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Original Article

Impact of Advanced External Beam Radiotherapy on Second Haematological Cancer Risk in Prostate Cancer Survivors

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Abstract

Aims: External beam radiotherapy (EBRT) for prostate cancer (PCa) has rapidly advanced over the years. Advanced techniques with altered dose distributions may have an impact on second haematological cancer (SHC) risks. We assessed SHC risk after EBRT for PCa and explored whether this risk has changed over the years.

Materials and methods: Patients diagnosed with a T1-T3 PCa between 1990 and 2015 were selected from the Netherlands Cancer Registry. Patients treated with EBRT were assigned to EBRT eras based on the date of diagnosis. These eras represented two-dimensional radiotherapy (2D-RT; 1991–1996), three-dimensional conformal radiotherapy (3D-CRT; 1998–2005) or advanced EBRT (2008–2015). Standardised incidence ratios (SIR) and absolute excess risks (AER) were calculated overall and by EBRT era. Sub-hazard ratios (sHRs) were calculated for the comparison of EBRT versus radical prostatectomy and active surveillance.

Results: PCa patients with EBRT as the primary treatment ($n = 37\,762$) had an increased risk of developing a SHC (SIR = 1.20; 95% confidence interval 1.13–1.28) compared with the Dutch male general population. Estimated risks were highest for the 2D-RT era (SIR = 1.32; 95% confidence interval 1.14–1.67) compared with the 3D-CRT era (SIR = 1.16; 95% confidence interval 1.05–1.27) and the advanced EBRT era (SIR = 1.21; 95% confidence interval 1.07–1.36). AER were limited, with about five to six extra cases per 10 000 person-years. Relative risk analysis (EBRT versus radical prostatectomy/active surveillance) showed significant elevation with EBRT versus active surveillance (sHR = 1.17; 95% confidence interval 1.03–1.33; $P = 0.017$), but not for EBRT versus radical prostatectomy (sHR = 1.08; 95% confidence interval 0.94–1.23; $P = 0.281$).

Conclusion: Increased SHC risks after EBRT for PCa cancer were observed for all EBRT eras compared with the general Dutch male population. Excess risks for EBRT versus other PCa treatment groups were found for only EBRT versus active surveillance.

Key words: Intensity-modulated radiotherapy; prostate cancer; second haematological cancer; survivorship; three-dimensional conformal radiotherapy; volumetric modulated arc therapy

Introduction

External beam radiotherapy (EBRT) is one of the cornerstones in the primary treatment of prostate cancer (PCa) and a known risk factor for the development of a second primary cancer (SPC) [1–6]. In the past decades, EBRT for PCa evolved from simple two-dimensional rectangular pelvic fields to more conformal fields targeting the prostate, with or without seminal vesicles, with a three- to four-beam arrangement. This technique subsequently evolved to a multiple-beam, intensity-modulated technique with tighter safety margins around the target volume [7].

Specifically, organs in the pelvis, such as the bladder and rectum, are at risk for SPC development [3,4,8,9]. Several studies have also reported heightened second haematological cancer (SHC) risk for patients irradiated in the pelvic

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area [4,10,11]. However, most of those studies are limited in their sample size and follow-up and do not explore specific SHC subtypes. Therefore, it remains unclear how EBRT impacts SHC development in the long term.

In adult patients, more than one-third of the proliferating haematopoietic stem cells in the bone marrow can be found in the pelvis [12]. Due to changes in the applied EBRT techniques over time, in particular field sizes and beam arrangements, the percentage and dose levels of bone marrow irradiated changed over time, which may impact SHC risks over time. Some of the more recent cohort studies take into consideration the evolvements in EBRT technique [7,13]. There is a general consensus that changes in EBRT may have an impact on SPC risks, which is confirmed by some cohort studies with respect to solid tumours, although other studies report no obvious impact of advanced radiotherapy techniques on SPC risks [7,10,13,14]. With respect to SHC risks, the impact of EBRT techniques has not yet been investigated in large PCa cohorts, to our knowledge.

Here we used nationwide cancer data to assess the risk of developing SHCs in a cohort of PCa patients who received EBRT in different EBRT eras to explore how the risk of developing SHC changed over the years, in particular with respect to the current era of advanced EBRT.

Materials and Method

Study Design and Population

For this cohort study, nationwide data from the Netherlands Cancer Registry (NCR) was used. The NCR, established in 1989 with nationwide coverage, contains data on all new cancer diagnoses in the Netherlands. Relevant patient and tumour characteristics, such as age, date of PCa diagnosis, disease stage (TNM classification) and primary treatment, were obtained from the NCR. All patients diagnosed with stage T1-T3 PCa without positive lymph nodes and without distant metastases were identified. Only patients who received either EBRT ± hormonal therapy, radical prostatectomy, active surveillance or brachytherapy as their primary treatment and who were diagnosed between 1990 and 2014, with no prior cancer history except for non-melanoma skin cancer, were included in the study. Patients were included regardless of whether they received hormonal therapy, because in a previously carried out single-centre study we found at sensitivity analysis that hormonal therapy did not affect the risk of developing a SPC [13]. This study aimed to explore SHC risk after treatment with EBRT. This was carried out by comparing PCa patients who received EBRT with the Dutch male general population and to radical prostatectomy and active surveillance reference cohorts. To minimise the effect of subsequent EBRT in the radical prostatectomy and active surveillance cohort, only patients with T1-T2 PCa were included.

Definition of Second Haematological Cancers, Time Periods and Follow-up

All SHC occurring 1 year after PCa diagnosis were included. The latency period of 1 year was applied to exclude synchronous cancers and to reduce surveillance bias. SHCs were divided into two different categories: myeloid and lymphoid malignancies. These categories were further subdivided into the most common haematological malignancies. This classification is based on the updated World Health Organization (WHO) classification of haematological malignancies [15].

Patients treated with EBRT were assigned to an EBRT era based on the date of diagnosis. Time periods were defined and used as a proxy for the EBRT eras. The following EBRT eras were defined: 1991–1996 representing the two-dimensional radiotherapy (2D-RT) era, 1998–2005 the three-dimensional conformal radiotherapy (3D-CRT) era and finally 2008–2014 the advanced EBRT era encompassing intensity-modulated radiotherapy (IMRT) and/or volumetric modulated arc therapy (VMAT). With respect to dose and fractionation protocols during the EBRT eras in the Netherlands, we can generally state that standard fractionation was around 2 Gy per fraction, and prescribed dose levels increased from about 66–70 Gy in the first two eras to 74–78 Gy in the advanced EBRT era. Follow-up was defined as the time between PCa diagnosis until date of SHC, date of death, date of emigration or end of study (31 December 2020), whichever occurred first.

Statistical Analysis

Descriptive analyses of the patient and tumour characteristics were carried out. Standardised incidence ratios (SIRs) and absolute excess risks (AERs) were calculated for the EBRT, radical prostatectomy and active surveillance cohorts. The radical prostatectomy and active surveillance cohorts were used as reference populations for further exploring the impact of EBRT on SHC risk.

SIR analysis was carried out for all SHC together and the subgroups as described earlier. The SIR describes the risk of developing a SHC by dividing the observed number of cancers by the expected number of cancers in the general population matched on age and calendar period. The expected number is calculated based on population number Statistics Netherlands (CBS) and incidence rates (NCR). Poisson regression was used to compute 95% confidence intervals. For measuring the excess burden of SHC, AERs were calculated. The AER represents the additional incidence beyond the background incidence found in the general population matched on age and calendar period. It is defined as the absolute difference between the observed and the expected number of patients with a SHC, divided by the number of person-years at risk, multiplied by 10 000. The expected number for both calculations is based on the sex-,

Table 1
Patient and tumour characteristics for prostate cancer patients who received external beam radiotherapy (EBRT) ± hormone therapy, radical prostatectomy, active surveillance or brachytherapy as primary treatment

	EBRT cohort		Radical prostatectomy cohort		Active surveillance cohort		Brachytherapy cohort	
	Patients		Patients		Patients		Patients	
	n	%	*n*	%	*n*	%	*n*	%
Total	37762	100	26187	100	24140	100	8025	100
Median age (interquartile range)	70.0 (65.0–74.0)		64.0 (59.0–67.0)		71.0 (65.0–77.0)		65.0 (61.0–70.0)	
Age group (years)								
<60	2910	7.71	7024	26.82	2316	9.59	1562	19.46
60–69	14772	39.12	15735	60.09	8140	33.72	4299	53.57
70–79	18850	49.92	3381	12.91	10205	42.27	2126	26.49
80+	1230	3.26	47	0.18	3479	14.41	38	0.47
Time period								
1991–1997 (2D-RT)	6630	20.33	2189	9.59	1925	9.23	99	1.52
1998–2005 (3D-CRT)	13746	42.16	7799	34.15	5430	26.04	2272	34.80
2006–2014 (advanced EBRT)	12232	37.51	12847	56.26	13494	64.72	4157	63.68
Disease stage								
T1-2 N0/X, M0/X	25778	68.26	26187	100	24140	100	7940	98.9
T3 N0/X, M0/X	11984	31.74	–	–	–	–	85	1.1

2D-RT, two-dimensional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy.

age- and calendar-specific incidence rates in the Netherlands. SIRs and AERs for the EBRT cohort were calculated for the previously defined EBRT eras, age groups (≤70 or >70 years) and follow-up years, in order to evaluate evolvement over time since diagnosis. SIRs and AER were estimated shortly after diagnosis (1–5 years), in the subsequent 5–10 years and >10 years after PCa diagnosis. When comparing groups, the point estimate of a SIR was considered significantly different when it was outside the 95% confidence interval of the SIR to which it was compared to. All abovementioned analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

A relative risk analysis was carried out using the Fine and Gray method (sub-hazard ratios; sHRs) for comparing the EBRT cohort versus the radical prostatectomy cohort and the active surveillance cohort [16]. The sHR for EBRT versus radical prostatectomy and active surveillance was estimated for the complete EBRT cohort and separately for the EBRT eras. The models were adjusted for the year of diagnosis and age. Significance was set at $P < 0.05$. The sHR analyses were carried out using STATA version 14 (STATA Corp., Texas, USA).

Results

Patient/Tumour Characteristics

Patient and tumour characteristics for PCa patients having received EBRT are summarised in Table 1. The median age of PCa diagnosis is this cohort was 70.0 years (interquartile range 65.0–74.0). Most patients (68.26%) were diagnosed with a T1-2 N0/X, M0/X PCa and 31.74% with a T3 N0/X, M0/X PCa. Patient and tumour characteristics for patients having undergone radical prostatectomy, active surveillance or brachytherapy can be found in Table 1.

Second Haematological Cancer Risk for the External Beam Radiotherapy Cohort

A significant increased risk for developing any SHC was observed in the EBRT cohort (SIR = 1.20; 95% confidence interval 1.13–1.28; AER = 4.98) (Table 2). The risk for second myeloid malignancies (SIR = 1.34; 95% confidence interval 1.21–1.49); AER = 2.71) was significantly elevated, with an increase found for all three subtypes: acute myeloid leukaemia (AML; SIR = 1.33; 95% confidence interval 1.07–1.64; AER = 0.66), myeloproliferative neoplasms (SIR = 1.30; 95% confidence interval 1.06–1.59; AER = 0.65) and myelodysplastic syndrome (MDS; SIR = 1.38; 95% confidence interval 1.18–1.59; AER = 1.42). The risk for second lymphoid malignancies was also significantly increased (SIR = 1.14; 95% confidence interval 1.06–1.24; AER = 2.42), attributed to the elevated risk of second plasma tumours (SIR = 1.28; 95% confidence interval 1.09–1.48; AER = 1.08) (Table 2).

Standardised Incidence Ratios and Absolute Excess Risk for Prostate Cancer Patients Treated with External Beam Radiotherapy by Different Duration of Follow-up

The risk of developing any SHC after EBRT for PCa was significantly increased in the first 1–5 years of follow-up (SIR = 1.21; 95% confidence interval 1.10–1.33; AER = 4.58) (Figure 1, Table 3). In the 5–10-year follow-up period it decreased (SIR = 1.15; 95% confidence interval 1.04–1.28; AER = 4.15) and then increased again after >10 years of follow-up (SIR = 1.25; 95% confidence interval 1.10–1.42; AER = 10.15). For myeloid malignancies, the risk was highest in the first 5 years of follow-up (SIR = 1.50; 95% confidence interval 1.28–1.75; AER = 3.17). In the second follow-up period, the risk reduced (SIR = 1.16; 95% confidence interval 0.95–1.39; AER = 1.40) and then significantly

Table 2
Standardised incidence ratios (SIR) and absolute excess risks (AER) for prostate cancer patients treated with external beam radiotherapy (EBRT) ± hormone therapy

Tumour sites	EBRT cohort			
	Observed	Expected	SIR	AER
All haematological	1019	848.6	**1.20 (1.13–1.28)**	4.98
Myeloid malignancies	365	271.6	**1.34 (1.21–1.49)**	2.71
Acute myeloid leukaemia	91	68.3	**1.33 (1.07–1.64)**	0.66
Myeloproliferative neoplasms	96	73.6	**1.30 (1.06–1.59)**	0.65
Myelodysplastic syndrome and myelodysplastic/myeloproliferative neoplasms	179	130.1	**1.38 (1.18–1.59)**	1.42
Lymphoid malignancies	658	575.0	**1.14 (1.06–1.24)**	2.42
Hodgkin lymphoma	9	11.6	0.78 (0.38–1.47)	−0.08
Indolent non-Hodgkin lymphoma	107	89.4	1.20 (0.99–1.45)	0.51
Plasma cell tumours	172	134.7	**1.28 (1.09–1.48)**	1.08
Aggressive non-Hodgkin lymphoma	191	176.6	1.08 (0.94–1.24)	0.42
B-cell chronic lymphocytic leukemia (B-CLL)/small lymphocytic lymphoma	132	129.6	1.02 (0.85–1.21)	0.07
Other	51	36.5	**1.40 (1.04–1.84)**	0.42

Bold numbers indicate significant SIRs.

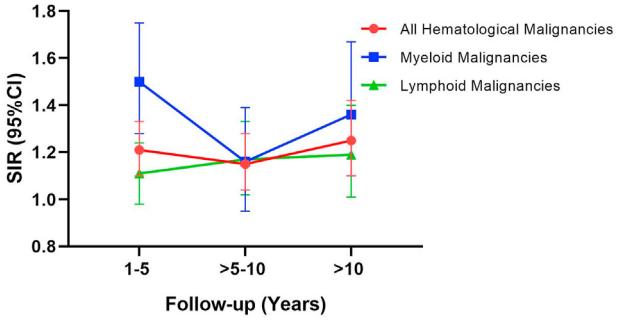

Fig 1. Standardised incidence ratios (SIR) for prostate cancer patients treated with external beam radiotherapy ± hormone therapy for different follow-up years.

increased again after >10 years of follow-up (SIR = 1.36; 95% confidence interval 1.10–1.67; AER = 3.74). A similar pattern was observed for second lymphoid malignancies. The SIR and AER for additional haematological tumour sites can be found in Table 3.

Standardised Incidence Ratios and Absolute Excess Risk for Prostate Cancer Patients Treated with External Beam Radiotherapy Stratified by External Beam Radiotherapy Era and Age

For the first EBRT era (2D-RT), a significant increased risk for developing any SHC was observed (SIR = 1.32; 95% confidence interval 1.14–1.67; AER = 6.61) (Table 4, Figure 2). A subtype-specific analysis revealed an increased risk for second myeloid cancers (SIR = 1.59; 95% confidence interval 1.19–2.10; AER = 3.24). In the era of 3D-CRT, the overall risk of developing any SHC was also increased (SIR = 1.16; 95% confidence interval 1.05–1.27; AER = 3.99). The risk for second myeloid malignancies was elevated (SIR = 1.35; 95% confidence interval 1.15–1.57; AER = 2.92), attributed to an increased risk for AML (SIR = 1.41; 95% confidence interval 1.02–1.91; AER = 0.84) and MDS (SIR = 1.30; 95% confidence interval 1.03–1.62; AER = 1.27). Furthermore, the risk of developing second plasma cell tumours (SIR = 1.34; 95% confidence interval 1.06–1.68; AER = 1.34) was increased in this era. A significant decreased risk was observed for second B-cell chronic lymphocytic leukemia (B-CLL) cancers (SIR = 0.72; 95% confidence interval 0.52–0.98; AER = −1.09). In the advanced EBRT era, the risk of developing any SHC was significantly elevated (SIR = 1.21; 95% confidence interval 1.07–136; AER = 5.37). The risk for second myeloid cancers (SIR = 1.38; 95% confidence interval 1.17–1.73; AER = 3.19) was increased. This increase can be linked to a significant increase in MDS (SIR = 1.58; 95% confidence interval 1.19–2.05; AER = 2.27). During the period 1990–2015, the risk of developing any SHC persisted. It slightly decreased in the second EBRT era and then increased again in the advanced EBRT era. The risk of developing MDS was highest in the advanced EBRT era (Table 4).

Patients aged ≤70 years had a slightly higher risk of developing any SHC (SIR = 1.23; 95% confidence interval 1.13–1.34; AER = 5.09) and myeloid malignancies (SIR = 1.45; 95% confidence interval 1.26–1.67; AER = 2.97), as opposed to patients aged >70 years. The risk of developing lymphoid malignancies was comparable for both age groups (Table 5). Similar observations were made for the EBRT eras (Table 5).

Standardised Incidence Ratios and Absolute Excess Risk for Prostate Cancer Patients Treated with Radical Prostatectomy, Active Surveillance or Brachytherapy

The risk of developing any SHC was significantly increased in the radical prostatectomy cohort (SIR = 1.19; 95% confidence interval 1.09–1.30; AER = 3.72) and not in the active surveillance cohort (SIR = 1.09; 95% confidence interval 0.99–1.20; AER = 0.22). For the brachytherapy cohort, the risk of developing any SHC was SIR = 1.15; 95% confidence interval 1.00–1.32; AER = 3.41. Detailed information on SHC risk for the complete radical prostatectomy, active surveillance and brachytherapy cohort can be found in Supplementary Table S1. Additionally, Supplementary

Table 3
Standardised incidence ratios (SIR) and absolute excess risks (AER) analysis for prostate cancer patients treated with external beam radiotherapy ± hormone therapy for different follow-up years

Tumour sites	1–5 years				>5–10 years				>10 years			
	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER
All haematological	444	366.1	**1.21 (1.10–1.33)**	4.58	339	293.7	**1.15 (1.04–1.28)**	4.15	236	188.8	**1.25 (1.10–1.42)**	7.49
Myeloid malignancies	162	107.9	**1.50 (1.28–1.75)**	3.17	113	97.6	1.16 (0.95–1.39)	1.40	90	66.1	**1.36 (1.10–1.67)**	3.74
Acute myeloid leukaemia	46	29.9	**1.54 (1.13–2.05)**	0.94	27	23.3	1.16 (0.76–1.69)	0.34	18	15.1	1.19 (0.71–1.89)	0.45
Myeloproliferative neoplasms	38	30.5	1.25 (0.88–1.71)	0.44	33	26.2	1.26 (0.87–1.77)	0.62	25	16.9	1.48 (0.96–2.18)	1.26
Myelodysplastic syndrome and myelodysplastic/myeloproliferative neoplasms	78	47.7	**1.64 (1.29–2.04)**	1.77	53	48.2	1.10 (0.82–1.44)	0.44	48	34.2	**1.40 (1.04–1.86)**	2.15
Lymphoid malignancies	284	256.7	1.11 (0.98–1.24)	1.60	228	195.7	**1.17 (1.02–1.33)**	2.95	146	122.6	**1.19 (1.01–1.40)**	3.69
Hodgkin lymphoma	5	5.9	0.85 (0.28–1.98)	−0.05	2	3.7	0.54 (0.07–1.95)	−0.15	2	2.0	1.00 (0.12–3.61)	0.00
Indolent non-Hodgkin lymphoma	42	40.0	1.05 (0.76–1.42)	0.12	35	30.5	1.15 (0.80–1.60)	0.41	30	18.9	**1.59 (1.07–2.27)**	1.73
Plasma cell tumours	82	59.4	**1.38 (1.10–1.71)**	1.32	57	46.0	1.24 (0.94–1.61)	1.00	33	29.3	1.13 (0.78–1.58)	0.58
Aggressive non-Hodgkin lymphoma	70	76.1	0.92 (0.72–1.16)	−0.36	78	60.6	**1.29 (1.02–1.61)**	1.58	43	39.9	1.08 (0.78–1.45)	0.48
B-cell chronic lymphocytic leukemia (B-CLL)/small lymphocytic lymphoma	59	43.7	**1.35 (1.03–1.74)**	0.21	46	43.7	1.05 (0.77–1.40)	0.21	27	25.9	1.04 (0.69–1.52)	0.17
Other	26	16.0	**1.63 (1.06–2.38)**	0.58	12	12.5	0.96 (0.50–1.68)	−0.05	13	8.0	1.63 (0.87–2.78)	0.78

Bold numbers indicate significant SIRs.

Table 4
Standardised incidence ratios (SIR) and absolute excess risk (AER) for prostate cancer patients treated with external beam radiotherapy (EBRT) ± hormone therapy for different EBRT eras

Tumour sites	1991–1996				1998–2005				2008–2015			
	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER
All haematological	160	121.5	**1.32 (1.14–1.67)**	6.61	428	370.0	**1.16 (1.05–1.27)**	3.99	276	228.9	**1.21 (1.07–1.36)**	5.37
Myeloid malignancies	51	32.0	**1.59 (1.19–2.10)**	3.24	166	123.3	**1.35 (1.15–1.57)**	2.92	107	74.8	**1.38 (1.17–1.73)**	3.19
Acute myeloid leukaemia	18	11.1	1.62 (0.96–2.56)	1.18	42	29.7	**1.41 (1.02–1.91)**	0.84	17	17.6	0.97 (0.56–1.55)	−0.07
Myeloproliferative neoplasms	10	7.0	1.43 (0.69–2.63)	0.51	45	33.0	1.36 (0.99–1.83)	0.82	31	22.2	1.40 (0.95–1.98)	1.00
Myelodysplastic syndrome and myelodysplastic/myeloproliferative neoplasms	23	14.3	**1.61 (1.02–2.41)**	1.48	80	61.4	**1.30 (1.03–1.62)**	1.27	55	34.9	**1.58 (1.19–2.05)**	2.27
Lymphoid malignancies	108	88.9	1.21 (1.00–1.47)	3.27	264	246.7	1.07 (0.94–1.21)	1.19	176	153.7	1.15 (0.98–1.33)	2.53
Hodgkin lymphoma	2	1.6	1.25 (0.15–4.52)	0.07	3	4.9	0.61 (0.12–1.79)	−0.13	2	3.1	0.65 (0.08–2.33)	−0.12
Indolent non-Hodgkin lymphoma	11	12.5	0.88 (0.44–1.58)	−0.26	39	37.1	1.05 (0.75–1.44)	0.13	32	26.6	1.20 (0.82–1.70)	0.61
Plasma cell tumours	26	21.1	1.23 (0.80–1.81)	0.84	77	57.4	**1.34 (1.06–1.68)**	1.34	44	35.7	1.23 (0.90–1.66)	0.94
Aggressive non-Hodgkin lymphoma	35	28.1	1.25 (0.87–1.73)	1.18	80	76.0	1.05 (0.83–1.31)	0.27	48	46.2	1.03 (0.77–1.38)	0.20
B-cell chronic lymphocytic leukemia (B-CLL)/small lymphocytic lymphoma	30	20.3	1.48 (1.00–2.11)	1.66	41	57.0	**0.72 (0.52–0.98)**	−1.09	41	32.6	1.26 (0.90–1.71)	0.95
Other	5	5.2	0.96 (0.31–2.24)	−0.03	25	15.6	**1.60 (1.04–2.37)**	0.64	11	9.8	1.12 (0.56–2.01)	0.14

Bold numbers indicate significant SIRs.

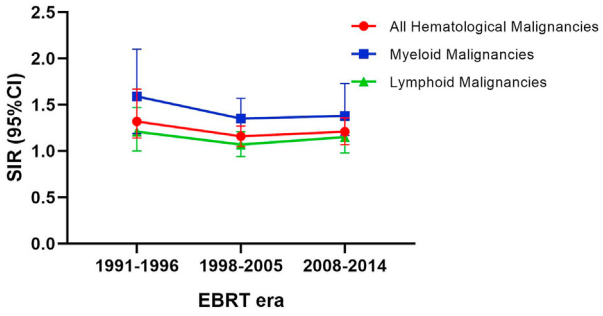

Fig 2. Standardised incidence ratios (SIR) for prostate cancer patients treated with external beam radiotherapy (EBRT) ± hormone therapy for different EBRT eras.

Table S2 shows the risk of developing a SHC after radical prostatectomy or active surveillance in patients aged below or above 70 years. Supplementary Figure S1 depicts the risk of developing any SHC, myeloid malignancies or lymphoid malignancies after radical prostatectomy or active surveillance over different follow-up years.

Comparison of the External Beam Radiotherapy Cohort to the Radical Prostatectomy Cohort and the Active Surveillance Cohort

The adjusted sHR (95% confidence interval) for EBRT versus radical prostatectomy for developing any SHC was 1.08 (95% confidence interval 0.94–1.23; $P = 0.281$), for myeloid malignancies 1.13 (95% confidence interval 0.91–1.41; $P = 0.261$) and for lymphoid malignancies 1.03 (95% confidence interval 0.87–1.22; $P = 0.727$) (Table 6). For any SHC, analysis stratified by EBRT era resulted in a sHR of 1.30 (95% confidence interval 0.91–1.86; $P = 0.153$) for the first era; 0.95 (95% confidence interval 0.78–1.15; $P = 0.574$) for the second era and 1.12 (95% confidence interval 0.86–1.47; $P = 0.390$) for the last era. Additional sHRs for the different tumour endpoints and time periods are depicted in Table 6. The sHR for the EBRT cohort versus the active surveillance cohort for any SHC was 1.17 (95% confidence interval 1.03–1.33; $P = 0.017$). For second myeloid malignancies it was 1.30 (95% confidence interval 1.06–1.60; $P = 0.014$). The biggest difference was observed for MDS (sHR = 1.74; 95% confidence interval 1.27–2.40; $P = 0.001$) and for plasma tumours (sHR = 1.73; 95% confidence interval 1.26–2.39; $P = 0.001$). Analysis stratified by EBRT era revealed a significant difference for the advanced EBRT era for second myeloid malignancies (sHR = 1.47; 95% confidence interval 0.97–1.47; $P = 0.023$) (Table 6).

Discussion

To the best of our knowledge, this is the first nationwide cohort study exploring SHC risk after EBRT for localised PCa, while considering advances in EBRT. Overall, we observed a significantly higher risk of developing a SHC in patients treated with EBRT, as opposed to the general population. We observed a limited difference in the estimated risk when comparing the different EBRT eras. Even though the risk for SHCs seemed lower in the advanced EBRT era, as opposed to the 2D-RT era (which might be related to reduced volumes treated and dose to bone marrow with advanced techniques), we still observed a significant increased risk. These findings suggest that advances in EBRT techniques did not necessarily lower the incidence of SHC. About 40% of all bone marrow in adults is located within the bones of the pelvis, making related haematological side-effects a major risk in patients having received pelvic EBRT [17]. The occurrence of haematological side-effects is associated with the volume of irradiated pelvic bone marrow [18]. With current advanced EBRT, bone marrow sparing planning strategies have become more feasible. With the introduction of IMRT and VMAT, radiation exposure to surrounding nearby healthy tissues and organs can be reduced, at the expense of larger volumes of normal tissue being exposed to low-dose radiation. Tissues receiving low doses are prone to developing secondary malignancies because low doses result in mutations rather than cell kill [19]. This is supported by a study presenting a linear model, which shows that low-dose radiation is insufficient to kill cells, thus allowing cells to maintain the potential to turn malignant at a later stage [14]. This model, however, is based on a one-time exposure event, which is not the case in EBRT. From a biological perspective, it is plausible that the low-dose radiation from advanced EBRT, such as IMRT and VMAT, leads to cell mutation rather than cell death, thereby increasing the risk of developing a SHC [20]. The limited studies exploring SHC risk focus mainly on the most common endpoints, namely myeloid malignancies. A population-based study carried out by Wang *et al.* [11] assessing the risk of developing MDS and AML after PCa, observed an increased risk for MDS/AML only in the patient cohort treated with IMRT. In our study, we observed a higher risk of developing a myeloid malignancy in the advanced EBRT era, as opposed to the 3D-CRT era. This risk was particularly evident for second MDS. No increased risk for AML was observed. However, similar to the study by Wang *et al.* [11], we found MDS and AML to be rare endpoints, especially in the EBRT-specific analysis.

This study is the first to explore the effect of advances in EBRT on haematological tumour endpoints other than AML and MDS. We found a significantly increased risk for lymphoid malignancies in PCa patients treated with EBRT. This increased risk was attributed to the significant elevation in second plasma cell tumours. Plasma cell tumours are a group of disorders involving mature B-cells [21]. Multiple myeloma is the most common subtype of plasma cell tumour and, similar to MDS/AML, arises from the bone marrow [21]. Thus, the mechanism of therapy-related multiple myeloma might be comparable to the aetiology of therapy-related MDS/AML. A study by Wright *et al.* [22] found no association between pelvic EBRT and multiple myeloma. Most patients included in their study received pelvic radiation to the cervix, uterus and rectum, and did not include patients who received pelvic radiation to the prostate.

Table 5
Standardised incidence ratios (SIR) and absolute excess risks (AER) for prostate cancer patients treated with external beam radiotherapy (EBRT) ± hormone therapy for the complete cohort and for the different EBRT eras stratified by age

	EBRT cohort				1991–1996				1998–2005				2008–2015			
Tumour sites	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER	Observed	Expected	SIR	AER
All haematological																
≤70 years	538	435.7	**1.23 (1.13–1.34)**	5.09	90	67.6	**1.33 (1.07–1.64)**	6.47	242	203.2	**1.19 (1.05–1.35)**	4.38	118	94.9	**1.24 (1.03–1.50)**	5.07
>70 years	481	412.9	**1.16 (1.06–1.27)**	4.81	70	54.2	**1.29 (1.01–1.63)**	6.68	186	167.1	1.11 (0.96–1.29)	3.34	158	134.5	1.17 (1.00–1.37)	5.57
Myeloid malignancies																
≤70 years	193	132.9	**1.45 (1.26–1.67)**	2.97	30	18.3	**1.64 (1.11–2.34)**	3.36	97	64.5	**1.50 (1.22–1.84)**	3.64	42	28.2	**1.50 (1.07–2.01)**	3.01
>70 years	172	138.6	**1.24 (1.06–1.44)**	2.34	21	14.0	1.50 (0.93–2.29)	2.95	69	58.6	1.18 (0.92–1.49)	1.82	61	46.5	1.31 (1.00–1.69)	3.41
Lymphoid malignancies																
≤70 years	346	302	**1.15 (1.03–1.27)**	2.18	59	48.8	1.21 (0.92–1.56)	2.94	146	138.6	1.05 (0.89–1.24)	0.83	77	65.9	1.17 (0.92–1.46)	2.43
>70 years	312	273.4	**1.14 (1.02–1.28)**	2.72	49	39.9	1.23 (0.91–1.62)	3.84	118	108.0	1.09 (0.90–1.31)	1.76	99	87.8	1.13 (0.92–1.37)	2.64

Bold numbers indicate significant SIRs.

Additionally, we explored the endpoint Hodgkin lymphoma and indolent non-Hodgkin lymphoma. We found both to be rare endpoints, especially after stratification by time period. We were therefore not able to confirm the findings from a large long-term study by Kim *et al.* [23], which investigated the risk of non-Hodgkin lymphoma after radiotherapy for solid cancer. In their study, they found a significant elevation of non-Hodgkin lymphoma in patients treated with radiotherapy for PCa. However, their study lacked detail on the applied EBRT technique.

We found that age plays a role in the development of a SHC. For the complete EBRT cohort, relative to the general population, both age groups had an increased risk of developing a SHC. Stratification by EBRT era revealed a higher risk of developing myeloid malignancies in patients aged ≤70 years. For clinical decision making it is important to consider this increased risk, as younger patients are likely to survive for a longer duration after treatment. The phenomenon of younger people being more susceptible to radiation exposure has been observed in other epidemiological cohort studies for solid cancer endpoints [13,24–27].

The risk of developing a SHC was already significantly increased in the first 1–5 years of follow-up. The latency period of developing a SHC is shorter than that of developing any solid SPC. These findings are in line with the results of the Life Span Atomic Bomb study, which observed that radiation-related excess of leukaemias would be expected to occur largely within the first 5 years of diagnosis [28]. In a study by Journy *et al.* [10], exploring SPC after IMRT versus 3D-CRT, they concluded that the development of leukaemia and/or MDS may occur as soon as 2 years after radiation. This is a relevant consideration in the follow-up of cancer patients.

In addition to the SIR and AER analysis, we compared SHC risk after EBRT versus radical prostatectomy and active surveillance. The radical prostatectomy cohort and the active surveillance cohort were used as reference populations. Due to the small number of events observed in the brachytherapy cohort, no comparison was carried out between EBRT versus brachytherapy. For both the radical prostatectomy and the active surveillance cohorts we limited the PCa tumour stages, in order to minimise the effect of subsequent EBRT treatment. Unlike with the comparison EBRT versus active surveillance, we observed no significant difference when comparing EBRT versus radical prostatectomy, despite the fact that patients who underwent radical prostatectomy were younger. However, it is common for patients who undergo radical prostatectomy to receive salvage radiotherapy at a later stage, in case of recurrent disease [29]. The NCR does not record additional treatment received. Therefore, we are unable to correct for this potential confounding factor. Additional research is required to further understand why we observe an increased risk for SHC after radical prostatectomy for PCa. The major strength of this study is its large sample size, which enabled us to explore several specific endpoints. Moreover, the data were obtained from the NCR, which has nationwide coverage and contains data on all new cancer

Table 6
Sub-hazard ratios (sHR) analysis for the external beam radiotherapy (EBRT) cohort ± hormone therapy versus the radical prostatectomy cohort and the active surveillance cohort

Tumour sites	EBRT	Radical prostatectomy	sHR	*P*-value	EBRT	Active surveillance	sHR	*P*-value
All haematological	760	470	1.08 (0.94–1.23)	0.281	760	383	1.17 (1.03–1.33)	**0.017**
Myeloid malignancies	308	171	1.13 (0.91–1.41)	0.261	308	142	1.30 (1.06–1.60)	**0.014**
Acute myeloid leukaemia	80	36	1.40 (0.89–2.19)	0.145	80	40	1.08 (0.72–1.60)	0.717
Myeloproliferative neoplasms	80	70	0.84 (0.59–1.20)	0.342	80	47	1.01 (0.69–1.48)	0.971
Myelodysplastic syndrome and myelodysplastic/ myeloproliferative neoplasms	148	65	1.27 (0.89–1.82)	0.184	148	55	1.74 (1.27–2.40)	**0.001**
Lymphoid malignancies	447	297	1.03 (0.87–1.22)	0.727	447	239	1.09 (0.93–1.29)	0.292
Hodgkin lymphoma	8	8	0.81 (0.28–2.29)	0.685	8	11	0.34 (0.12–0.92)	**0.033**
Indolent non-Hodgkin lymphoma	87	70	1.14 (0.78–1.66)	0.501	87	57	0.95 (0.67–1.36)	0.793
Plasma cell tumours	155	109	0.86 (0.65–1.14)	0.295	155	54	1.73 (1.26–2.39)	**0.001**
Aggressive non-Hodgkin lymphoma	156	88	1.04 (0.77–1.41)	0.795	156	103	0.86 (0.66–1.12)	0.263
Other	41	22	1.65 (0.97–2.82)	0.065	41	14	1.75 (0.93–3.32)	0.085
All haematological								
1991–1996	119	54	1.30 (0.91–1.86)	0.153	119	32	0.97 (0.65–1.44)	0.867
1998–2005	339	217	0.95 (0.78–1.15)	0.574	339	113	1.12 (0.90–1.40)	0.320
2008–2014	186	129	1.12 (0.86–1.47)	0.390	186	169	1.20 (0.97–1.47)	0.088
Myeloid malignancies								
1991–1996	49	16	1.86 (1.02–3.40)	**0.042**	49	11	1.18 (0.60–2.30)	0.633
1998–2005	138	86	0.93 (0.67–1.27)	0.633	138	47	1.09 (0.77–1.54)	0.640
2008–2014	83	42	1.31 (0.84–2.05)	0.227	83	61	1.47 (1.06–2.05)	**0.023**
Lymphoid malignancies								
1991–1996	69	37	1.05 (0.66–1.66)	0.836	69	21	0.84 (0.51–1.38)	0.488
1998–2005	198	131	0.94 (0.74–1.20)	0.635	198	65	1.14 90.85–1.54)	0.364
2008–2014	102	87	1.12 (0.86–1.47)	0.390	102	108	1.03 (0.79–1.35)	0.811

Bold numbers indicate significant *P*-values.

diagnoses in the Netherlands. The time periods defined act as a proxy for the different EBRT eras. This enabled us to assess trends over time and further explore the impact different EBRT modalities have on SHC risk. By doing a dual comparison, EBRT versus the general population as well as radical prostatectomy and active surveillance, we were able to verify patterns of SHC risk.

Patients diagnosed with a cancer undergo more surveillance (e.g. more imaging), which increases the probability of diagnosing a second (or synchronous) cancer. In this study we limited the risk of surveillance bias, by excluding haematological cancer diagnosis within 1 year of a PCa diagnosis. Furthermore, by limiting our patient population to patients without lymph node involvement or distant metastasis, we were able to significantly reduce the likelihood that patients received whole pelvis radiotherapy. Whole pelvis radiotherapy is associated with larger volumes receiving radiation, thus could significantly impact SHC risk.

One inherent weakness of this study is that the development of a SHC is a rare endpoint. Therefore, analyses stratified by tumour subtype, EBRT era and follow-up years are limited in their statistical power. This becomes especially apparent when looking at the event rates for the different study cohorts. Furthermore, this study made use of a large population-based dataset that does not contain specific information on the EBRT characteristics. Over the years, there have been advances in the field of EBRT besides the technique, such as the dose-fractionation schedule applied and the energy used for delivering treatment. These factors could have an impact on the risk of developing a SHC. Despite the fact that we limited the comparisons with the radical prostatectomy cohort and the active surveillance cohort to T1-T2 patients, we cannot completely avoid subsequent EBRT and its effect. Additionally, we do not have treatment data beyond 1 year post-diagnosis. The active surveillance group might ultimately have received some form of treatment.

For the elective irradiation of gynaecological cancers, techniques are currently being developed that focus on minimising pelvic bone dose. Current clinical practice for the irradiation of PCa does not yet take this into consideration. There might be options to also implement this for PCa irradiation dose planning, which could impact SHC risk, although bladder and rectum dose constraints will remain the most important and should be kept optimal when looking at dose reduction to the pelvic bone area. The findings from this study warrant future research, exploring the effect advanced EBRT has on the risk of developing a SHC. Advanced EBRT has been widely adopted in recent years to treat PCa. Analysis containing more detailed EBRT characteristics could provide further valuable insight into what aspects of advanced EBRT precisely contribute to the persisting SHC risk.

In conclusion, we showed that PCa patients who received EBRT have an increased risk of developing a SHC. The risk persisted in patients treated in the advanced EBRT era. Despite the absolute number of SHC being limited, these findings are a relevant consideration for healthcare professionals, considering the high survival prospects of this patient population.

Author Contributions

KKHA, WDH, LI, MH and MD are guarantors of integrity of the entire study. M-CJ, KKHA, WDH, CJ, MvdP, AGD and RN were responsible for study concepts and design.

KKHA, WDH, CJ, MvdP and AGD were responsible for literature research. M-CJ and KKHA were responsible for experimental studies/data analysis. M-CJ and KKHA carried out the statistical analysis. All authors were responsible for preparing and editing the manuscript.

Ethics

According to the Central Committee of Research involving Human Subjects (CCMO), this descriptive type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry (K20.067).

Data Availability

The raw data supporting the conclusions of this study will be made available by the authors, without undue reservation.

Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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