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Original article

Short- and long-term risks of cardiovascular disease following radiotherapy in rectal cancer in four randomized controlled trials and a population-based register

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ABSTRACT

Aim: A population-based cohort and four randomized trials enriched with long-term register data were used to clarify if radiotherapy in combination with rectal cancer surgery is associated with increased risks of cardiovascular disease (CVD).**Methods:** We identified 14,901 rectal cancer patients diagnosed 1995–2009 in Swedish nationwide registers, of whom 9227 were treated with preoperative radiotherapy. Also, we investigated 2675 patients with rectal cancer previously randomized to preoperative radiotherapy or not followed by surgery in trials conducted 1980–1999. Risks of CVD overall and subtypes were estimated based on prospectively recorded hospital visits during relapse-free follow-up using multivariable Cox regression. Maximum follow-up was 18 and 33 years in the register and trials, respectively.**Results:** We found no association between preoperative radiotherapy and overall CVD risk in the register (Incidence Rate Ratio, IRR = 0.99, 95% confidence interval (CI) 0.92–1.06) or in the pooled trials (IRR = 1.07, 95% CI 0.93–1.24). We noted an increased risk of venous thromboembolism among irradiated patients in both cohorts (IRR_{register} = 1.41, 95% CI 1.15–2.72; IRR_{trials} = 1.41, 95% CI 0.97–2.04), that remained during the first 6 months following surgery among patients treated 2006–2009, after the introduction of antithrombotic treatment (IRR_{6 months} = 2.30, 95% CI 1.01–5.21). However, the absolute rate difference of venous thromboembolism attributed to RT was low (10 cases per 1000 patients and year). **Discussion:** Preoperative radiotherapy did not affect rectal cancer patients' risk of CVD overall. Although an excess risk of short-term venous thromboembolism was noted, the small increase in absolute numbers does not call for general changes in routine prophylactic treatment, but might do so for patients already at high risk of venous thromboembolism.

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Survival from rectal cancer has increased during recent years [1–3]. Whereas surgery is the main treatment modality for cure, pre- or postoperative radiotherapy (RT) reduces the risk of local recurrence by at least 50% [4–9]. In Sweden, preoperative RT is recommended to rectal cancer patients at risk of local recurrence including those with intermediate risk tumours, and, together with chemotherapy, to patients with locally advanced cancer who can tolerate this treatment [9].

Concerns of elevated risks of cardiovascular disease (CVD), particularly venous thromboembolism, due to RT in combination

with rectal cancer surgery have been raised in a few randomized controlled trials (RCTs) [10–14], although with mixed results regarding associated CVD type(s) and timing of risk. Pollack et al. reported an increased risk of CVD overall among 139 RT-treated rectal cancer patients at a mean follow-up of 15 years after surgery [12], whereas Birgisson et al. observed an increased risk confined to the first 6 months among 1147 patients [13]. Two other studies showed a higher CVD risk comparing preoperative RT with surgery alone at 60 days in 1399 patients [10] or 6 months after surgery in 557 patients [11], respectively. The radiation techniques and the target volumes used in the abovementioned RCTs varied considerably, but often resulted in large irradiated volumes and were thus more harmful than techniques used in recent years. Also, a limited number of patients were included (<1500) and prophylaxis against venous thromboembolism after surgery was not routinely

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administered. Furthermore, the investigated CVD types differed across studies.

We aimed to clarify the relationship between preoperative RT in rectal cancer and CVD risk among 17,576 Swedish rectal cancer patients recorded in national registers (1995–2009) or included in historic RCTs (conducted between 1980 and 1999) followed up to 33 years.

Materials and methods

The study population consisted of rectal cancer patients recorded in the Swedish Colorectal Cancer Register (SCRCR) and patients in four Swedish RCTs conducted with the primary aim of investigating the influence of RT on local recurrence and survival. Ethical approval was obtained from the regional ethical committee in Uppsala, Sweden.

Data sources

SCRCR

SCRCR was initiated in 1995 and its coverage is >98% nationwide [15,16]. Between 1995 and 2009, 24,271 rectal cancer patients were registered. After excluding patients diagnosed with stage IV or unknown stage ($n = 7554$), not treated with abdominal surgery ($n = 862$), treated with postoperative RT ($n = 219$), with erroneous relapse date ($n = 12$) or aged >85 years at surgery ($n = 723$), 14,901 patients remained. We collected information on pathological TNM stage (I–III); operation types (anterior resection, abdominoperineal resection, Hartmann's procedure); types of (planned) oncological treatment (preoperative RT/preoperative chemotherapy (CT)/preoperative chemoradiotherapy (CRT)/adjuvant CT); relapse status (yes/no), types and dates (local recurrence and/or distant metastasis). The preoperative RT regimen used during the register period was usually identical as in the trials, whereas CRT meant a dose of about 50 gray (Gy) given during 5–6 weeks combined with fluoropyrimidine (i.v. 5-fluorouracil or p.o. capecitabine). A few patients received 50 Gy without CT and very few received oxaliplatin plus capecitabine.

RCTs

Patients with resectable rectal cancer diagnosed 1980–1999 were randomized to short-course preoperative RT (5×5 Gy in one week) followed by surgery, or to surgery alone.

The Stockholm I trial (1980–1987) included 849 patients [17], of whom 752 from the Stockholm region were included in the present study. The Swedish Rectal Cancer Trial (1987–1990) included 1168 patients aged ≤ 80 years [8], of whom 1146 were available. The Stockholm II Trial (1987–1993) enrolled 558 patients aged ≤ 80 years (of whom 316 were included before February 1990 and also enrolled in the Swedish Rectal Cancer Trial [11]). The Dutch multicentre Total Mesorectal Excision (TME) trial (1996–1999) included 219 Swedish patients randomized to short-course preoperative RT plus TME or TME alone [5]. After pooling, 2675 patients were included.

Radiotherapy (RT)

Patients were classified as exposed if they were treated with preoperative RT or CRT (RT⁺), and unexposed if they were treated with surgery alone (RT⁻). The treatment adherence in the RCTs was $\geq 99\%$ [18]. In the SCRCR, the recorded oncological treatment plans represent administered treatment for >95% of the patients [15]. The RT techniques were 3 or 4 beams except in the Stockholm I trial where 2 anterior–posterior beams were used [18].

Cardiovascular disease (CVD)

Data regarding CVD were retrieved from the Swedish National Patient Register (NPR) [19] where hospital discharge information has been recorded since 1987. The primary outcome was main diagnoses of CVD at discharge recorded at any time point between surgery and end of follow-up. Subtypes of CVD assessed included coronary heart disease, arrhythmias and heart failure, stroke, peripheral vascular disease, and venous thromboembolism (including pulmonary embolism and deep vein thrombosis) using International Classification of Diseases (ICD) codes (Supplementary Table 1). Additionally, the NPR records non-primary care outpatient visits since 2001. In a sub-cohort of SCRCR (patients diagnosed 2001–2009), outpatient visits for CVD were added in the outcome assessment.

Covariates

Through the NPR, we assessed CVD history up to 10 years before rectal cancer surgery. For the register patients, we also obtained highest attained level of education ($\leq 9/10$ – $12/12+$ years) and residential region at diagnosis from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) kept by Statistics Sweden [20]. For all patients, emigration dates were extracted from the Total Population Register [21], and death dates from the Cause-of-Death Register [22].

Statistical analyses

Analyses were performed separately in the SCRCR cohort and in the pooled RCTs. Unadjusted event rates per 1000 person-years (py) for time-to-first event, and time-to-multiple events were calculated. Start of follow-up was the date of surgery. End of follow-up was the date of first CVD admission (in time-to-first-event analyses), relapse, death, emigration, or December 31st 2012, whichever happened first.

The main analyses assessed time-to-first CVD comparing incidence rates of overall CVD and subtypes among RT⁺ and RT⁻ patients. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were estimated using Cox regression models. Due to non-proportional hazards, we defined five follow-up periods, 0–<0.5, 0.5–<5, 5–<10, 10–<15 years, and ≥ 15 years (≥ 15 years in RCTs only), and estimated separate IRRs of CVD within each follow-up period.

In the pooled RCTs, the Cox regression models were stratified by specific RCTs to account for trial heterogeneity in baseline CVD risk. Due to imbalance of previous CVD by RT status in one RCT, we adjusted for previous CVD. In the SCRCR analyses, besides adjusting for previous CVD, we further adjusted for sex, age, calendar period of surgery, education level, and residential region.

To compare incidence rates of multiple CVD events during follow-up we used Andersen-Gill regression models [23]. The number needed to harm of venous thromboembolism due to preoperative RT was also calculated [24].

All statistical analyses were performed in SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) and STATA (StataCorp, release 14.1, College Station, TX, USA).

Results

In the SCRCR cohort of 14,901 patients with stage I–III rectal cancer, 9227 patients (62%) were treated with preoperative RT (RT⁺) and 5674 with surgery alone (RT⁻). Among 2675 patients included in the four RCTs, 1309 (49%) were randomized to preoperative RT (RT⁺) and 1366 to surgery alone (RT⁻) (Table 1). Median age at rectal cancer surgery was 70 years in the SCRCR and 69 years

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