)**	**168(57·3)**	**293(100)**	**49 (36·8)**	**84 (63·2)**	**133 (100)**

Abbreviations: ICD 10= International Classification of Diseases, Tenth Revision, ET=Endocrine therapy, RT= Radiotherapy, N= Number, NA=not applicable

Data in parentheses are percentages.

Supplementary table 2. Cumulative incidence (probability) of main endpoints 5, 10, 15 and 20 years after randomization.

	Probability %	
Second cancer risk	**ET**	**ET+RT**
5-year follow-up	9·3 (6·8 – 12·2)	8·9 (6·4 – 11·8)
10- year follow-up	16·7 (13·4 – 20·4)	18·5 (15·0 – 22·3)
15-year follow-up	22·5 (18·7 – 26·6)	27·1 (23·0 – 31·4)
20-year followw-up	24·8 (20·6 – 29·3)	34·6 (29·6 – 39·6)
Overall survival		
5-year follow-up	87·5 (84·0 – 90·3)	90·7 (87·5 – 93·1)
10- year follow-up	64·3 (59·6 – 68·6)	73·4 (68·9 – 77·3)
15-year follow-up	39·9 (35·2 – 44·5)	51·8 (46·9 – 56·4)
20-year follow -up	20·6 (14·9 – 27·0)	31·6 (25·8 – 37·6)

Abbreviations: ET= Endocrine therapy, RT= Radiotherapy.

Data in parentheses are 95 % confidence intervals.

Supplementary Figure 1. Time to salvage radiotherapy, Norwegian patients randomized to ET (n= 324).