Radiotherapy and Oncology 131 (2019) 150–159

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

Volume effects of radiotherapy on the risk of second primary cancers: A systematic review of clinical and epidemiological studies

Neige Journy [a,*], Imène Mansouri [a], Rodrigue S. Allodji [a], Charlotte Demoor-Goldschmidt [a,b], Debiche Ghazi [a], Nadia Haddy [a], Carole Rubino [a], Cristina Veres [a], Wael Salem Zrafi [a], Sofia Rivera [c,d,e], Ibrahima Diallo [a], Florent De Vathaire [a]

[a] INSERM U1018, Paris-Sud XI University, Paris-Saclay University, Centre for Research in Epidemiology and Population Health (CESP), "Cancer & Radiations" Group, Gustave Roussy Cancer Campus, Villejuif; [b] Department of Pediatric Onco-hematology, CHU Angers, Angers; [c] Department of Radiation Oncology, Gustave Roussy Cancer Campus; [d] INSERM 1030 Molecular Radiotherapy, Villejuif; and [e] Paris-Saclay University, Paris-Sud Medical School, Le Kremlin-Bicêtre, France

ARTICLE INFO

Article history:
Received 28 May 2018
Received in revised form 19 September 2018
Accepted 24 September 2018
Available online 10 October 2018

Keywords:
Radiotherapy
Neoplasms, radiation-induced
Radiation dosage
Dose–response relationship, radiation
Review

ABSTRACT

As modern radiotherapy, including intensity-modulated techniques, is associated with high dose gradients to normal tissues and large low-to-moderate dose volumes, the assessment of second primary cancer (SPC) risks requires quantification of dose–volume effects. We conducted a systematic review of clinical and epidemiological studies investigating the effect of the irradiated volume or dose–volume distribution to the remaining volume at risk (RVR) on SPC incidence. We identified eighteen studies comparing SPC risks according to the irradiated volume (i.e., in most studies, the size or number of fields used), and four studies reporting risk estimates according to the dose distribution to the RVR (after whole-body dose reconstruction). An increased risk of SPCs (mainly breast and lung cancers) with extended radiotherapy was observed among patients treated for Hodgkin lymphoma or childhood cancers. However, normal tissue dose distribution was not estimated, limiting the interpretation of those results in terms of volume effects on organs at risk. Studies considering whole-body exposures quantified dose–response relationships for point dose estimates, without accounting for dose–volume distributions. Therefore, they disregarded possible tissue effects (e.g. bystander and abscopal effects, stem cell repopulation) which may play a role in the induction of SPCs. Currently, there is no clinical or epidemiological information about a possible role of high dose gradients in surrounding organs, or increasing volumes of distant tissues exposed to low doses, in the risk of SPCs. Opportunities for future research nevertheless now exist, since methods and tools for estimating individual whole-body dose–volume distributions in large patient populations have been developed.

Second primary cancers (SPCs) occur in 3–40% of cancer survivors within 10 to more than 40 years after diagnosis of the first cancer [1–7], in part as late effects of treatments. Cancer survivors initially treated with radiotherapy (RT) at age ≥18 years have long-term risks of SPC incidence (all sites combined) 1.1–3 times higher than the general population [8], and the estimated risks relative to the general population are 5–10 after childhood cancers [8,9].

Modern RT techniques, including intensity modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT) and particle therapy, can deliver highly conformal dose distributions allowing dose escalation and dose homogeneity improvement to the target volume while reducing doses to normal tissues within the irradiated volume (i.e. the volume receiving ≥20% of the prescribed dose). However, with IMRT and SBRT, it is at the expense of a larger volume of distant tissues receiving low-to-moderate doses (<1 Gy) compared to 3D-RT, with whole-body dose distributions varying according to the technique used [10,11]. The late effects, particularly SPCs (which mainly occur 10 to >25 years after RT), subsequent to large low-to-moderate dose volumes with modern RT techniques remain poorly quantified due to short follow-up times [12–14].

While awaiting for accumulating epidemiological data on modern techniques with a sufficient follow-up time, simulation studies have compared predictions of long-term SPC incidence between treatment techniques. They used dose–response estimates derived from epidemiological studies on past RT techniques and other sources of radiation exposures, and mechanistic models [15–19]. Most of them suggested that increasing low-to-moderate dose volumes with IMRT may be associated with higher risks of SPC com-

* Corresponding author at: INSERM U1018, Centre for Research in Epidemiology and Population Health (CESP), "Cancer & Radiations" Group, Gustave Roussy Cancer Campus, 39 rue Camille Desmoulins, 94800 Villejuif, France.
E-mail address: neige.journy@gustaveroussy.fr (N. Journy).

https://doi.org/10.1016/j.radonc.2018.09.017
0167-8140/

pared to 3D-RT, despite a dose reduction to surrounding tissues [15–19]. The dose–response models used for these simulations were derived from studies considering mean organ doses after homogeneous exposures to low linear energy transfer radiation (e.g. among Hiroshima and Nagasaki a-bombing survivors), or dose estimates at the SPC location (or, less frequently, mean organ doses) after radiotherapy. The risk of SPC at a given organ/tissue was then simulated as the sum of "local" risks at different point estimates of dose, generally using the concept of organ equivalent dose [20,21]. This approach thus did not consider systemic ("volume") effects of radiation on tissues (e.g. bystander and abscopal effects, and stem cell repopulation) [22–25] and the potential biological effects of different dose gradients within organs. At the present time, it remains uncertain to which extent those risk predictions, which are inherently based on simplified modeling of the biological mechanisms underlying SPC development, correlate to clinical outcomes in patients receiving modern RT.

We hypothesized that evidence of the existence, or not, of volume effects on SPC risks may be available among the numerous published studies on patients treated with past RT techniques who have now been followed for decades, and conducted a systematic review of clinical and epidemiological studies. This review reports estimated risks of SPC incidence according to the irradiated volume (i.e. treatment and organ-at-risk volumes that are delineated for treatment planning [26]), or as a function of dose–volume distribution to the remaining volume at risk (RVR – not delineated organs/tissues for treatment planning [26]).

Material & methods

Search strategy and study selection. Studies were identified through a systematic search in the PubMed/MEDLINE database (the search terms are listed in Appendix). The reference lists of eligible articles were also reviewed to identify studies which we might have missed by searching terms in the titles and abstracts. We included articles published in English up to 31 August 2017 which reported results of randomized controlled trials (RCTs) or observational (cohort or case-control) studies. We excluded stud-

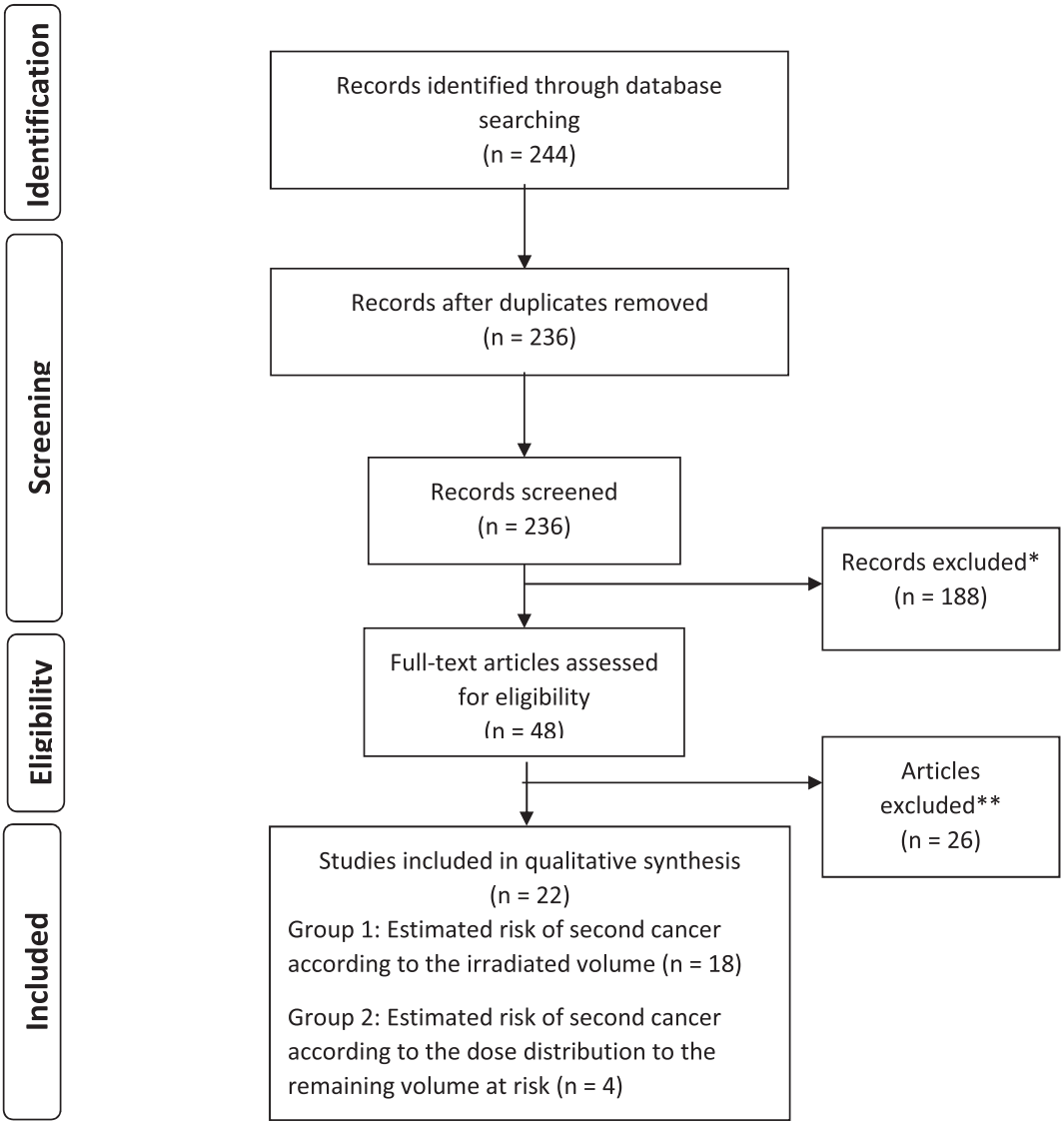

Fig. 1. PRISMA Flow Diagram.
Reasons for exclusion: *did not match inclusion criteria (i.e. clinical and epidemiological studies investigating the effect of the irradiated volume or dose–volume distribution to the remaining volume at risk in the risk of second primary cancers, $n = 188$), **no full-text available ($n = 4$), no information about the irradiated volume or dose distribution to the remaining volume at risk ($n = 4$), total number of second cancers < 10 ($n = 13$), study population included in a meta-analysis/another publication with extended follow-up ($n = 4$), cancer mortality analysis only ($n = 1$).

Table 1a
Study settings, population, treatment characteristics and methods of follow-up and statistical analyses of the 22 included studies.

Refs.	Study settings	Study design	1st Cancer	2nd Cancer	N (# SPC) or Case/ Contr.	Years of treatment	Median age at 1st diagnosis (range)	Radiotherapy modalities (for initial treatment)	Median follow-up (range)	Case ascertainment	Statistical methods
(a) Eighteen studies estimating risks of SPC according to the irradiated volume											
[31]	GELA-EORTC H8 trial (91 centers)†	RCT	Hodgkin L. (stage I–II)	all SPCs	1538 (55)	1993–1999	30–33 (15–70)	H8-F, Arm 1: 36- to 40-Gy STNI (mantle + spleen and para-aortic nodes), Arm 2: IFRT; H8-U, Arm 1: 36- to 40-Gy IFRT; Arm 2: 36- to 44-Gy IFRT; H8-U, Arm 3: 36- to 44-Gy STNI	8 (0–12)	Hospital	Kaplan–Meier, log-rank test
[30]	UK, BLNI-sponsored trial§	RCT	Hodgkin L. (stage I–II)	all SPCs	603 (87)	1970–1979	30* (15–78)	Stage IA-IIA, Arm 1: 40-Gy IFRT; Arm 2: 35- to 40-Gy EFRT (mantle); Stage IB-IIB, Arm 1: 35- to 40-Gy IFRT (mantle or inverted-Y); Arm 2: 35- to 40-Gy EFRT (mantle plus inverted-Y)	25 (N/R-32)	Hospital, national cancer registry	Kaplan–Meier, log-rank test
[29]	Cochrane systematic review (10 studies)†	Meta-analysis (RCTs)	Hodgkin L. (stage I–IV)	all SPCs	3221 (201)	1966–1998	N/R	Arm1: extended field, Arm 2: involved-field	<10	Hospital, cancer registries†	Peto's OR and cumulative incidence
[34]	USA, Minnesota Hospital (1 center)	cohort	Hodgkin L. (stage I–III)	all SPCs (excl. in situ and basal cell carcinomas)	210 (33)	1970–1986	N/R	Cobalt-60 or 4–10 MV photons; Stage I and II: 40- to 45-Gy with mantle + peri-aortic field or TNI wi/wo 12–20 Gy lung irradiation; Stage III: 40- to 45-Gy mantle + inverted-Y field wi/wo 20–35 Gy splenic irradiation wi/wo 12–20 Gy lung wi/wo 18–20 Gy liver irradiation.	16 (0–27)	Hospital-based tumor registry	SIR, annual excess rate
[40]	Netherlands, population-based cancer registries and centers	cohort	Hodgkin L. (stage I–IV)	all SPCs (excl. NMSC)	3905 (908)	1965–2000	29 (15–50)	Cobalt-60/orthovoltage therapy or photons linear accelerators, 2D treatment planning, 36- to 44-Gy mantle, modified-mantle wi/wo supraclavicular/neck, involved-field wi/wo individual blocks	19 (5–47)	Hospital, GPs, national cancer registry	Cox's regression model
[36]	USA, Harvard (5 centers)	cohort	Hodgkin L. (stage I–IV)	all SPCs	961 (161)	1969–1997	25 (N/R)	36- to 40-Gy total nodal, mantle + paraaortic, mantle alone or pelvic + paraaortic fields wi/wo individualized blocks	12 (10- N/R)	Hospital, referring physicians, patient/family's interview	SIR, Chi-square test
[38]	USA, Yale-New Haven (1 center)	cohort	Hodgkin L. (stage I–IV)	all SPCs	404 (42)	1970–2004	N/R	20- to 25-Gy involved-field with CT vs. 36- to 43-Gy extended field with no CT	17 (3–40)	Hospital-based tumor registry	SIR
[32]	Italy, Florence University (1 center)	cohort	Hodgkin L. (stage I–IV)	all SPCs (excl. NMSC and myelodysplasia)	1121 (73)	1960–1988	35 (N/R)	No RT/involved-field or mantle/lumbar bar/ inverted-Y or subtotal nodal/total nodal	>9 (N/R)	Hospital	Cox's regression model
[39]	UK, national program of breast cancer counseling	cohort	Hodgkin L. (stage I–IV)	breast (incl. in situ)	5002 (373)	1956–2003	N/R (N/R-35)	Mantle, modified mantle or other fields wi/wo pelvic irradiation	x (N/R-53)	Hospital, national cancer center network, cancer registries, self-reported questionnaires, radiologist reports (parallel screening study)	SIR, p-trend
[33]	USA, SUNY (1 center)	cohort	Hodgkin L. (stage I–IV)	breast (incl. in situ)	136 (11)	1962–1988	31 (N/R)	Cobalt-60 or 4–6 MeV photons; 25- to 40.25 Gy mantle/modified mantle, total nodal or supradiaphragmatic wi/wo periaortic field wi/wo splenic irradiation.	15 (N/R-26)	Hospital	Log-rank test, multiple linear regression model
[37]	Italy, Florence University (1 center)	cohort	Hodgkin L. (stage I–IV)	breast	725 (39)	1960–2003	30 (10–85)	36–40 Gy supradiaphragmatic wi/wo infradiaphragmatic complementary extended field or 30-Gy supradiaphragmatic involved field or infradiaphragmatic field alone	16 (0.5–48)	Hospital	Kaplan–Meier, log-rank test, Cox's regression model

Table 1a (*continued*)

Refs.	Study settings	Study design	1st Cancer	2nd Cancer	N (# SPC) or Case/ Contr.	Years of treatment	Median age at 1st diagnosis (range)	Radiotherapy modalities (for initial treatment)	Median follow-up (range)	Case ascertainment	Statistical methods
(a) Eighteen studies estimating risks of SPC according to the irradiated volume											
[35]	UK, BCHD cohort§	nested case-control	Hodgkin L. (stage I–IV)	lung	88/176	1963–1993	>=40 years in 78% of cases	35 to 40 Gy involved field (0–10% of total lung volume in the field) or mantle (>10% of total lung volume in the field)	>=10 years in 31% of cases#	Hospital, regional cancer registries	Logistic regression model
[41]	USA, Yale New Haven (1 center)	cohort	Breast (stage I–II)	all SPCs	1029 (117)	1970–1990	N/R	4–6 MeV photons/13 MeV electrons, 46- to 54-Gy tangential field (local) or 46- to 54-Gy tangential field + 46-Gy regional nodal irradiation (locoregional) + 10- to 18-Gy electron boost	15 (9- N/R)	Hospital-based tumor registry	life-table, Mantel-Haenszel test
[43]	Canada, British Columbia (4 centers)	cohort	Breast (stage I–II)	all SPCs (excl. NMSC)	12,836 (1119)	1989–2005	N/R (20–79)	Cobalt-60 or 4–10-MV photon 3D-CRT, 50- to 50.4-Gy breast/chest wall field (local) or 42.5-Gy supraclavicular fossa wi./wo. axilla field wi./wo. 40-Gy regional nodal irradiation (locoregional) + 10- to 18-Gy boost	8 (3–20)	Regional cancer registry	Fine and Gray's regression model‡
[42]	Italy, Florence University (1 center)	cohort	Breast (stage I–IV)	all SPCs	5-year survivors: 3080 (167)ǂ	1965–1994	55* (N/R)	No RT/cobalt-60/6 MV photons/12-MeV electrons, up to 60 Gy with breast field alone or internal mammary chain, supraclavicular nodes, axillary lymph nodes and/or chest wall fields	8* (5ǂ-30)	Hospital, regional cancer registry	Cox's regression model
[7]	USA/Canada, CCSS (26 centers)	cohort	Childhood (stage I–IV)§	Breast (incl. in situ)	1230 (203)	1970–1986	13 (0–20)	Chest RT: mantle (median dose, 40 Gy, range, 5–54), mediastinal (incl. IFRT, median dose, 30; range, 3–54), whole lung (median dose, 14; range, 2–20), other one-sided anterior (median dose, 41; range, 10–61), posterior chest (median dose, 31; range, 6–54), abdominal (median dose, 20; range, 4–40), total body (median dose, 12; range, 4–16) wi/wo pelvic irradiation	26 (8–41)	Self/proxy-report, national death registry	Poisson regression model
[44]	USA, St Jude Hospital	nested case-control	Childhood (stage I–IV)	Colon and rectum	19/148	1960–2009	10 (0–20)	Median local received dose = 29 (in cases), 33 (in controls), range: 10–50 Gy	25 (5–39)	Clinic visits, Hospital-based tumor registry, national death registry	Logistic regression model
[45]	USA, Fox Chase Cancer Center (1 center)	cohort	Prostate (stage I–III)	all SPCs	543 (31)	1973–1993	70 (N/R)	2D conventional or 3D conformal; 10 –18 MV photons; 70–72 Gy to the prostate only or the whole pelvis	4 (0–21)	Hospital	Kaplan–Meier, log-rank test

BCHD: British collaborative Hodgkin's disease cohort, which includes patients from the British National Lymphoma Investigation (BNLI) cohort, the Royal Marsden Hospital and St Bartholomew's Hospital.
BLNI: British National Lymphoma Investigation; CCSS: Childhood Cancer Survivor Study; EFRT: extended field radiotherapy; EORTC: European Organisation for Research and Treatment of Cancer.
GHSG: German Hodgkin's Lymphoma Study Group; GP: general practitioner; IFRT: involved field radiotherapy; N/R: not reported; NHSCR: National Health Service central register; NMSC: non-melanoma skin cancer.
RCT: randomized controlled trial; RT: radiotherapy; SPC: second primary cancer; STNI: subtotal nodal irradiation; SUNY: State University of New York Health Science Center.
*mean age/time; †the follow-up methods differed in each individual trial; ‡relapse and death as competing risks; additional analyses were performed on leukemia risks (8 cases) among 4716 2-year survivors; §tumors of the central nervous system, leukemia, Hodgkin or non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue or bone sarcoma, others #Interval time between first cancer diagnosis and the date of SPC diagnosis (among cases).

Table 1b
Fours studies estimating risks of SPC according to dose-distributions to the remaining volume at risk.

Refs.	Study settings	Study design	1st Cancer	2nd Cancer	N (# SPC) or Case/Contr.	Years of treatment	Median age at 1st diagnosis (range)	Radiotherapy modalities (for initial treatment)	Median follow-up (range)	Case ascertainment	Statistical methods
(b) Eighteen studies estimating risks of SPC according to the irradiated volume											
[46]	IRSCCP	nested case-control	Cervical (stage I–IV)	Leukemia	133/500	1920->1965	52* (x-x)	No RT/orthovoltage, cobalt-60, linear accelerator, Betatron	≥5 yrs. in 70% of cases#	N/R	Logistic regression model
[47]	France, SFOP	case-control	Childhood (stage I–IV)	Leukemia, myelodysplasia, myeloproliferative syndrome	61/196	1980–1997	8 (0–<18)	No RT/orthovoltage, cobalt-60, linear accelerator (photon and electrons), Betatron, brachytherapy	3 (1–13) #	National radiotherapy center network, regional cancer registries	Logistic regression model
[49]	France-UK, Euro2K	cohort	Childhood (stage I–IV)	Bone sarcoma	4171 (39)	1942–1985	4 (0–20)	No RT/orthovoltage, cobalt-60, linear accelerator (photon and electrons), Betatron, brachytherapy	27 (5–62)	Hospital, GPs, self-reported questionnaire, national death registry	Cox's regression model
[48]	France-UK, Euro2K	case-control	Childhood (stage I–IV)	Leukemia	35/140	1964–2000	6 (0–<17)	No RT/orthovoltage, cobalt-60, linear accelerator (photon and electrons), Betatron, brachytherapy	6 (2–36) #	Hospital, GPs, self-reported questionnaire, national death registry	Logistic regression model; Proportional marginal means model

*Mean age/time; N/R: not reported; SPC: second primary cancer; RT: radiotherapy #Interval time between first cancer diagnosis and the date of SPC diagnosis (among cases).

ies with less than 10 SPC cases, which did not report information on the irradiated volume or dose–volume distribution to the RVR, or which did not collect information on observed SPC cases (i.e. simulation studies or studies on SPC mortality only). No exclusion was made on the earliest publication date, first/second cancer site, treatment period and place, patient characteristics, RT technique, other treatment modalities, or methods of patient follow-up. The results of the identification and selection process are displayed in a flow diagram (Fig. 1), as proposed in the PRISMA statement [27].

Data extraction and study quality assessment. Information on study settings and design, population characteristics, treatments modalities, patient follow-up and statistical analysis were extracted from the primary article, using a predefined data extraction form (Tables 1a, 1b). When necessary, companion or previous reports were also reviewed to retrieve more information on treatments and methods for patient selection and follow-up. The methodological quality and potential biases of the included studies were assessed using a pre-defined list of items that we considered to be the most important for a reliable assessment of dose–volume effects on the risk of SPCs (Table 2). This approach mainly addresses the United Nations Scientific Committee on the Effects of Atomic Radiation's recommendations for reviews of epidemiological studies of radiation exposures [28]. Data extraction and study quality assessment were performed independently by two reviewers (NJ, IM), who then cross-checked their reports to validate the reported information and reach a consensus on quality assessment.

Data synthesis. We summarized the methodological strengths, limitations and main results of the included studies in Table 3 (and Table S1), and reported detailed results from the original articles in Table S2. We only considered methods and results related to dose–volume effects on SPC risks, even though some of the reviewed studies were primarily designed for other purposes.

Results

Selected studies

Among 235 non-duplicated articles screened, 47 eligible articles were fully reviewed against our inclusion criteria. After exclusions, 22 studies (publication date: 1991–2015) were included (Fig. 1). Eighteen studies compared the incidence of SPCs according to the irradiated volume (i.e., in most studies, the size or number of fields used) for treatment of Hodgkin lymphoma ($n = 12$), breast ($n = 3$), childhood ($n = 2$) or prostate ($n = 1$) cancer (Table 1a). Four studies reported risk estimates according to the dose distribution to the RVR for treatment of cervical ($n = 1$) or childhood ($n = 3$) cancer (Table 1b). The number of patients included in each study ranged from 124 to 12,836, and the number of SPCs from 11 to 1,119 after widely variable follow-up times (Tables 1a, 1b). Treatments mainly involved photon non-conformal or 3D RT (cobalt-60, 4- to 10-MV photon linear accelerator).

Risk of SPCs according to the irradiated volume

Hodgkin lymphoma

Several RCTs were conducted between 1966 and 1999 to evaluate survival and toxicity rates associated with involved-field (IF) versus extended field (EF) RT into adjacent clinically uninvolved areas (i.e. inverted-Y or mantle field with, possibly, additional irradiation of the spleen and para-aortic, abdominal and/or pelvic lymph nodes) (Table 1a). Prescribed doses were highly standardized, usually ranging from 35 to 45 Gy. A meta-analysis combined individual data of 3221 stage I–IV patients included in 10 RCTs [29]. With a median follow-up time <10 years, no significant difference in the risk of all SPCs was observed between IFRT and EFRT

Table 2
Reviewing check list to assess quality and potential biases in the included studies.

item#	Description and rating
1	Large number of cases, especially by cancer site[†] *Poor*: <10 cases by cancer site & treatment group (all groups) *Medium*: ≥10 cases by cancer site & treatment group (all groups) *High*: ≥30 cases by cancer site & treatment group (all groups)
2	Adequate data collection, estimation and reporting of irradiated volumes *Poor*: individual radiotherapy fields or irradiated volumes not adequately assessed and reported *Medium*: individual radiotherapy fields adequately assessed and reported *High*: individual volumes to organ(s) at risk adequately assessed and reported
3	Adequate data collection, estimation and reporting of radiation doses *Poor*: no dose reported, or inadequately assessed *Medium*: highly standardized doses to the treated volume or, if doses not highly standardized, individual dose variability to the treated volume adequately estimated and reported *High-*: individual doses to organ(s) at risk adequately assessed, estimated and reported (dose reconstruction based on medical records – no imaging) *High+*: individual doses to organ(s) at risk adequately assessed, estimated and reported (dose estimation based on patient's imaging)
4	Adequate duration of follow-up to estimate risks of second primary cancers *Poor*: <10 years *Medium*: ≥10 years *High*: ≥20 years
5	High-quality follow-up: high overall rate of completeness and non-differential method by treatment group (in randomized controlled trials or cohort studies) or between cases and controls (in case-control studies) *Poor*: differential follow-up and completeness rate <90% *Medium*: non-differential follow-up and completeness rate <90%, or completeness rate ≥90% *High*: non-differential follow-up and completeness rate ≥90% (typically, population-based cancer and death registries with a nationwide coverage)
6	Randomization, stratification or adjustment for confounding factors *Poor*: no randomization, stratification or adjustment for important confounding factors (e.g. age, time since radiotherapy, chemotherapy as primary treatment, smoking history in studies on lung cancer, etc.) *Medium*: randomization, stratification or adjustment for important confounding factors, but some potential confounding factors are not considered (e.g. treatments at relapse, lifestyle factors other than smoking history in studies on lung cancer) *High*: randomization, stratification or adjustment for important or potentially important confounding factors
7	Adequate statistical methods and analyses stratified by cancer site or in-/out-field sites of second primary cancers *Poor*: comparison to incidence rates in the general population or no proper comparison between treatment groups *Medium-*: multivariate regression models (or other more appropriate methods to specific study designs[‡]) with no stratification on second cancer site *Medium*: multivariate regression models (or other more appropriate methods to specific study designs[‡]) with stratification on second cancer site *Medium+*: accounting for competing risks (e.g. death) *High*: multivariate regression models assessing the effect of irradiated volume with adjustment for radiation dose, assessing the joint effect of dose and volume or assessing the effect of dose–volume distribution

[†] These quality criteria are arbitrary and should be ideally based on statistical power (which is however missing in all included articles) [‡]For instance, Peto's method for meta-analyses.

(Table 3, Table S1). After 15 years or more since treatment, there was a trend toward a higher SPC (all sites combined) incidence with EFRT (25-year cumulative incidence after early stage disease: 34%) than with IFRT (25-year cumulative incidence after early stage disease: 22%), among the few patients who were followed for such a long time. The meta-analysis also showed a significantly 3-fold increased risk of breast cancer after EFRT compared to IFRT. Other trials, which were not included in Franklin et al's meta-analysis [29] (because individual patient data were not available or the results have been published more recently), did not report increased risks of all SPCs with EFRT [30,31], even after a median follow-up of 25 years [30] (Table 1a). These RCTs nevertheless involved small numbers of SPCs (Table 1a) [30,31] (Table 3).

Beside RCTs, nine observational studies compared SPC risks in patients treated between 1960 and 2003 according to the extent of EFRT (total or subtotal nodal irradiation vs. mantle or modified mantle field), or between EFRT and IFRT (which has progressively replaced EFRT in routine practice since the 1990s for early-stage patients) [32–40] (Table 1a). Most of those studies had a mean/median follow-up time >10 years [32–34,36–38,40]. Five studies reported lower risks of all SPCs [32,36], all solid cancers [32,38,40], breast cancer [39,40] and non-Hodgkin lymphoma [40] with reduced RT fields (Table 3). The risk of all SPCs was reduced by 45–65% with mantle fields versus total nodal irradiation [32,36,38], and the risk of breast cancer by 50–60% with modified mantle fields compared to full mantle RT (Table S2) [39,40]. The estimated 25-year cumulative incidence of all solid SPCs decreased from 16% with total nodal irradiation to 9% with mantle RT [38]. No significant effect of reducing the RT fields was reported on the risk of leukemia or myelodysplasia [32,36,38,40], but most studies involved few cases (11–23 for all treatment groups in each study) [32,36,38]. Out of these five studies reporting a positive association between the extent of RT fields and SPC risks, three studies accounted for chemotherapy [32,36,40] and one for smoking status [40]. The latter one also benefited from a high-quality follow-up of 40 years after treatment [40]. However, none accounted for prescribed or delivered radiation doses which may vary among individuals and across time periods [32,36,38–40].

Three studies found no significant association between the risk of SPC and irradiated volume [33,35,37], but they included few cases [33,37], and had a possibly incomplete and differential follow-up between treatment groups [33,37] and no adjustment for possible confounders [33] (Table 1a, Table 3). The risk of second lung cancer was nevertheless non-significantly increased by 20% after EFRT compared to IFRT (results remaining consistent after adjustment for smoking when the information was available) [35] (Table S2). One study reported an incidence rate of all SPCs in patients treated with one field twice as high as in patients treated with two fields, which was probably due to a longer follow-up of high-risk patients treated in the earliest years with less extended RT [34].

Breast cancer

Three cohort studies compared the risk of non-breast and contralateral breast SPCs in women with breast cancer treated between 1965 and 2005 with local RT (breast or chest wall tangential fields)

Table 3
Review summary of study quality, potential biases and main findings of 22 studies investigating volume effects of radiotherapy on the risk of second primary cancer.

Study [ref.]	Sample size	Volume assessment	Dose assessment	Follow-up time	Case ascertainment	Confounding factors	Statistical methods	Main findings about volume effects/dose–volume distribution & risk of second primary cancer
GELA-EORTC H8 [31]	Low	Medium	Medium	Low	Medium‡	Medium	Low	No association with the irradiated volume
BLNI [30]	Medium	Low	Medium	High	Medium‡	Medium	Medium	No association with the irradiated volume
Cochrane [29]	Low	Medium	Low	Low	Medium	Medium	Medium+	No association with the irradiated volume
Minnesota [34]	Low	Low	Medium	Medium	Medium	Low	Low	Increasing risk with reduced irradiated volume
Netherlands [40]	Medium	Medium	Low	High	High	Medium	Medium	Decreasing risk with reduced irradiated volume
Harvard [36]	Medium‡	Medium	Medium	Medium	Not rated‡	Medium-	Low	Decreasing risk with reduced irradiated volume
Yale (Hodgkin_1) [38]	Low	Medium	Medium	Medium	Not rated‡	Medium	Low	Decreasing risk with reduced irradiated volume
Florence (Hodgkin_1) [32]	Low‡	Medium	Low	Medium‡	Not rated‡	Medium-	Medium-	Decreasing risk with reduced irradiated volume
UK_breast_counseling [39]	High	Medium	Low	Medium‡	High	Medium	Low	Decreasing risk with reduced irradiated volume
SUNY [33]	Low	Medium	Medium	Medium	Not rated‡	Medium-	Low	No association with the irradiated volume
Florence (Breast_2) [37]	Low	Medium	Medium	Medium	Not rated‡	Low	Low	No association with the irradiated volume
BCHD [35]	Medium‡	Medium	Medium	Not rated‡	High	Medium	Medium	No association with the irradiated volume
Yale (Breast_1) [41]	Low	Low	Low	Medium	Low	Low	Low	No association with the irradiated volume
British Columbia [43]	High	Medium	Medium	Low	High‡	Medium-	Medium+	No association with the irradiated volume
Florence (Breast_1) [42]	Low	Medium	Low	Low	Medium‡	Medium-	Medium	Ambiguous results
CCSS [7]	High	Medium	Medium	High	Not rated‡	Medium‡	High	Decreasing risk with reduced irradiated volume
StJude [44]	Not rated‡	High	High-	High	Not rated‡	Low‡	Medium	Decreasing risk with reduced irradiated volume
Fox Chase [45]	Low	Medium	Low	Low	Medium	Low	Low	No association with the irradiated volume
IRSCCP [48]	High‡	None	High-‡	Not rated‡	Not rated‡	Low‡	Medium	Risk depends on dose–volume distribution
SFOP [49]	Low	None	High-‡	Not rated‡	Not rated‡	High	Medium	No association with dose–volume distribution
Euro2K_ Bone [51]	Low	None	High-‡	High	Not rated‡	High	Medium	No association with dose–volume distribution
Euro2K_ Leukemia [50]	Low	None	High-‡	Not rated‡	Not rated‡	High‡	Medium	No association with dose–volume distribution
No. with medium/high rate	*8*	*15*	*15*	*13*	*10*	*16*	*13*	

‡ Rating is tentative due to missing/partial information in the original article. Some articles are not rated for quality items because we found insufficient information in the original articles. NB: The study quality criteria and potential biases assessed only concerns dose–volume analyses on the risk of second primary cancer after radiotherapy, which may not be the main objective of the original publications. The reviewed studies may have been designed for other purposes.

vs. loco-regional RT (including nodal areas), after radical or conservative surgery and in combination or not with adjuvant treatments [41–43] (Table 1a). Two studies found no difference between local and loco-regional RT on the risk of SPCs [41,43], at in-field or out-of-field organs [43] (Table 3, Table S2). A non-significantly higher 15-year cumulative incidence rate for all SPCs (19% vs. 15%) was observed with regional RT including internal mammary lymph nodes as compared to tangential fields only [41]. This study possibly had, however, an incomplete follow-up through a single-hospital database and lacked information on potential confounders including age at treatment. The other study had many methodological strengths (a large sample size, unbiased follow-up through the regional cancer registry, detailed information on treatments and potential confounders), but probably had a too short follow-up time (median: 8 years) to evaluate risks of SPC [43] (Table 3). With a similar follow-up time (mean: 8 years), a third study suggested a 3-fold increased risk of all SPCs with loco-regional RT as compared to local RT, mainly driven by contralateral breast cancers, after adjustment for major potential confounders (Table 3, Table S2) [42]. Among women with loco-regional RT, there was a significant trend toward a reduced risk with the use of a higher number of fields for nodal irradiation, but the lack of detailed information on the irradiation fields and adjustment for prescribed/delivered doses limited the interpretation of these results.

Childhood cancers

Moskowitz et al compared incidence rates of breast cancer according to the irradiated chest volume among 1230 children and adolescents, with a median follow-up time of 26 years [7] (Table 1a). The analyses were adjusted for the maximal delivered dose (in addition to age and calendar year) to account for the variability of clinical indications and treatment modalities (Table 3, Table S2). The study showed a significantly 2-fold increased risk of breast cancer among girls treated with mantle fields (cumulative incidence by age 45 years: 21%) as compared to girls treated with mediastinal fields (cumulative incidence by age 45 years: 9%) who received similar doses to the target volume. Breast cancer risk was even higher after whole lung irradiation (cumulative incidence by age 45 years: 30%) which was typically associated with lower doses than mediastinal RT (Table S2). The number of cases was nevertheless relatively low in some treatment groups (20, 17 and 156 cases after, respectively, mediastinal, whole lung and mantle RT fields). Other limitations were a lack of data about blockings used with mantle/mediastinal fields that may reduce doses delivered to the breasts, a possibly substantial rate of loss to follow-up through self-reported questionnaires (though no details are provided in the original article) and a relatively young age at study exit (median: 37 years). With a median follow-up time of 25 years, Nottage et al also reported an increased risk of second colorectal cancer among children who were irradiated

to a larger volume of the colon, but the analyses were based on only 19 cases and not adjusted for radiation doses [44].

Prostate cancer

Movsas et al compared the risk of all SPCs according to treatment modalities for prostate cancer in a small-sized, single-institution cohort study with a median age at treatment of 70 years [45] (Table 1a). They found no difference in the risk of all SPCs after RT to the prostate +/− seminal vesicles compared to local RT plus irradiation of lower pelvic lymph nodes (Table 3, Table S2). The follow-up time (median: 4 years) was nevertheless too short to evaluate the risk of SPCs and only results of univariate analyses were reported.

Risk of SPCs according to dose distribution in the remaining volume at risk

Four studies estimated risks of leukemia [46–48] or bone sarcoma [49] associated with whole-body radiation exposures to active bone marrow [46–48] or bones [49] resulting from the primary beam and scattered radiations for treatment of cervical [46] or childhood [47–49] cancers (Table 1b). Individual whole-body dose distributions were defined as mean or local dose estimates to several compartments of the skeleton, which were retrospectively reconstructed by medical physicists using the patients' radiotherapy records, mathematical human phantoms and treatment planning systems to simulate treatment conditions. The approach differs from estimating isodoses in that dose compartments were defined based on anatomical substructures, rather than volumes that received a given dose level. SPC risks were estimated by tissue compartment (each one being considered to receive a relatively homogenous dose distribution), and then averaged at individual level in two studies while accounting for age-dependencies of the whole-body distribution of bone marrow [46,47].

In a study involving 133 cases of leukemia and 500 controls after RT for cervical cancer, Blettner et al reported a significant non-linear dose–response relationship compatible with a cell killing effect at high doses (Table 1b) [46]. This study showed that ignoring the whole-body dose distribution (but considering whole-body mean doses) would have yielded to an erroneous conclusion of lack of departure from linearity in the dose–response relationship. Studies after childhood cancers did not reject linearity, but they involved smaller numbers of cases (Table 1b) [47–49].

Discussion

Current evidence of dose–volume effects on SPC risks

Among patients treated for Hodgkin lymphoma within RCTs, the risk of SPCs appeared to be increased after extended vs. involved-field RT after 15 years or more after treatment, for organs located within or close to the irradiated volume (breast, lung) [29]. However, the short follow-up times in most studies prevented providing firm results. This conclusion was re-affirmed in an updated meta-analysis on RCTs for Hodgkin lymphoma management that was published after the end of data collection for the present review [50]. A follow-up of >40 years after treatment of Hodgkin lymphoma was achieved in several large observational studies that accounted for major risk factors [35,39,40]. In these studies, the risk of SPCs was increased with larger RT fields, mainly due to increased risks of breast [39,40] and lung [35,40] cancers, and non-Hodgkin lymphoma [40]. Increased incidence risk of breast and colorectal cancers with larger irradiated volumes was also reported after radiotherapy for childhood cancers [7,44]. No evidence of an association between the irradiated volume and risks of SPC at organs located within the RVR was reported, based on few cases [40]. Thus, most of the increased risks were seen at organs located close to the clinical target volume, which were, by definition, exposed to higher doses when larger fields were used. Dose–volume distributions in normal tissues were nevertheless not estimated in those studies. As a consequence, they did not allow to disentangle dose and volume effects, and investigate whether the risk of SPCs increased (or decreased) when a larger amount of normal tissues was exposed at given dose levels.

Other observational studies reconstructed whole-body exposures and estimated dose-distributions in normal tissues within and outside the irradiated volume [46–48,51]. Unlike many other studies that only considered local doses at the SPC site (or matched site for controls) [52], they considered the dose distribution within entire organs/tissues. In one study, this approach demonstrated the non-linearity of the dose–response relationship for risk of second leukemia [46]. In other situations where the dose–response relationship is linear, the sum of risks at each tissue/organ compartment would equal the risk associated with the averaged dose to the tissue/organ. The method of "compartmental dose-risk" analysis was thus useful to investigate the shape of the dose–response relationship for particular endpoints. However, it did not allow to investigate the effects of the exposed volume *per se*, at the tissue level. It should also be noted that, the RT-associated risks might be have been concealed by high proportions of patients treated with chemotherapy, in particular in leukemia analyses [46–48]. Other major limitations frequently observed in the 22 included studies were a small number of SPC cases, and an incomplete and potentially differential follow-up between treatment groups or insufficient information provided in the original articles on follow-up methods and completeness (Table 3, Table S1). Several studies also lacked information on treatments at relapse/progression, and most of them did not account for death as a competing risk.

Biological mechanisms potentially underlying volume effects on SPC risks

Cellular effects of radiation include DNA damages and chromosomal aberrations, repair mechanisms and cell killing/repopulation effects, which have been described by a linear-quadratic-exponential (LQE) model that applies to doses per fraction <5–6 Gy [53]. This model has been the conceptual framework of simulation studies predicting risks of SPC after different RT techniques [15–19], and was also the basis of the "compartmental dose-risk" approach [46]. Shuryak et al extended the LQE model (described by the authors as reflecting short-term biological processes) by incorporating the long-term kinetics of the cell population to predict lifetime rates of spontaneous and radiation-induced pre-malignant stem cells that will grow as malignant clones, in a mechanistic "initiation-inactivation-proliferation-migration" model [54,55].

Non-targeted tissue effects also play a role on radiation-induced cancers [22–25]. Radiation-induced genomic instability transmitted by irradiated cells to their progeny can lead to chromosomal aberrations, gene mutations and malignant transformation in the clonal cells that received themselves no radiation exposure [22,23,25]. Bystander and abscopal effects also induce genetic damages in non-irradiated cells located in close proximity or farther from irradiated cells, through intercellular communication and signaling pathways, inflammatory processes and immune response [22,23,25]. Radiation-induced bystander and abscopal effects are believed to have a greater influence on radiation-induced SPCs in tissues receiving low doses than in highly irradiated tissues, because a smaller proportion of cells are actually hit by ionizing particles and a larger proportion of cells remain alive. Another important factor in the influence of irradiated volume is the migration of non-irradiated stem cells [24]. In-vivo experi-

ments demonstrated that irradiated active bone marrow can be repopulated by hematopoietic stem cells circulating in the blood or recruited from non-irradiated bone marrow [24,55]. Similarly, the radiosensitivity of epithelial cells with a high cellular migratory capacity (such as skin and intestinal epithelium) decreases with reduction of the irradiated volume [24]. This type of volume effect is related to the organ architecture. Serial or tubular organs (in which high doses to a small volume can impair the function of the whole organ) are more likely to be repopulated by non-irradiated, or less irradiated surrounding tissues than parallel organs (in which functional damages depend on the dose–volume distribution in the entire organ) [24]. It should however be noted that these effects related to the organ architecture were described for functional and structural damages, not carcinogenesis.

In summary, tissue effects (kinetics of the cell population, radiation-induced genomic instability, bystander and abscopal effects, and stem cell repopulation) influence the development of radiation-induced cancers, beyond the sole cellular effects, and may modify the effect of ionizing particles to individual cells according to the volume of the organ/tissue irradiated and to the doses received by others tissues. Volume effects likely depend on the cell types and organs/tissues considered, and vary among individuals.

Opportunities for future epidemiological studies

Diallo et al reported that, among 115 patients who developed a solid SPC after RT for childhood cancer, 66% of the SPCs were located at the border of the beam and 22% in distant tissues (>5 cm outward from the edge of the irradiated volume) that received doses ranging from 0 to 3 Gy (median: 0.3 Gy) [56]. These results suggest that estimating dose–volume-response relationships for SPCs requires considering both normal tissues receiving high dose gradients (beam-bordering tissues) and those receiving low-to-moderate doses (distant tissues).

In order to investigate dose–volume effects in epidemiological studies, precise in-field and out-of-field dosimetry is needed. This implies that detailed information on treatment plans are collected, and that patient's anatomy modeling (in the absence of imaging for each individual, in particular of out-of-field organs) and particle-transport simulation (including primary beam, leakage and scatter radiation) are sufficiently automated to be applied for large cohorts of patients and can provide accurate whole-body dose–volume distributions. Such efforts have already been made [57–59], providing methods and tools for further dose–volume risk analyses. It should nevertheless be noted that these methods have only been applied so far to photon non-conformal and 3D RT, and further progresses are needed to reconstruct organ doses for more advanced conformal techniques, such as IMRT and SBRT, and particle therapy.

Unlike previous epidemiological studies which estimated SPC risks as a function of point dose estimates (dose estimates at the SPC location or at various locations within the skeleton) or mean organ doses, multivariate models including dose–volume histogram parameters and other clinical parameters can now be developed. Applying the methodological framework of normal tissue complication probability models for early and non-SPC late toxicities [60] to define dose–volume constraints (or indexes) is one possible option, which may have important implications for treatment planning to reduce risks of SPCs. To understand the respective effect of reducing doses and/or the irradiated volume, statistical methods for dose–volume interaction modeling in the presence of spatial correlations should be considered. In exploratory analyses, non-parametric approaches have been tested (e.g. [61]). The combined effect of RT and chemotherapy and additional radiation exposures due to repeated imaging for patient positioning during image-guided radiotherapy are also important aspects to consider.

Conclusion

Current evidence from clinical and epidemiological studies suggests that risks of SPC at organs/tissues located within or close to the target volume increase with larger RT fields. Most of them, however, did not have sufficient sample size or follow-up time to assess risks at distant organs exposed to low doses, and none investigated the effect of dose–volume distribution on normal tissues. Those studies thus did not allow to quantify risks associated with different dose gradients in surrounding organs or increasing distant tissue volumes exposed to low-to-moderate doses. Opportunities for research on this topic now exist, with the availability of methods and tools for estimating individual whole-body dose–volume distributions in large populations. Future studies could use data that have been accumulated in large cohorts of patients who were treated in the past, including with conformal RT, and followed for decades after their initial treatment. Dose–volume analyses in such cohorts may provide useful information to attempt predicting SPC risks from modern techniques of radiotherapy, provided that there is a sufficient variability of treatment plans among the included patients and that risk models can be validated against prospective data.

Funding

This work has been supported by the Fondation ARC pour la recherche sur le cancer (grant n° PDF20161205256).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.09.017.

References

[1] Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011;12:353–60.
[2] Chaturvedi AK, Engels EA, Gilbert ES, Chen BE, Storm H, Lynch CF, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst 2007;99:1634–43.
[3] Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 2007;25:1489–97.
[4] Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27:2356–62.
[5] Olsen JH, Moller T, Anderson H, Langmark F, Sankila R, Tryggvadottir L, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 2009;101:806–13.
[6] Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst. 2001;93:618–29.
[7] Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Novetsky Friedman D, et al. Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncology 2014;32:2217–23.
[8] Curtis R, Freedman D, Ron E, Ries LAG, Hacker DG, Edwards BK, et al. New malignancies among cancer survivors: SEER cancer registries, 1973-2000. NIH Publ. No. 05-5302. Bethesda, MD, USA: National Cancer Institute; 2006.
[9] de Vathaire F, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, et al. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. Br J Cancer 1999;79:1884–93.
[10] Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 2003;56:83–8.
[11] Purdy JA. Dose to normal tissues outside the radiation therapy patient's treated volume: a review of different radiation therapy techniques. Health Phys 2008;95:666–76.
[12] Journy NM, Morton LM, Kleinerman RA, Bekelman JE, Berrington de Gonzalez A. Second primary cancers after intensity-modulated vs 3-dimensional conformal radiation therapy for prostate cancer. JAMA Oncol 2016;2:1368–70.
[13] Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 2013;87:46–52.

[14] Mizumoto M, Murayama S, Akimoto T, Demizu Y, Fukushima T, Ishida Y, et al. Proton beam therapy for pediatric malignancies: a retrospective observational multicenter study in Japan. Cancer Med 2016;5:1519–25.
[15] Murray L, Henry A, Hoskin P, Siebert FA, Venselaar J. ESTRO BPgotG. Second primary cancers after radiation for prostate cancer: a review of data from planning studies. Radiat Oncol 2013;8:172.
[16] Zwahlen DR, Bischoff LI, Gruber G, Sumila M, Schneider U. Estimation of second cancer risk after radiotherapy for rectal cancer: comparison of 3D conformal radiotherapy and volumetric modulated arc therapy using different high dose fractionation schemes. Radiat Oncol 2016;11:149.
[17] Brodin NP, Munck Af Rosenschold P, Aznar MC, Kiil-Berthelsen A, Vogelius IR, Nilsson P, et al. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. Acta Oncol 2011;50:806–16.
[18] Filippi AR, Ragona R, Piva C, Scafa D, Fiandra C, Fusella M, et al. Optimized volumetric modulated arc therapy versus 3D-CRT for early stage mediastinal Hodgkin lymphoma without axillary involvement: a comparison of second cancers and heart disease risk. Int J Radiat Oncol Biol Phys 2015;92:161–8.
[19] Johansen S, Cozzi L, Olsen DR. A planning comparison of dose patterns in organs at risk and predicted risk for radiation induced malignancy in the contralateral breast following radiation therapy of primary breast using conventional, IMRT and volumetric modulated arc treatment techniques. Acta Oncol 2009;48:495–503.
[20] Schneider U, Zwahlen D, Ross D, Kaser-Hotz B. Estimation of radiation-induced cancer from three-dimensional dose distributions: Concept of organ equivalent dose. Int J Radiat Oncol Biol Phys 2005;61:1510–5.
[21] Schneider U, Sumila M, Robotka J. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. Theor Biol Med Model 2011;8:27.
[22] Little JB. Principal cellular and tissue effects of radiation. In: Kufe DW, Pollock RE, Weichselbaum RR, editors. Holland-Frei cancer medicine. Hamilton (ON): BC Decker; 2003.
[23] Marcu LG. Photons – radiobiological issues related to the risk of second malignancies. Phys Med 2017;42:213–20.
[24] Dorr W, Van der Kogel A. In: Basic clinical radiobiology. Hodder Arnold: London, UK; 2009. p. 191–206.
[25] Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol. 2009;10:718–26.
[26] ICRU. ICRU Report 83: Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Bethesda, MD, USA: International Commission on Radiation Units and Measurements; 2010. p. 1–106.
[27] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:W64.
[28] UNSCEAR. Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure. In: Sources, Effects and Risks of Ionizing Radiation, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2017 Report2018.
[29] Franklin JG, Paus MD, Pluetschow A, Specht L. Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk. Cochrane Database Syst Rev 2005:CD003187.
[30] Hoskin PJ, Smith P, Maughan TS, Gilson D, Vernon C, Syndikus I, et al. Long-term results of a randomised trial of involved field radiotherapy vs extended field radiotherapy in stage I and II Hodgkin lymphoma. Clin Oncol (R Coll Radiol) 2005;17:47–53.
[31] Ferme C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007;357:1916–27.
[32] Biti G, Cellai E, Magrini SM, Papi MG, Ponticelli P, Boddi V. Second solid tumors and leukemia after treatment for Hodgkin's disease: an analysis of 1121 patients from a single institution. Int J Radiat Oncol Biol Phys 1994;29:25–31.
[33] Chung CT, Bogart JA, Adams JF, Sagerman RH, Numann PJ, Tassiopoulos A, et al. Increased risk of breast cancer in splenectomized patients undergoing radiation therapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys 1997;37:405–9.
[34] Lee CK, Aeppli D, Nierengarten ME. The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. Int J Radiat Oncol Biol Phys 2000;48:169–79.
[35] Swerdlow AJ, Schoemaker MJ, Allerton R, Horwich A, Barber JA, Cunningham D, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. J Clin Oncol 2001;19:1610–8.
[36] Ng AK, Bernardo MV, Weller E, Backstrand K, Silver B, Marcus KC, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002;100:1989–96.
[37] Meattini I, Livi L, Saieva C, Marrazzo L, Rampini A, Iermano C, et al. Breast cancer following Hodgkin's Disease: the experience of the University of Florence. Breast J 2010;16:290–6.
[38] Omer B, Kadan-Lottick NS, Roberts KB, Wang R, Demsky C, Kupfer GM, et al. Patterns of subsequent malignancies after Hodgkin lymphoma in children and adults. Br J Haemat 2012;158:615–25.
[39] Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol 2012;30:2745–52.
[40] Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. N Engl J Med 2015;373:2499–511.
[41] Obedian E, Fischer DB, Haffty BG. Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. J Clin Oncol 2000;18:2406–12.
[42] Zhang W, Becciolini A, Biggeri A, Pacini P, Muirhead CR. Region of Treatment in Radiotherapy and Second Malignancies in Breast Cancer Patients. J Cancer Ther 2012;3:768–76.
[43] Hamilton SN, Tyldesley S, Li D, Olson R, McBride M. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? Int J Radiat Oncol Biol Phys 2015;91:977–85.
[44] Nottage K, McFarlane J, Krasin MJ, Li C, Srivastava D, Robison LL, et al. Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 2012;30:2552–8.
[45] Movsas B, Hanlon AL, Pinover W, Hanks GE. Is there an increased risk of second primaries following prostate irradiation? Int J Radiat Oncol Biol Phys 1998;41:251–5.
[46] Blettner M, Boice Jr JD. Radiation dose and leukaemia risk: general relative risk techniques for dose-response models in a matched case-control study. Stat Med 1991;10:1511–26.
[47] Allard A, Haddy N, Le Deley MC, Rubino C, Lassalle M, Samsaldin A, et al. Role of radiation dose in the risk of secondary leukemia after a solid tumor in childhood treated between 1980 and 1999. Int J Radiat Oncol Biol Phys 2010;78:1474–82.
[48] Allodji RS, Schwartz B, Veres C, Haddy N, Rubino C, Le Deley MC, et al. Risk of subsequent leukemia after a solid tumor in childhood: impact of bone marrow radiation therapy and chemotherapy. Int J Radiat Oncol Biol Phys 2015;93:658–67.
[49] Schwartz B, Benadjaoud MA, Clero E, Haddy N, El-Fayech C, Guibout C, et al. Risk of second bone sarcoma following childhood cancer: role of radiation therapy treatment. Radiat Environ Biophys 2014;53:381–90.
[50] Franklin J, Eichenauer DA, Becker I, Monsef I, Engert A. Optimisation of chemotherapy and radiotherapy for untreated Hodgkin lymphoma patients with respect to second malignant neoplasms, overall and progression-free survival: individual participant data analysis. Cochrane Database Syst Rev 2017;9. CD008814.
[51] Nguyen F, Rubino C, Guerin S, Diallo I, Samand A, Hawkins M, et al. Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields. Int J Radiat Oncol Biol Phys 2008;70:908–15.
[52] Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol Biol Phys 2013;86:224–33.
[53] Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. Proc Natl Acad Sci USA 2005;102:13040–5.
[54] Shuryak I, Hahnfeldt P, Hlatky L, Sachs RK, Brenner DJ. A new view of radiation-induced cancer: integrating short- and long-term processes. Part I: approach. Radiat Environ Biophys 2009;48:263–74.
[55] Shuryak I, Sachs RK, Hlatky L, Little MP, Hahnfeldt P, Brenner DJ. Radiation-induced leukemia at doses relevant to radiation therapy: modeling mechanisms and estimating risks. J Natl Cancer Inst 2006;98:1794–806.
[56] Diallo I, Haddy N, Adjadj E, Samand A, Quiniou E, Chavaudra J, et al. Frequency distribution of second solid cancer locations in relation to the irradiated volume among 115 patients treated for childhood cancer. Int J Radiat Oncol Biol Phys 2009;74:876–83.
[57] Veres C, Allodji RS, Llanas D, Vu Bezin J, Chavaudra J, Mege JP, et al. Retrospective reconstructions of active bone marrow dose-volume histograms. Int J Radiat Oncol Biol Phys 2014;90:1216–24.
[58] Lee C, Jung JW, Pelletier C, Pyakuryal A, Lamart S, Kim JO, et al. Reconstruction of organ dose for external radiotherapy patients in retrospective epidemiologic studies. Phys Med Biol 2015;60:2309–24.
[59] Lamart S, Stovall M, Simon SL, Smith SA, Weathers RE, Howell RM, et al. Radiation dose to the esophagus from breast cancer radiation therapy, 1943–1996: an international population-based study of 414 patients. Int J Radiat Oncol Biol Phys 2013;86:694–701.
[60] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10–9.
[61] Benadjaoud MA, Blanchard P, Schwartz B, Champoudry J, Bouaita R, Lefkopoulos D, et al. Functional data analysis in NTCP modeling: a new method to explore the radiation dose-volume effects. Int J Radiat Oncol Biol Phys 2014;90:654–63.