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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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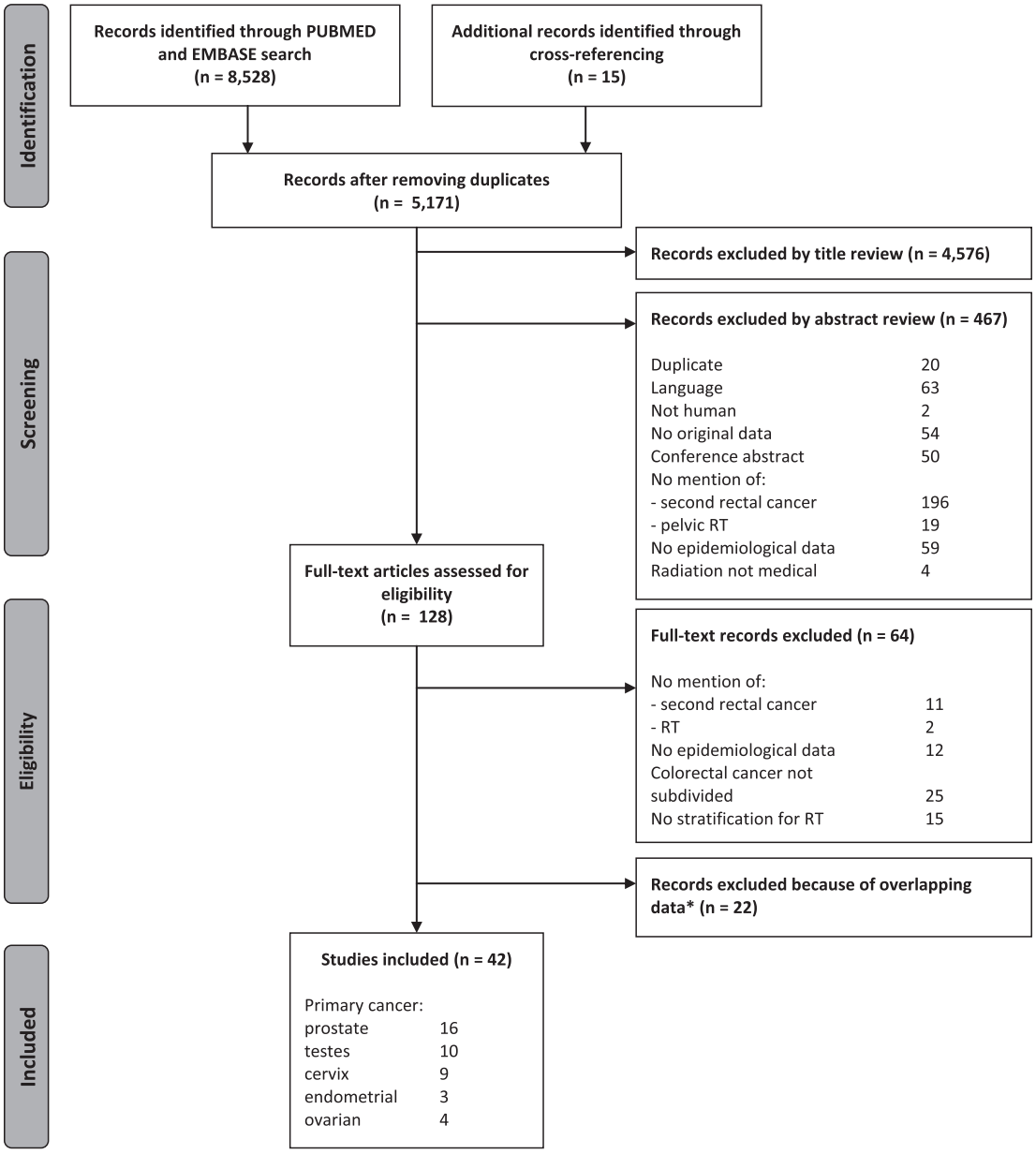

Fig. 1. Flowchart of the search strategy for systematic review. *In case of considerable overlap in data/subjects between studies, the study with the largest population was included in the meta-analysis. A reference list of studies that were excluded due to overlap in data is provided in Supplementary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