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Original Article

Advances in radiotherapy and its impact on second primary cancer risk: A multi-center cohort study in prostate cancer patients

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ABSTRACT

Background: Modelling studies suggest that advanced intensity-modulated radiotherapy may increase second primary cancer (SPC) risks, due to increased radiation exposure of tissues located outside the treatment fields. In the current study we investigated the association between SPC risks and characteristics of applied external beam radiotherapy (EBRT) protocols for localized prostate cancer (PCa).
Methods: We collected EBRT protocol characteristics (2000–2016) from five Dutch RT institutes for the 3D-CRT and advanced EBRT era (N = 7908). From the Netherlands Cancer Registry we obtained patient/-tumour characteristics, SPC data, and survival information. Standardized incidence ratios (SIR) were calculated for pelvis and non-pelvis SPC. Nationwide SIRs were calculated as a reference, using calendar period as a proxy to label 3D-CRT/advanced EBRT.
Results: From 2000-2006, 3D-CRT with 68–78 Gy in 2 Gy fractions, delivered with 10–23 MV and weekly portal imaging was the most dominant protocol. By the year 2010 all institutes routinely used advanced EBRT (IMRT, VMAT, tomotherapy), mainly delivering 78 Gy in 2 Gy fractions, using various kV/MV imaging protocols. Sixteen percent (N = 1268) developed $\geq$ 1 SPC. SIRs for pelvis and non-pelvis SPC (all institutes, advanced EBRT vs 3D-CRT) were 1.17 (1.00–1.36) vs 1.39 (1.21–1.59), and 1.01 (0.89–1.07) vs 1.03 (0.94–1.13), respectively. Nationwide non-pelvis SIR was 1.07 (1.01–1.13) vs 1.02 (0.98–1.07). Other RT protocol characteristics did not correlate with SPC endpoints.
Conclusion: None of the studied RT characteristics of advanced EBRT was associated with increased out-of-field SPC risks. With constantly evolving EBRT protocols, evaluation of associated SPC risks remains important.

External beam radiotherapy (EBRT) for localized prostate cancer (PCa) is nowadays delivered using intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), frequently combined with online imaging of the target volume. With these advanced techniques a more conformal dose distribution to the target is achieved while reducing moderate to high-dose volumes to normal tissues neighboring the target, in particular the rectum and bladder [1]. The biggest defect of advanced EBRT is its association with increased exposure to low-dose radiation [2,3]. Concerns have been raised that this might increase second primary cancer (SPC) risk, especially in (very) low-dose regions further away from the primary target. Since PCa patients have a good life expectancy, most patients will be at risk for long-term side effects, such as the development of a SPC [4].

With state-of-the-art EBRT, non-uniform fluence intensities are generated in comparison to conformal radiotherapy (RT), which used uniform beam intensities. The intensity modulating property of IMRT requires longer beam-on times, yielding higher out-of-field doses [3,5,6]. Additionally, to improve dose conformity to the target multiple beam angles are generally used in advanced EBRT, exposing larger volumes of normal tissue to low dose radiation [2]. For safe application of advanced EBRT, image guidance

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(daily of weekly) using either kV or MV imaging of the dose delivery to the target plays a vital role. The imaging beam may be somewhat extended beyond the target, resulting in additional dose in the targeted area, potentially increasing SPC risks [5,6].

Modelling studies have expressed concerns that aspects of advanced EBRT are associated with an up to a 2-fold increased SPC risk [3,7–9]. More recently, patient cohort studies have shown conflicting results on the risk of developing a SPC after advanced EBRT, with some studies observing increased SPC risks [10–12]. Other cohort studies, however, did not observe such increased risks [1,13]. Which aspects of advanced EBRT specifically lead to increased SPC risks have yet to be determined.

In this study, we investigated the relationship between applied advanced EBRT protocols and SPC risks in the pelvic and non-pelvic region in five Dutch RT institutes. We hypothesized that differences in SPC risks in the non-pelvic region exist between the applied RT protocols, due to differences in exposure to scatter and low-dose volumes.

Methods

Study design

Five Dutch RT institutes participated in this retrospective cohort study. The following RT protocol information was collected from each institute: EBRT technique (three-dimensional conformal RT (3D-CRT) or advanced intensity-modulated EBRT, prescribed dose (Gy) per fraction, energy (MV), type of image-guidance (cone beam computed tomography (CBCT), portal imaging), planning system, and linac (vendor). For each year 2000–2016, the centers were asked to indicate the most dominant protocol aspects applied (for $\geq$ 80% of patients). Advanced EBRT consisted in most institutes of either IMRT or VMAT. All institutes delivered IMRT using step-and-shoot; only for the final year included in this study, institute A delivered IMRT using dynamic leaves. Institute E, was the only institute, which delivered advanced EBRT using tomotherapy (Table 1). All PCa patients who received EBRT between 2000–2016 in one of those five centers were identified through the Netherlands Cancer Registry (NCR). From the NCR, we retrieved for each patient the primary PCa characteristics and data on SPCs. Each PCa patient was linked to the respective RT protocol information, based on the institute where he received treatment, and the year he was diagnosed with PCa. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry (K20.067).

Definition of SPC and follow-up

We defined time at risk for SPC from one year after PCa diagnosis. The one year was used as a surrogate, since start of RT is not captured as a required field in the NCR database. All invasive SPC and non-invasive bladder cancers, except for non-melanoma skin cancers were included in the analysis. Analyses were carried out for all SPC, all solid SPC, all haematological SPC, and SPC within different anatomical regions, such as pelvis versus non-pelvis. In general, only the first SPC was included. However, for all analyses focusing on a specific subgroup (i.e., solid cancers, haematological cancers, anatomical region, or specific subsite), the first SPC cancer within that group was included. Follow-up was defined as the time between PCa diagnosis until the date of SPC diagnosis, date of death, date of emigration, or end of study (31.12.2020), whichever occurred first. New cancers diagnosed within one year after the initial PCa diagnosis were excluded, as these are likely to represent synchronous cancers.

Statistical analysis

Standardized incidence ratios (SIR) were calculated to evaluate the risk of developing a SPC in the PCa patient cohort compared to the general Dutch male population. SIRs were computed by dividing the observed number of SPC by the expected number of cases based on the cancer incidences in the Netherlands. To consider potential regional fluctuations in the expected cancer cases, SIR analysis was also carried out using regional cancer incidences as a reference. The SIR analysis is based on the sex, age, and calendar specific incidence rates in the Netherlands. Poisson regression was used to compute 95% confidence intervals (CI). The excess burden of SPC was measured by calculating the absolute excess risks (AER). The AER is defined as the difference between the observed and the expected number of patients with a SPC, divided by the number of person years (py) at risk, multiplied by 10,000. It represents the additional incidence beyond the background incidence found in the Dutch general population. SIR and AER analyses were carried out for the complete PCa patient cohort, for patients treated with conformal RT versus patients treated with advanced RT, for different age groups ($\leq$70 or > 70 years), and for SPC subsites. For reference purposes, we calculated nationwide reference values (including all patients diagnosed with a PCa in the Netherlands). For the nationwide comparison, we used time periods (2000–2005 3D-CRT (N = 11760), 2008–2016 advanced EBRT (N = 18693) as a proxy for the different EBRT modalities used in the Netherlands, similar to our previous study [12]. SIR and AER analysis was carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

The Dutch Cancer Society which had no further say in the design, analyses or description of the results, provided financial support for this study (project grant 12009).

Table 1
RT protocol information summarized per institute.

Institute	N PCa Survivors	Calendar Period	Technique	Dose (Gy/fraction)	Energy (MV)	Imaging procedure
3D-CRT						
A	2171	2000–2010	3D-CRT	68/2, 72/2	18|23	no
B	531	2000–2006	3D-CRT	68/2, 78/2	10|18	no, weekly 3D cone beam
C	260	2000–2007	3D-CRT	72/2	10	no
D	25	2000–2004	3D-CRT	67.5/2.5	18|23	no
E	291	2000–2006	3D-CRT	76/2, 78/2	10	no
Advanced EBRT						
A	1169	2010–2016	IMRT/VMAT	78/2	10|18	2D portal imaging
B	1464	2006–2016	IMRT/VMAT	78/2, 77/2.2	10	Weekly 3D cone beam
C	896	2007–2016	IMRT/VMAT	78/2, 70/2.5	10	2D portal imaging
D	679	2004–2016	IMRT/VMAT	67.5/2.5, 70/2.5	10	2D portal imaging
E	422	2006–2016	Tomotherapy	78/2, 80.5/2.3	6	Daily 3D cone beam

Results

Patient Characteristics and RT protocol information

Patient, tumor, and treatment characteristics for each RT institute are depicted in Table 2**.** The complete cohort consisted of 7908 PCa patients. The median age at diagnosis was 70 (Interquartile range (IQR) 65–74) years. The majority of patients (62.1%) were diagnosed with a T1-2 N0/X, M0/X PCa. A distinction was made between the RT protocols for 3D-CRT and advanced EBRT (Table 1). For all RT institutes combined, 3278 (41.5%) PCa patients received 3D-CRT. The administered dose prescription (total dose/fraction dose) was predominantly 78/2 Gy (Table 1). The applied beam energies ranged from 10 MV to 23 MV. Only institute B used for selected patients weekly 3D cone beam imaging during delivery of 3D-CRT; other institutes applied 2D imaging of the bony anatomy within the treatment fields with an electronic portal imaging device (EPID). From the year 2004 onwards, the first RT institute introduced IMRT/VMAT. By the year 2010, all five RT institutes routinely delivered radiation using advanced EBRT, either IMRT or VMAT (Table 1). For all RT institutes combined, 4630 (58.5%) PCa patients received advanced EBRT up until 2016. Most institutes used 10 MV and all institutes applied setup verification using either 2-dimensional portal imaging or weekly/daily 3D cone beam acquisition (Table 1).

Second primary cancers (SPC)

A total of 1268 solid SPCs were observed in the complete EBRT study cohort of the five RT institutes. The estimated SIR (95% confidence interval) for any solid SPC, regardless the RT protocol or institute was 1.06 (0.99–1.12); AER = 10.36) (Table 3). Table 3 further summarizes SPC risk for the complete EBRT cohort and for different age groups. We observed a significant increased risk for second pelvis cancers for the complete EBRT cohort, regardless of the age (SIR = 1.28 (1.16–1.42); AER = 12.61). The risk for developing a pelvis SPC was SIR = 1.34 ((1.16–1.42); AER = 12.36) for patients aged 70 or below, compared to SIR = 1.24 ((1.08–1.42); AER = 12.89) for patients aged above 70 years (Table 3). For the 3D-CRT cohort, the estimated SIR for developing any solid SPC was 1.11 (1.03–1.20); AER = 20.06), compared to a nationwide reference SIR of 1.08 ((1.04–1.12); AER = 15.61) (Table 4). For the advanced EBRT cohort, the estimated SIR was 1.01 (0.93–1.09); AER = 0.83), compared to a nationwide reference SIR of 1.08 (1.04–1.14); AER = 15.48) (Table 4 **&** Supplementary Table S1). For 3D-CRT, the risk of developing a solid SPC was significantly increased for institutes A (SIR = 1.13 (1.03–1.24); AER = 23.49) and C (SIR = 1.35 (1.05–1.72); AER = 69.29). For institute A, the risk of developing a solid SPC was significantly increased for the advanced EBRT protocol (SIR = 1.23 (1.04–1.44); AER = 40.35) (Table 4 **&** Fig. 1) as well.

Non-pelvis SPC risk

The risk of developing a non-pelvis SPC was similar in the complete cohort regardless of RT protocol (SIR = 1.00 (0.94–1.07); AER = 0.56) (Table 4). This also applied to the 3D-CRT (SIR = 1.03 (0.94–1.13); AER = 4.73) and advanced EBRT cohorts (SIR = 1.01 (0.89–1.07); AER = -3.59). For institute A, the risk of developing a non-pelvis SPC increased from SIR = 1.05 ((0.94–1.17); AER = 7.09) in the 3D-CRT cohort to SIR = 1.21 ((1.00–1.45); AER = 27.41) in the advanced EBRT cohort. An increased nationwide reference SIR was observed for the advanced EBRT period (SIR = 1.07 (1.01–1.13); AER = 9.47) (Fig. 1 **&** Supplementary Table S1).

Table 2
Patient, tumor and treatment characteristics for the complete cohort and for each institute.

	Complete cohort		Institute A		Institute B		Institute C		Institute D		Institute E	
	n	%	n	%	n	%	n	%	n	%	n	%
Patient	7908	100	3340	100	1995	100	1156	100	704	100	713	100
Age at radiotherapy												
50–69	3849	48.7	1614	48.3	1057	53.0	509	44.0	335	47.6	334	46.8
70–79	4059	51.3	1726	51.7	938	47.0	647	56.0	369	52.4	379	53.2
Median Age (IQR)	70 (65–74)		70 (65–74)		69 (64–73)		71 (66–75)		70 (66–73)		70 (66–74)	
Birth cohort												
< 1935	2267	28.7	1112	33.3	490	24.6	300	26.0	124	17.6	241	33.8
1935–1940	2497	31.6	985	29.5	637	31.9	380	32.9	251	35.7	244	34.2
> 81940	3144	39.8	1243	37.2	868	43.5	476	41.2	329	46.7	228	32.0
Tumor & treatment												
Disease Stage												
T1-2 N0/X, M0/X	4914	62.1	2461	73.7	1110	55.6	578	50.0	394	56.0	371	52.0
T3 N0/X, M0/X	2990	37.8	877	26.3	885	44.4	577	49.9	310	44.0	341	47.8
EBRT technique												
3D-CRT	3278	41.5	2171	65.0	531	26.6	260	22.5	25	3.6	291	40.8
IMRT/VMAT	4208	53.2	1169	35.0	1464	73.4	896	77.5	679	96.4	0	0.0
Tomotherapy	422	5.3	0	0.0	0	0.0	0	0.0	0	0.0	422	59.2
Median follow-up (IQR)	8.13 (5.37–11.83)		8.36 (5.27–12.40)		8.51 (5.66–12.03)		7.50 (5.20–10.87)		7.96 (5.89–10.89)		7.66 (5.08–11.89)	

Table 3
SIR and AER for the complete EBRT cohort and for different age groups.

Tumor Sites	All Ages				≤70 years		>70 years	
	Obs	Exp	SIR	AER	SIR	AER	SIR	AER
All SPC	1404	1331.2	1.05 (1.00–1.11)	11.13	1.08 (1.00–1.16)	13.05	1.04 (0.96–1.11)	8.86
All solid	1268	1199.8	1.06 (0.99–1.12)	10.36	1.06 (0.97–1.15)	8.55	1.06 (0.98–1.14)	12.51
Non-Pelvis	930	926.3	1.00 (0.94–1.07)	0.56	1.00 (0.90–1.10)	−0.48	1.01 (0.92–1.10)	1.78
Pelvis	387	301.2	**1.28 (1.16–1.42)**	12.61	**1.34 (1.16–1.42)**	12.36	**1.24 (1.08–1.42)**	12.89
All hematological	160	146.5	1.09 (0.93–1.28)	1.96	**1.33 (1.06–1.64)**	5.70	0.91 (0.71–1.14)	−2.44
Anatomical Regions								
Head & Neck	92	84.4	1.09 (0.88–1.34)	1.09	1.06 (0.78–1.42)	0.73	1.12 (0.82–1.50)	1.51
Chest	392	380.7	1.03 (0.93–1.14)	1.64	1.04 (0.89–1.21)	1.92	1.02 (0.89–1.17)	1.30
Lung & Bronchus	308	300.9	1.02 (0.91–1.15)	1.03	1.08 (0.91–1.27)	2.86	0.98 (0.83–1.14)	−1.13
Abdomen	391	393.9	0.99 (0.90–1.10)	−0.43	0.94 (0.81–1.10)	−2.66	1.03 (0.90–1.18)	2.21
Esophagus	50	52.7	0.95 (0.70–1.25)	−0.39	0.89 (0.57–1.34)	−0.73	1.00 (0.66–1.46)	0.01
Stomach	31	31.9	0.97 (0.66–1.38)	−0.13	0.71 (0.32–1.35)	−0.97	1.14 (0.71–1.73)	0.86
Colon	192	193.2	0.99 (0.86–1.15)	−0.17	0.98 (0.78–1.21)	−0.56	1.01 (0.83–1.22)	0.28
Liver	22	16.8	1.31 (0.82–1.98)	0.75	1.08 (0.49–2.04)	0.17	1.54 (0.82–2.65)	1.43
Pancreas	52	47.8	1.09 (0.81–1.43)	0.60	0.87 (0.52–1.36)	−0.77	1.27 (0.88–1.79)	2.21
Kidney	53	47.6	1.11 (0.83–1.46)	0.78	1.02 (0.65–1.51)	0.10	1.21 (0.81–1.74)	1.21
Renal Pelvis	9	11.4	0.79 (0.36–1.50)	−0.35	0.59 (0.12–1.73)	−0.55	0.94 (0.34–2.04)	−0.11
Ureter	10	11.7	0.85 (0.41–1.57)	−0.25	0.99 (0.32–2.33)	−0.01	0.75 (0.24–1.74)	−0.53
Pelvis								
Male genital organs	6	6.3	0.95 (0.35–2.07)	−0.05	0.7 (0.08–2.49)	−0.23	1.15 (0.31–2.93)	0.17
Bladder	265	202.2	**1.31 (1.16–1.48)**	9.17	**1.30 (1.07–1.57)**	6.91	**1.31 (1.12–1.54)**	11.85
Urethra	4	4.6	0.86 (0.24–2.23)	−0.09	1.58 (0.33–4.61)	0.29	0.37 (0.01–2.06)	−0.54
Rectum & Rectosigmoid	117	87.7	**1.33 (1.10–1.60)**	4.23	**1.52 (1.17–1.94)**	5.86	1.16 (0.87–1.52)	2.33

*bold numbers indicate significantly increased SIRs; observed (Obs); expected (Exp).

Pelvis SPC risk

For the complete cohort, a significant increased SPC risk in the pelvis region was observed for all RT institutes combined (SIR = 1.28 (1.16–1.42) (Table 4). This number was quite similar to the corresponding nationwide calculated SIR of 1.35 (Fig. 1 **&** Supplementary Table S1**).** For the 3D-CRT cohort the risk for pelvic SPC was increased for all institutes combined (SIR = 1.39 (1.21–1.59); AER = 18.08), institute A (SIR = 1.40 (1.17–1.65); AER = 18.05), institute B (SIR = 1.43 (1.02–1.96); AER = 19.90), and institute C (SIR = 1.80 (1.14–2.70); AER = 39.19) (Table 4 **&** Fig. 1). For the advanced EBRT cohort, the estimated SIR of 1.17 for the institutes combined did not reach significance (95% CI of 1.00–1.36); the corresponding nationwide SIR of 1.21 (1.11–1.32) was however highly significant. For none of the institutes the calculated SIRs of the advanced EBRT cohort reached significance and estimates varied considerably (range 0.82–1.36). Results for additional tumor subsites are depicted in Table 4.

RT protocol characteristics

Within the 3D-CRT cohort, institute C and E used lower energies (10 MV) compared to the other institutes. Observed SIRs for Institute C in this 3DCRT cohort are relatively high compared to A, B, D, however, for institute E this is not the case (Fig. 1**,** Table 3). None of the participating institutes used daily cone beam CT for IMRT/VMAT treatment, only weekly CBCT was performed by institute B which showed relatively low SIRs for all endpoints compared to the other institutes (Fig. 1). Institute E had a deviating advanced EBRT protocol applying tomotherapy with daily (MV) scanning: corresponding SIRs were relatively low but had large confidence intervals (Table 3, Fig. 1). Institute D used mild hypofractionation with 2.5 Gy fractions for the majority of the advanced EBRT patients, whereas the other institutes mainly prescribed 2 Gy fractions for this group; corresponding SIRs show no deviating patterns comparing institute D with the other institutes (Fig. 1).

Nationwide reference

All estimated SIRs (solid, pelvis, non-pelvis, 3D-CRT, advanced EBRT) for the participating five RT institutes combined, are within the 95% CI range of the calculated nationwide SIRs, except for solid SPC of advanced EBRT: nationwide SIR of 1.08 (1.04–1.14) vs 1.01 (0.93–1.09) for the institutes (Fig. 1**,** Supplementary Table S1**,** Table 3). With respect to solid SPCs, the institutes show a trend of a lower SIR for advanced EBRT vs 3D-CRT (1.01 vs 1.11) whereas the nationwide numbers (where we used calendar period as a proxy) suggest similar levels of solid SPCs for advanced EBRT vs 3D-CRT (both SIR of 1.08). For pelvis SPC the nationwide numbers and the participating institutes combined both show similar trends of lower SIRs for advanced EBRT. For non-pelvis SPC nationwide numbers suggest an increase with advanced EBRT (1.07 vs 1.02 for 3D-CRT) which was not observed for the participating institutes (1.01 vs 1.03 for 3D-CRT).

Calculations with regional cancer incidence data

SPC risk analysis using regional data generally resulted in similar risk patterns as to what was observed using national reference data (Supplementary Table S2).

Risks for different follow-up periods

Fig. 2 **&** Supplementary Table S3 show estimated SIRs for 3D-CRT and advanced EBRT for different follow-up periods. It should be noted that the statistical power for this additional analysis is limited (especially for estimates > 10 years) and plotted confidences intervals for advanced EBRT and 3D-CRT are all overlapping. For non-pelvis SPC no clear trend was observed. For pelvis SPC, data show a trend of increasing risks with increasing follow-up time. Furthermore, we noticed that for the follow-up period > 5–10 years point estimates for 3D-CRT and advanced EBRT were very similar.

Discussion

To the best of our knowledge, this is the first study exploring potential differences in SPC risks between 3D-CRT and more advanced EBRT for PCa, through linking RT specific protocol data from RT institutes to data from a nationwide cancer registry. The nationwide reference numbers show a small, but significant

Table 4
SIR and AER for the different RT institutes - for all EBRT techniques combined and by EBRT technique.

Tumor Sites	Complete Cohort				3D-CRT Cohort		Advanced EBRT	
	Obs	Exp	SIR	AER	SIR	AER	SIR	AER
All Solid SPC								
All Institutes	1268	1199.8	1.06 (0.99–1.12)	10.36	**1.11 (1.03–1.20)**	20.06	1.01 (0.93–1.09)	0.83
Institute A	595	516.5	**1.15 (1.06–1.25)**	27.72	**1.13 (1.03–1.24)**	23.49	**1.23 (1.04–1.44)**	40.35
Institute B	300	306.8	0.98 (0.87–1.10)	−3.95	0.99 (0.81–1.20)	−2.17	0.97 (0.84–1.12)	−4.84
Institute C	190	164.3	1.16 (1.00–1.33)	29.08	**1.35 (1.05–1.72)**	69.29	1.07 (0.89–1.28)	13.32
Institute D	88	103.1	0.85 (0.68–1.05)	−26.62	1.11 (0.41–2.42)	20.68	0.84 (0.67–1.04)	−29.06
Institute E	95	109.2	0.87 (0.70–1.06)	−24.18	0.97 (0.73–1.28)	−3.84	0.76 (0.55–1.03)	−43.2
Non-Pelvis								
All Institutes	930	926.3	1.00 (0.94–1.07)	0.56	1.03 (0.94–1.13)	4.73	1.01 (0.89–1.07)	−3.59
Institute A	434	398.8	1.09 (0.99–1.20)	12.14	1.05 (0.94–1.17)	7.09	1.21 (1.00–1.45)	27.41
Institute B	222	237.6	0.93 (0.82–1.07)	−8.91	0.88 (0.69–1.11)	−16.17	0.96 (0.81–1.13)	−5.23
Institute C	139	127	1.09 (0.92–1.29)	13.25	1.24 (0.91–1.65)	35.72	1.03 (0.83–1.27)	4.31
Institute D	61	79.7	**0.77 (0.59–0.98)**	−32.24	0.95 (0.26–2.43)	−7.24	**0.76 (0.57–0.98)**	−33.55
Institute E	74	83.5	0.89 (0.70–1.11)	−15.57	1.02 (0.74–1.38)	3.23	0.76 (0.52–1.07)	−33.24
Pelvis								
All Institutes	387	301.2	**1.28 (1.16–1.42)**	12.61	**1.39 (1.21–1.59)**	18.08	1.17 (1.00–1.36)	7.19
Institute A	181	130.4	**1.39 (1.19–1.61)**	17.27	**1.40 (1.17–1.65)**	18.05	1.36 (0.98–1.85)	14.90
Institute B	94	76.6	1.23 (0.99–1.50)	9.83	**1.43 (1.02–1.96)**	19.90	1.11 (0.84–1.45)	4.77
Institute C	58	41.3	**1.41 (1.07–1.82)**	18.31	**1.80 (1.14–2.70)**	39.19	1.23 (0.86–1.71)	9.95
Institute D	31	25.4	1.22 (0.83–1.73)	9.69	2.16 (0.44–6.26)	56.38	1.17 (0.78–1.69)	7.28
Institute E	23	27.7	0.83 (0.53–1.25)	−7.71	0.84 (0.43–1.47)	−7.53	0.82 (0.41–1.47)	−7.87
Head & Neck								
All Institutes	92	84.4	1.09 (0.88–1.34)	1.09	1.16 (0.86–1.54)	1.95	1.02 (0.74–1.37)	0.23
Institute A	42	36.4	1.15 (0.83–1.56)	1.88	0.95 (0.62–1.39)	−0.63	**1.79 (1.03–2.92)**	9.52
Institute B	25	21.9	1.14 (0.74–1.69)	1.73	1.48 (0.74–2.66)	5.86	0.97 (0.53–1.62)	−0.38
Institute C	13	11.5	1.13 (0.60–1.93)	1.64	1.19 (0.32–3.01)	2.37	1.11 (0.51–2.11)	1.35
Institute D	3	7.2	0.41 (0.09–1.22)	−7.14	2.77 (0.06–13.93)	22.05	0.29 (0.04–1.05)	−8.64
Institute E	9	7.5	1.20 (0.55–2.28)	2.46	1.89 (0.76–3.90)	11.1	0.52 (0.06–1.90)	−5.82
Lung & Bronchus								
All Institutes	308	300.9	1.02 (0.91–1.15)	1.03	1.03 (0.88–1.20)	1.28	1.02 (0.86–1.20)	0.77
Institute A	146	130.8	1.12 (0.94–1.31)	5.08	1.08 (0.89–1.31)	3.73	1.23 (0.86–1.71)	9.18
Institute B	62	76.6	0.81 (0.62–1.04)	−8.1	0.64 (0.38–1.01)	−16.53	0.91 (0.66–1.22)	−3.79
Institute C	53	40.8	1.30 (0.97–1.70)	13.1	1.31 (0.76–2.09)	15	1.29 (0.90–1.79)	12.35
Institute D	24	25.1	0.96 (0.61–1.42)	−1.88	2.12 (0.44–6.26)	54.8	0.89 (0.55–1.35)	−4.79
Institute E	23	27.5	0.84 (0.53–1.26)	−7.4	1.04 (0.58–1.71)	1.74	0.61 (0.26–1.20)	−16.23
Abdomen								
All Institutes	391	393.9	0.99 (0.90–1.10)	−0.43	1.04 (0.90–1.19)	2.42	0.94 (0.81–1.09)	−3.27
Institute A	181	169.6	1.07 (0.92–1.24)	3.86	1.09 (0.92–1.29)	5.47	0.98 (0.70–1.34)	−1.02
Institute B	98	100.9	0.97 (0.79–1.18)	−1.60	0.95 (0.65–1.33)	−3.14	0.99 (0.76–1.26)	−0.82
Institute C	49	54.3	0.90 (0.67–1.19)	−5.77	1.03 (0.60–1.66)	2.17	0.84 (0.58–1.19)	−8.98
Institute D	28	33.7	0.83 (0.55–1.20)	−9.72	0.55 (0.01–3.10)	−27.35	0.85 (0.56–1.23)	−8.78
Institute E	35	35.5	0.99 (0.69–1.37)	−0.83	0.90 (0.52–1.47)	−5.88	1.07 (0.64–1.67)	4.04
Colon								
All Institutes	192	193.2	0.99 (0.86–1.15)	−0.17	1.05 (0.86–1.28)	1.57	0.93 (0.74–1.15)	−1.91
Institute A	88	83.4	1.05 (0.85–1.30)	1.53	1.11 (0.87–1.40)	3.08	0.88 (0.51–1.41)	−3.15
Institute B	46	49.4	0.93 (0.68–1.24)	−1.88	0.80 (0.44–1.34)	−5.71	1.00 (0.69–1.42)	0.08
Institute C	28	26.6	1.05 (0.70–1.52)	1.54	1.33 (0.66–2.37)	10.30	0.93 (0.54–1.49)	−1.99
Institute D	13	16.4	0.79 (0.42–1.36)	−5.74	-	-	0.84 (0.45–1.43)	−4.43
Institute E	17	17.4	0.98 (0.57–1.56)	−0.69	1.01 (0.47–1.94)	0.52	0.93 (0.40–1.83)	−1.86
Bladder								
All Institutes	265	202.2	**1.31 (1.16–1.48)**	9.17	**1.40 (1.18–1.64)**	12.28	**1.22 (1.01–1.46)**	6.08
Institute A	126	87.6	**1.44 (1.20–1.71)**	13.00	**1.42 (1.15–1.74)**	12.86	**1.49 (1.01–2.13)**	13.40
Institute B	67	51.2	**1.31 (1.01–1.66)**	8.88	**1.53 (1.02–2.21)**	16.14	1.19 (0.84–1.62)	5.20
Institute C	37	27.8	1.33 (0.94–1.84)	9.99	1.49 (0.80–2.56)	16.08	1.26 (0.81–1.87)	7.52
Institute D	22	16.9	1.30 (0.82–1.97)	8.66	2.15 (0.27–8.03)	37.34	1.25 (0.76–1.93)	7.19
Institute E	13	18.7	0.70 (0.37–1.19)	−9.27	0.83 (0.36–1.63)	−5.50	0.55 (0.18–1.30)	−12.91
Rectum								
All Institutes	117	87.7	**1.33 (1.10–1.60)**	4.23	**1.45 (1.12–1.84)**	5.60	1.21 (0.90–1.60)	2.59
Institute A	55	38	**1.45 (1.09–1.88)**	5.70	**1.46 (1.06–1.97)**	6.07	1.39 (0.72–2.44)	4.60
Institute B	25	22.5	1.11 (0.72–1.64)	1.39	1.24 (0.59–2.27)	3.20	1.04 (0.58–1.72)	0.46
Institute C	19	11.9	1.60 (0.96–2.49)	7.65	**2.44 (1.11–4.62)**	19.88	1.22 (0.58–2.24)	2.71
Institute D	9	7.4	1.22 (0.56–2.31)	2.75	2.43 (0.06–13.93)	19.88	1.15 (0.49–2.25)	1.85
Institute E	9	7.9	1.13 (0.52–2.16)	1.75	0.73 (0.15–2.13)	−3.68	1.57 (0.58–3.44)	7.01

*bold numbers indicate significantly increased SIRs; observed (Obs); expected (Exp).

increase in non-pelvis SPC risk with the introduction of advanced EBRT. We also observed this in our previous study on this topic, where we identified in particular an increased non-pelvis SPC risk in the advanced EBRT era for patients aged $\leq$ 70 years at time of diagnosis [12]. In the current study, exploring data at the RT institute level and acquiring detailed RT protocol data, we were unable to establish a clear pattern in non-pelvis SPC risks. Similarly to the trend observed at the nationwide level, we found that the risk for pelvis SPC decreased as EBRT advances, especially with respect to bladder SPC. Between RT institutes considerable variations in SPC risks were observed; at the same time statistical power and therefore confidence intervals were large at the institute level. Furthermore, one must keep in mind that (inherent to the observational nature of the study), observations of (excess) SPC risks in different

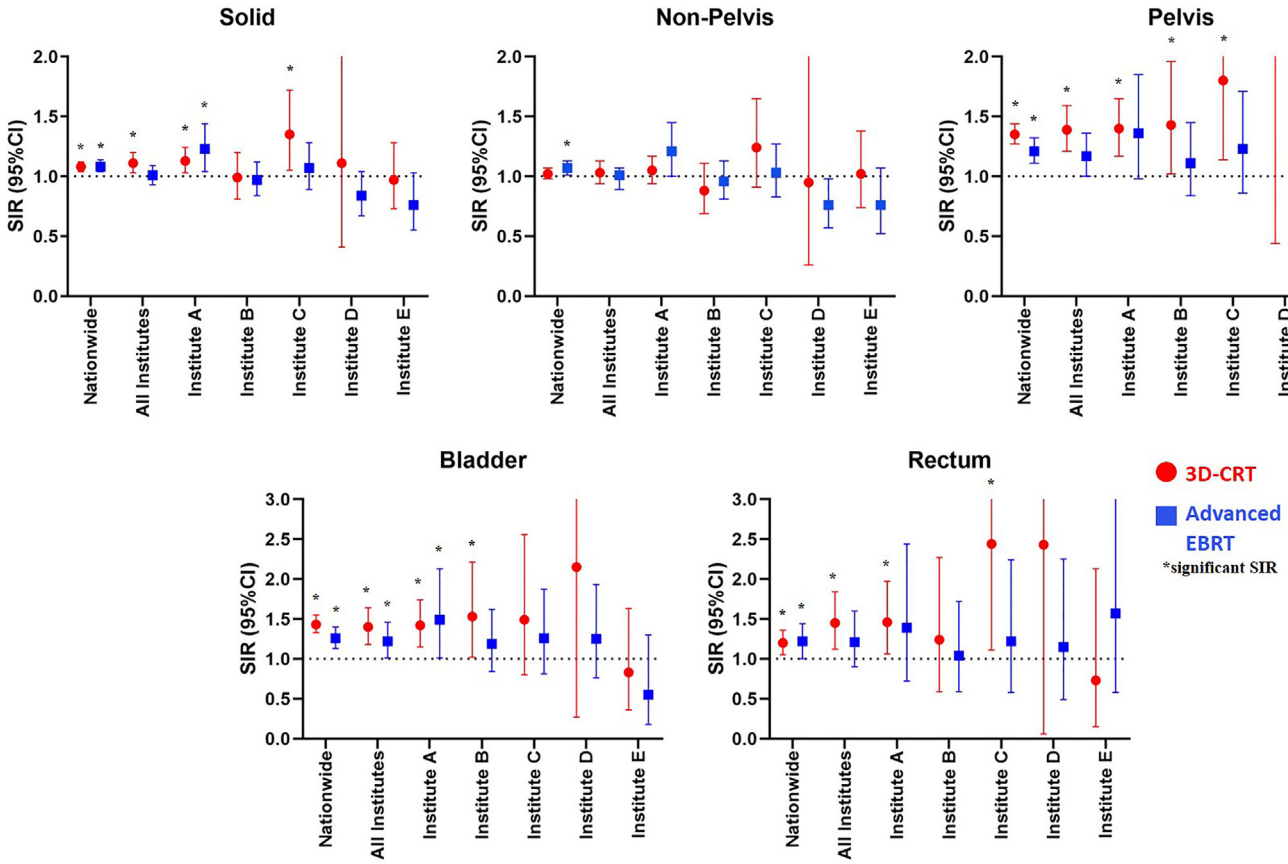

Fig. 1. SIR for the 3D-CRT cohort and the advanced EBRT cohort, for a nationwide reference value, all RT institutes combined and for the different RT institutes.

cohorts do not necessarily reflect underlying causal relationships between radiation and SPC.

Previous modelling studies have predicted that IMRT increases the risk of developing a SPC [3,8,9,14]. This increase is related to the increased low dose regions and the increased radiation exposure of tissues located outside the treatment fields. This aspect was considered of particular importance for patients with long life expectancy after cancer diagnosis, such as the PCa patient population. However, more recent modelling studies have demonstrated that this increased risk may have been overestimated, and that the proposed risk might in fact be reduced with advanced techniques [14–17].

To date, observational cohort studies show conflicting results. Zelefsky and colleagues (2012) report a reduced SPC risk with the introduction of advanced EBRT, especially in areas close to the prostate, such as the bladder and the rectum [13]. Conversely, a study by Buwenge et al. (2020) suggests a correlation between the use of modulated techniques and the incidence of second pelvic tumors [10]. Studies by Journy et al. (2016) and Xiang et al., (2020) found no difference in SPC incidence after 3D-CRT versus IMRT [1,18]. In a recent nationwide cohort study we found that SPC risks after advanced EBRT persists, and is even increased for second cancers in the non-pelvis region [12]. This nationwide study included all PCa patients diagnosed in the Netherlands, and calendar period was used as a proxy to label RT technique.

All institutes, except for institute E, used IMRT/VMAT for advanced EBRT. In addition, institute E was the only institute that used 6 MV for delivery of advanced EBRT. Institute E introduced tomotherapy as a successor of 3D-CRT. Similarly to VMAT, tomotherapy is an arc-based approach for delivering IMRT [19]. We observed for this institute a significantly lower SIR for non-pelvic tumors compared to the general population, which suggests that the applied RT protocol is safe with respect to unfavorable out-of-field dose. From literature it is known that tomotherapy results in better organs at risk sparing compared to other advanced techniques, such as VMAT [20,21]. With respect to the used energy, 6 MV and 10 MV are both considered optimal energies for delivering intensity-modulated EBRT, since they are both associated with a low neutron contribution, and treatment plans have comparable plan quality [22]. Further research is therefore needed to assess SPC risks with respect to tomotherapy versus other advanced EBRT techniques.

Looking at second tumor sites in the pelvis region specifically, pelvic SPC (and in particular bladder SPC) show consistently lower SIRs for the advanced EBRT cohort. However, we also observed that for estimated risks beyond 5 years of follow-up, estimated risks were similar. With respect to variations in bladder SPCs, we know that the dose distribution with advanced EBRT is quite different from 3D-CRT, with larger very low-dose volumes and smaller intermediate to high-dose volumes [23]. Also dose constraints might have an impact on potential risk differences between RT protocols. The identification of potential underlying relationships is subject of further research.

The strengths of this study are that it made use of RT protocol specific information. The NCR does not routinely collect information on specific treatment-related characteristics. By linking the RT protocol information obtained from each institute to the NCR data, we were able to have a more accurate representation of the exact treatment administered. By limiting our patient selection to patients with no regional lymph node involvement or distant metastasis, we can assume that patients did not receive elective lymph node irradiation. Furthermore, we were able to explore how the risk of developing a SPC differed between RT institutes, and how this risk compared to nationwide reference numbers.

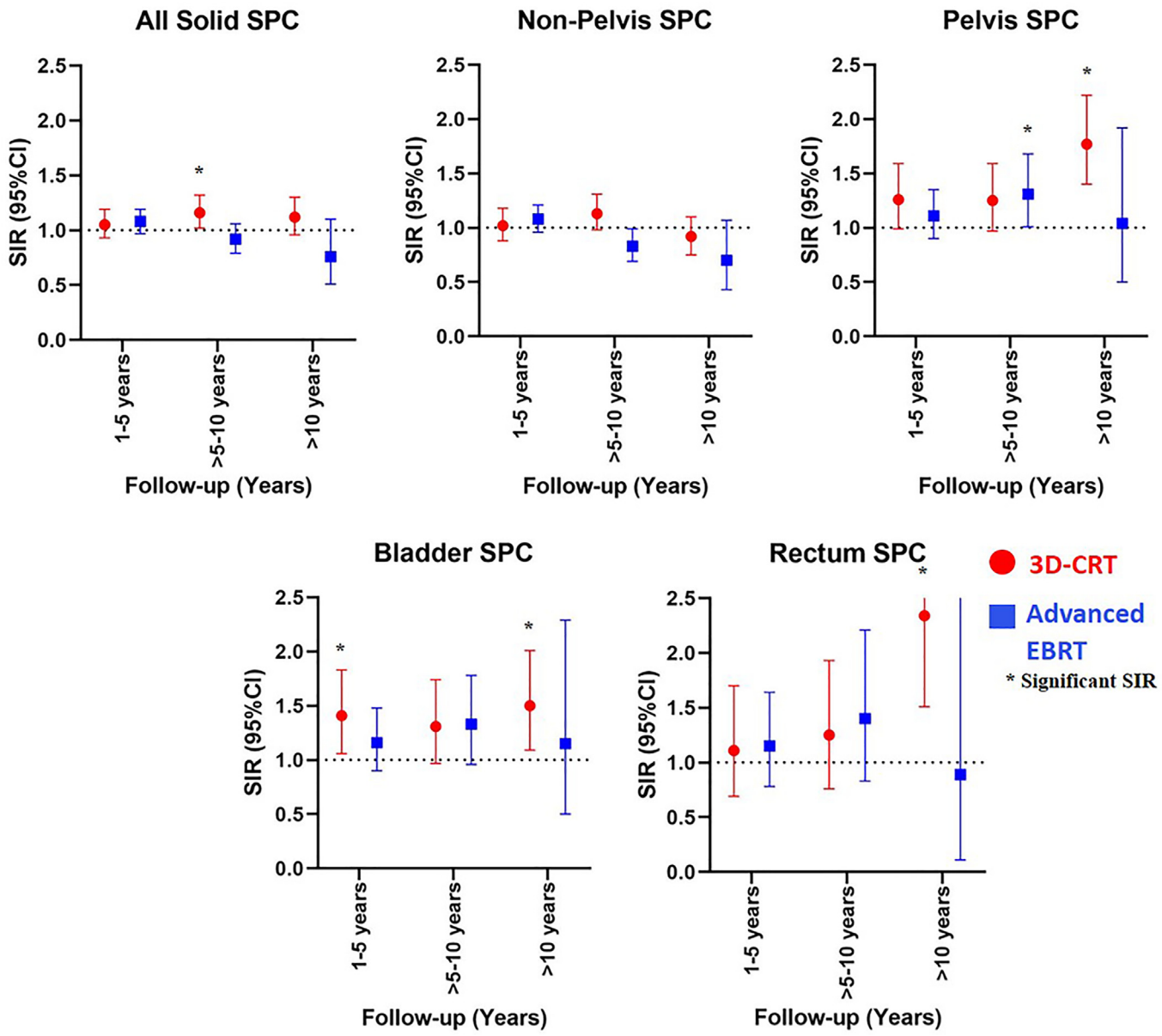

Fig. 2. SIR per EBRT technique for all RT institutes combined for different follow-up years.

Our risk analysis was based on nationwide cancer incidences. However, between the different regions of the Netherlands there is variation in cancer incidences, due to differences in sociodemographic status. In order to control for regional differences in cancer incidences, we verified our analysis using regional cancer incidences.

One inherent weakness of this study is the available follow-up for the advanced EBRT cohort. For studying SPC trends after EBRT, sufficient follow-up is essential. Studies have shown that the development of a solid SPC is in particular increased after five year follow-up [11,24,25]. In our study we observed for the advanced EBRT cohort no significantly increased SPC risks for the period 1–5 year. For the period 5–10 years of follow-up, we observed a significant increased risk for second pelvis cancers. We were unable to observe clear patterns of SPC risk beyond 10 years, in particular for SPC sites such as the pelvis and organs within the pelvis, due to the small number of observed events. Therefore repeating this analysis in the future with a longer follow-up for the advanced techniques is essential to establish clear risk patterns over time. Additionally, for some tumor site specific analyses, we had limited statistical power to establish excess risk patterns. This was particularly evident for analysis stratified by RT institute. Therefore, the results of institutes with small sample sizes must be interpreted with caution.

Advances in the field of EBRT have resulted in better biochemical disease control and reduced treatment-related toxicity, improving the overall wellbeing of the patient [12]. Current advances in EBRT are focused around improving IGRT, with the use of MR-guided radiotherapy, as well as the introduction of hypofractionation protocols [26]. It would be interesting to explore the impact these advances have on the risk of developing a SPC once sufficient follow-up data become available.

In conclusion, in the current multi-center cohort we were unable to explain by means of RT specific information the small, but significant increased risk in second non-pelvis SPCs that we previously observed at a nationwide level [12]. For pelvic cancers, in particular bladder SPC, we observed consistent lower risks for advanced EBRT compared to the previous 3D-CRT era. This was

however mainly caused by lower risks in the follow-up period 1–5 years, with similar estimated risks for the period > 5 years when radiation-induced solid SPCs are more likely to occur then < 5 year follow-up. Therefore this result should be interpreted with caution. Overall the outcomes of this study suggest that the risk of developing a SPC after advanced EBRT is not as substantial as certain modelling studies have suggested. Our findings further indicate that the risk of developing a secondary cancer is especially in older patients not as concerning as previously thought. Therefore, despite the current results indicating limited excess SPC risks for advanced EBRT techniques (with low absolute numbers of SPC and low estimated AERs), further research with longer follow-up for the advanced EBRT cohort is needed to explore potential associations between specific aspects of advanced EBRT and SPC risk, in order to establish risk estimates for younger patients. In addition, with constantly evolving EBRT protocols (like the introduction of hypofractionation, new imaging protocols), awareness and studies addressing SPC risks remain important.

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Data Availability Statement

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109659.

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