Review Article

Late Sequelae of Radiotherapy

The Effect of Technical and Conceptual Innovations in Radiation Oncology

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Summary

Background: Approximately half of all patients with tumors need radiotherapy. Long-term survivors may suffer from late sequelae of the treatment. The existing radiotherapeutic techniques are being refined so that radiation can be applied more precisely, with the goal of limiting the radiation exposure of normal tissue and reducing late sequelae.

Methods: This review is based on the findings of a selective search in PubMed for publications on late sequelae of conventional percutaneous radiotherapy, January 2000 to May 2020. Late sequelae affecting the central nervous system, lungs, and heart and the development of second tumors are presented, and radiobiological mechanisms and the relevant technical and conceptual considerations are discussed.

Results: The current standard of treatment involves the use of linear accelerators, intensity-modulated radiotherapy (IMRT), image-guided and respiratory-gated radiotherapy, and the integration of positron emission tomography combined with computed tomography (PET-CT) in radiation treatment planning. Cardiotoxicity has been reduced with regard to the risk of coronary heart disease after radiotherapy for Hodgkin's lymphoma (hazard ratio [HR] 0.44 [0.23; 0.85]). It was also found that the rate of radiation-induced pneumonitis dropped from 7.9% with conformal treatment to 3.5% with IMRT in a phase III lung cancer trial. It is hoped that neurocognitive functional impairment will be reduced by hippocampal avoidance in modern treatment planning: an initial phase III trial yielded a hazard ratio of 0.74 [0.58; 0.94]. It is estimated that 8% of second solid tumors in adults are induced by radiotherapy (3 additional tumors per 1000 patients at 10 years).

Conclusion: Special challenges for research in this field arise from the long latency of radiation sequelae and the need for large-scale, well-documented patient collectives in order to discern dose–effect relationships, and take account of cofactors, when the overall number of events is small. It is hoped that further technical and conceptual advances will be made in the areas of adaptive radiotherapy, proton and heavy-ion therapy, and personalized therapy.

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Now that the number of long-term cancer survivors is increasing, the late sequelae of cancer treatment have taken on new importance, and about half of all patients with cancer are treated with radiotherapy (1, e1).

The late sequelae of radiotherapy manifest themselves with a latency of three months to several decades after the completion of treatment; unlike acute sequelae, they are generally irreversible (1, e2). Their latency and severity depend on the nature of the affected organ or tissue, the applied radiation dose (total and per fraction), and the irradiated volume and are modulated by concomitant treatments and other characteristics of the patient.

There have been recent advances in radiotherapeutic techniques, treatment planning, and the integration of modern imaging methods with the goal of limiting the radiation exposure of normal tissue in order to lessen toxicity, or else enable raising the dose delivered to the tumor without increasing toxicity (1, 2). These developments include linear accelerators with intensity-modulated radiotherapy or volumetrically modulated arc therapy (VMAT) (e3), image-guided radiotherapy, and stereotactic radiotherapy *(Box)*. Modern imaging techniques are also being

BOX

Technical developments in radiotherapy

- **Intensity-modulated radiotherapy (IMRT) or volume-modulated arc therapy (VMAT)**
  The use of multiple, irregularly shaped radiation fields that are dynamically altered for radiotherapy in complex target regions
  Benefit: – Dose reduction in the tumor and its vicinity and in the surrounding normal tissue (2, 27, 28, 34)

- **Image-guided radiotherapy**
  The use of integrated imaging units on the linear accelerator to monitor the position of the patient
  Benefit: – safe dose application, reduced safety margins (dose reduction)
  – ability to analyze the anatomy of the tumor and the surrounding tissue during the entire treatment, often with low-dose cone beam computerized tomography (CT)
  – adaptability of treatment planning to the current anatomical situation (e.g., tumor remission) (32)

- **Stereotactic radiotherapy**
  High-precision radiotherapy of small tumor volumes with a narrow safety margin; requires precise imaging for planning and execution of treatment
  Benefit: – enables the application of high individual doses (e.g., as radiosurgery), with high tumor-control rates (e20)

- **Breathing-controlled radiotherapy with the breath-holding technique**
  Radiotherapy only during a specified phase of breathing (deep inspiration)
  Benefit: – In radiotherapy (RT) of left-sided breast cancer, the heart is kept away from the radiated field by the expanded lung, and the dose to the heart is reduced.
  – In RT of lung cancer, respiratory movements are reduced and the irradiated volume of lung tissue is thereby reduced as well (e7, e8, 21–23, 32).

- **Breathing-controlled radiotherapy with gating**
  Implementation of radiotherapy only when the (mobile) tumor is found in the target region; requires a camera system that pursues the mobile patient or organ
  Benefit: – the irradiated volume of lung tissue is reduced (32)

- **Adaptive radiotherapy, "plan of the day"**
  daily alteration of the radiotherapy treatment plan depending on the patient's anatomy
  Benefit: – The technique accounts for organ movement, variable filling states, and changes in the tumor volume. The technique is currently under clinical evaluation (32, e4).

- **Proton-beam therapy**
  irradiation with particles that yield a maximum dose in a narrow range of depth within the tissue.
  Benefit: – Particularly useful for the irradiation of deep-lying tumors or those that are immediately adjacent to critical structures (e.g., the brainstem); available only in specialized centers, for specified indications (1)

- **MR accelerator**
  Coupling of a magnetic resonance imaging (MRI) unit with a linear accelerator for image-guided radiotherapy using images of diagnostic quality
  Benefit: – This method is now being clinically implemented and evaluated (e4).

increasingly applied in order to delimit tumors more precisely in the planning and execution of radiotherapy (2, e4). The ideal goal of zero radiation exposure of the normal tissue is not attainable even in principle. The dose distribution always represents a compromise, where the physicians and radiation physicists must collaborate in weighing the probability of late sequelae against the tumor control rate for each individual patient.

In this review, we present current clinical and biological data on the late sequelae of percutaneous radiotherapy for selected organs at risk and discuss the implications of recent technical developments with regard to these sequelae. For more information on treatment and prevention of radiation side effects, the reader is referred to the German S3 guideline on supportive therapy for cancer patients (*Supportive Therapie bei onkologischen PatientInnen*, Ref. 3).

Radiation biological principles of the late sequelae of radiotherapy

The late sequelae of radiotherapy reflect changes in organ parenchyma, in the vasculature, or in the connective tissue, which lead to a loss of function within the irradiated volume. The immune system participates in this process with inflammatory reactions, the degradation of damaged cells, and the generation of pro-inflammatory and pro-fibrogenic cytokines (4). The sequelae of radiotherapy depend on tissue architecture. In serially constructed organs, such as the gastrointestinal tract and the vascular system, radiation exposure at any site in the system affects the function of distally located compartments as well. In organs that are constructed in parallel, such as the liver or lung, the radiation exposure must affect a significant portion of the overall volume to have any adverse clinical effects. Late sequelae arise after at least a few months, with the latency being inversely related to the biologically effective dose (e5). Relative biological effectiveness (RBE) is a parameter that can be used to predict what doses of two different types of ionizing radiation (e.g., electrons and protons) will be equally biologically effective (5).

Late sequelae in normal tissue arise in 5–10% of patients who undergo radiotherapy (6, 7). Multiple factors, including cellular composition, degree of differentiation, cell replication capacity, and cellular radiation sensitivity, determine the extent of the sequelae. Patient-related factors, too, are important co-determinants of the risk (8). The reaction of human beings to ionizing radiation is individual and variable and is affected by age, smoking behavior, illnesses such as diabetes mellitus, collagenoses, and vascular diseases, and the genotype (8). The molecular basis of individual sensitivity to radiation is complex and poorly understood. There is currently no reliable biological marker that can predict severe radiation sequelae. Only in the case of breast and prostate cancer is there an observed, significant association between the nucleotide polymorphism (SNP) rs1801516 of the ataxia-telangiectasia gene, which is

found in ca. 10% of the population, and the severity of late sequelae (odds ratio [OR] 1.2; 95% confidence interval [0.81; 2.27]) (9, 10). Further SNPs are also of predictive value in prostate cancer. Other epigenetic changes in relevant genes are being studied as well. Genetic factors such as DNA repair, oxidative stress, radiofibrogenesis, and endothelial cell damage all play a role in the late sequelae of radiotherapy (11).

Methods

In this review, we present the late sequelae of conventional percutaneous radiotherapy in the central nervous system (CNS), lungs, and heart, as well as the generation of second tumors. A selective literature search was carried out in PubMed covering the period from 2000 to May 2020. Publications of the following kinds were considered: systematic reviews, meta-analyses, and population-based studies with late toxicity as a primary endpoint. We also considered relevant phase III trials of dose escalation and/or de-escalation in which data on the patient population, applied dose/technique, and classification of toxicity were reported. Empirical documentation of the clinical effects of recent technical and conceptual innovations will only be possible many years after their introduction; thus, model calculations will be used as a surrogate and will be presented for a number of illustrative situations.

Specific late sequelae of radiotherapy

Cardiotoxicity

The types of damage to the heart that can arise after mediastinal irradiation include coronary heart disease (CHD), cardiomyopathy, valvular disease, disturbances of the intracardiac conducting system, and pericardial disease (1, 12). They are caused by diffuse interstitial fibrosis and collagen deposition, as well as by narrowing of the lumen of arteries and arterioles through the accumulation of myofibroblasts. The site and magnitude of the applied dose determine the type, extent, and latency of the clinical sequelae. Individual substructures display different dose–response relationships: the risk of coronary heart disease depends linearly on the median cardiac dose (relative risk [RR]: 7.4%/Gy [2.9; 14.5]) (13). The rate of additional events (excess rate ratio, ERR) compared to cohorts from the general population is 0.04 [0.02; 0.06] after radiotherapy for breast cancer or Hodgkin's lymphoma (13–15). In contrast, the rate of radiation-induced valvular disease rises exponentially beyond an exposure of 30 Gy (cumulative incidence figures at 30 years: 3.0% [≤ 30 Gy], 6.4% [31–35 Gy], 9.3% [36–40 Gy], 12.4% [≥ 40 Gy]) (14, e6).

Current consensus recommendations stratify risk categories according to the median cardiac dose and urge the avoidance of dose maxima in the coronary arteries (16–18). Measures that were implemented over the period 1970–1999 to lower the radiation exposure of patients with Hodgkin's lymphoma and thereby lessen cardiotoxicity were indeed accompanied by a significant lowering of the 20-year incidence of CHD: cumulative incidence 0.99% [0.67; 1.48] in the 1970s, versus 0.42% [0.20; 0.88] with hazard ratio (HR) 0.44 [0.23; 0.85] in the 1990s (12).

Similar developments can be seen in adjuvant radiotherapy for patients with breast cancer who were treated in the period 2000–2012. They did not have a higher risk than the general population for acute coronary events or cardiac death (19, 20). Developments such as the possibility of irradiating only during deep inspiration have lowered the cardiac dose still further (e7, e8). The German Society for Radiation Oncology recommends this technique for the treatment of left-sided breast cancer (17). Comparative dosimetric evaluations have shown that this technique lowers the median cardiac dose by 1.3–3.45 Gy in lymphoma treatment as well (21–23).

Lung toxicity

Subacute pneumonitis and chronic pulmonary fibrosis are potential side effects of radiotherapy in the chest. Pneumonitis arises 1–6 months after treatment, with manifestations ranging from asymptomatic changes visible on a chest CT, to moderately severe cough, dyspnea, and sometimes fever, to rare severe courses with respiratory insufficiency. Pulmonary fibrosis can arise as a long-term complication (1).

Irradiation initiates a complex mechanism involving damage to the alveolar epithelium through inflammation, DNS damage, cell senescence, and subsequent fibrosis (24). Pneumonitis can lead to pulmonary fibrosis through a mechanism that has yet to be fully explained, but is thought to involve radiation-induced oxidative stress and free-radical production, leading to an inflammatory reaction and DNA injury. A resulting high concentration of circulating growth factors may induce fibroblast proliferation and migration, leading to collagen deposition (25). The incidence and severity of pneumonitis depend on the magnitude of the applied dose, the volume of lung tissue irradiated, and the dose per fraction (26).

A meta-analysis of studies on the prediction of symptomatic pneumonitis that were published over the period 1993–2010 contained an evaluation of individual data on 836 patients who had undergone radiotherapy (and sometimes chemotherapy as well) with curative intent for non-small-cell lung cancer, at a median dose of 60 Gy (IMRT or conformal technique). After a median follow-up time of 2.3 years, pneumonitis of grade 2 or worse was seen in 29% of the patients (26). In contrast, in the phase III trials of conventional radiotherapy for lung cancer that were published in the period 2016–2020 (27)—partly with simultaneous dose escalation (2, 28)—grade 3 pneumonitis was seen in only 0–7.5% of the patients. The follow-up times were 21–29 months and thus similar to those of the previous studies included in the meta-analysis mentioned above (26).

The risk of pneumonitis is increased by advanced patient age, simultaneous chemotherapy (particularly

TABLE 1

Overview of studies on neurocognitive functional impairment after radiotherapy (with or without chemotherapy)*

Authors / year of publication	Question	Design	Method, tumor entity	Collective / treatment year	Result
Gehrke et al. 2013 (e35)	post-therapeutic neurocognitive function of patients with malignant intrinsic brain tumors compared to the population without cancer	comparison of patients with controlled brain tumor vs. the normal population (matched pairing)	systematic review malignant intrinsic brain tumors	4 studies (195/20/17/10 pts) 40–80% with RT 2002–2012	demonstrable cognitive deficits mainly pertaining to attention, cognitive control, and flexibility; effect of individual treatments not studied
Lawrie et al. 2019 (e13)	neurocognitive function ≥ 2 yr after glioma treatment	analysis of studies of RT vs. observation, RT +/- chemotherapy, low- vs. high-dose RT, conventional vs. stereotactic RT	Cochrane - analysis glioma	RT vs. observation 2 observational studies 195 pts /1997–2000/ 5yr FU 31 pts/1989–93/ 2yr FU	RT vs. observation cognitive impairment (mainly in attention, information processing, and memory) 41/104 pts vs. 24/91 pts, RR 1.38 (95% confidence interval [0.92; 2.06]) 1/17 pts vs. 0/14 pts, RR 2.5 [0.11; 56.9] very low reliability of both conclusions (GRADE)
van der Meulen et al. 2018 (33)	effect of primary cerebral lymphoma and treatment modalities on neurocognitive function	analysis of studies on neurocognitive function in primary cerebral lymphoma	systematic review primary cerebral lymphoma	9 studies with RT 12–80 pts studies up to 2018	up to 6 months after treatment, stable or improved neurocognitive function; 2 yr after RT, worsened neurocognitive function compared to at end of treatment risk factor: total dose > 40 Gy
Zeng et al. 2020 (e19)	risk factors for impaired neurocognitive function after PCI	analysis of RCTs prophylactic RT of the brain (PCI) vs. observation	systematic review PCI in lung carcinoma	8 RCT, 8 observational studies 3553 pts published 1995–2019	neurocognitive functional impairment: present at baseline in 23–95% of patients risk factors: total dose, RT twice per day, simultaneous chemotherapy; questionable: age
Liu et al. 2020 (e33)	efficacy and toxicity of PCI in lung carcinoma	analysis of RCTs of PCI vs. observation	systematic review PCI in lung carcinoma	study RTOG 0214: 93 pts 2002–2007 (Sun et al. 2010) study NVALT-11: 195 pts 2009–105 (De Ruysscher et al. 2018)	neurocognitive functional impairment (memory) RT vs. observation RTOG 0214 1yr FU HVALT 10/48 pts (26%) vs. 3/45 Pat (7%) p = 0.03 pts self-assessed EORTC QLQC30/BN20 15/37 pts (41%) vs. 12/47 pts (25%) p = 0.02 NVALT-11 summative medical CTCAE v3.0 grade 1–2 26/86 pts (30%) vs. 7/88 pts (8%) p = 0.001 pts self-assessed EORTC QLQC30/BN20 in all grades 48/87 pts (55%) vs. 46/88 pts (52%)

*Except for one study on prophylactic radiotherapy of the brain (de Ruysscher et al. 2018, in [e33]), studies are included in this table only if they employed neuropsychological measuring instruments (rather than screening tests, such as the Mini Mental Status Examination [MMSE]) and documented a baseline evaluation. Two Cochrane analyses of the effects of early vs. delayed radiotherapy for low-grade glioma (e34) and of RT for highly malignant glioma (e14) are not included here, as the data were insufficient to permit any conclusion.

CTCAE, Common Terminology Criteria for Adverse Events; the higher the grade, the more severe the manifestations, on a scale from 0 to 5; EORTC QLQC30/BN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core tool /brain module; FU, follow-up time; GRADE,Grading of Recommendations Assessment, Development and Evaluation; HVALT, Hopkins Verbal Learning Test; NVALT, Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose; pts, patient(s); PCI, prophylactic cranial irradiation; RCT, randomized controlled trial; RR, relative risk; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; vs., versus; yr, year(s)

if it includes taxanes), and a positive smoking history (26, 29). In contrast, it is probably lowered by smoking during radiotherapy (30, 31, e9, e10).

Various technical developments have enabled a lowering of radiation exposure. In one of the phase III trials mentioned above, pneumonitis of grade 3 or worse arose significantly less commonly after IMRT than after conformal radiotherapy (3.5% vs. 7.9%; p = 0.039) (28). In the technique of PET-CT, the morphological display of anatomy with CT is combined with a nuclear-medical study revealing tissue functionality. Usually, radioactively labeled glucose is injected to demonstrate intratumoral metabolic activity. The integration of PET-CT in radiation planning to

reduce the target volume has enabled isotoxic dose escalation (2). In radiotherapy planning studies involving patients with lymphoma, the breath-hold technique lowered median pulmonary exposure by 1.5–2.4 Gy (21–23). Moreover, with the aid of an imaging unit combined with the linear accelerator for the generation of verification images during radiotherapy (so-called on-board imaging), day-to-day anatomical changes such as tumor remission, atelectasis, or pleural effusions can be visualized and the volume to be irradiated can be tailored during treatment (adaptive planning) (32). Daily adaptation of the treatment plan to generate a "plan of the day" requires not only rapid on-board imaging, but also precise fusion of these images with the planning images, as well as the availability of appropriate staff to carry out the re-planning. This technique is currently under development (32).

Neurotoxicity

The late sequelae of radiotherapy in the CNS include, above all, neurocognitive functional impairment and, rarely, brain necrosis.

The risk of neurocognitive functional impairment after radiotherapy of the brain is particularly disturbing for patients and for the specialists who treat them. Such problems tend to affect the domains of verbal and nonverbal memory, problem-solving ability, attention, and information-processing speed. Changes that are demonstrable in neuropsychological tests are not always clinically relevant (33), and a dementia syndrome is rare. Neurocognitive impairment arising from four months to several years after radiotherapy (with or without chemotherapy) is generally irreversible (e11, e12) *(Table 1)*. Reliable data on the frequency of neurocognitive impairment after radiotherapy are hard to obtain because of the small patient collectives, short follow-up times, cross-sectional studies without reporting of baseline data, inappropriate test instruments (e.g., the Mini Mental Status Test), poor test compliance, and the confounders tumor progression and treatment with antiepileptic drugs (33, e13–e15). Patients whose glioma was well controlled suffered more often from neurocognitive functional impairment if they had received radiotherapy than if they had not (17/32 patients [53%] versus 4/17 [24%]). However, tumor recurrence is the main risk factor for functional impairment, in patients with brain metastases as well (e11, e12, e16).

The risk of toxicity is increased by fraction doses > 2 Gy (in conventional radiotherapy), antiepileptic drugs (e11, e12, e17), chemotherapy, the administration of BRAF inhibitors (e18), and either very young or very old age (e11, e12, e17, e19). The risk of neurocognitive impairment after prophylactic whole-brain radiotherapy in patients with lung cancer is of particular clinical significance. Neurocognitive impairment is already present in 23–95% of patients before radiotherapy and worsens in 8–89% after radiotherapy, compared to 3–42% after observation alone (e19).

Some memory tasks are thought to be localized to the hippocampus. The IMRT and VMAT techniques enable reduction of the radiation dose that is delivered to the hippocampus. In the first phase III trial of whole-brain radiotherapy for brain metastases with or without hippocampal sparing, the frequency of cognitive impairment (memory/language) at four months was significantly lower in the group with hippocampal sparing than in the control group (52% versus 65%, 211/517 patients studied, HR 0.74 ([0.58; 0.94]) (34). Further study findings on the functional effect of hippocampal sparing, and on tumor control despite dose reduction, are currently pending.

Brain necrosis in tumor-free brain tissue has become a rare event (<1%) since the introduction of IMRT/VMAT and stereotactic radiotherapy. Necrosis arises in high-dose regions of radiotherapy for brain tumors or metastases from 10 months to approximately 3 years after treatment in 1–12% of patients, with the frequency depending on the total dose, fraction dose, and treatment volume (e20, e21). Patients present with focal symptoms that depend on the neuroanantomical location of the necrosis; large areas of necrosis can also exert mass effect, producing symptoms of intracranial hypertension. The differential diagnosis of tumor progression versus "pseudoprogression" (i.e., radionecrosis) can be made by magnetic resonance tomography with perfusion and diffusion studies and spectroscopy, supplemented, if indicated, by combined positron emission tomography and computed tomography (PET-CT) employing an amino-acid tracer such as ^{18}F-fluoroethyl-L-tyrosine (sensitivity 83–87%, specificity 81–85%) (e22). The clinical course of cerebral radionecrosis varies, ranging from spontaneous remission, to stable clinical manifestations and magnetic resonance findings, to continuing progression.

Technical innovations such as stereotactic radiotherapy now enable escalation of the dose delivered to the tumor without any increase in toxicity. For brain metastases, tumor control rates above 80% have been achieved (e20).

The induction of second tumors

After the successful treatment of the primary tumor, a small number of patients develop second tumors (or multiple further tumors) later on in life *(Table 2, eTable)*. The incidence of such tumors can be estimated from the findings of cohort studies (with large, heterogeneous patient groups) or meta-analyses of randomized, controlled trials (with narrowly defined but small patient groups); it is reported as a standardized incidence rate (SIR) compared to the normal population, as an absolute excess rate (AER) of cases per 10 000 patient-years, or as a relative risk in comparison to a control group. Aside from the radiotherapy undergone by the patient, the risk factors for a second tumor include the same factors that likely played a role in the development of the primary tumor:

TABLE 2

Studies on second tumors

Author	Type of study	Question	Patient collective, treatment years, follow-up	Number of studies, number of patients	Results
Berrington de Gonzalez et al. 2011 (35)	Cohort study	Calculation of radiotherapy-induced solid second tumors (SecT)	population-based cohort study 15 tumor types 5-year survivors 1973–2002 FU ≥ 5 yr	647 672 pts RT dose and distance to RT field assumed to be according to standard protocol	AER RT-associated tumors 8% [7; 9]), AE 3266/42 294 patients rectal cancer (primary tumor) AE 112/21 841 pts, AER 7 % [3; 12]) RT vs. no RT RR* 1.33 [1.03; 1.7] breast cancer (primary tumor) AE 660/12 450 pts. AER 5 % [4; 7]); RT vs. no RT RR* 1.42 [1.24; 1.62] prostate cancer (primary tumor) AE 1131/11 292 pts, AER 10% [8; 12]) RT vs. no RT RR* 1.59 [1.41; 1.8]
Wiltink et al. 2015 (38)	pooled analysis of phase III studies individual patient data	long-term probability of a second tumor after rectal or endometrial carcinoma in patients with and without RT	RT in patients with rectal or endometrial carcinoma 1990–2006 median FU 7.5–13 yr	3 phase III studies (TME, PORTEC-1, PORTEC-2) 2554 patients	cumulative incidence: 10 yr 16%, 15 yr 26% no difference between RT and no RT SIR for SecT overall 2.98 [2.82; 3.14] no difference between RT and no RT
Wallis et al. 2016 (e32)	meta-analysis	risk of carcinoma of the rectum, colon, bladder, or lung or a hematological disease after RT for prostate cancer	patients with prostate cancer 1973–2010 median FU 3–12 yr	13 studies with surgery, 8 studies with no RT as control group 199 049 pts	carcinoma of the rectum (second tumor) RT vs. no RT, latency 10 years absolute difference in incidence/100 pts 0.2 [0.2; 0.3] carcinoma of the bladder (second tumor) absolute difference in incidence/100 pts 0.6 [0.5; 0.7]
Taylor et al. 2017 (15)	meta-analysis individual patient data	assessment of the absolute risk of modern radiotherapy for carcinoma of the breast: second tumors in the lungs in smokers and nonsmokers	patients with carcinoma of the breast published 2010–2015	214 studies one cohort study each for lung cancer among smokers and nonsmokers	calculation of mortality from lung cancer compared to the normal population up to age 80 50 yr at time of RT, never smoked, 0.8 vs. 0. 5% 50 yr at time of RT, active smoker, 13.8 vs. 9.4%

This table contains the summarized findings of selected studies on the incidence of second tumors after radiotherapy in adulthood and on the observation/risk estimationof second tumors after modern radiotherapy. For more comprehensive information, see the *eTable*; square brackets, 95% confidence interval; *10–14 years follow-up

AE, absolute excess, i.e., the absolute number of additional events; AER, absolute excess risk, i.e., the risk of additional events; FU, follow-up time; Gy, Gray; HR, hazard ratio; pts, patients; PORTEC, Post-Operative Radiation Therapy in Endometrial Carcinoma; RR, relative risk; RT, radiotherapy; SecT, solid second tumor; SIR, standard incidence ratio (compared to age-matched normal population); SurvT, survival time;TME, Total Mesorectal Excision; Tu, tumor; vs., versus; yr, year(s).

- lifestyle (35% of second malignancies are in patients who consume alcohol, tobacco, or both)
- environmental factors
- genetic factors (hereditary ovarian carcinoma, hereditary non-polypoid colorectal carcinoma, breast cancer (BRCA) 1/2 mutation (35–37).

Patients who have had a first cancer have an elevated risk of developing a second cancer with or without radiotherapy (SIR after cancer of the rectum or endometrium 2.98 [38], after breast cancer 1.08 [39]). An estimated 8% of solid second tumors in adults, corresponding to 3 additional tumors per 1000 patients in 10 years, are thought to be induced by radiotherapy (35).

Tumors induced by radiotherapy (e23) are mainly solid tumors arising after a latency of at least 5–10 years, with an incidence that never reaches a plateau (35, 39). Critical factors for the development of second tumors include both the irradiated volume in and immediately adjacent to the tumor and the volume of tissue outside the tumor that is irradiated at a much lower dose. After radiotherapy for prostate cancer, 50% of the second tumors in the low-dose region (doses less than 1–3 Gy) arise in the lung and the other 50% in the bone marrow, while the tumors in the high-dose region arise in portions of the bladder and rectum that are adjacent to the prostate (e24). The underlying radiobiological processes that give rise to cancer are chronic inflammatory reactions in the high-dose region and an elevated mutation rate and epigenetic changes in the low-dose region.

Second tumors arise more frequently in patients with genetic syndromes, Li-Fraumeni syndrome, hereditary retinoblastoma, Gorlin syndrome, and Wilms tumor (36). Women who have undergone radiotherapy for breast cancer have a higher risk of a second tumor compared to the general population if they carry a missense mutation with loss of function of the ataxia-telangiectasia mutated (ATM) gene; on the other hand, no elevation of the risk is demonstrable in women carrying mutations of the BRCA1/2 genes (e25). Lifestyle factors potentiate the risk: the RR of developing lung cancer after chemo- or radiotherapy

for Hodgkin's lymphoma is five times higher in intense smokers than in nonsmokers or persons who smoke very little (37). For patients who underwent radiotherapy in childhood or adolescence, the risk of a second tumor is greater in those who were irradiated at younger ages (especially under the age of 5 years) (e26). Radiotherapy involving or confined to the CNS elevates the risk of glioma (AER 3, compared to chemotherapy with AER 2.6) and meningioma, while mediastinal radiotherapy for Hodgkin's lymphoma elevates the risk of breast cancer (SIR 13–55) (40) (*eTable*, e27–e29). It follows that all persons who underwent radiotherapy in childhood or adolescence should have annual follow-up examinations by a multidisciplinary team for the rest of their lives, including, among other things, lifestyle counseling and, in women who underwent radiotherapy of the chest, intensified screening for breast cancer (e30).

The dose-response curve for the induction of second tumors is linear (except in the case of thyroid cancer), with an excess relative risk per Gy of 0.01–0.2 for adults, and, for children, excess relative risks ranging from 0.08–0.33 (highly malignant glioma) to 1.06 (meningioma) (40).

The calculated estimate of the hazard ratio for carcinoma of the rectum after radiotherapy for prostate cancer in the years 1973–2010 is 1.43 for irradiated versus non-irradiated patients (e31), or an additional two carcinomas of the rectum per 1000 patients (e32). In contrast, phase III trials conducted in the period 1990–2006 in which modern, conformal radiotherapy was used, did not reveal any elevation of the rate of second tumors in a small group of patients who had undergone pelvic radiotherapy (38).

In an analysis of clinical cohort studies of patients with breast cancer, conducted from 1935 to 2007, the standardized incidence rate of second tumors ten years after treatment, compared to the normal population, was 1.5 in patients who had undergone radiotherapy of the breast, and 1.16 in patients who had not (39). The variables radiation dose, radiation technique, and smoking could not be considered in the analysis. A lower risk of second tumor can be expected with the types of normal-tissue-sparing radiotherapy that are available today. Because of the long latency, however, the effect can only be estimated with models for the time being. For women with breast cancer, the estimated mortality from lung cancer is 0.8% with radiotherapy vs. 0.5% without (in never-smokers), and 13% vs. 9% (in active smokers) (15). The expected effect cannot yet be seen in the German studies on Hodgkin's lymphoma, in which the radiation dose and volume were systematically reduced.

Conclusion and overview

Conceptual and technical advances in radiotherapy over the past twenty years have enabled reduction of the radiation dose delivered to normal tissue and/or escalation of the dose delivered to the tumor. Further improvements are expected from advances in proton and heavy-ion beam therapy and adaptive radiotherapy, and from the integration of tumor-biological predictive tests. Special challenges for research are posed by the long latency of sequelae and the need (because these sequelae are fairly rare) to collect data from large, well-documented patient cohorts to be able to evaluate cofactors such as systemic tumor therapy, patient-related risk factors, and the primary malignancy itself.

Conflict of interest statement
The authors state that they have no conflict of interest.

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► **Supplementary material**

eReferences, eTable:
www.aerzteblatt-international.de/m2021.0024

Erratum

For the clinical snapshot "Squamous Cell Carcinoma Arising From an Interdigital Pilonidal Sinus" by Haiduk et al. on page 212 in issue 12/2019: In the course of the ongoing dermatologist's procedure, all histology specimens were put under the microscope again. As a result the finding of squamous cell carcinoma, which had initially been established by two histopathology labs, was revised and classified as a pseudocarcinomatous epithelial hyperplasia in pilonidal sinus. *MWR*

Erratum

In the CME article "Non-Substance Addiction in Childhood and Adolescence: The Internet, Computer Games and Social Media" by Olga Geisel et al. in issue 1–2/2021, it was not possible to answer question 7—"How many of the DSM-5 criteria have to be met to be able to diagnose 'Internet Gaming Disorder'?"—unequivocally. What is correct is that at least five criteria have to be met. In agreement with the certifying recognition/accreditation body for continuing medical education measures in the Medical Association of North Rhine, we therefore allow answers b) and c). *MWR*

Supplementary material to:

Late Sequelae of Radiotherapy

The Effect of Technical and Conceptual Innovations in Radiation Oncology

by Ulrike Hoeller, Kerstin Borgmann, Michael Oertel, Uwe Haverkamp, Volker Budach, and Hans Theodor Eich

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eTABLE

Overview of studies on second tumors

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Radiotherapy in adulthood					
Berrington de Gonzalez et al. 2011 (35)	cohort study	calculation of solid second tumors (SecT) due to radiotherapy	population-based cohort study SEER, 15 tumor types, 5-year survivors USA 1973–2002 FU: only pts who survived at least 5 years were included	64 672 pts assuming RT dose and distance to RT field according to standard protocols: < 3 cm > 5 Gy, 3–10 cm 1–5 Gy, > 10 cm < 1 Gy	AER RT-assoc. tumors 8% [7; 9], SecT 3266/42 294 pts RR RT vs. no RT 10–14 yr FU (results for >14 yr FU) carcinoma of the rectum (primary tumor) SecT AE 112/21 841 pts, AER 7% [3; 12] RR 1.33 [1.03; 1.7], (RR 0.91 [0.2; 1.27]) carcinoma of the breast (primary tumor) SecT AE 660/12 450 pts, AER 5% [4; 7] RR 1.42 [1.24; 1.62], (RR 1.5 [1.34; 1.81]) carcinoma of the prostate (primary tumor) SecT AE 1131/11 292 pts, AER 10% [8; 12]) RR 1.59 [1.41; 1.8], (RR 1.91 [1.53; 2.38] The rise of RR with increasing FU is significant. cervical carcinoma (primary tumor) SecT AE 214/1289 pts, AER 17% [10; 23] RR 1.55 [1; 2.4] (RR 2.59 [1.84; 3.68]) The rise of RR with increasing FU is significant. endometrial carcinoma (primary tumor) SecT AE 286/3296 pts, AER 9% [5; 12] RR 1.99 [1.6; 2.47], (RR 2.18 [1.78; 2.65]) The rise of RR with increasing FU is significant. seminoma (primary tumor) SecT AE 150/628 pts, AER 24% [9; 37] RR 1.43 [1.13; 1.84]
Rombouts et al. 2018 (e31)	systematic review and meta-analysis	risk and latency of carcinoma of the rectum after pelvic RT	studies reporting carcinoma of the rectum (SecT) after the treatment of pelvic Tu +/- RT mainly national cancer registries (SEER/ USA, Netherlands, Israel, Denmark) 1935–2011	meta-analysis 18 studies pelvic RT: 403 243 pts no RT: 615 530 pts primary tumor: carcinoma of the prostate 9 studies ovarian carcinoma 3 studies cervical carcinoma 6 studies	overall patient cohort frequency of carcinoma of the rectum as a SecT RT 0.4% (1622/403 243 pts) no RT 0.36% (2261/615 530 pts) RR 1.43 [1.18; 1.72; p = 0.0006 carcinoma of the prostate (primary tumor) RT 0.48% (1140/232 120 pts) no RT 0.41% (1983/487 703 pts) RR 1.36 [1.10; 1.67] cervical carcinoma (primary tumor) RT 0.28% (371/134 725 pts) no RT 0.18% (69/38 688 pts) RR 1.61 [1.10; 2.35] ovarian carcinoma (primary tumor) no difference RT vs. no RT

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Wiltink et al. 2015 (38)	pooled analysis of phase III studies individual patient data	long-term probability of a second tumor after carcinoma of the rectum or endometrial carcinoma in patients with and without RT	adjuvant RT in patients with carcinoma of the rectum (TME study) endometrial carcinoma (PORTEC-1/-2 studies) Netherlands 1990–2006 median FU 13 yr (1.8–21.2) TME 14 yr (2–16) PORTEC-1 12.6 yr (2.8–21.1) PORTEC-2 7.5 yr (1.8–10.5)	3 phase III studies (TME, PORTEC-1, PORTEC-2) 2554 pts TME 1413 pts PORTEC-1 714 pts PORTEC-2 427 pts	759 carcinomas in 549/2554 pts among which 268 carcinomas of the skin 75 carcinomas of the breast 55 lung carcinomas 52 colon carcinomas cumulative incidence in 10 yr 16%, 15 yr 26% no difference RT vs. no RT SIR SecT overall (no difference RT vs. no RT) 2.98 [2.82; 3.14] AER 154/10 000 patient-years 15 yr cumulative incidence, age-dependent pts ≤ 60/> 60 yr 27% vs.. 23.9%; p = 0.01, no difference RT vs. no RT SIR pts ≤ 60 yr 5.47 [4.73; 6.31] pts > 60 yr 2.76 [2.6; 2.9], no difference RT vs. no RT
Zhu et al. 2018 (e36)	systematic review	risk of rectum or colon carcinoma after RT of a carcinoma of the prostate	patients with carcinoma of the prostate (RT, OP, endocrine therapy, watchful waiting) USA, China, Korea, Europe (Netherlands, Germany, Switzerland), Israel 1973–2011; median FU 3.5–12 yr	16 studies (9 SEER, 7 further registries) 357 752 pts	carcinoma of the rectum (second tumor) RT vs. no RT, latency 10 yr HR 1.64 [1.39; 1.94] percutaneous radiotherapy vs. OP HR 1.45 [0.99; 2.12]
Wallis et al. 2016 (e32)	meta-analysis	risk of rectum, colon,bladder, or lung carcinoma or hematologic disease after RT for carcinoma of the prostate	pts with carcinoma of the prostate USA, Canada, Europe (UK, Netherlands, Switzerland), Israel 1973–2010 median FU 3 to 12 yr	18 multicenter, 3 monocenter 13 studies OP as a comparison group, 8 studies “no RT” as a comparison group 199 049 pts	carcinoma of the rectum (second tumor) RT vs. no RT, latency 10 yr HR 1.79 [1.34; 2.38] absolute difference in incidence/100 pts 0.2 [0.2; 0.3] carcinoma of the bladder (second tumor) 1.67 [1.55; 1.80] absolute difference in incidence/100 pts 0.6 [0.5; 0.7]
Taylor et al. 2017 (15)	meta-analysis of individual patient data	estimation of the absolute risk after modern radiotherapy for carcinoma of the breast: lung cancer, AER for smokers and non-smokers	women with carcinoma of the breast USA, Canada, Europe old RT: randomized studies RT vs. no RT, randomization year before 2000, median 1983 (1974–89), median FU 10 yr modern RT: studies published 2010–2015	old RT: 75 randomized studies, 40 781 patients modern RT: 214 studies, 647 different treatment regiments one population-based cohort study each for lung carcinoma in smokers and non-smokers as comparison groups for the background rate of lung carcinoma	old studies RT vs. no RT lung carcinoma 94/194 957 pts vs. 40/180 250 pts relative risk 2.1 [1.48; 2.98], EER/Gy 0.11 [0.05; 0.2] determination of the relative risk/Gy of lung carcinoma on the basis of the radiation dose given in the publication and reconstruction in an illustrative RT plan for a fictitious patient; in old studies, the ERR/Gy is calculated as (relative risk –1)/(mean overall pulmonary dose) (not individual, no information on smoking status) calculation of average dose for modern vs. old RT overall lung, 5.7 Gy (interquartile span 3.4–8.3) vs. 10 Gy calculation of mortality due to lung cancer compared to the normal population up to age 80: 50-year-old with RT, never smoked: 0.8% vs. 0.5%, absolute difference 0.3% 50-year-old with RT, active smoker: 13.8 vs. 9.4%. absolute difference 4.4% 50-year-old with RT, active smoker only up to RT: absolute difference 1.3%

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Grantzau et al. 2016 (39)	meta-analysis	risk of a second carcinoma in women with breast cancer with and without adjuvant radiotherapy compared to the normal female population	women with carcinoma of the breast USA, Canada, Europe 1935–2007 mean FU 8.5 yr	22 studies 16 population-based and 6 monocenter cohort study 522 739 pts (47% with RT)	all SecT (not carcinoma of the breast), SecT in lung, esophagus, or thyroid, sarcoma pts with RT all SecT SIR 1.23 [1.12; 1.13] latency ≥ 10 yr 1.51 [1.21; 1.88] lung SIR 1.09 [0.94; 1.25], p = 0.264 latency ≥ 10 yr 1.58 [1.21; 2.05], p = 0.001 esophagus SIR 1.46 [1.18; 1.79], p < 0.001 latency ≥ 10 yr 2.82 [1.45; 5.49], p = 0.002 thyroid SIR 1.28 [1.0; 1.65], p = 0.054 latency ≥ 10 yr 2.15 [1.03; 4.51], p = 0.043 sarcoma SIR 4.59 [2.19; 6.94], p < 0.001 latency ≥ 10 yr 6.54 [3.54; 12.1], p < 0.001 pts without RT all SecT SIR 1.08 [1.03; 1.36] latency ≥ 10 yr 1.16 [1.1; 1.24] lung 0.93 [0.82; 1.05], not significant latency ≥ 10 yr 1.17 [0.86; 1.58], not significant esophagus SIR 1.14 [0.97; 1.34], not significant thyroid SIR 1.21 [1.03; 1.4], p = 0.017 sarcoma SIR 1.42 [1.18; 1.71], p < 0.001 latency ≥ 10 yr 1,63 [0.76; 3.49]
Radiotherapy in childhood or adulthood					
Berrington de Gonzalez et al. 2013 (40)	meta-analysis	dose-effect relationship for fractionated RT with > 5 Gy absorbed organ dose	epidemiologic studies on second tumors and with adequate information on RT dose UK, USA published 1988–2010	28 studies, including 25 case-control in cohort studies (16 studies on pediatric tumors) 3343 pts	There is a linear dose-effect relationship except for thyroid cancer, which displays a bell effect (rise up to 20 Gy, fall thereafter) excess relative risk/Gy: lung carcinoma (SecT) 0.15–0.2 after treatment in childhood and adolescence: carcinoma of the breast (SecT) 0.13–0.27 brain tumor (SecT) glioma/PNET 0.33–0.8 meningioma (SecT) 1.06–5

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Franklin et al. 2017 (Cochrane) (e37)	meta-analysis	1. secondary malignancies after the treatment of Hodgkin's lymphoma in childhood or adulthood 2. risk of secondary malignancy after chemotherapy vs. identical chemotherapy + radiotherapy 3. risk of secondary malignancy after chemotherapy + involved field RT vs. identical chemotherapy + extended field (early stages) 4. risk of secondary malignancy after chemotherapy + low-dose RT vs. chemotherapy + higher-dose RT (early stages)	patients with Hodgkin's lymphoma randomized, controlled studies USA, Europe 1984 –2007	21 studies, 16 with individual patient data, 3–4 studies per question, with 1101 –2996 pts	1. risk of secondary malignancy OR 0.43 [0.23; 0.82], mainly secondary acute leukemia, low-quality evidence SecT 4% vs. 8%, HR 0.71 [0.42; 1.1], questionable effect on overall survival, high-quality evidence 2. risk of secondary malignancy OR 0.86 [0.64; 1.16], low-quality evidence overall survival HR 0.89 [0.72; 1.12] progression-free survival HR 1.2 [0.81; 1.21] high-quality evidence 3. risk of secondary malignancy OR 1.03 [0.71; 1.5], low-quality evidence overall survival HR 0.91 [0.65; 1.28] high-quality evidence 4. insufficient data to draw any conclusion
Radiotherapy in childhood and adolescence					
Taylor et al. 2010 (e27)	cohort study and case-control studies	risk of second tumors in the CNS after tumor treatment in childhood correlation of this risk with treatment and genetic susceptibility	children < 15 yr at time of treatment UK 1940–1991 FU to 2002 mean FU, 17.3 yr	13,211 5-year survivors case-controls, 247 pts with SecT and 243 pts without SecT not stratified according to RT	247 SecT mean interval from treatment to SecT: PNET 9 yr, glioma 17 yr, meningioma 23 yr SIR glioma overall 10.8 [8.5; 13.6] AER glioma 10 000 patient-years RT 3.0 [2.1; 3.8] no RT 1.2 [0.3; 2] chemotherapy 2.6 [1.6; 3.6] no chemotherapy 2.3 [1.5; 3.2] case-controls, 162 pts glioma 10–20 Gy RR 0.5 [0.1; 23] 20–30 Gy RR 2.6 [0.9; 8] > 39 Gy RR 4.4 [1.2; 16.4] meningioma RR adjusted for intrathecal methotrexate 10–20 Gy RR 8.4 [6.4; < 10.7] 20–30 Gy RR 51.6 [5.5; < 69.5] > 39 Gy RR 479 [25; < 657] the risk of glioma is correlated with age and genetic susceptibility intrathecal methotrexate elevates the risk of meningioma

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Taylor et al. 2008 British Childhood Cancer Survey (e38)	cohort study individual patient data	risk of a second tumor after treatment of a Wilms tumor in 5-year survivors compared to the normal population	pts with Wilms tumor children < 15 yr, 5-year survivors or older than 20 yr UK diagnosis 1940–91 FU to 2002	1441 pts	number of events: 81 SecT, incl. 52 solid Tu (50 pts with RT), 26 basal-cell Ca, 3 AML solidTu AER 10 000 patient-years male 13 [6.7; 19.3], female 18 [10.8; 26.6] SIR 6.7 [5; 8.8] overall SIR depending on length of FU: 0–9 yr; 10–19 yr; > 29 yr 9.4 [4.7; 16.8]; 7.8 [4.4; 12.9]; 3.6 [1.7; 6.9] Remark: Solid Tu mainly in patients with RT, mainly in or near the RT field; very large RT fields were applied
Bowers et al. 2013 (e29)	systematic review	risk of a CNS tumor after cranial RT for cancer in childhood	pts who underwent cranial RT before age 20, survived, and went on to develop a CNS tumor USA, Europe (UK, Netherlands, Italy, Scandinavia) published up to 2011 treatment years1940–2005	16 retrospective cohort studies (4 population-based) 2 case-control studies compared with Central Brain Tumor Registry, USA 959 CNS Tu as SecT in >150 000 survivors	risk of CNS Tu (SecT) after treatment with or without RT (no stratification) SIR glioma 8.9–24.3 AER glioma 2.1–3.4/10 000 patient-years meningioma (including schwannoma) 41–714/10 000 patient-years
Bavle et al. 2018 (e39)	systematic review	risk of a second tumor after craniospinal RT for medulloblastoma in childhood	patients with medulloblastoma USA, Europe (UK, Netherlands, Scandinavia) 1963–2008 median FU 9 yr	2 prospective / 5 retrospective monocenter studies, 1 retrospective cohort (55 pts) 1114 patients	10 yr cumulative incidence malignant SecT 3.7 [2.7; 4.9] benign SecT 3.1 [1.4; 5.3] 40% of the tumors were in the radiation exit field, including 40% thyroid carcinomas

Authors	Type of study	Question being studied	Patient population, country, years of treatment, follow-up interval	Number of studies, number of patients	Results
Bhatti et al. 2010 (e26)	cohort study	risk of thyroid carcinoma after treatment for (non-)Hodgkin's lymphoma, a renal tumor, a bone tumor, neuroblastoma, or soft-tissue sarcoma	children/adolescents < 21 yr USA, Netherlands 1970–1986	Childhood Cancer Survivor Study 12,547 pts, 118 thyroid carcinomas RT details known	linear-exponential dose-response curve up to a maximum at 20 Gy, with declining incidence thereafter (the so-called bell effect) risk higher with young age, female sex (high background incidence) age during treatment < 5 yr AER < 5 yr 8.3 SIR 17.2 [12.2; 24.3] age during treatment 5–9 yr AER 5–9 yr 4.2 SIR 15.7 [10.7; 23] compared to age < 5 yr during treatment: 5–9 yr 0.7 [0.4; 1.2] > 14 yr 0.2 [0.1; 0.4]
Henderson et al. 2010 (e28)	systematic review	1. What is the incidence of carcinoma of the breast after chest/mantle-field/similar RT in childhood or adolescence, up to age 30? 2. Do these breast carcinomas differ from the sporadic breast carcinomas seen in the general population?	women who underwent RT of the chest in childhood or early adulthood USA 7000 pts 1960–2000	11 retrospective cohort studies 3 case-control studies	1. SIR 13.3 –55 AER 18.6–79/10 000 patient-years no difference whether RT was received before puberty or during adolescence 2. At the time of diagnosis of breast carcinoma, patients who received RT in childhood or adolescence are younger than those in the normal population, and they more frequently have bilateral carcinomas (12 vs. 3–5%). No differences with respect to histology, node status, or estrogen receptors. In both groups, the probability of survival is determined by the disease stage at the time of the initial diagnosis.

95% confidence intervals are given in square brackets.
AE, absolute excess, i.e., the absolute number of additional events; AER, absolute excess risk, i.e., the risk of additional events; AML, acute myelogenous leukemia; assoc., associated; Ca, carcinoma; dos, dosed; ERR, excess rate ratio/Gy; FU, follow-up time; Gy, Gray; HR, hazard ratio; OP, operation; OR, odds ratio; pts, patients; PORTEC, Post-Operative Radiation Therapy in Endometrial Carcinoma; RR, relative risk; RT, radiotherapy; SecT, solid second tumor; SEER, Surveillance, Epidemiology, and End Results Program; SIR, standard incidence ratio (compared to age-matched normal population); TME, total mesorectal excision; Tu, tumor; vs., versus; yr, year(s)

Questions on the article in issue 12/2021:

cme plus+

Late Sequelae of Radiotherapy—The Effect of Technical and Conceptual Innovations in Radiation Oncology

The submission deadline is 25 March 2022. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

What does the abbreviation IMRT stand for?

a) intensive modular radiotherapy
b) invasive modulated radiotherapy
c) intelligence-modulated radiotherapy
d) intensity-modulated radiotherapy
e) included modulated radiotherapy

Question 2

What is the designation of the parameter that describes the ratio of intensities of two different types of ionizing radiation that is needed for them to have the same biological effect?

a) relative histological effectiveness
b) relative biological effectiveness
c) relative radiological effectiveness
d) relative morphological effectiveness
e) relative therapeutic effectiveness

Question 3

What percentage of patients who have undergone radiotherapy develop late sequelae of radiotherapy in normal tissue?

a) 2–4%
b) 13–15%
c) 5–10%
d) 10–12%
e) 15–18%

Question 4

Whole-brain radiotherapy (WBRT) can be followed by neurocognitive functional impairment. In a phase III trial, WBRT with dose reduction (tissue sparing) in a particular region of the brain was found to be associated with less severe cognitive impairment four months after treatment than WBRT without dose reduction. What is the brain region in question?

a) the amygdala
b) the pyramidal tract
c) the frontal cortex
d) the corpus callosum
e) the hippocampus

Question 5

In a meta-analysis by Taylor et al. concerning estimation of the risk of a second tumor in the lungs after radiotherapy for breast cancer, the mortality due to lung cancer up to age 80 was determined among women who had been so treated compared to the normal population. What risk was found for women who, at the time of radiotherapy (with a dose of 5 Gy to the lungs), were 50 years old and had never smoked, compared to female non-smokers in the normal population (0.5% risk)?

a) 0.05%
b) 0.5%
c) 0.8%
d) 9.4%
e) 13.8%

Question 6

According to an analysis of clinical cohort studies of women with breast cancer who did or did not undergo radiotherapy to the breast in the years 1935–2007, by what factor was the rate of second tumors elevated ten years after treatment, in comparison to the normal population (SIR)?

a) 1.5 in irradiated patients, 1.16 in non-irradiated patients
b) 1.2 in irradiated patients, 2 in non-irradiated patients
c) 0.8 in irradiated patients, 0.5 in non-irradiated patients
d) 2 in irradiated patients, 2.5 in non-irradiated patients
e) 2.2 in irradiated patients, 1.5 in non-irradiated patients

Question 7

What is a major advantage of stereotactic radiotherapy for small tumor volumes?

a) it enables compensation for organ movement during radiotherapy
b) it does not require very precise imaging
c) it corrects for the patient's respiratory movements during radiotherapy
d) its spatial precision enables the application of high individual doses
e) treatment planning is easily accomplished and is not labor-intensive

Question 8.

Which of the following techniques is still in the initial phase of clinical evaluation?

a) breathing-controlled radiotherapy with breath-holding technique
b) breathing-controlled radiotherapy with gating
c) proton-beam therapy
d) stereotactic radiotherapy
e) MR accelerators

Question 9

The rs1801516 polymorphism of the ataxia-telangiectasia gene, which is present in about 10% of the population, has been found to be significantly associated with the degree of severity of late sequelae of radiotherapy for certain types of cancer. What are these types of cancer?

a) non-Hodgkin's lymphoma and ependymoma
b) breast and prostate cancer
c) hepatocellular carcinoma and basal-cell carcinoma
d) gingival and renal-cell carcinoma
e) pancreas and lung cancer

Question 10

What is the estimated percentage of solid second tumors in adults that are attributable to radiotherapy?

a) approximately 0.5%
b) approximately 1%
c) approximately 3%
d) approximately 5%
e) approximately 8%