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Original Research

Increased risk for second primary rectal cancer after pelvic radiation therapy☆

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Vaginal cancer;
Ovarian cancer;
Bladder cancer

Abstract ***Background:*** The aim of this study was to analyse the association between pelvic radiation therapy (RT) and the development of rectal cancer as a second primary cancer.
Methods: Data on patients treated for a primary pelvic cancer between 1989 and 2007 were retrieved from the population-based Netherlands Cancer Registry. Patients treated for more than one pelvic cancer were excluded. To estimate the cumulative incidence of rectal cancer, Fine and Gray's competing risk model was used with death as a competing event. Survival was calculated using multivariable Cox regression.
Results: A total of 192,658 patients were included, of which 62,630 patients were treated with RT for their pelvic cancer. Primary tumours were located in the prostate (50.1%), bladder (19.2%), endometrium (13.9%), ovaries (10.0%), cervix (6.4%) and vagina (0.4%). At a median interval of 6 years (range 0–24), 1369 patients developed a rectal cancer. Overall, the risk for rectal cancer was increased in patients who underwent RT for the previous pelvic cancer (sub-hazard ratio [SHR]: 1.72, 95% confidence interval [CI]: 1.55–1.91). Analysis for each tumour location specifically showed an increased risk in patients who received RT for prostate (SHR: 1.89, 95% CI: 1.66–2.16) or endometrial cancer (SHR: 1.50, 95% CI: 1.13–2.00). A protective effect of RT was observed for patients with bladder cancer (SHR 0.67, 95% CI: 0.47–0.94). There was no survival difference between patients with rectal cancer with or without previous RT (hazard ratio: 0.94, 95% CI: 0.79–1.11).

☆ The results of this manuscript have been presented as a poster presentation at the ESCP yearly conference of 2018 in Nice.

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Conclusions: Patients who received RT for a previous pelvic cancer were at increased risk for rectal cancer. The risk was modest and pronounced in patients receiving RT for prostate and endometrial cancer.

1. Introduction

Compared with the general population, cancer survivors have an increased risk of developing new malignancies [1,2]. This is the result of a combination of factors such as lifestyle, genetic susceptibility and type of treatment for their previous cancer [3,4]. Radiation therapy (RT) is part of the treatment regimen in at least 50% of all patients with cancer and has been associated with the development of second primary cancers [3–5]. However, recent studies have shown that in some cases, RT does not increase the risk for a second primary cancer and might even have a preventive effect [2,6,7].

When RT is administered for a tumour located in the pelvis, the rectum is likely to be within the irradiation field and is therefore prone to early and late toxicity [8,9]. Recently, a systematic review and metaanalysis on the incidence of second primary rectal cancer after RT for a primary pelvic tumour demonstrated a small increase in rectal cancer incidence after pelvic RT [10]. However, given the sparse evidence in the literature regarding several primary tumour sites (e.g., bladder and vaginal cancer), this hypothesis warrants further study and validation using population-based data.

A second primary rectal cancer after RT to the pelvic region has implications for rectal cancer treatment. One of the difficulties is whether additional courses of RT can be given because reirradiation has been associated with an excess of toxicity [11]. In addition, it is not clear whether radiation-induced rectal cancer is equally sensitive to RT compared with a sporadic rectal cancer. Yet, recent studies suggest that reirradiation can be of added value and that toxicity seems to be acceptable [12–15]. In addition, fibrosis due to previous RT can be associated with more challenging surgery and possibly increased surgical complications [15,16]. As a result, there might be a difference in outcomes between patients with rectal cancer who did or did not receive RT as part of the treatment for their previous cancer located in the pelvis.

The aim of the present study was to compare the incidence of rectal cancer as a second primary cancer in patients with or without RT as treatment for their previous pelvic cancer. Moreover, data on survival of patients with rectal cancer as a second primary cancer were analysed.

2. Material and methods

Data on all patients treated for a primary cancer located in the pelvis, excluding primary rectal and anal cancer, between 1989 and 2007 were retrieved from the population-based Netherlands Cancer Registry (NCR). The NCR collects all newly diagnosed tumours. Cancers are staged according to the TNM (tumour-node-metastasis) classification and topography, and morphology of tumours is coded using the International Classification of Diseases for Oncology (ICD-O). The NCR adheres to the ICD-O guidelines to identify multiple primary cancers and to the clinical assessment for the distinction of primary cancer from recurrent disease. The NCR performs at least annual updating on survival status. In the study period, the NCR did not differentiate between types of radiation therapy (i.e., external beam radiation therapy, brachy therapy etc.) and dosages were not registered.

Tumours of the prostate, bladder, endometrium, ovaries and vagina were included as first pelvic primary cancers. Patients who were treated for more than one pelvic cancer (other than their second primary rectal cancer) and patients whose tumour was found during autopsy were excluded (N = 3329 and N = 72, respectively). Rectal cancers that were not classified as adenocarcinoma, mucinous adenocarcinoma or signet ring cell carcinoma were excluded (N = 24). Information on vital status and incidence of rectal cancer as a second primary cancer was complete up to January 31st 2016 by linkage to the nationwide municipal population registries network.

2.1. Statistical analysis

Statistical significance was defined as $p < 0.05$. SPSS statistics (version 20.0; IBM) was used for characteristics and survival analyses. Baseline characteristics were analysed using the independent sample *t*-test, χ^2 test, or in case of an expected cell count <5, the Fisher exact test. Survival outcomes were calculated using Kaplan–Meier curves, and log-rank test was used for comparison of these curves. Cox regression was used for multivariable analysis, and variables were entered into the model in case of a p-value <0.1 in univariable analyses or when considered clinically relevant. Survival

time was calculated as the time between diagnosis of the rectal tumour and the date of vital status.

Fine and Gray's competing risk model was used to estimate the cumulative incidence of developing rectal cancer as a second primary cancer. The model incorporates death as a competing event for the development of a second cancer. This was performed using the Stata software (version 13.1). Subhazard ratios (SHRs) obtained from the Fine and Gray's competing risk model describe the relative effect of covariates on the subdistribution hazard function. Follow-up was defined as the time between incidence of the first primary tumour and date of a second primary rectal tumour or the last date of study follow-up or death. Estimation of standardised incidence ratios (SIRs) was performed using SAS (version 9.2). SIRs were defined as the ratio of observed secondary rectal cancers to expected cases in the Dutch general population. Results were stratified by gender, age and calendar time; 95% confidence intervals (CIs) were calculated by Poisson regression. The absolute excess risk per 10,000 person-years was also calculated (i.e., number of observed secondary rectal cancers minus the number of expected cases divided by person-years of follow-up).

3. Results

A total of 192,658 patients were included in the study, of which 62,630 patients (32.5%) were treated with RT for a primary pelvic cancer. Primary cancers were located in the prostate (50.1%), bladder (19.2%), endometrium (13.9%), ovaries (10.0%), cervix (6.4%) and vagina (0.4%; Table 1). Median follow-up was 6.8 years (range 0–27). After 10 years of follow-up, 65,992 (40.7%) patients were alive, and after 20 years, 9593 (20.9%) patients were alive. Characteristics of the previous pelvic cancers are depicted in Table 2. A total of 1369 patients (0.7%) developed rectal cancer as a second primary cancer after a median interval of 6 years (range 0–24). The crude incidence of rectal cancer was 1.0% in patients who received RT for their previous pelvic cancer and 0.6% in patients who did not receive RT ($p < 0.001$). Multivariable analysis (correcting for age, gender, clinical TNM stage, treatment for their previous pelvic cancer [surgery and chemotherapy], vital status, incidence year of their previous cancer and location of their previous tumour) confirmed the increased risk for rectal cancer as a second primary cancer in patients who received RT (hazard ratio [HR]: 1.19, 95% CI: 1.03–1.37).

Table 1
Characteristics of the previous pelvic cancer.

	RT N = 62,630 (%)	NRT N = 130,028 (%)
Second primary rectal cancer		
Yes	618 (1.0)	751 (0.6)
No	62,012 (99.0)	129,277 (99.4)
Location of previous pelvic tumour		
Prostate	36,427 (58.2)	60,150 (46.3)
Bladder	8916 (14.2)	28,128 (21.6)
Endometrium	10,009 (16.0)	16,694 (12.8)
Ovaries	348 (0.6)	18,931 (14.6)
Cervix	6372 (10.2)	5983 (4.6)
Vagina	558 (0.9)	142 (0.1)
Age, median (range)	69 (0–100)	69 (0–102)
0–14	6 (0.0)	101 (0.1)
15–29	216 (0.3)	902 (0.7)
30–44	1952 (3.1)	6373 (4.9)
45–59	8871 (14.2)	24,006 (18.5)
60–74	37,157 (59.3)	57,002 (43.8)
>75	14,428 (23.0)	41,644 (32.0)
Gender		
Male	43,128 (68.9)	82,021 (63.1)
Female	19,502 (31.1)	48,007 (36.9)
Incidence year		
1989–1992	9239 (14.8)	21,160 (16.3)
1993–1996	11,240 (17.9)	26,847 (20.6)
1997–2000	12,930 (20.6)	27,711 (21.3)
2001–2004	15,782 (25.2)	30,297 (23.3)
2005–2007	13,439 (21.5)	24,013 (18.5)
Tumour differentiation		
Well	9829 (15.7)	19,725 (15.2)
Intermediate	24,287 (38.8)	42,652 (32.8)
Poor	18,366 (29.3)	43,913 (33.8)
Undifferentiated	461 (0.7)	969 (0.7)
Unknown	9687 (15.5)	22,769 (17.5)
Treatment		
Surgery	19,161 (30.6)	82,194 (63.2)
Radiation therapy	62,630 (100)	–
Chemotherapy	2057 (3.3)	23,869 (18.4)
Immunotherapy	50 (0.1)	4057 (3.1)
Hormonal therapy	13,049 (20.8)	45,361 (34.9)

RT, radiation therapy; NRT, no radiation therapy.

3.1. Standardised incidence ratios

When compared with the general Dutch population, patients with a history of pelvic cancer were at increased risk for the development of rectal cancer as a second primary cancer. The increased risk was caused by RT treatment, as evident by a SIR in this group of 1.20 (CI: 1.10–1.30), compared with the group of RT-naïve patients (SIR: 0.99, CI: 0.91–1.06). The latter have a similar risk as the general Dutch population. In patients with a history of RT, the excess risk accounts for 17 cases per 100,000 patients per year.

3.2. Crude incidence ratio

The crude incidence ratio of rectal cancer was increased in patients who received RT for primary prostate cancer (1.3% versus 0.7%; $p < 0.001$) or endometrial cancer (0.9% versus 0.6%; $p = 0.002$) compared with patients who did not receive RT as part of their treatment. There was no statistically significant difference in the crude incidence ratio of rectal cancer based on previous RT for treatment of cervical (0.4% versus 0.3%, $p = 0.757$), vaginal (0.4% versus 0.7%; $p = 0.494$) or ovarian cancer (0.9% versus 0.3%; $p = 0.080$). There was less rectal cancer in the patient group with RT-treated bladder

Table 2
Characteristics of the previous pelvic cancer divided per organ.

	Prostate		Bladder		Endometrial		Ovarian		Cervical		Vaginal	
	RT+ N = 36,427	RT− N = 60,150	RT+ N = 8916	RT− N = 28,128	RT+ N = 10,009	RT− N = 16,694	RT+ N = 348	RT− N = 18,931	RT+ N = 6372	RT− N = 5983	RT+ N = 558	RT− N = 142
Second rectal cancer												
Yes	462 (1.3)	404 (0.7)	39 (0.4)	180 (0.6)	89 (0.9)	94 (0.6)	3 (0.9)	53 (0.3)	23 (0.4)	19 (0.3)	2 (0.4)	1 (0.7)
No	35,965 (98.7)	59,746 (99.3)	8877 (99.6)	27,948 (99.4)	9920 (99.1)	16,600 (99.4)	345 (99.1)	18,878 (99.7)	6349 (99.6)	5694 (99.7)	556 (99.6)	141 (99.3)
Age, median (range)	69 (4−92)	72 (2−99)	74 (1−98)	71 (0−101)	67 (0−95)	65 (0−102)	57 (14−94)	62 (0−98)	58 (19−100)	40 (12−95)	69 (2−95)	63 (0−95)
0−14	2 (<0.01)	2 (<0.01)	1 (<0.01)	13 (<0.01)	1 (<0.01)	2 (<0.01)	1 (0.3)	79 (0.4)	–	2 (<0.01)	1 (0.2)	3 (2.1)
15−29	2 (<0.01)	3 (<0.01)	5 (0.1)	29 (0.1)	4 (<0.01)	19 (0.1)	6 (1.7)	433 (2.3)	188 (3.0)	414 (6.9)	11 (2.0)	4 (2.8)
30−44	27 (0.1)	80 (0.1)	129 (1.4)	572 (2.0)	173 (1.7)	499 (3.0)	51 (14.7)	1712 (9.0)	1536 (24.1)	3486 (58.3)	36 (6.5)	24 (16.9)
45−59	3950 (10.8)	6856 (11.4)	951 (10.7)	4507 (16.0)	2060 (20.6)	5363 (32.1)	139 (39.9)	5840 (30.8)	1654 (26.0)	1407 (23.5)	117 (21.0)	33 (23.2)
60−74	26,138 (71.8)	29,388 (48.9)	3609 (40.5)	13,026 (46.3)	5310 (53.1)	6575 (39.4)	118 (33.9)	7464 (39.4)	1789 (28.1)	518 (8.7)	193 (34.6)	31 (21.8)
>75	6308 (17.3)	23,821 (39.6)	4221 (47.3)	9981 (35.5)	2461 (24.6)	4236 (25.4)	33 (9.5)	3403 (18.0)	1205 (18.9)	156 (2.6)	200 (35.8)	47 (33.1)
Incidence year												
1989−1992	3142 (8.6)	8340 (13.9)	2285 (25.6)	4627 (16.4)	2083 (20.8)	2756 (16.5)	200 (57.5)	4052 (21.4)	1406 (22.1)	1347 (22.5)	123 (22.0)	38 (26.8)
1993−1996	5710 (15.7)	12,687 (21.1)	2071 (23.2)	5437 (19.3)	1969 (19.7)	3165 (19.0)	72 (20.7)	4159 (22.0)	1304 (20.5)	1369 (22.9)	114 (20.4)	30 (21.1)
1997−2000	7599 (20.9)	12,835 (21.3)	1766 (19.8)	6019 (21.4)	2074 (20.7)	3504 (21.0)	41 (11.8)	4039 (21.3)	1353 (21.2)	1279 (21.4)	97 (17.4)	35 (24.6)
2001−2004	10,605 (29.1)	14,706 (24.4)	1642 (18.4)	6499 (23.1)	2129 (21.3)	4052 (24.3)	20 (5.7)	3922 (20.7)	1261 (19.8)	1091 (21.4)	125 (22.4)	27 (19.0)
2005−2008	9371 (25.7)	11,582 (19.3)	1152 (12.9)	5546 (19.7)	1754 (17.5)	3217 (19.3)	15 (4.3)	2759 (14.6)	1048 (16.4)	897 (15.0)	99 (17.7)	12 (8.5)
Clinical tumour stage												
cT0, cTis, cTA	2 (<0.01)	146 (0.2)	6 (0.1)	196 (0.7)	66 (0.7)	238 (1.4)	4 (1.1)	101 (0.5)	37 (0.6)	265 (4.3)	3 (0.5)	2 (1.4)
cT1	9363 (25.8)	9858 (16.4)	434 (4.9)	11,386 (40.5)	4553 (45.5)	7749 (46.4)	177 (50.9)	4224 (22.3)	1773 (27.8)	4112 (68.7)	152 (27.2)	46 (32.4)
cT2	17,612 (48.3)	27,695 (46.0)	3736 (41.9)	5886 (20.9)	657 (6.6)	404 (2.4)	67 (19.3)	1928 (10.2)	2438 (38.3)	256 (4.3)	150 (26.9)	6 (4.2)
cT3	8104 (22.2)	10,845 (18.0)	1825 (20.5)	1694 (6.0)	489 (4.9)	450 (2.7)	44 (12.6)	9892 (52.3)	1260 (19.8)	60 (1.0)	85 (15.2)	5 (3.5)
cT4	838 (2.3)	6481 (10.8)	1202 (13.5)	1174 (4.2)	93 (0.9)	193 (1.2)	–	–	414 (6.5)	46 (0.8)	85 (15.2)	6 (4.2)
cTX/Unknown	508 (1.4)	5125(8.5)	1713 (19.2)	7792 (27.7)	4151 (41.5)	7660 (45.9)	56 (16.1)	2786 (14.7)	450 (7.1)	1253 (20.9)	83 (14.9)	77 (45.2)
Clinical node stage												
cN0	22,299 (61.4)	17,189 (29.5)	5373 (60.7)	9520 (34.0)	4551 (48.3)	6535 (42.4)	191 (55.4)	6961 (37.0)	2757 (43.6)	2335 (39.4)	308 (59.2)	50 (55.6)
cN+	649 (1.8)	6656 (11.4)	701 (7.9)	1513 (5.4)	329 (3.5)	333 (2.2)	14 (4.1)	1988 (10.6)	1204 (19.0)	141 (2.4)	82 (15.8)	8 (8.9)
cNX	13,399 (36.9)	34,395 (59.1)	2785 (31.4)	16,955 (60.6)	4543 (48.2)	8558 (55.5)	140 (40.6)	9865 (52.4)	2365 (37.4)	3448 (58.2)	130 (25.0)	32 (35.6)
Clinical metastasis stage												
cM0	28,798 (79.2)	26,551 (45.6)	7156 (80.8)	19,719 (70.5)	7215 (76.6)	10,485 (68.0)	266 (77.1)	11,258 (59.8)	4735 (74.8)	3455 (58.3)	389 (74.8)	55 (61.1)
cM1	407 (1.1)	18,335 (31.5)	400 (4.5)	1116 (4.0)	161 (1.7)	520 (3.4)	12 (3.5)	2802 (14.9)	343 (5.4)	117 (2.0)	23 (4.4)	12 (13.3)
cMX	7143 (19.7)	13,355 (22.9)	1304 (14.7)	7154 (25.6)	2047 (21.7)	4420 (28.7)	67 (19.4)	4754 (25.3)	1248 (19.7)	2353 (39.7)	108 (20.8)	23 (25.6)
Tumour differentiation												
Well	7253 (19.9)	8285 (13.8)	85 (1.0)	1368 (4.9)	2137 (21.4)	7426 (44.5)	30 (8.6)	2164 (11.4)	285 (4.5)	473 (7.9)	39 (7.0)	9 (6.3)
Moderate	16,416 (45.1)	23,833 (39.6)	1249 (14.0)	8352 (29.7)	4094 (40.9)	5196 (31.1)	123 (35.3)	3786 (20.0)	2245 (35.2)	1457 (24.4)	160 (28.7)	28 (19.7)
Poor	6577 (18.1)	18,198 (30.3)	6757 (75.8)	16,088 (57.2)	2678 (26.8)	1877 (11.2)	85 (24.4)	6627 (35.0)	2135 (33.5)	1107 (18.5)	134 (24.0)	16 (11.3)
Undifferentiated	65 (0.2)	242 (0.4)	202 (2.3)	304 (1.1)	79 (0.8)	73 (0.4)	9 (2.6)	288 (1.5)	96 (1.5)	58 (1.0)	10 (1.8)	4 (2.8)
Unknown	6116 (16.8)	9592 (15.9)	623 (7.0)	2016 (7.2)	1021 (10.2)	2122 (12.7)	101 (29.0)	6066 (32.0)	1611 (25.3)	2888 (48.3)	215 (38.5)	85 (59.9)
Treatment												
Surgery	1035 (2.8)	16,825 (28.0)	6094 (68.3)	27,044 (96.1)	9651 (96.4)	16,103 (96.5)	327 (94.0)	16,262 (85.9)	1959 (30.7)	5832 (97.5)	95 (17.0)	128 (90.1)
Radiation therapy	36427 (100)	–		–	10009 (100)	–	348 (100)	–	6372 (100)	–	558 (100)	–
Chemotherapy	66 (0.2)	704 (1.2)	481 (5.4)	8535 (30.3)	112 (1.1)	499 (3.0)	56 (16.1)	13,900 (73.4)	1269 (19.9)	212 (3.5)	73 (13.1)	19 (13.4)
Immunotherapy	2 (<0.01)	3 (<0.01)	46 (0.5)	4041 (14.4)	–	1 (<0.01)	1 (0.3)	12 (0.1)	1 (<0.01)	–	–	–
Hormonal therapy	12,987 (35.4)	44,342 (73.7)	6 (0.1)	35 (0.1)	122 (1.2)	792 (4.7)	4 (1.1)	171 (0.9)	19 (0.3)	20 (0.3)	1 (0.2)	1 (0.7)

RT, radiation therapy; NRT, no radiation therapy.

cancer compared with patients with RT-naïve bladder cancer (crude incidence 0.4% versus 0.6%; p = 0.018).

3.3. Competing risk analysis

Competing risk analysis was performed to correct for death as a competing event (see Fig. 1). For all first tumour locations taken together, RT increased the risk for rectal cancer as a second primary cancer (SHR: 1.72, 95% CI: 1.55–1.91). Age did not influence this relation. Competing risks were also calculated for each primary tumour location specifically. The risk for rectal cancer was increased in patients who received RT for prostate cancer (SHR: 1.89, 95% CI: 1.66–2.16) or endometrial cancer (SHR: 1.50, 95% CI: 1.13–2.00). Yet, a protective effect of RT was observed for patients who received RT for bladder cancer (SHR: 0.67, 95% CI: 0.47–0.94). There was no interaction with gender. No effect was observed in patients who received RT for cervical cancer (SHR: 1.17, 95% CI: 0.64–2.15), ovarian cancer (SHR:

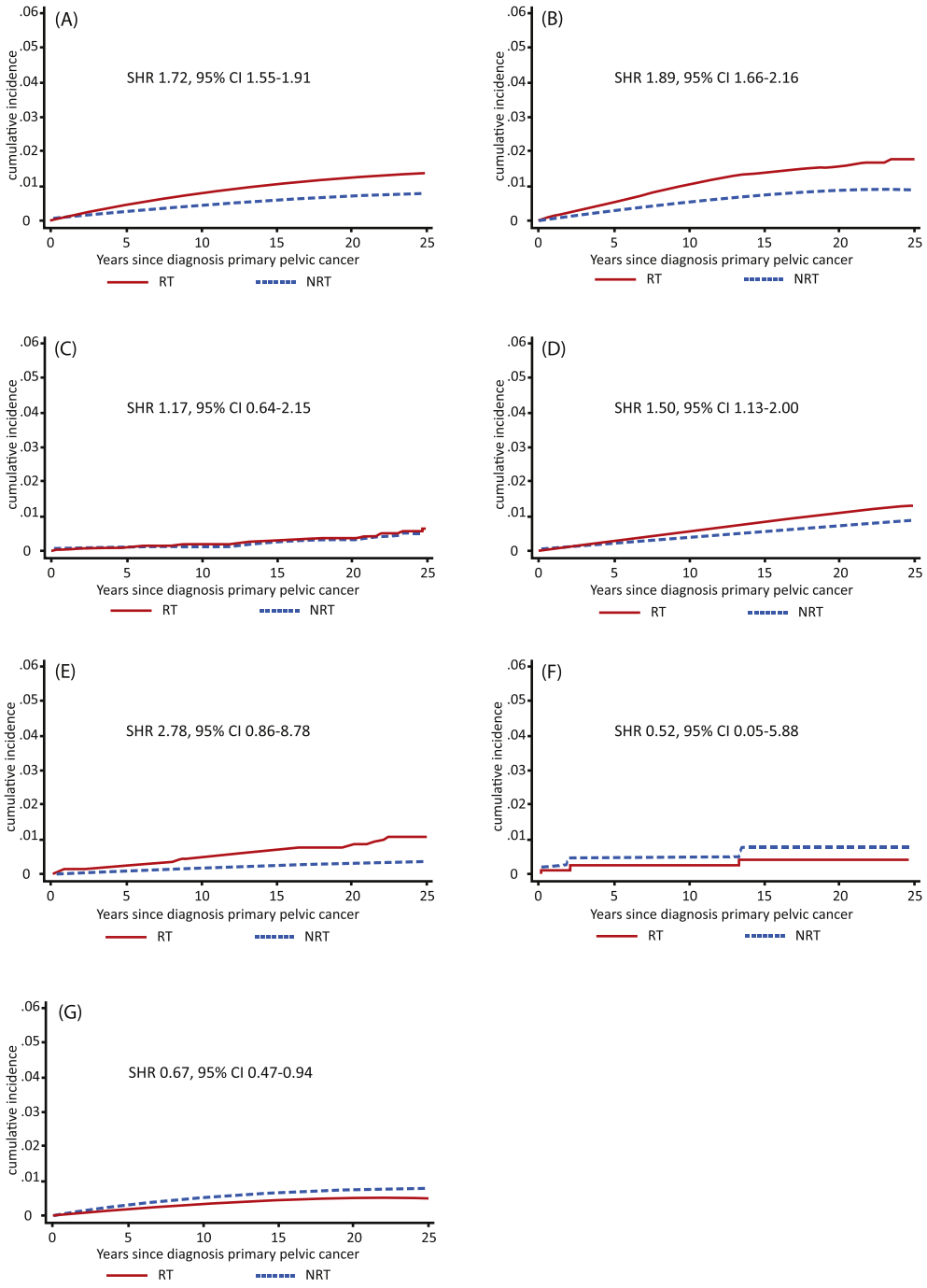

Fig. 1. Cumulative incidence of second primary rectal cancer RT after RT for (A) any pelvic cancer; (B) prostate cancer; (C) cervical cancer; (D) endometrial cancer; (E) ovarian cancer; (F) vaginal cancer and (G) bladder cancer. RT radiation therapy; NRT, no radiation therapy.

2.78, 95% CI: 0.86–8.78) or vaginal cancer (SHR: 0.52, 95% CI: 0.05–5.88).

3.4. Characteristics of rectal cancer and survival analysis

The median age at the time of diagnosis of rectal cancer was 75 years (range, 44–97), and most patients with a rectal cancer were men (77.4%). Clinical TNM stage, differentiation grade and histology were similar between the groups (Table 3). Patients who received RT for their previous pelvic cancer were less likely to undergo additional RT for the rectal cancer (15.6% versus 46.8%, respectively, $p < 0.001$). Subsequently, patients who were treated with RT for the primary pelvic cancer were diagnosed with higher pathological T-stage of the rectal cancer (Table 4). There were no differences in pathological nodal stage or metastasis stage for rectal cancer in patients treated with or without RT for the primary pelvic cancer.

Table 3
Characteristics of rectal cancer as a second primary cancer.

	RT for previous pelvic cancer N = 618 (%)	NRT for previous pelvic cancer N = 751 (%)	p-value
Age, median (range)	75 (45–97)	75 (44–95)	0.002
Gender			0.014
Male	497 (80.4)	562 (74.8)	
Female	121 (19.6)	189 (25.2)	
Incidence year			0.541
1989–1992	10 (3.0)	16 (3.4)	
1993–1996	31 (9.2)	48 (10.1)	
1997–2000	53 (15.8)	90 (19.0)	
2001–2004	90 (26.8)	133 (28.1)	
2005–2008	152 (45.2)	187 (39.5)	
Histology			0.511
adenocarcinoma	566 (91.6)	675 (89.9)	
mucinous carcinoma	46 (7.4)	69 (9.2)	
signet ring cell carcinoma	6 (1.0)	7 (0.9)	
Tumour differentiation			0.182
well	26 (5.7)	31 (6.4)	
moderate	359 (78.7)	357 (73.8)	
poor	67 (14.7)	94 (19.4)	
undifferentiated	4 (0.9)	2 (0.4)	
not applicable/ unknown	162	267	
Treatment			<0.001
Sx	365 (59.1)	258 (34.4)	
Sx + CT	27 (4.4)	23 (3.1)	
Sx + RT	42 (6.8)	221 (29.4)	
Sx + CRT	33 (5.3)	70 (9.3)	
CT	24 (3.9)	24 (3.2)	
RT	12 (1.9)	48 (6.4)	
CRT	10 (1.6)	15 (2.0)	
No Sx or (C)RT	105 (17.0)	92 (12.3)	
Clinical tumour stage			0.797
cT0/cTis	1 (0.3)	2 (0.6)	
cT1	20 (6.1)	23 (6.7)	
cT2	79 (24.0)	77 (22.5)	
cT3	149 (45.3)	167 (48.8)	
cT4	80 (24.3)	73 (21.3)	
cTx/unknown	272	394	
Clinical node stage			0.113
cN0	259 (70.4)	274 (65.1)	
cN+	109 (29.6)	147 (34.9)	
cNx/unknown	233	314	
Clinical metastasis stage			0.881
cM0	449 (82.2)	521 (82.6)	
cM1	97 (17.8)	110 (17.4)	
cMx/unknown	55	105	

RT, radiation therapy; NRT, no radiation therapy; Sx, surgery; CT, chemotherapy; CRT, chemoradiation.

Univariable analysis showed no statistically significant difference in overall survival between patients with rectal cancer based on their history of RT: 5-year overall survival after diagnosis of rectal cancer was 33.7% (95% CI: 29.6–37.8) in patients treated with RT for their previous pelvic cancer versus 39.1% (95% CI: 35.4–42.8) in patients without RT (Fig. 2). Multivariable analysis, correcting for age, gender, incidence year, stage and treatment of the rectal cancer, confirmed this (HR: 0.94, 95% CI: 0.79–1.11).

4. Discussion

A recent systematic review and metaanalysis showed an increased risk of rectal cancer after RT for a variety of pelvic cancers [10]. Stratification for origin of the first cancer showed that the risk for rectal cancer was increased after treatment for prostate, cervical or endometrial cancer. The present nationwide study is the largest patient cohort in the literature and analysed the association between RT as treatment for pelvic cancer and the development of rectal cancer as a second primary cancer. The current data confirms that patients who receive RT for a primary pelvic cancer are at increased risk for the development of rectal cancer as a second primary cancer. Analysis of each primary cancer location specifically showed an increased risk for patients who received RT for a primary prostate or endometrial cancer. In contrast, a small preventive effect of RT on rectal cancer development was seen for patients who received RT for bladder cancer and no influence of RT was observed for patients who received RT for the other gynaecological cancers.

Little is known about the aetiology of rectal cancer in relation to a history of RT. RT effects can be divided into set and random effects according to the probability of occurrence [17]. Set effects, such as teratogenesis, occur above a threshold dose and the severity increases with increasing the dose. In contrast, the probability for a random effect such as carcinogenesis increases as the dose increases. In that case, there is no minimal threshold dose, and the severity is independent of the dose. Since the introduction of intensity-modulated radiation therapy (IMRT), and even more volumetric

Table 4
Pathological tumour stage of rectal cancer as a second primary cancer.

		RT for previous pelvic cancer N = 382 (%)	NRT for previous pelvic cancer N = 277 (%)	p-value
No (chemo)radiation for rectal cancer	Pathological tumour stage			<0.001
	pT1	40 (11.0)	69 (26.4)	
	pT2	115 (31.6)	82 (31.4)	
	pT3	186 (51.1)	100 (38.3)	
	pT4	23 (6.3)	10 (3.8)	
	pTx/unknown	18	16	
	Pathological nodal stage			0.937
	pN0	179 (61.5)	107 (61.1)	
	pN+	112 (38.5)	68 (38.9)	
	pNx/unknown	91	102	
	Metastasis stage			0.858
	M0	319 (93.0)	213 (92.6)	
	M1	24 (7.0)	17 (7.4)	
	Mx/unknown	39	47	
		RT for previous pelvic cancer N = 75 (%)	NRT for previous pelvic cancer N = 291 (%)	p-value
No (chemo)radiation for rectal cancer	Pathological tumour stage			0.001
	ypT0	5 (6.9)	11 (4.0)	
	ypT1	1 (1.4)	30 (10.8)	
	ypT2	23 (31.9)	87 (31.3)	
	ypT3	34 (47.2)	142 (51.1)	
	ypT4	9 (12.5)	8 (2.9)	
	ypTx/unknown	3	13	
	Pathological nodal stage			0.106
	ypN0	46 (69.7)	150 (58.8)	
	ypN+	20 (30.3)	105 (41.2)	
	ypNx/unknown	9	36	
	Metastasis stage			0.427
	M0	62 (91.2)	254 (93.7)	
	M1	6 (8.8)	17 (6.3)	
	Mx/unknown	7	20	

Pathological tumour stage of patients who underwent surgery for rectal cancer, with or without (chemo)radiation. Fourteen patients underwent neoadjuvant chemotherapy without radiation and are not taken into consideration in this table. RT, radiation therapy; NRT, no radiation therapy.

IMRT, where the high-dose region is geometrically more shaped around the target volumes at a cost of a so-called low-dose bath to a larger volume of non-target tissue, it was argued that these differences in RT dose distribution might increase the risk for induction of second cancers [10,18–20]. However, little data are available to support this.

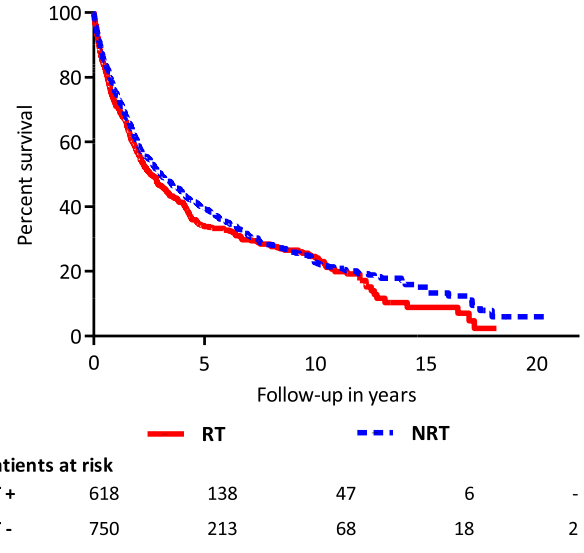

Fig. 2. Kaplan–Meier curve for overall survival after diagnosis of rectal cancer. RT radiation therapy for previous pelvic cancer; NRT, no radiation therapy for previous pelvic cancer.

There are several other possible explanations for the observed discrepancies in rectal cancer risks between the primary irradiated organs. Firstly, genetic susceptibility is likely to play a role. For instance, patients with endometrial cancer with Lynch syndrome have a 50% chance of developing a subsequent colorectal cancer [21]. In addition, DNA mismatch repair (MMR) status has been associated with radio sensitivity and long-term toxicity [22]. Increase in MMR expression is related to low-dose rate sensitivity, whereas MMR deficiency is related to high-dose rate sensitivity and possibly increased risk of carcinogenesis [22].

Secondly, because of its fixed location in the pelvis, the rectum is prone for toxicity after RT, and chronic proctitis occurs in 2–20% of patients receiving RT to the pelvis [23]. Hypothetically, RT-induced late toxicity leading to inflammation could create a precancerous environment, as is observed in patients with inflammatory bowel diseases (IBD) [24–26]. Carcinogenesis of IBD-related colorectal cancer differs from sporadic

colorectal cancer [25,26]. Sporadic colorectal cancer typically develops via the adenoma-carcinoma sequence, characterised by a series of molecular alterations (e.g., RAS mutation or p53 mutation). In IBD-related colorectal cancer, the 'inflammation-dysplasia-carcinoma' sequence shows a different pattern of molecular alterations [27]. Carcinogenesis in patients with IBD is characterised by a rapid development of high-grade dysplasia. Because RT is associated with chronic proctitis, we hypothesise that the development of rectal cancer after RT might be similar to colorectal cancer in patients with IBD. If that is the case, the incidence of rectal cancer would be related to toxicity experienced by patients after RT. For example, late grade ≥2 toxicity (following the Radiation Therapy Oncology Group [RTOG] and the European Organization for Research and Treatment of Cancer [EORTC]. radiation morbidity scoring schema) occurs in approximately 3–7% of patients with bladder cancer, 5–20% in patients with prostate cancer, 10–20% in patients with cervical cancer and up to 22% in patients with endometrial cancer [28–33]. In combination with the findings in the present study, it could be hypothesised that this may be an explanation for the increased risk of rectal cancer in patients with prostate and endometrial cancer.

Another reason of the higher incidence of rectal cancer in patients with prostate cancer might be the dose/volume characteristics of up to 70Gy to a small part of the anterior rectal wall in prostate cancer versus 45–50Gy to much larger volumes for most other pelvic tumours.

On the other hand, numbers between groups varied and observed risk differences were small. Lack of power in the smaller groups might be one of the reasons for the lack of effect of RT for cervical, vaginal and ovarian cancer. Theoretically, differences in RT techniques, that is, external beam radiation versus brachytherapy might also play a role, but this could not be confirmed in our recent review of the literature [10]. In the NCR, no data were available on RT techniques used. In the earlier years most patients in the Netherlands received pelvic RT according to the traditional 'box' technique. During the 1990s, 3D conformal computed tomography (CT)–based techniques were gradually introduced, enabling individualisation to volume- instead of field-based RT. However, during multivariable analysis, incidence year of the primary cancer was not a significant predictor for the development of a rectal cancer.

Differences in predisposing lifestyle factors such as smoking might also play a role in the development of second cancers. Hegemann *et al.* [34] have studied the incidence of second cancers after treatment for prostate cancer and concluded that the lack of information on smoking is one of the major limitations in the available literature. They reported on an increased risk for second rectal cancer in patients who were treated with RT only, but no increase in second rectal cancer was found in patients treated with surgery followed by RT or surgery only. The authors hypothesised that the difference in second rectal cancer incidence might be due to differences in age and lifestyle habits such as smoking. In the present study, 36,427 patients with prostate cancer who received RT and 60,150 RT-naïve patients were analysed. In contrast to the study by Hegemann *et al.* [34], age was not a significant predictor for the incidence of second rectal cancer. Unfortunately, information on smoking habits is not available in the NCR, and therefore, a possible confounding effect could not be studied.

There was no significant difference in survival after the diagnosis of rectal cancer depending on the patients' history of RT. Clinical stage of the second primary rectal cancers was comparable and perhaps even favourable to clinical stage reported in the literature for primary rectal cancer [35,36]. Notwithstanding, survival rates were lower than those reported for the general population (34–39% versus 51–65%) [36,37]. Patients with rectal cancer in the present study were slightly older than patients with a sporadic rectal cancer described in the literature [35,36]. Moreover, the fact that these patients have a history of cancer and cancer treatment, which might have affected their fitness and outcome, could explain the difference in overall survival. Another hypothesis could be that, tumours of patients who present with a second primary cancer might have different biological behaviour and/or might be more aggressive than tumours in patients who present with a first primary cancer [38]. This is supported by the advanced T-stage of patients with a history of RT and the relative high number of ypT4 cases after reirradiation in the present study.

This nationwide study provides unique long-term data on the incidence and outcomes of second primary rectal cancer after RT for primary pelvic cancer. One of the strengths of our study is that, it contains a large cohort of patients with more than 65,000 patients having more than 10 years of follow-up and 9500 patients more than 20 years of follow-up. However, the nature of the study needs to be taken into account when interpreting the data. To diminish the influence of confounding factors, multivariable analysis was conducted. However, for some of the known predisposing factors, such as genetic susceptibility and lifestyle factors, no data were available, which is considered a limitation of the study. Only few patients underwent RT for a primary ovarian or vaginal cancer, and therefore, we could not establish whether RT for the primary cancer was related to an increased risk of second rectal cancer. However, because of the low number of patients with ovarian and vaginal cancer receiving RT, a possible relation between RT and second primary rectal cancer would not be clinically relevant.

5. Conclusions

Patients who received RT for pelvic cancer were at increased risk for rectal cancer as a second primary

cancer. However, its incidence is low and analysis per primary pelvic organ specifically showed an increased risk after prostate and endometrial cancer treatment only. Patients with previous RT for bladder cancer had a decreased risk for rectal cancer. There was no difference in survival after diagnosis of rectal cancer depending on their history of RT.

Conflict of interest statement

There are no conflicts of interest to declare. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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