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Systematic or Meta-analysis Studies

Does pelvic radiation increase rectal cancer incidence? – A systematic review and meta-analysis☆

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ABSTRACT

Background: One of the late complications associated with radiation therapy (RT) is a possible increased risk of second cancer. In this systematic review, we analysed the incidence of rectal cancer following primary pelvic cancer irradiation.

Methods: A literature search was conducted using the PubMed and EMBASE libraries. Original articles that reported on secondary rectal cancer after previous RT for a primary pelvic cancer were included. Sensitivity analyses were performed by correcting for low number of events, high risk of bias, and outlying results.

Results: A total of 5171 citations were identified during the literature search, 23 studies were included in the meta-analyses after screening. A pooled analysis, irrespective of primary tumour location, showed an increased risk for rectal cancer following RT (N = 403.243) compared with non-irradiated patients (N = 615.530) with a relative risk (RR) of 1.43 (95% confidence interval [CI] 1.18–1.72). Organ specific meta-analysis showed an increased risk for rectal cancer after RT for prostate (RR 1.36, 95%CI 1.10–1.67) and cervical cancer (RR 1.61, 95% CI 1.10–2.35). No relation was seen in ovarian cancer patients. The modality of RT did not influence the incidence of rectal cancer.

Conclusions: This review demonstrates an increased risk for second primary rectal cancer in patients who received RT to the pelvic region. This increased risk was modest and could not be confirmed for all primary pelvic cancer sites. The present study does not provide data to change guidelines for surveillance for rectal cancer in previously irradiated patients.

Introduction

Approximately 50% of all cancer patients undergo radiation therapy (RT) as part of their primary treatment regimen [1]. During RT, high dosages of ionizing radiation are delivered which generate oxygen-derived free radicals. These radicals induce DNA damage and eventually cause apoptosis [2,3]. The addition of RT to a treatment regimen is generally associated with a reduction in recurrences and improvement of prognosis in many types of cancer [4–8]. However, RT is also known to cause acute and late toxicity. One form of late toxicity is a potentially increased risk of secondary tumours in the irradiated field.

During RT for cancer of one of the pelvic organs, the rectum is usually within the field of irradiation, and secondary rectal cancer has been reported. Studies show conflicting data with respect to increased risk on rectal cancer following pelvic radiation [9–14]. Lack of power and variations in study design might explain these conflicts partially. Moreover, all patients with a history of cancer, including those who did not undergo RT, are at increased risk for the development of second primary cancer [15]. Although secondary cancer development is a multifactorial process, the exact role of RT in this remains unclear.

One of the challenges in the interpretation of studies on second cancer incidence is that different latency period thresholds are being used. Latency periods represent the time from radiation exposure until diagnosis of a subsequent cancer and latency period thresholds have been introduced to second cancer analyses to reduce possible bias from synchronous tumours. Between studies, latency period thresholds vary

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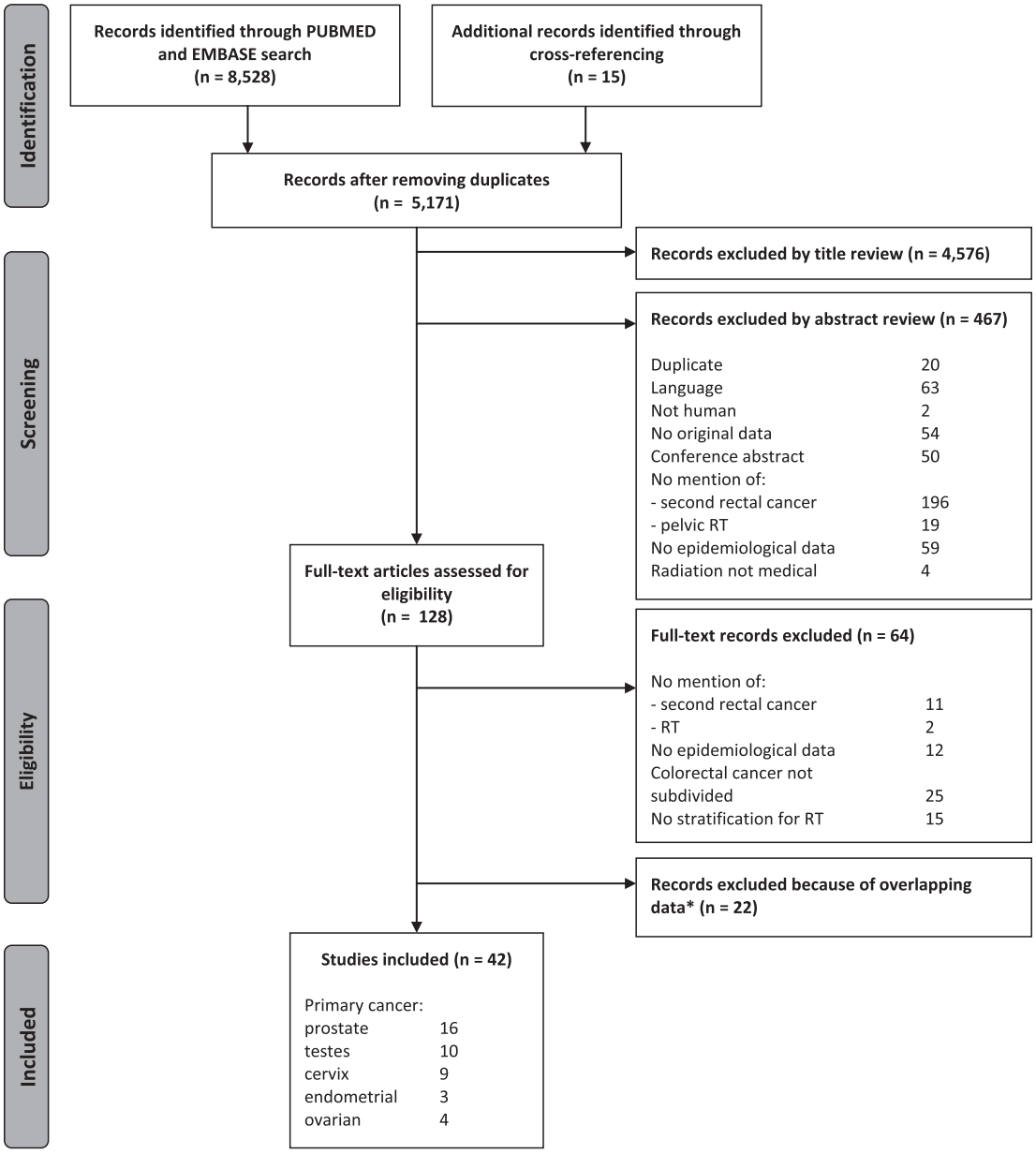

Fig. 1. Flowchart of the search strategy for systematic review. *In case of considerable overlap in data/subjects between studies, the study with the largest population was included in the meta-analysis. A reference list of studies that were excluded due to overlap in data is provided in Supplementary File 3.

from 1 month up to 10 years [16,17].

This systematic review generates insight into the incidence and latency period of subsequent rectal cancer following primary pelvic cancer irradiation through an overview of the literature and a meta-analysis.

Methods

Literature search and selection criteria

A systematic search of all peer-reviewed literature was conducted using the PubMed and EMBASE libraries on April 14th 2017. Reference lists of selected studies were checked for relevant articles. The Boolean search strategy is provided in Supplementary File 1 and included the following terms and their synonyms: [“second primary neoplasm” OR “radiation-induced neoplasm”] AND [“rectal neoplasm”] AND [(“ureteral” OR “urinary bladder” OR “genital” OR “gynaecological” OR “ovarian” OR “uterine” OR “endometrial” OR “cervical” OR “vaginal” OR “vulvar” OR “prostate” OR “testicular”) AND “neoplasm”]. All studies were reviewed for inclusion by two independent reviewers (AR and JvB or NH). A title and abstract screening was performed followed by full-text review. Any discrepancies were resolved through a consensus discussion. Only original articles in the English language that reported on second rectal cancer after previous RT for a primary pelvic cancer were included. Studies were excluded if ‘colorectal cancer’ was not subdivided into colon and/or rectal cancer. In case of considerable overlap in data/subjects between studies, the study with the largest population was included in the meta-analysis.

Data extraction

The goal was to compare patients who received RT for their primary cancer with patients who did not receive RT for the primary cancer. Therefore, we calculated the number of patients in each group and the corresponding number of second rectal cancers. Data was extracted for male and female patients separately. Some studies applied a threshold

Table 1
Studies included in the meta-analysis on second rectal cancer in male patients.

Study (year)	Period	Registry	Latency period	Total no. of patients	Study group (RT)	Control group (No RT)	Mean age (yr) (study/control)	Median follow-up in years (study/control)	No. of second rectal cancers (study/control)	SIR (95% CI) (study/control)
Prostate cancer										
Boorjian et al.[17]	1989–2003	CaPSURE	1 mo	9681	2471[A]	4608[F]	67–70	3.3	11/20	–
Rapiti et al.[30]	1980–1998	Geneva cancer registry	5 yrs	1134	264[B]	870	68/71	7.8/7.3	2/4	2.0 (0.2–7.2)/1.2 (0.3–3.1)
Huo et al.[27]	1973–2005	SEER (17 registries)	Not used	635,910	211,882[A]	424,028	69.4	5.38[ǂ]	941/1687	1.04 (0.97–1.11)/0.95 (0.91–1.00)
Bhojani et al.[32]	1983–2003	Quebec health plan	5	17,845	3079[A]	6037[F]	69.6/64.6	–	33/43	–
Hinnen et al.[14]	1989–2005	The Netherlands	1 yr	1888	1187[C]	701[F]	66.5/62.6[*]	7.1/8.7	9/9	0.90 (0.41–1.72)/1.50 (0.68–2.85)
Margel et al.[33]	1982–2005	Israel cancer registry	6 mo	8925	2163[A]	6762[F]	69.4/70.2[*]	11.2	26/41	1.81 (1.2–2.5)/1.22 (0.85–1.65)
Hamilton et al.[35]	1998–2010	British Columbia cancer agency	Not used	5061	2418[C]	2643[F]	66/62[*]	5.8/6.4	19/11	–
Joung et al.[31]	1993–2011	Korean central cancer registry	2 mo	55,378	3407[A]	27,765[F]	69.8	3.5[ǂ]	17/83	1.03 (–)/0.67 (–)[†]
Hegemann et al.[65]	1988–2008	Munich cancer registry	1 yr	19,538	3883[A] 1366[D]	14,289[F]	70.3[A]/64.4[D]/65.2[*]	9.6[A]/8.8[D]/10.2	42/4[D]/85	1.75[†] (1.18–2.60)/1.90[†] (1.27–2.85)[d]/1.00 (–)

RT, Radiation therapy; SEER, Surveillance Epidemiology and End Results Registry; mo, month(s); yr, year; SIR, standardized incidence ratio; CI, confidence interval.
[A]Radiation therapy not further specified; [B]External beam radiation therapy (EBRT); [C]Brachytherapy; [D]Radiation therapy not further specified in combination with surgery; [E]Radiation therapy not further specified in combination with chemotherapy; [F]Surgery only; [G]Chemotherapy only.

[*] Median (instead of mean).

[ǂ] Mean (instead of median).

[†] $p < 0.05$.

Table 2
Studies included in the meta-analysis on second rectal cancer in female patients.

Study (year)	Period	Registry	Latency period	Total no. of patients	Study group (RT)	Control group (No RT)	Mean age (yr)	Median follow-up in years (study/control)	No. of second rectal cancers (study/control)	SIR (95% CI) (study/control)
Cervix cancer										
Clarke et al. [22]	1960–1975	Ontario Cancer Institute	1 mo	7535	7113[A]	422	52.1	6	13/0	0.77/–
Boice et al. [41]	1960–1970	International Radiation Study of Cervical Cancer (15 registries)	Not used	96,789	82,616[A]	14,173	–	7.6[‡]/6.6[‡]	198/29	1.3[†]/1.3
Hiyama et al. [23]	1966–1970	Osaka cancer registry	3 mo	3144	1767[A]	1377	–	7.2[‡]/9.0[‡]	9/2	4.82[†]/1.35
Storm et al. [66]	1943–1982	Danish Cancer Registry	1 yr	24,970	20,160[A]	4810	–	–	85/17	1.2/1.2
Arai et al.[21]	1961–1981	China, Tokyo and Matsumoto	Not used	11,855	7694[A]	4161[F]	–	8.2/11.4	25/3	1.91[†]/0.54
Kleinerman et al. [11]	1935–1990	SEER (Denmark, Finland, Norway, Sweden, Connecticut, Iowa)	2 mo	66,541	49,828[A]	16,713	–	10.4	340/58	1.7 (1.5–1.8)/1.3 (1.0–1.7)
Ovarian cancer										
Reimer et al. [25]	1935–1972	End Results Program	Not used	13,309	6596[A]	6713	56	3.5	2/10	RR 0.3 (0.0–0.9)/1.1 (0.5–1.9)
Prior et al. [24]	1957–1976	Birmingham and west midlands	1 yr	3300	1030[A] 414[E]	1,229 627[G]	–	7–26	0[A]/2[E]/2[G] Other: 8	6.7[E,†]/2.1[†]/2.9[G]
Freedman et al. [26]	1973–2000	SEER (9 registries)	2 mo	74,185	3462[A]	38,027	60.4[*]	–	9/57	1.54/1.45[†]

RT, Radiation therapy; SEER, Surveillance Epidemiology and End Results Registry; mo, month(s); yr, year; SIR, standardized incidence ratio; CI, confidence interval.
[A]Radiation therapy not further specified; [B]External beam radiation therapy (EBRT); [C]Brachytherapy; [D]Radiation therapy not further specified in combination with surgery; [E]Radiation therapy not further specified in combination with chemotherapy; [F]Surgery only; [G]Chemotherapy only.
[*] Median (instead of mean).
[‡] mean (instead of median).
[†] $p < 0.05$.

for the latency period to reduce bias from synchronous tumours when multiple incidences were given for different threshold latency periods, all were extracted. In addition, data on RT regimen, follow-up, age, and standardized incidence risk (SIR) were extracted when available.

Quality assessment

Risk of bias was assessed by the 'Newcastle-Ottawa Scale (NOS) [18], a tool designed for quality assessment of non-randomised studies for meta-analysis (Table 3). Studies are rated on a 0–9 scale on items regarding selection, comparability of subjects and exposure. The quality of most reviewed studies was high (NOS score 7–9), only one study had a high risk of bias (NOS score 5). Publication bias was analysed by testing for funnel plot symmetry (Supplementary Fig. 1).

Statistical analysis

Patients who received RT were compared with patients who did not receive RT. Studies in which a non-irradiated control group was lacking and studies with zero events were excluded from meta-analysis and are summarized in supplementary Table 1. Heterogeneity was tested by Chi-square analysis and was defined as present in case of a p-value $<$ 0.10. To assess the impact of heterogeneity on the meta-analysis, I^2 (the percentage of variability in effect estimates that is due to heterogeneity rather than chance) was calculated. Furthermore, a random-effects model with inverse variance weighting of studies was used for meta-analysis. This model incorporates heterogeneity by giving a weight to each study equal to the inverse of the variance of the effect estimate. Results are depicted as risk ratios (RR) alongside a 95% confidence interval (CI). Sensitivity analyses were performed to assess the robustness of the results by correcting for low number of events (≤ 5 events per group), high risk of bias (total score $<$ 6), and outlying results. Subgroup analysis was performed to compare the different primary cancer sites and different RT modalities (external beam radiation therapy versus brachytherapy), and to analyse the influence of used fixed latency periods. Review Manager version 5.3 was used for the meta-analysis (Copenhagen, the Nordic Cochrane Centre) [19].

Registration

The study design was registered and published at the PROSPERO International prospective register of systematic reviews [20]. Registration number: CRD42017046045.

Results

Search results

A total of 5171 citations were identified during the literature search (Fig. 1). After screening titles and abstracts, 128 studies were selected, and 64 studies were selected on the basis of their full text. Studies with overlapping data were excluded (n = 22). Studies without a non-irradiated control group (n = 15) and studies with zero events (n = 4) are summarized in supplementary Table 1.

Subgroup analyses were performed for the different primary cancer sites. In male patients, the literature search revealed 16 studies that reported on the risk of rectal cancer after RT for prostate cancer, and 10 studies after RT for testicular cancer. Nine and two studies were eligible for meta-analysis, respectively. In female patients, nine studies were identified after primary cervical cancer, of which six studies were eligible for meta-analysis. Three studies were identified after primary endometrial cancer, and all three were eligible for meta-analysis. The literature search revealed four studies that investigated the risk of rectal cancer after RT for ovarian cancer, of which three were included in the meta-analysis. No studies were identified investigating the risk for second primary rectal cancer following treatment for bladder or vaginal

Table 3
Assessment of methodological quality of included studies for meta-analysis based on the Newcastle-Ottawa Scale for cohort studies.

Location primary tumour	Study (year)	Selection	Comparability	Outcome/exposure	Total (max 9)
Prostate	Boorjian et al. [17]	★★★★	★★	★★	8
	Rapiti et al. [30]	★★★★	★★	★★	8
	Huo et al. [27]	★★★★	★★	★★★	9
	Bhojani et al. [32]	★★★★	★★	★★	8
	Hinnen et al. [14]	★★★	★★	★★	7
	Margel et al. [33]	★★★★	★	★★	7
	Hamilton et al. [35]	★★★★	★★	★★	8
	Joung et al. [31]	★★★★		★★	6
	Hegemann et al. [65]	★★★★	★	★★	7
Cervix	Clarke et al. [22]	★★★★		★★	6
	Boice et al. [41]	★★★		★★★	6
	Hiyama et al. [23]	★★★★		★★★	7
	Storm et al. [66]	★★★★	★	★★	7
	Arai et al. [21]	★★★★		★★	6
	Kleinerman et al. [11]	★★★★		★★	6
Ovaries	Reimer et al. [25]	★★★★		★★★	7
	Prior et al. [24]	★★★★		★★★	7
	Freedman et al. [26]	★★★★		★	5

cancer. Data on studies that were included in the meta-analysis (n = 18) are summarized in Table 1 for male patients and in Table 2 for female patients. Data from studies reporting on testicular and endometrial primary cancers are provided in the supplementary files only (Supplementary file 2).

All primary cancer sites

A pooled analysis for all studies suitable for meta-analysis, irrespective of primary cancer location, showed an increased risk for rectal cancer as a second primary in previously irradiated patients (N = 403.243), compared with patients who did not undergo RT (N = 615.530; RR 1.43, 95% CI 1.18–1.72; Fig. 2a). Heterogeneity was substantial (I^2 = 59%). Sensitivity analysis, excluding studies with ≤ 5 events per group [17,21–25], high risk of bias [26], or outlying results [27] did not change the results nor the level of heterogeneity (RR 1.44, 95%CI 1.21–1.72; I^2 = 59%). Subgroup analyses were performed for the different primary cancer sites.

Male patients

Prostate cancer

RT is used as definitive treatment for prostate cancer in approximately 25% of localized prostate cancer patients [28]. Dosages up to 80 Gy are delivered to the prostate, and as a result, the rectum, is exposed to significant dosages of radiation as well [29]. Patients who underwent RT for prostate cancer (N = 232,120) were at increased risk for rectal cancer compared with patients who did not undergo RT as part of their initial treatment (N = 487,703). The incidence of second rectal cancer was 0.48% (N = 1104) in irradiated patients and 0.41% (N = 1983) in non-irradiated patients (RR 1.36, 95% CI 1.10–1.67; Fig. 2b). However, considerable heterogeneity was observed between studies (I^2 = 44%). Sensitivity analyses, the exclusion of studies with ≤ 5 events per group [30], high risk of bias [31], or outlying result [14], did not alter the outcomes.

Some studies reported an increased risk for rectal cancer after prostate irradiation [27,31–34], whereas others found no association [14,17,30,35]. Possible reasons for this discrepancy are a limited sample size or short follow-up, differences in lag time periods and

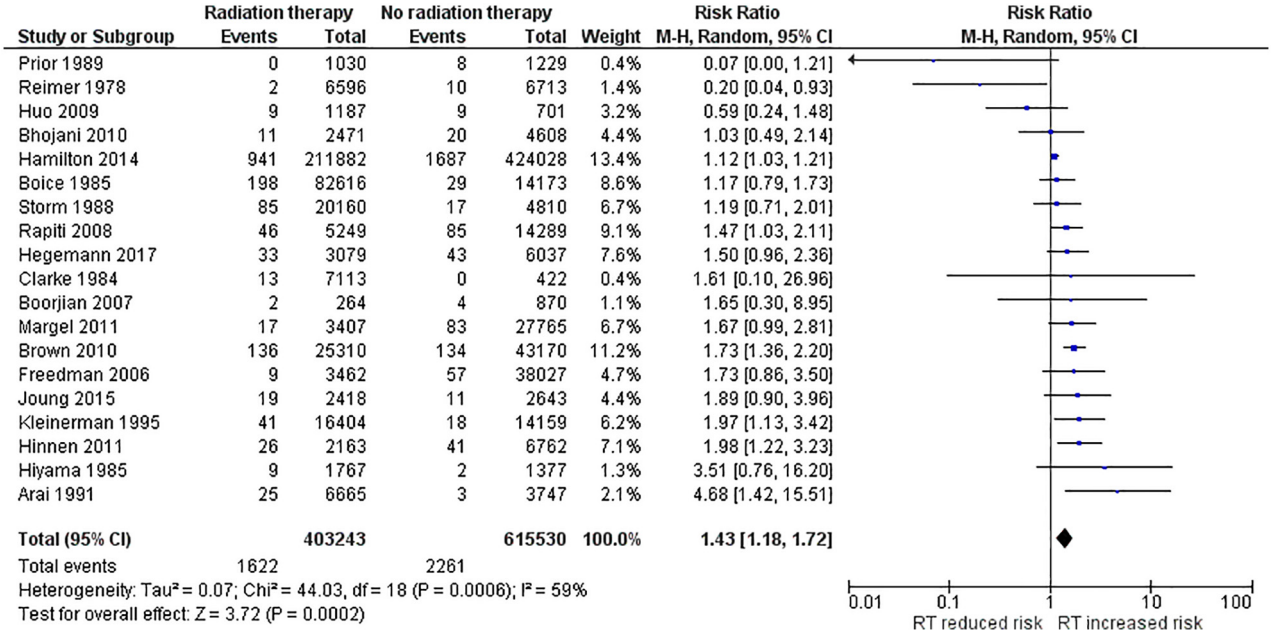

Fig. 2a. Assessment of risk ratio of second primary rectal cancer following irradiation for a pelvic tumour, all primary cancer sites. RT, radiation therapy.

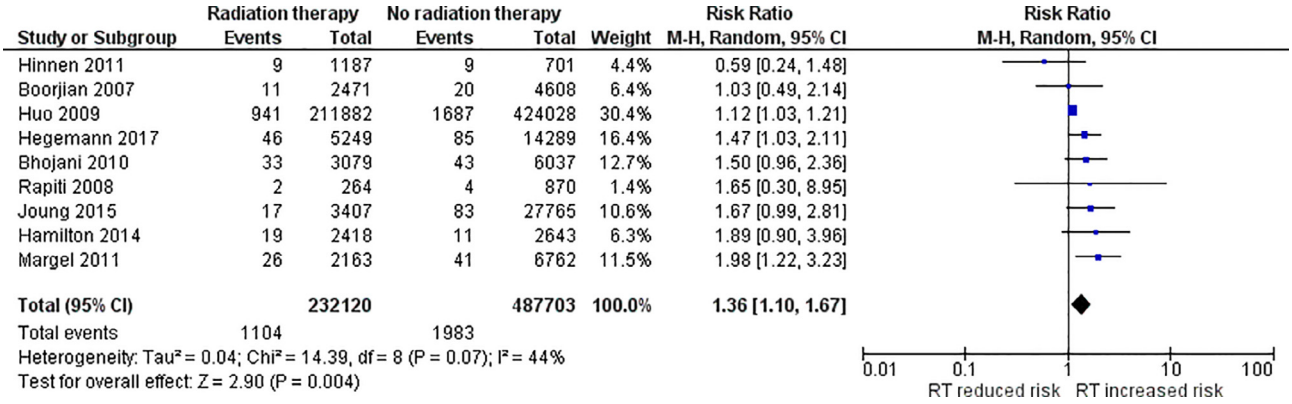

Fig. 2b. Assessment of risk ratio of second primary rectal cancer following irradiation for prostate cancer. RT, radiation therapy.

variation in statistical methods. The latter is illustrated by the fact that Baxter et al. reported an 1.7-fold increased risk of rectal cancer for prostate cancer patients treated with RT compared to those treated surgically [9], while Kendal et al. did not find an increased risk using the same SEER data [36]. Huo et al. expanded the SEER data until 2005 and demonstrated that there was indeed an increased risk for rectal cancer, but only after > 10 years of follow-up [27]. In addition, prostate cancer usually affects men at older age (median 67–71 years in the reviewed studies) which resulted in a limited follow-up time in some of the studies.

Female patients

Cervical cancer

Approximately half of cervical cancer patients receive RT as part of their treatment regimen [37]. A case-control study estimated that the rectum receives 30–60 Gy of irradiation during RT for cervical cancer [38]. Overall 5-year survival is up to 85% for early stage cervical cancer, depending on the stage of disease [39]. Meta-analyses showed an increased incidence of rectal cancer in patients treated with RT (N = 134,725) compared with non-irradiated patients (N = 38,688). The incidence of second rectal cancer was 0.28% (N = 371) in irradiated patients and 0.18% (N = 69) in non-irradiated patients (RR 1.61, 95% CI 1.10–2.35; Fig. 2c). Heterogeneity was moderate (I^2 = 37%). Excluding studies with ≤ 5 events per group [21–23] during sensitivity analysis lowered heterogeneity to 20% and results were no longer statistically significant but showed a trend towards an increase of rectal cancer after previous RT (RR 1.35, 95% CI 0.99–1.83). Studies that could not be included into the meta-analysis also found an increased incidence of rectal cancer in patients that received RT for a primary cervical cancer, compared with the general population [11,16,21,23,40,41].

Ovarian cancer

Less than 10% of primary ovarian cancer patients are treated with RT as a component of the primary treatment [42]. Ovarian cancer is relatively rare and the related mortality is high. Most patients present with a late stage of disease and the 5-year survival rate is only 45–50% [43,44].

The literature search revealed four studies that investigated the risk of rectal cancer after RT for ovarian cancer, of which three were included in the meta-analysis. The meta-analysis showed no statistically significant difference in the incidence of rectal cancer between irradiated (N = 11,088) and non-irradiated patients (N = 45,969). Second rectal cancer occurred in 0.10% (N = 11) of irradiated patients and in 0.16% (N = 75) of non-irradiated patients (RR 0.38; 95%CI 0.05–3.11; Fig. 2d). It should be taken into account that heterogeneity was high between the studies (I^2 = 83%). Excluding studies with ≤ 5 events per group for sensitivity analysis would only leave one study for meta-analysis and this study [26] had a relatively high risk of bias. In the study that was excluded from the meta-analysis, the number of patients included in the study (n = 93) was too small to draw any conclusions [45].

Type of radiation

The technique that is used to administer RT might influence the probability of developing a second rectal cancer. This was suggested in several studies [46–48] and might be related to differences in radiation doses to which the rectum is exposed. Lönn et al. studied organ-specific dose distributions of RT for endometrial cancer and estimated that the average dose received by the rectum was 50 Gy for external beam RT and 35 Gy for brachytherapy [49].

To further investigate this hypothesis, a subgroup analysis was performed, including the studies in which information regarding the type of radiation was given (Supplementary Fig. 2). External beam RT (N = 196,329) was compared with the application of brachytherapy

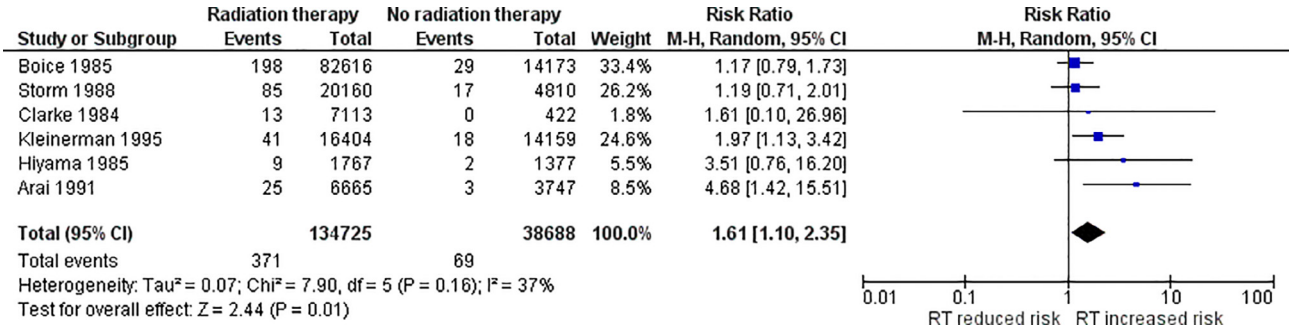

Fig. 2c. Assessment of risk ratio of second primary rectal cancer following irradiation for cervical cancer. RT, radiation therapy.

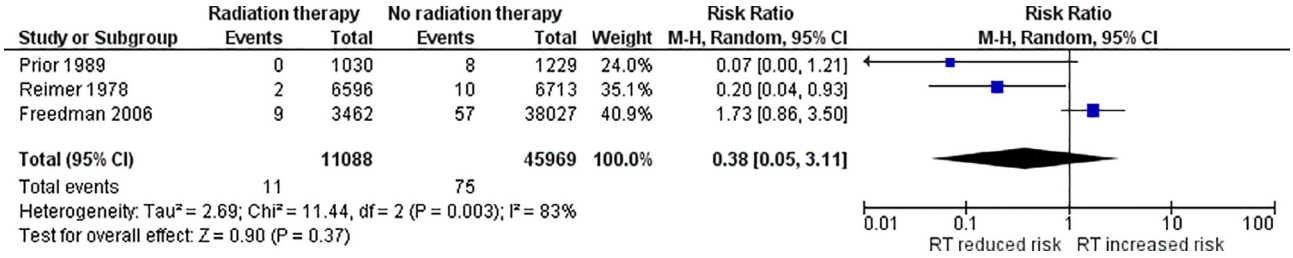

Fig. 2d. Assessment of risk ratio of second primary rectal cancer following irradiation for ovarian cancer. RT, radiation therapy.

(N = 188,828). A relation between the type of RT and the incidence of rectal cancer could not be confirmed. The RR for developing rectal cancer was 1.36 (95% CI 1.19–1.56) in the external beam RT group and 0.98 (95%CI 0.43–2.21) in the brachytherapy group (P = 0.43). Heterogeneity was high (I^2 = 90%) due to inconsistent findings in the brachytherapy group. Results did not change during sensitivity analysis. Unfortunately, information on RT doses was not provided in the majority of the studies and this could therefore not be analysed.

Latency period

Several studies suggested that the incidence of rectal cancer might increase with time [11,21,27,40,50]. A subgroup analysis was performed according to the threshold of follow-up that was used, excluding all rectal cancer events prior to the following time points: 0–2 months (N = 868.907), and 5 (N = 9918), 10 (N = 98,877), or 20 years (N = 28,926; Supplementary Fig. 3). Some studies reported on multiple fixed latency periods and could therefore be entered into the meta-analysis repetitively. There was a significant increase of rectal cancers in time since primary treatment with calculated RRs for developing rectal cancer of 1.31 (95% CI 1.104–1.66), 1.51 (95% CI 0.97–2.33), 1.95 (95% CI 01.51–2.53), and 2.49 (95% CI 1.48–4.19), for 0–2 moths, up to 5 years, up to 10 years and up to 20 years respectively (P = 0.0006). The test for subgroup differences showed a heterogeneity level (I^2) of 61.8%. By performing sensitivity analysis, studies with ≤ 5 events per group were excluded [22,25,30,51], as well as one study with high risk of bias [26]. This did not change the results.

Discussion

Pelvic RT has been associated with a potentially increased risk for secondary tumours. Especially the rectum, which is in close anatomical relation to several pelvic target organs, is likely to be within the field of irradiation and can consequently receive relatively high doses of radiation. The aim of this systematic review and meta-analysis was to study the incidence of a second primary rectal cancer after previous RT for a primary pelvic cancer. A pooled analysis, irrespective of primary cancer location, showed an increased risk for rectal cancer following RT (N = 403.243) compared with non-irradiated patients (N = 615.530) with a RR of 1.43 (95% CI 1.18–1.72). Organ specific meta-analysis showed a statistically significant increased risk for rectal cancer after RT for prostate and cervical cancer. No relation was seen in ovarian cancer patients. A possible explanation for this is that studies on the incidence of rectal cancer following RT for ovarian cancer were scarce due to a low incidence rate of the primary cancer itself, and the low number of patients receiving RT. Also, the irradiation field in ovarian cancer is probably less likely to include the rectum. Finally, only few studies have studied rectal cancer as a second primary tumour specifically; a number of studies had to be excluded since data on second colorectal cancers were not further subdivided into rectal cancer cases. However, in the majority of these studies, colorectal cancer risk following RT was not increased [52–56]. There were no studies that investigated the risk for second primary rectal cancer following treatment for bladder or vaginal cancer.

The results show that the incidence of rectal cancers after pelvic radiation increases with time. The majority of tumours developed after the regular follow-up period. However, given the relatively small increase of rectal cancers due to RT, it does not seem beneficial to introduce a surveillance program for irradiated patients. Although the risk for second rectal cancer is relatively small, it is important for physicians and patients to be aware of this late complication of RT, especially given the fact that it may alter treatment of rectal cancer due to limitations in the possibility of additional use of RT [57,58].

In a previous nationwide study, with a median age of 66 and a median follow-up of 8.1 years (range 0–27) in the irradiated group, we showed that the incidence of second primary pelvic cancers was not increased following RT for a primary rectal cancer [15]. Instead, a protective effect was seen for some of the cancer sites, predominantly for the development of second primary prostate cancer. This has also been observed by other study groups [13,59–61] and contrasts with the current findings in which RT for a primary pelvic cancer results in an increased risk for a second primary rectal cancer. In other words, pelvic radiation seems to result in an increased risk for rectal cancer, but not for other pelvic cancers. There is no clear explanation for this. The bowel is prone to radiation toxicity with late/chronic proctitis occurring in 5–20% of patients [62]. This condition might create a precancerous microenvironment, similar to chronic inflammatory bowel diseases [63] such as Crohn's or ulcerative colitis. Induction of chronic inflammation by RT is less common in other organs. Hypothetically, differences in RT fields or in doses of delivered scatter radiation might also play a role, however, insufficient data are available. Finally, differences in age at onset of the primary cancer might play a role. One could postulate that older patients have less chance to develop second cancers due to a limited life expectancy. Although age was often not subdivided for irradiated and non-irradiated patients in the included studies, the mean age of patients did not seem to differ greatly from the previous nationwide study (Tables 1 and 2).

The quality of the reviewed studies was high, with low risks of bias. This is probably related to the fact that most studies included data from well-known population-based cancer registries, among which were different SEER registries and the Dutch, Danish and Israeli nationwide cancer registries. The current study was limited by the absence of uniformity in defined latency periods (between radiation exposure and diagnosis of rectal cancer) that were used in the reviewed studies. Second malignancies diagnosed within a short time period after diagnosis of the initial cancer are often regarded as independent events (synchronous tumours), also resulting from intensified medical surveillance [33]. Therefore, a fixed latency period is often introduced to reduce the chances of such bias. The latency periods in the reviewed studies varied between 1 month up to 10 years, often without evidence supporting the time thresholds. This may have led to heterogeneity in the results.

Another possible bias arises from the uncertainty whether non-irradiated patients received any kind of pelvic radiation after treatment for the primary cancer. For example, in the study of Curtis et al., 70% of patients had advanced endometrial cancer and some of these patients might have received RT in any subsequent courses of treatment [12]. Mettlin et al. previously studied the completeness of cancer registries

and found that in 6% of prostate cancer patients, subsequent RT was given after the primary treatment, but was not registered [64]. This could have led to an underestimation of the influence of RT in the development of second rectal cancer. In addition, information on other possible predisposing factors, such as lifestyle factors or genetic susceptibility was not available in the reviewed studies. However, this possible bias is expected to affect both groups equally.

Conclusions

This systematic review and meta-analysis demonstrates an increased risk for second primary rectal cancer in patients who received irradiation to the pelvic region. This increased risk was modest and could not be confirmed for all different types of primary pelvic cancer. Further research, using large nationwide cohorts with more detailed information should be performed to specifically study the incidence of rectal cancer after treatment for other primary pelvic cancers. The present study does not provide data to change guidelines for surveillance for rectal cancer in previously irradiated patients.

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Conflict of interest

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2018.05.008.

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