Systematic review

Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients

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Abstract

Background and purpose: Radiotherapy for breast cancer both decreases loco-regional recurrence rates and improves overall survival. However, radiotherapy has also been associated with increased second cancer risk at exposed sites. In this meta-analysis, we estimated the risk of second non-breast cancers after radiotherapy for breast cancer. Material and methods: The databases Medline/Pubmed, Cochrane, Embase and Cinahl were systematically searched, for cohort studies on second cancer after radiotherapy for breast cancer, from inception to August 1st 2013. Included studies were to report the relative risk (RR) of second cancers comparing irradiated female breast cancer patients to unirradiated patients. Primary endpoints were all second non-breast-cancers and second cancers of the lung, esophagus, thyroid and second sarcomas. RRs were pooled using random-effects meta-analysis. Results: Thirteen studies comprising 762,468 breast cancer patients were included in the meta-analysis. Five or more years after breast cancer diagnosis radiotherapy was significantly associated with an increased risk of second non-breast cancer RR 1.12 (95% confidence interval [CI] 1.06–1.19), second cancer of the lung RR 1.39 (95% CI 1.28–1.51), esophagus RR 1.53 (95% CI 1.01–2.31) and second sarcomas RR 2.53 (95% CI 1.74–3.70). The risk increased over time, and was highest 15 or more years after breast cancer diagnosis, for second lung RR 1.66 (95% CI 1.36–2.01) and second esophagus cancer RR 2.17 (95% CI 1.11–4.25). There was no significant association between radiotherapy and second thyroid cancer. Conclusions: Radiotherapy for breast cancer is significantly associated with increased risks of second non-breast cancer, overall and in organs adjacent to the previous treatment fields. Despite a relative small absolute risk, the growing number of long-time survivors after breast cancer warrants the need for normal tissue sparing radiotherapy techniques.

Breast cancer continues to be the most prevalent cancer among women in the Western world [1] with a cumulative probability of more than 10% in North America and several Western European countries [2]. In the last twenty years advances in breast cancer treatment, have led to prolonged survival-times and the majority of breast cancer patients are now cured of the disease and are becoming long-time survivors. Adjuvant radiotherapy plays an essential role in modern breast cancer treatment and has been shown to both decrease loco-regional recurrence rates and improve overall survival [3–7]. The changes in surgical procedures of early breast cancer have furthermore lead to an increased number of patients receiving breast conserving surgery, thus the majority of patients today will receive radiotherapy as part of their adjuvant treatment.

During the last decade there has been an increased awareness as to radiation induced second cancers [8], and both large-scale cancer registry based studies [9–12] and smaller single institutional studies [13,14] have shown, that radiotherapy for breast cancer is associated with an increased risk of second cancer. Smaller studies have however due to limited population size and observation time at times resulted in ambiguous results. The 2005 Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview of clinical trials is the only former published study with pooled risk estimates of second cancers after radiotherapy for breast cancer [5]. Therefore, to obtain more knowledge on the risk of second cancers after radiotherapy for breast cancer we conducted the following systematic review and meta-analysis.

Two larger cohort studies [9,10] have previously reported that second cancers after radiotherapy for breast cancer particularly develop in organs adjacent to the previous treatment fields i.e. the organs that receive the highest dose of radiation exposure. The objective of the current analysis was therefore, to examine the risk of second cancers of the lung, esophagus, and soft tissues
together with the total risk estimate of all second non-breast cancers, comparing female breast cancer patients treated with radiotherapy to those not treated with radiotherapy. Second thyroid cancer was also included as an outcome, due to its potential close location to the former treatment fields. The risk of second cancer by time since breast cancer diagnosis was additionally examined.

Materials and methods

Study eligibility

The following study was conducted applying the PRISMA [15] guidelines for a systematic review and meta-analysis. Only cohort studies examining the risk of second non-breast cancers, comparing primary early breast cancer patients treated with radiotherapy with those patients not allocated to radiotherapy were eligible for inclusion. This analysis was restricted to the following predefined second cancer sites: lung, esophagus, thyroid, and soft tissues and the combined group of all second non-breast cancers. The included studies had to report the relative risk (RR) or equivalents together with the corresponding 95% confidence interval (CI). Only original published data were considered i.e. no overviews or reviews. The following type of studies were excluded: studies on patients treated with protons or light ions, studies based on cancer mortality data, studies on patients exposed during childhood, and studies where the number of patients treated with radiotherapy was determined by approximation.

Search strategy and selection criteria

The Medline/Pubmed, Cochrane and Cinahl databases were systematically searched for eligible studies, from inception to August 1st 2013, using the following Medical Subject Headings (MeSH) ‘breast neoplasm’ and ‘radiotherapy’. The terms were combined with ‘neoplasm’, ‘second primary’, ‘radiation-induced’ and ‘comparative study’ using the Boolean operator ‘and’. The search strategy included no language restriction. The reference lists of the included studies were additionally carefully reviewed in the search for additional studies.

Definition of outcomes

The primary endpoints were all second non-breast cancers, second cancers of the lung, esophagus, thyroid, and second sarcomas. The primary metrics were the pooled RRs of second cancer comparing breast cancer patients treated with radiotherapy to those who were not. To evaluate the risk over time the RRs were pooled, both in a total risk estimate, and for the time intervals \( \geq 5 \), \( \geq 10 \) and \( \geq 15 \) years following breast cancer diagnosis. The interval from primary breast cancer diagnosis to the beginning of the observation time varied between zero and five years throughout the different studies. Therefore, in the meta-analysis we defined a ‘total pooled RR’ estimate to only included studies where the observation-time was counted from \( \leq 2 \) years after breast cancer diagnosis and onward. We did this, as we judged these RRs to be sufficiently similar for pooling of data. All other risk estimates were pooled according to the appropriate second cancer latency periods: \( \geq 5 \), \( \geq 10 \) and \( \geq 15 \) years following breast cancer diagnosis, respectively. This was done regardless of the total observation time in the studies.

Data extraction and statistical analysis

The RRs with the corresponding 95% CI were extracted directly from each included study. For studies reporting both unadjusted and adjusted risk estimates the most adjusted estimate was included. Risk ratios were pooled using the DerSimonian and Laird random-effects model to obtain RRs with associated 95% CI [16]. Each study was weighted by the inverse of its variance. The standard errors (SE) were derived from the reported 95% CI, by applying the equation \( SE = \ln (upper\ limit\ of\ 95\%\ CI/lower\ limit\ of\ 95\%\ CI)/(1.96 \times 2) \). In the event of studies reporting zero observations of second cancers the study was omitted from the final analyses, as no risk estimate was reported. \( I^2 \) statistics were used to quantify heterogeneity between study results, where \( I^2 \) is the percentage of total variation across studies due to heterogeneity rather than chance. Statistically significant heterogeneity was defined as \( I^2 \) statistic greater than 50%. All analyses were carried out using STATA IC 11.2. (Statistical Software, TX, USA). The pooled risk estimates according to time after breast cancer diagnoses (\( \geq 5 \), \( \geq 10 \), and \( \geq 15 \) years) were, if possible, extracted directly from the included studies. However, if not originally presented, we derived them from the risk estimates 1–4, 5–9, 10–14, and \( \geq 15 \) years after breast cancer diagnosis, if presented in the studies. These risk estimates were pooled, as described above. The pooled risk estimates and the corresponding forest plots for the 5-year increments: 1–4, 5–9, 10–14 years following breast cancer diagnosis for second lung, esophagus and thyroid cancer are presented in the appendix as appendix Supplementary Figs. 1–3. The risk according to type of breast cancer surgery was additionally estimated.

Results

Description of the studies

The systematic search indentified 812 potentially relevant references (Fig. 1). Of these, 99 studies qualified for full text review of which 80 did not meet the eligibility criteria of this study. A second careful examination of the remaining 19 potential candidates led to the exclusion of further six studies: One study as only the standardized incidence rate ratios were reported [17] and further five studies due to overlapping cohorts: two on second lung cancer [18,19] one on second lung and thyroid cancer [20], and two on second sarcomas [21,22]. The descriptive characteristics of the five excluded studies are listed in the appendix Supplementary Table 1.

A total of 13 original studies were included in the final analysis [9–14,23,24,25–29], nine population based cohort studies, three single institution cohort studies and one regional prospective study. Of the 13 included studies, several reported risk estimates according to various second cancer sites [9–14,23] occasionally leading to the fact that studies despite the primary exclusion of overlapping cohorts would refer to the same population and, or had overlapping cohorts. In such case, the largest study was included in the meta-analysis.

All of the included studies happened to be based on European or North American populations of female breast cancer patients treated in the period between 1954 and 2007. The cumulative sample size including all 13 studies was 1,644,488 women. After eliminating overlapping cohorts the analysis included a total of 762,468 breast cancer patients, of which 321,143 (42%) received radiotherapy whereas 441,325 (58%) did not. The age at primary breast cancer diagnosis was: mean 59 years, based on 5 studies and median 57 years, based on 2 studies. 6 studies reported no exact age at breast cancer diagnosis [10–12,23,24,26]. The reported mean and median follow-up time was 8 years based on 11 studies. Two studies provided no follow-up time [11,23]. The descriptive characteristics of the included studies are listed in Table 1. The reported RRs with corresponding 95% CI of second cancers used in the meta-analysis according to cancer site along with the number of included patients and observed second cancers are listed in the appendix Supplementary Table 2.
All second non-breast cancers

Seven studies [9,10,12,14,23,26,29] reported the endpoint of all second non-breast cancers. These studies included a total of 299,883 patients, of which 44% received radiotherapy for breast cancer whereas 56% did not. The treatment years ranged between 1954 and 2007. In the total pooled RR estimate, radiotherapy was significantly associated with an increased risk of second non-breast cancers with a RR of 1.22 (95% CI 1.06–1.41), based on five studies [9,12,14,23,26] including 5465 incidences of second cancers (Fig. 2). The risk remained significantly elevated ≥5 years after breast cancer diagnosis with a RR of 1.12 (95% CI 1.06–1.19), but non-significantly ≥10 years after breast cancer diagnosis RR 1.20 (95% CI 0.88–1.64). These estimates were based on 10,517 (not reported in one study[29]) and 790 second cancers, respectively. The total pooled RR estimate showed significant heterogeneity between study results, $I^2 = 66\%$.

Risk of second cancer by organ site

Second lung cancer

Seven studies [9–13,23,27] reported risk estimates on second lung cancer. They included a total of 631,021 patients, of which 40% received radiotherapy, whereas 60% did not. The treatment years ranged between 1961 and 2007. The total pooled RR estimate yielded a significant association between radiotherapy and second lung cancer with a RR of 1.23 (95% CI 1.07–1.43), based on six studies [9,11–13,23,27] and 4016 incidences of second lung cancer (Fig. 3). The risk of second lung cancer increased gradually by time following breast cancer diagnosis with pooled estimates of 1.39 (95% CI 1.28–1.51), 1.59 (95% CI 1.39–1.81), and 1.66 (95% CI 1.36–2.01) for the latency periods ≥5, ≥10 and ≥15 years after breast cancer diagnosis, respectively. These risk estimates were based on 2899, 1128, and 512 second lung cancers, respectively.

Second esophageal cancer

Four studies [9,11,12,28] reported the endpoint second esophageal cancer (Fig. 4). The studies included a total of 413,650 patients, of which 39% were treated with radiotherapy, whereas 61% was not. The treatment years ranged between 1961 and 2007. The risk of second esophageal cancer was non-significantly increased in the total pooled RR estimate, with a RR of 1.17 (95% CI 0.89–1.54). Five or more years following breast cancer diagnosis, radiotherapy however became significantly associated with second esophageal cancer and furthermore increased by each 5 year increment in time. Thus 5, 10 and 15 or more years after breast cancer diagnosis the RRs were 1.53 (95% CI 1.01–2.31), based on 255 second cancers, 1.56 (95% CI 1.03–2.38) based on 147 second cancers and 2.17 (95% CI 1.11–4.25) based on 46 second cancers, respectively.

Second thyroid cancer

For the endpoint second thyroid cancer four studies [9,11,13,24] were included, comprising a total of 322,461 breast cancer patients (Fig. 5). Patients were treated in the years between 1961 and 2007 and radiotherapy was given to 37% of the patients, whereas 63% received no radiotherapy. There was no significant association between radiotherapy and second thyroid cancer neither in the

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**Fig. 1.** Consort diagram of the study selection. SIR: Standardized incidence ratio. If the studies referred to the same population or in the case of overlapping cohorts the largest study and/or with the most relevant information was included in the meta-analysis.
Table 1
Clinical and baseline characteristics for the 13 studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author, year &amp; country</th>
<th>Treatment years</th>
<th>Data source</th>
<th>Number of patients</th>
<th>Mean/median age at BC years (range)</th>
<th>Mean/median Follow-up (years) &amp; Inclusion from (years)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roychoudhuri (2004) [11]</td>
<td>UK 1961–2000</td>
<td>The Thamsen Cancer Registry</td>
<td>64,782</td>
<td>NR (up to 85)</td>
<td>NR Inclusion from BC diagnosis. RRs used in meta-analysis based on estimates from 1 y after BC diagnosis</td>
<td>Women treated with adjuvant CTX were excluded in the study Mastectomy &amp; BCS No information on surgery or radiation dose</td>
</tr>
<tr>
<td>Zhang (2011) [29]</td>
<td>Italy 1965–1994</td>
<td>Hospital Records from 1984 including the Tuscany Cancer Registry</td>
<td>5,248</td>
<td>Mean 55</td>
<td>Mean 8 Inclusion from 2 y after BC diagnosis</td>
<td>Mastectomy &amp; BCS No information on dose Mastectomy &amp; BCS No information on dose Mastectomy &amp; BCS</td>
</tr>
</tbody>
</table>

Abbreviations: BC: Breast cancer; DBCG: Danish Breast Cancer Cooperative Group; NR: Not reported; SEER: Surveillance, Epidemiology, and End Results Program, BCS: Breast conserving surgery; RT: Radiotherapy; DCIS: Ductal carcinoma in situ; CTX: Chemotherapy; CCCN: Comprehensive Cancer Centers North-Netherlands, CCS: Cancer Center South; y: years; mo: months.
Second cancer after radiotherapy for breast cancer: a systematic review and meta-analysis

Fig. 2. Second non-breast cancer: Random effects meta-analysis of the relative risk (RR) of second non-breast cancer according to follow-up since primary breast cancer diagnosis among radiotherapy treated breast cancer patients compared to those not treated with radiotherapy. Pooled relative risks for second non-breast cancer after first breast cancer, comparing patients treated with radiotherapy to those not treated with radiotherapy. The RR is reported as a total pooled RR estimate and according to time since breast cancer diagnosis. Solid squares represent the RR for each study with corresponding 95% confidence intervals. The Diamonds represents the pooled estimate. Each study is weighted (%) by the inverse of its variance. In the two studies by Berrington de Gonzalez et al. [10] and Grantzau et al. [9] risk estimates were solely based on second non-breast cancers, in the study by Zhang et al. [29] non-melanoma skin cancers but not second leukemia were included as an outcome and in the study by Schaapveld et al. [12] meningiomas were not included as an outcome.

Second sarcomas

Four studies [9,12,13,25] on second sarcomas were included in the analysis for the total pooled RR estimate. The studies comprised a total of 684,104 patients treated between 1973 and 2007 (Fig. 6). Radiotherapy was given to 41% of the patients whereas 59% received no radiotherapy. In the total pooled RR estimate, the association between radiotherapy and second sarcomas was significantly and more than two fold increased with a RR of 2.41 (95% CI 1.41–4.13), based on 1048 incidence cases. The risk remained significantly elevated ≥5 years after breast cancer diagnosis with a RR of 2.53 (95% CI 1.74–3.70) based on 124 incidences of second sarcomas. The reported risk estimates were based on all second sarcomas that were observed in the cohorts, regardless of the anatomical location of these second cancers. Two studies, based on data from the SEER database, also estimated the risk specifically for angiosarcomas with reported RRs of 7.63 (95% CI 4.9–11.9) [25] among +1-year survivors and 13.7 (95% CI 4.0–95.6) [10] among +5-year survivors of breast cancer (see Appendix Supplementary Table 2).

Second cancer risk by breast cancer surgery type

In the study by Berrington de Gonzalez et al. [10], the risk according to breast cancer surgery type, was estimated for the combined group of second cancers potentially receiving the highest radiation dose, i.e. the lung, esophagus, pleura, bone, and soft tissues. We also estimated the risk according to surgery type in the Danish cohort study [9] by applying the same combined group of second cancers as Berrington de Gonzalez et al. [10]. For patients diagnosed with one of these second cancers five or more years after breast cancer diagnosis the pooled RRs including both studies [9,10] were significantly increased both after a mastectomy RR 1.64 (95% CI 1.42–1.89) and after a lumpectomy RR 1.29 (95% CI 1.16–1.43). See appendix Supplementary Fig. 4.

Discussion

In this meta-analysis of female early breast cancer patients, radiotherapy was significantly associated with and increased risk of second non-breast cancers. The strength of this study is its large size, including more than 700,000 patients. The study was furthermore conducted following the PRISMA [15] guidelines of systematic reviews and meta-analysis providing a reliable and comprehensive assessment of second cancer risk after radiotherapy for early breast cancer. For patients with a latency time of at least five years, from breast cancer diagnosis to second cancer diagnosis, radiotherapy was significantly associated with an increased risk of second non-breast cancers overall and specifically
for second cancers of the lung, esophagus, and second sarcomas. For these second cancers the risk increased gradually by each five year increment in time since breast cancer diagnosis. There was no significant association between radiotherapy and second thyroid cancer.

The 2005 EBCTCG overview of randomized trials is currently the only other study reporting pooled estimates on second cancer risk after radiotherapy for early breast cancer [5]. This overview was based on trials that began in the mid 1970s and included a total of 31,800 female breast cancer patients and 1351 second cancers. The annual risk ratios comparing irradiated women with unirradiated women were significantly increased for second lung cancer (2.06, p = 0.05). There was no excess risk of second thyroid cancer reported in the EBCTCG overview analysis due to some degree of overlap between patients of the overall and the included cohorts of this study and furthermore as estimates in the EBCTCG were reported as annual risk ratios.

We found no significant association between radiotherapy for breast cancer and second thyroid cancer, neither in the total estimate, nor over time since breast cancer diagnosis. Increased risks of second thyroid cancer have predominantly been reported in adult breast cancer patients, it is too low to be detectable in a cohort of over 300,000 women.

In the two studies by Zablotska et al. [27,28], included in the current analysis, the risk of second lung and esophagus cancer was reported separately for patients treated with either post-mastectomy or post-lumpectomy radiotherapy. The studies were based on data from the SEER database and covered the treatment years 1973–1998/2000. In both studies only radiotherapy after mastectomy was significantly associated with increased risks. Notably though, as breast conserving surgery first became common during...
on individual patient data, potential methodological limitations and the study by Grantzau et al. that there is evidence of second cancers of the lung, esophagus, pleura, bone, and soft tissues. Though, if of significance this would probably primarily affect the total pooled risk estimates and would diminish over time following breast cancer diagnosis. Solid squares represent the pooled estimate. Each

The risk estimates were given for the combined group of second cancers of the lung, esophagus, pleura, bone, and soft tissues and the comparison group included all unirradiated patients regardless of the type of breast cancer surgery. Using this combined group of second cancers, we further showed in the pooled estimates, including the study by Berrington de Gonzalez et al. and the study by Grantzau et al. [9], that there is evidence of a significantly increased risk after both post-lumpectomy and post-mastectomy radiotherapy. It therefore appears that radiotherapy to the conserved breast, like radiotherapy after mastectomy, carries a risk of second cancer induction.

As this meta-analysis was based on summary results and not on individual patient data, potential methodological limitations in our analysis are primarily inherited from the design of the included studies, such as, duration of observation-time and study populations. Studies were further not standardized as to radiation treatment techniques or systemic adjuvant treatment. However, all included studies came from European and North American institutions, thus the included cohorts were fairly compatible according to applied diagnostic criteria’s, adjuvant treatments and western lifestyle and therefore judged sufficiently similar to allow pooling of data. Information on smoking status, alcohol consumption, BMI, genetic factors, and other potential confounders that could affect second cancer risks was not available in any of the studies. It is well known that smoking is the leading cause of lung cancer and in the combination with heavy alcohol consumption the primary cause of squamous-cell carcinoma of the esophagus [34]. Increased risks of esophagus cancer have also been linked to obesity [35]. However, it is typically not possible to adjust for these confounders in large cohort studies. Not all second tumors in the studies were histopathologically confirmed and it is possible that some of these cancers were misclassified metastatic breast cancers. Though, if of significance this would probably primarily affect the total pooled risk estimates and would diminish over time following breast cancer diagnosis.

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**Fig. 4. Second esophagus cancer: Random effects meta-analysis of the relative risk (RR) of second esophageal cancer according to follow-up since primary breast cancer diagnosis among radiotherapy treated breast cancer patients compared to those not treated with radiotherapy.** Pooled relative risks for second esophagus cancer after first breast cancer, comparing patients treated with radiotherapy to those not treated with radiotherapy. The RR is reported as a total pooled RR estimate and according to time since breast cancer diagnosis. The RRs and weights were calculated using random-effects models.

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<table>
<thead>
<tr>
<th>Author, Country &amp; Year</th>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Relative Risk [95% CI]</th>
<th>RR ES [95% CI]</th>
<th>Weight %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>33,763 / 156,517</td>
<td>1.23 [0.75, 2.01]</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Zablotska LB et al. USA, 2005</td>
<td>BCS</td>
<td>46,120 / 153,322</td>
<td>0.93 [0.46, 1.87]</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Schapaeveld M et al. Netherlands, 2008 &lt; 50 y</td>
<td>Tot. 14,678</td>
<td>0.64 [0.16, 2.48]</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schapaeveld M et al. Netherlands, 2008 &gt; 50 y</td>
<td>Tot. 43,390</td>
<td>0.85 [0.49, 1.48]</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grantzau T et al. Denmark, 2013</td>
<td>Mast</td>
<td>22,549 / 23,627</td>
<td>1.17 [0.56, 2.44]</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td><strong>1.17 [0.89, 1.54]</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Latency ≥ 5 years      |          |                    |                        |                |
| Roychoudhuri R et al. UK, 2004 | NR       | 1.19 [0.60, 2.35]   | 26             |
| Zablotska LB et al. USA, 2005 | Mast     | 2.21 [1.42, 3.45]   | 42             |
| Zablotska LB et al. USA, 2005 | BCS      | 0.91 [0.37, 2.25]   | 17             |
| Grantzau T et al. Denmark, 2013 | Mast   | 1.46 [0.57, 3.76]   | 16             |
| **Subtotal**           |          |                    | **1.53 [1.01, 2.31]** | **100**        |

| Latency ≥ 10 years     |          |                    |                        |                |
| Roychoudhuri R et al. UK, 2004 | NR       | 1.48 [0.62, 3.53]   | 23             |
| Zablotska LB et al. USA, 2005 | Mast     | 1.81 [1.03, 3.19]   | 55             |
| Zablotska LB et al. USA, 2005 | BCS      | 0.64 [0.17, 2.39]   | 10             |
| Grantzau T et al. Denmark, 2013 | Mast   | 1.89 [0.57, 6.30]   | 12             |
| **Subtotal**           |          |                    | **1.56 [1.03, 2.38]** | **100**        |

| Latency ≥ 15 years     |          |                    |                        |                |
| Roychoudhuri R et al. UK, 2004 | NR       | 1.925 / 4,625      | 87             |
| Grantzau T et al. Denmark, 2013 | Mast   | 2.19 [1.07, 4.49]   | 87             |
| **Subtotal**           |          |                    | **2.17 [1.11, 4.25]** | **100**        |

*Percentages may not add up to 100 due to rounding.

Fig. 4. Second esophagus cancer: Random effects meta-analysis of the relative risk (RR) of second esophageal cancer according to follow-up since primary breast cancer diagnosis among radiotherapy treated breast cancer patients compared to those not treated with radiotherapy. Pooled relative risks for second esophagus cancer after first breast cancer, comparing patients treated with radiotherapy to those not treated with radiotherapy. The RR is reported as a total pooled RR estimate and according to time since breast cancer diagnosis. Solid squares represent the pooled estimate. Each study is weighted (%) by the inverse of its variance. Abbreviations: RT: Radiotherapy; ES: Estimate; Mast: Mastectomy; BCS: Breast Conserving Surgery; y: years; Tot: Total; NR: Not reported. Data on second esophagus cancer by time since treatment in the study by Grantzau et al. [9] are previously unpublished.
The level of heterogeneity for each analysis was often either low or moderate. As the overall study period covered more than 50 years and included patients from several countries, some differences between studies in regard to radiotherapy techniques will inevitably exist, and would explain some of the observed inter-study heterogeneity. Substantial heterogeneity was however only observed in the total pooled RR estimate of all second non-breast cancers. This was most likely due to, that not all studies reported the outcome for all second non-breast cancer uniformly (see Fig. 2, footnote). It should also be noted, that only few studies reported data on second cancers developing ten or more years after breast cancer diagnosis, hence the pooled risk estimates were only based on two to three studies. However, with increasing time since breast cancer diagnosis the risk estimates became remarkably similar. The dose–response relation for second solid cancer induction after radiotherapy for breast cancer is currently only examined in few epidemiological studies. We have recently shown, that second lung cancer after radiotherapy for breast cancer is associated with the delivered dose to the lung [36]. The rate of lung cancer increased linearly with 8.5% per delivered Gray to the lung (95% CI 3.1% to 23.3%) among female ≥5 year survivors. In a similar study, on second esophageal cancer, Morton et al. [37] showed, that the excess odds ratio of second esophageal cancer also increased linearly with 9% per delivered Gray to the tumor location (95% CI 4% to 16%) among ≥5 year survivors of female breast cancer. Together, these epidemiological data indicate, that any dose reduction to the surrounding normal tissue would result in a beneficial risk reduction of second cancers in organs adjacent to the radiation fields. During the last 50 years breast cancer treatment has changed considerably. This includes changes in surgical procedures, more extensive use of systemic treatment, and changes in radiotherapy techniques including the change from two dimensional (2D) treatment planning to the currently used CT-guided techniques. Mastectomy has, since the mid 90’s, largely been replaced by breast conserving surgery resulting in an increasing number of patients receiving adjuvant radiotherapy. Whereas orthovoltage X-ray and Co\(^{60}\) have now been abandoned, in favor of photon and electron beams, the total breast dose has remained relatively constant. Over the last ten years though, an increasing number of new radiation therapy techniques, such as intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and intraoperative radiotherapy (IORT) have rapidly entered clinical practice. Due to insufficient follow-up time, no cohort studies have yet estimated the risk of second cancer using these more novel treatment tech-
and IORT remains an experimental approach in early breast cancer time of only five years these conclusions are however premature of getting a radiation induced second cancer 10–15 years after consequently improved overall survival by far outweigh the risk between radiotherapy and second thyroid cancer. Adjuvant radiotherapy (IORT), is another technique that recently has been released [41,42]. Both studies found a significantly higher The 5-year results of the IORT trials ELOIT and TARGIT-A have just been released [41,42]. The TARGIT-A investigators however, argued that IORT local recurrence rate after IORT compared with whole breast irradiation [42]. With a median follow-up reduced both cardiovascular and second cancer mortality com-
parison with conventional whole breast irradiation IORT reduces the treatment time, the irradiation field and the maximal doses to the surrounding normal tissues [40]. The 5-year results of the IORT trials ELOIT and TARGIT-A have just been released [41,42]. Both studies found a significantly higher local recurrence rate after IORT compared with whole breast irradiation. The TARGIT-A investigators however, argued that IORT reduced both cardiovascular and second cancer mortality compared to whole breast irradiation [42]. With a median follow-up time of only five years these conclusions are however premature and IORT remains an experimental approach in early breast cancer treatment. In conclusion, radiotherapy for breast cancer is associated with a small but significantly increased risk of second cancers of the lung, esophagus, and soft tissues. There was significant association between radiotherapy and second thyroid cancer. Adjuvant radiotherapy continues to be an essential part of breast cancer treatment and the benefits in regard to local tumor control and consequently improved overall survival by far outweigh the risk of getting a radiation induced second cancer 10–15 years after treatment. Thus, the emerging challenge in breast cancer treat-
ment is to optimize current and evolving radiotherapy techniques by reducing the normal tissue dose without compromising the target, and to improve the identification of patients that are most, or least, likely to benefit from adjuvant radiotherapy.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.10.004.

Reference


