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Radiotherapy for non-cancer diseases: Benefits and long-term risks

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Abstract

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Purpose: The discovery of X-rays was followed by a variety of attempts to treat infectious diseases and various other non-cancer diseases with ionizing radiation, in addition to cancer. There has been a recent resurgence of interest in the use of such radiotherapy for non-cancer diseases. Non-cancer diseases for which use of radiotherapy has currently been proposed include refractory ventricular tachycardia, neurodegenerative diseases (e.g., Alzheimer's disease and dementia), and Coronavirus Disease 2019 (COVID-19) pneumonia, all with ongoing clinical studies that deliver radiation doses of 0.5–25 Gy in a single fraction or in multiple daily fractions. In addition to such non-cancer effects, historical indications predominantly used in some countries (e.g., Germany) include osteoarthritis and degenerative diseases of the bones and joints. This narrative review gives an overview of the biological rationale and ongoing preclinical and clinical studies for radiotherapy proposed for various non-cancer diseases, discusses the plausibility of the proposed biological rationale, and considers the long-term radiation risks of cancer and non-cancer diseases.

Conclusions: A growing body of evidence has suggested that radiation represents a double-edged sword, not only for cancer, but also for non-cancer diseases. At present, clinical evidence has shown some beneficial effects of radiotherapy for ventricular tachycardia, but there is little or no such evidence of radiotherapy for other newly proposed non-cancer diseases (e.g., Alzheimer's disease, COVID-19 pneumonia). Patients with ventricular tachycardia and COVID-19 pneumonia have thus far been treated with radiotherapy when they are an urgent life threat with no efficient alternative treatment, but some survivors may encounter a paradoxical situation where patients were rescued by radiotherapy but then get harmed by radiotherapy. Further studies are needed to justify clinical use of radiotherapy for non-cancer diseases, and optimize dose to diseased tissue while minimizing dose to healthy tissue.

Introduction

Radiotherapy (RT) aims to deliver ionizing radiation doses to diseased tissue with minimal exposure of neighboring healthy tissues. Normal tissue complications following RT include cancer and non-cancer effects. Even taking into account possible practical dose thresholds for non-cancer effects of radiation that generally decrease with increasing post-irradiation time (ICRP 2012), the longer the post-radiotherapeutic survival of patients, the broader the spectrum of normal tissue complications of concern (Hamada 2023). Recent studies have demonstrated that radiation exposure might be used therapeutically for various non-cancer diseases such as arrhythmia, neurodegenerative diseases and diabetes (Zhang et al. 2021; Wilson et al. 2023; Paithankar et al. 2023), but can also increase risks of these non-cancer diseases (Errahmani et al. 2021, 2022; Azizova et al. 2020, 2023; Gillies et al. 2017; Laurent et al. 2023; Hayashi et al. 2003; de Vathaire et al. 2012), indicating that radiation represents a double-edged sword for non-cancer effects in addition to the cancer risks. As such, justification (to ensure that benefits outweigh the summed total of different types of effects, when they are appropriately weighted by quality of life (QOL) and years lived) and optimization of RT (to keep the dose as low as therapeutically achievable) would be important regardless of whether RT is used to treat cancer or non-cancer diseases to ensure adequate protection from harm in the long term.

In the first half of the 20th century, attempts were made to use RT for various non-cancer effects, such as cardiovascular diseases (CVD) (e.g., angina pectoris, myocarditis) (Sabrazès

and Rivière 1897), ocular diseases (e.g., cataracts) (Cohen and Levin 1919) and infectious diseases (e.g., viral or bacterial pneumonia) (Calabrese and Dhawan 2013): reported case series studies showed some success, but there appeared to be little ground for believing that such an approach might be effective (Desjardins 1931, 1932; Salomaa et al. 2020a, 2020b; Little et al. 2021). From the mid-20th century onwards, use of RT for non-cancer diseases has been increasingly restricted to painful degenerative skeletal diseases (e.g., osteoarthritis), musculoskeletal disorders (e.g., entesopathies), hyperproliferative disorders (e.g., keloids), symptomatic functional disorders (e.g., heterotopic ossification, trigeminal neuralgia), particularly in Germany where annually 50,000 patients receive such RT (Seegenschmiedt et al. 2015). However, there has recently been a surge of interest, and preclinical and clinical studies are ongoing that propose the use of RT for various non-cancer diseases, such as refractory ventricular tachycardia (VT), neurodegenerative diseases (e.g., Alzheimer's disease (AD) and dementia), and Coronavirus Disease 2019 (COVID-19) pneumonia, as detailed below.

This paper reviews the current knowledge relating to RT proposed for various non-cancer diseases in terms of the biological rationale and the ongoing preclinical or clinical studies, discusses plausibility of the proposed rationale, and considers the long-term radiation risk of cancer and non-cancer diseases. A particular focus is placed on RT for VT, neurodegenerative diseases and COVID-19 pneumonia, but one section is dedicated to RT for other various non-cancer diseases or conditions (e.g., vascular, skeletal, hyperproliferative, metabolic or autoimmune disorders).

Radiotherapy for refractory ventricular tachycardia

Relevant clinical findings

VT is a life-threatening heart arrhythmia that can arise from either ischemic heart disease (IHD) or non-IHD and has increased in prevalence with the global increase in heart disease. Monomorphic VT in particular is associated with cardiomyopathy and results when a scarred area of the heart (i.e., from myocardial infarction) cannot depolarize correctly and therefore creates an aberrant circuit around the scar (re-entry circuit).

First line management of monomorphic VT includes anti-arrhythmic medications, placement of an implantable cardioverter-defibrillator (ICD), and ultimately catheter ablation to both identify and destroy the re-entrant electrical circuit causing the arrhythmia. However, each of these approaches has their own risks with various control rates. The most common medication for VT, amiodarone, may not be tolerated by all patients, and may have to be stopped in the event of vision loss or pulmonary fibrosis. ICDs are life-saving devices that can electroconvert the patient back into a normal rhythm, but episodes of device firing can be associated with post-traumatic stress disorder and decreased QOL (Bostwick Sola 2007). Additionally, it is possible that there is excess mortality associated with catheter ablation (Lee et al. 2022). Complications that can be seen following catheter ablation include groin hematoma, cardiovascular collapse, damage to cardiac valves, cardiac perforation and stroke (Mathew et al. 2022; Pastapur et al. 2023). Furthermore, the risk of VT recurrence after a successful catheter ablation can be high, with series reporting recurrence rates ranging from 12% to >50% (Liang et al. 2015). Finally, not all VT patients

may be eligible for catheter ablation. Frequent reasons for unsuccessful catheter ablation include vascular disease prohibiting safe access and presence of VT in certain anatomical locations of the heart after cardiac surgery.

Due to the high recurrence rates of VT even after optimizing the gold standard trimodality approaches (i.e., medication, ICD placement, catheter ablation) described above, many patients with VT may require repeat catheter ablation procedures (Tzou et al. 2017). Given the ability of RT to provide a conformal dose in an ablative manner, interest turned to the use of stereotactic body RT (SBRT) to treat the VT circuit. The most common treatment approach in patients has been linear accelerator (LINAC) treatments with 6 MV photons and flattening filter free, but Cyberknife and protons have also been used. Early porcine models demonstrated that a single fraction of at least 25 Gy to the normal left ventricle could induce non-conductive scar tissue (Blanck et al. 2014). The first prospective study of RT for VT was ENCORE-VT, a phase I/II study for cardiac SBRT in patients with treatment-refractory monomorphic VT (Robinson et al. 2019). Of note, eligible patients were those who had recurrent VT despite previous catheter ablation, could no longer tolerate anti-arrhythmic medications, and/or were not candidates for repeat catheter ablation. This small study (n=19) demonstrated both safety and efficacy of cardiac SBRT (Robinson et al. 2019). 94% of patients had VT episode reduction and overall survival was 89% at 6 months and 72% at one year; this compares favorably with rates of one-year overall survival among patients with treatment refractory VT that is estimated at 50–60% (Robinson et al. 2019). Additionally, use of dual anti-arrhythmic drugs in the ENCORE-VT study decreased from 59% to 12% and significant improvements in QOL measures were also demonstrated.

There have been a number of additional studies of patients with VT treated with SBRT which show significant improvements after radiation (Cuculich et al. 2017; Neuwirth et al. 2019; Ninni et al. 2022; van der Ree et al. 2023a, 2023b). In other studies, however, there was only borderline significant or no improvement (Gianni et al. 2020; Lloyd et al. 2020; Carbucicchio et al. 2021; Qian et al. 2022), and in one study there was only a single case (Jumeau et al. 2018), making assessment unreliable. A recent systematic review and meta-analysis of 61 patients from seven studies (literature available by February 2023: Cuculich et al. 2017; Neuwirth et al. 2019; Robinson et al. 2019; Gianni et al. 2020; Chin et al. 2021; Lee et al. 2021; Carbucicchio et al. 2021) indicated that at 6 months after radiotherapy for VT, there were a 92% (95% confidence intervals (CI): 85, 100) reduction in the VT burden, an 86% (95% CI: 80, 93) reduction in the number of ICD shocks, the rates for improved left ventricular ejection fraction (LVEF) of 10%, overall survival of 89% (95% CI: 81, 97), the cardiac specific survival of 87% (95% CI: 81, 97), with late grade 3 toxicity in 2% (95% CI: 0, 5) and no grade 4–5 toxicity (Viani et al. 2023). With the results of ENCORE-VT and other institutions reporting VT reduction in a salvage setting, the use of LINAC as a treatment device for VT was granted compassionate use status, therefore facilitating SBRT for VT. These clinical trials had generally limited follow up (mostly <1 year) (Table 1), but longer-term follow-up data (>1 year) is beginning to emerge from both the ENCORE-VT trial and compassionate use populations. One of the most important outstanding questions if cardiac SBRT were to have wider adoption for VT treatment, or if it was performed in patients with less severe cardiac disease, is what is the incidence and severity of radiation-related toxicities. Discerning treatment-related late toxicities in this

patient population, as in groups treated with catheter ablation, is challenging, as patients already have significant heart disease with high cardiac mortality without treatment, and follow-up is limited. While radiation to the heart has long-term side effects (Little et al. 2023a), in these VT patients with known CVD (by definition of their VT arising from either IHD or non-IHD) it is unclear whether there is measurable excess cardiac risk from doses arising within the first few years after treatment. Indeed, series reporting outcomes for patients receiving RT for VT indicate high cardiovascular morbidity and mortality (Table 1), as would be expected. One recent retrospective analysis of 20 patients who received 20–25 Gy of RT to the planning target volume for VT examined LVEF and valvular disease after RT by assessing echocardiograms taken as part of clinical care. With median follow-up of 1.7 years (range of 0.9 to 3.9 years), they found no significant decrease in LVEF in any time period; however, 5 of the 20 patients experienced worsening of valvular function, with the aortic valve most commonly affected (van der Ree et al. 2023a). There was a significant difference in dose to the aortic valve between patients who had worsening function and those that did not (16.8 Gy vs. 7.2 Gy, p=0.03) (van der Ree et al. 2023a). More studies like this may lead to knowledge regarding risks and safer ways to deliver RT for VT.

The number of patients receiving cardiac SBRT is increasing globally, but it remains a very small population. It will take much larger series than presently exist, and with much longer follow-up, to determine the risk of long-term adverse side effects from radiation. In addition, much of the data on radiation-induced cardiotoxicity from other groups is associated with radiation exposure of patients with relatively healthy heart tissue without CVD (Little et al. 2023a). It is unclear how treatment with one very large dose of radiation to an already scarred portion of the heart in patients with heart failure relates to the findings from these other groups.

To date, the most commonly reported late toxicities from use of radiation treatment have included Grade 2 nausea, Grade 3 pericarditis and Grade 3 pneumonitis (Robinson et al. 2019; Neuwirth et al. 2019), but there have also been cases of Grade 4 gastropericardial fistula (Hayase et al. 2022) and Grade 4 heart failure exacerbation (Qian et al. 2022). Two small cohorts of patients receiving echocardiograms before cardiac SBRT, with follow-up between 3–12 months after treatment, showed no decline in LVEF after radiation (Robinson et al. 2019; Cuculich et al. 2017). Additionally serial electrocardiograms of patients pre- and post-cardiac SBRT showed that there could be a variety of changes in the duration of the QRS and QTc intervals for most patients (89%), with approximately 57% occurring within 3 days of treatment and 90% occurring within 3 months (Zhang et al. 2021). However, no patients in this series had any clinically significant conduction changes such as atrioventricular block or new arrhythmias. Continued monitoring of cardiac SBRT dosimetry will be important to collect both on and off trial, to determine if there are any correlations between late toxicities and target and/or organ at risk doses (Knutson et al. 2019).

Underlying mechanisms

There is considerable uncertainty regarding the underlying mechanisms by which SBRT may result in effective treatment of VT (Whitaker et al. 2022). It is important to note that while late cardiac toxicity from conventionally fractionated RT can result from chronic

fibrotic changes, the decrease in VT episodes following cardiac SBRT happens within days to weeks, much faster than would be expected with a fibrotic pathway (Dreyfuss et al. 2022). It has been shown that the clinical radiation dose of 25 Gy does not appear to increase fibrosis in the timeframe that decreased VT burden appears, and in murine models this dose of radiation enhances ventricular conduction (Zhang et al. 2021). Recent research using preclinical mouse models to elucidate the mechanisms of VT reduction and/or cessation following cardiac SBRT (25 Gy) suggested that increased expression of cardiac conduction proteins such as connexin 43 (a gap junction channel component) and voltage gated sodium channels via Notch signaling pathways shortly after cardiac radiation could contribute to the treatment effect (Zhang et al. 2021). Another group described the cardiac proteome changes (e.g., decreases of proteins involved in actin filament or fiber organization) that occurred within 7 days following cardiac SBRT (25 Gy) in a rat model (Kim et al. 2022). In addition, intriguing recent work suggests that in preclinical mouse models lower doses of radiation (5 Gy) may attenuate adverse cardiac remodeling in heart failure, and patient data in a small cohort of patients from the ENCORE-VT study also demonstrated improvements in LVEF and end diastolic function after SBRT for VT (Pedersen et al. 2023). Future studies on how lower doses of radiation can affect cardiac remodeling in heart failure patients are needed.

Further characterization of the mechanisms of VT reduction from cardiac SBRT continues and is an active area of research. Additional data is needed on long-term cardiac and non-cardiac toxicities for this patient population. Collaborations between centers performing these treatments to pool dosimetry data and patient outcomes in prospective registries will be required to fill this knowledge gap. Clinical trials continue to move forward in this field, the most recent being the multicenter RADIATE-VT phase II randomized trial (https://clinicaltrials.gov/ct2/show/study/NCT05765175) comparing cardiac SBRT to repeat catheter ablation for patients with recurrent monomorphic VT to help determine the optimal approach in this population. A Delphi review of these studies (Krug et al. 2021) has highlighted the groups of patients for whom SBRT may be useful. In particular, SBRT can be considered in patients with refractory VT who have optimal medical management and have failed prior catheter ablation, or who have contraindications to catheter ablation. The Delphi review indicated the importance of: treatment at centers with strong expertise in SBRT and VT patient management; patient selection, interdisciplinary processes, and teams for target definition; and optimal follow-up (Krug et al. 2021).

Radiotherapy for neurodegenerative diseases

Current clinical studies

A few clinical case reports of improved cognitive symptoms in AD patients receiving multiple head computed tomography (CT) scans and preclinical evidence (Wilson et al. 2023) led to at least four clinical trials being initiated to test the safety and tolerability of whole brain RT (WBRT, in one case with hippocampal sparing) in patients with AD. Although some trials included other treatment arms, all initially employed 5 or 10 daily fractions of 1.8 or 2 Gy (total dose ranging from 9–20 Gy), except three patients receiving 3 daily fractions of 1.8 Gy (total dose of 5.4 Gy) (Wilson et al. 2023). Two trials in the United States were terminated, due in part to the COVID-19 pandemic, with only 2 and

5 patients treated in Michigan (https://clinicaltrials.gov/ct2/show/results/NCT02359864) and Virginia (https://clinicaltrials.gov/ct2/show/results/NCT02769000), respectively. Of these, the results from the Virginia trial were recently reported: improvement in Mini-Mental State Examination (second edition) (MMSE-2) T scores and relative stability in other neuropsychological test endpoints was found in 3 of 5 patients over a 12 month observation period following fractionated megavoltage WBRT (Rogers et al. 2023). The status of two trials, one in Switzerland that includes control (non-irradiated) subjects (https://clinicaltrials.gov/ct2/show/study/NCT03352258), the other in South Korea (https://clinicaltrials.gov/ct2/show/NCT04203121), are not known, though some patient accrual may have occurred (Wilson et al. 2023). The results from all these trials have yet to be reported.

Relevant biological data

A recent review highlights preclinical studies that appear to demonstrate some beneficial effects of certain radiation dose regimens on key pathological endpoints in mouse models of AD (Wilson et al. 2023). These models are based on transgenic overexpression of mutated human genes associated with amyloid-β processing, which leads to deposition of amyloid plaques, or mutations in tau, a microtubule-stabilizing protein that becomes hyperphosphorylated in AD leading to accumulation of neurofibrillary tangles and neural loss/dysfunction. Depending on the model used, these studies include beneficial effects on amyloid plaque load as well as levels of hyperphosphorylated tau and provide some potential insights into mechanisms underlying such changes after irradiation (Kim et al. 2020; Yang et al. 2021; Ceyzériat et al. 2022).

While these findings are of potential utility in supporting the proposed clinical use of RT for AD, there is a large body of research highlighting the deleterious effects of radiation on the rodent central nervous system (CNS). One of these effects observed with single doses of 1–10 Gy is loss of synapses and dendritic complexity in the hippocampus (Chakraborti et al. 2012; Parihar and Limoli 2013; Hinkle et al. 2019), a recognized component of the neurodegeneration leading to AD dementia (Forner et al. 2017; Meftah and Gan 2023). Synaptic loss in AD and aging depends in part on complement activation and direct pruning by complement receptor bearing microglia (Shi et al. 2015, 2017; Hong et al. 2016). A similar mechanism appears to underlie synaptic loss following irradiation (~10 Gy), which depends on components of the complement system and is associated with increased expression of the microglial lysozyme protein CD68 involved in phagocytosis (Hinkle et al. 2019; Markarian et al. 2021). Moreover, pharmacologic depletion of microglia with colony stimulating factor 1 receptor (CSF1R) inhibitors also preserves cognitive capacity after low linear energy transfer (LET) (9 Gy) and high LET (0.3 Gy of 400 MeV/u ^{4}He or 0.5 Gy of 250 MeV/u ^{4}He) irradiation in mice (Acharya et al. 2016; Krukowski et al. 2018, 2021; Allen et al. 2020). Indeed, radiation induces changes in microglia and other brain cell types, including expression of genes also detected in AD, Parkinson’s disease (PD) and aging (Wang et al. 2021). These include genes associated with neuroinflammation, a complex reaction involving multiple cell types that can have both deleterious as well as beneficial effects in AD mouse models (Shaftel et al. 2008; McFarland et al. 2022).

There are also reports that directly examine the effects of radiation on AD pathology, some of which have demonstrated exacerbation of plaque pathology and increased cognitive dysfunction, particularly in male mice (Cherry et al. 2012; Schroeder et al. 2021). Although these observations were made with high energy particle irradiation mimicking aspects of space radiation, the findings clearly show that radiation can negatively impact mechanisms controlling plaque deposition in the same mouse models that were used to show benefits (Wilson et al. 2023) and may have specific implications for proton or heavy ion RT.

One of the key features of protocols showing benefits is the use of fractionated dosing schemes, with total doses of 10–20 Gy in mice (Wilson et al. 2023). These doses are likely to have effects on proliferating cell populations, including newly borne neurons in the hippocampus (Park et al. 2012; Sweet et al. 2016) and subventricular zones (Balentova et al. 2014) as well as proliferating oligodendrocyte precursor cells (Begolly et al. 2018). Given that hippocampal sparing is being investigated in brain irradiation paradigms to reduce cognitive decline (Rodriguez et al. 2021; Shang et al. 2022), the possibility that RT for AD may have similar adverse effects is concerning.

Radiation exposure can also lead to changes in endothelial cells and other cell populations associated with the vasculature and blood brain barrier (BBB) (Wang et al. 2021). Moreover, there is substantial evidence for increased risk of cerebrovascular disease (CeVD) in adult survivors of childhood brain tumors treated with radiation (Remes et al. 2020). Vascular and BBB dysfunction is well known in AD and may contribute to disease progression even at the very earliest stages (Nation et al. 2019; Barisano et al. 2022).

Importantly, amyloid plaque clearance alone is not likely to be beneficial for AD patients as demonstrated by the many failed trials of anti-amyloid therapies (Perneczky et al. 2023). Indeed, the only approved anti-amyloid therapies have profound effects on amyloid load, need to be given at regular intervals, and are associated with serious risks of vascular complications (Musiek et al. 2023). There is clearly a need for improvement in our ability to prevent and treat AD; it is unknown whether observations of potential radiation-associated benefits in preclinical studies will ever translate to the clinic.

Ultimately, for any therapeutic intervention one must consider potential risks and benefits. AD is a complex disorder characterized by neural and synaptic loss, neuroinflammation, pathological hallmarks, and BBB dysfunction. Most agree that AD must be treated early in the course of disease or even in preclinical phases to delay neurodegeneration and loss of cognitive capacity (Jack et al. 2018). Given known risks of radiation to the healthy brain, including clear effects on cognitive function, it seems unlikely that radiation will have a role in preventative AD treatment strategies. If used to treat individuals after clinical onset, randomized studies showing substantial improvement in QOL will be needed.

Potential long-term risk

The biological mechanisms behind long-term effects of radiation injury to the brain remain incompletely understood. Epidemiological studies of neurological effects have focused on risks of AD, PD, dementia and related causes. In 2012, a systematic review concluded that there were few population-based studies of radiation exposure and increased risk of

dementia and related outcomes, which provided conflicting evidence (Begum et al. 2012). Since then, new evidence emerged from population studies pointing to increased risks of dementia, including AD (Laurent et al. 2023) and PD (Azizova et al. 2020), after radiation exposures. In particular, a number of studies have noted radiation-induced cognitive injury (Pasqual et al. 2021).

Several recent meta-analyses summarized epidemiological evidence on radiation risks of cognitive disorders (Pasqual et al. 2020; Lopes et al. 2022a; Srivastava et al. 2023; Dauer et al. 2023), but only three are relevant to the doses in RT for AD (Lopes et al. 2022a; Srivastava et al. 2023; Dauer et al. 2023), the results of which are summarized in Table 2. Lopes et al. examined radiation risks for a broad grouping of non-malignant CNS diseases that also included PD (Lopes et al. 2022a). The meta-analysis of four studies (3 studies of nuclear industry workers and 1 study of medical radiation workers) showed a significantly increased excess relative risk (ERR) per 100 mGy for PD (ERR/100 mGy = 0.11; 95% CI: 0.06, 0.16), an order of magnitude higher than radiation risks of CeVD (ERR/100 mGy = 0.019; 95% CI: 0.009, 0.028) or to the larger group of CVD (ERR/100 mGy = 0.011; 95% CI: 0.008, 0.014) observed in a meta-analysis of 93 studies (Little et al. 2023a). However, a meta-analysis of standardized mortality ratios comparing observed outcomes to those expected based on the general population rates of PD showed no increase in risks (Lopes et al. 2022a). Several studies have suggested that various biological processes (e.g., inflammation, oxidative stress, apoptosis and tissue necrosis) are commonly affected both in radiation-induced neurodegenerative diseases and CVD (Begum et al. 2012; Chi et al. 2018), so a potential difference in the magnitude of radiation risks requires further careful investigation.

A recent meta-analysis by Srivastava et al. examined epidemiological studies of dementia, AD and PD after radiation exposure (Srivastava et al. 2023). It included 18 studies from five typical radiation exposure scenarios: (1) atomic bomb survivors; (2) RT patients; (3) nuclear industry workers; (4) populations receiving environmental radiation exposures, including background and accidental radiation; and (5) patients receiving CT scan and other diagnostic radiation. The final meta-analysis was based on 8 studies with low-to-moderate dose chronic radiation exposures only. Meta-analysis ERR/100 mGy were 0.11 (95% CI: 0.04, 0.18) for all dementia subtypes (which includes AD, PD, Huntington’s disease, vascular dementia, frontotemporal dementia, and other rarer types of dementia) and 0.12 (95% CI: 0.07, 0.17) for PD alone (Srivastava et al. 2023).

Ten other studies which did not have individual radiation dose estimates or had a high risk of bias were not included in the Srivastava et al. meta-analysis (Srivastava et al. 2023), but provide potentially useful information. Three (Chan et al. 2010; Golden et al. 2021; Boice et al. 2023) of the four studies in occupationally exposed nuclear fuel industry workers showed increased risks of dementia outcomes compared to the general population. One study reported higher risks of dementia after RT for nasopharyngeal cancer compared with the general population matched controls without cancer (Penn et al. 2021). Three studies from the Life Span Study (LSS) cohort of Japanese atomic bomb survivors were reviewed and reported no increase in risk of incident dementia (Yamada et al. 2009) or a decrease in

cognitive function after exposure to moderate to high doses of radiation (Yamada et al. 2016, 2021).

Srivastava et al. (Srivastava et al. 2023) highlighted evidence on potential protective effects against systemic amyloid deposits in AD after low dose RT (LDRT), as well as against chronic inflammatory diseases (Ceyzériat et al. 2020), although suggesting that currently there is not enough evidence to conclude whether radiation exposure causes or prevents dementia, AD and/or PD (Srivastava et al. 2023).

Several studies have shown a high level of mental disorders with an excess of cognitive dysfunction over 0.25 Gy in Chernobyl cleanup workers (Rahu et al. 2014; Bromet et al. 2011). Whether this association is due to the direct effects of radiation or to the effects of psychosocial stress associated with the nuclear accident is not clear (Bromet et al. 2012; Fukasawa et al. 2017, 2022).

One of the biggest problems with examination of mortality outcomes for dementia and related disorders is that death certificates often do not include dementia as the underlying cause of death, which could lead to underascertainment of dementia mortality (Stokes et al. 2020). Another significant limitation is the lack of evidence evaluating the effect of radiation on dementia progression over time. There is also very limited information on the association between radiation dose and dementia severity.

A recent meta-analysis of PD mortality in 6 cohorts of US radiation workers and veterans in the Million Person Study (MPS) of low dose effects reported a significantly increased risk (ERR at 100 mGy = 0.17; 95% CI: 0.05, 0.29) (Dauer et al. 2023). MPS workers were exposed primarily to low LET γ- and X-rays, but some workers received internal exposure to radionuclides and external neutrons. Increased but non-significant risks were seen in five out of the six MPS cohorts which contributed to the meta-analysis. The authors noted that no specific mechanism have been identified to explain the association between radiation exposure and PD mortality and suggested that the observed association could be due in part or in full to as-yet-unknown confounding factors (Dauer et al. 2023).

Collectively, the three recent meta-analyses of radiation risks of various types of neurodegenerative diseases from low-dose exposures reported increased risks of various outcomes (Lopes et al. 2022a; Srivastava et al. 2023; Dauer et al. 2023) and the magnitude of estimated risks was comparable across the studies.

Cancer is also a potential adverse effect following irradiation of the brain. A systematic review and meta-analysis showed no increase in the risk of brain and CNS cancer (ERR/100 mGy = –0.01; 95% CI: –0.05, 0.04) for occupational, environmental, or accidental exposure to low to moderate doses during adulthood (Lopes et al. 2022b). One of the few studies to report significant increases was that of Brenner et al. (Brenner et al. 2020) who examined the risk of brain tumors by histological type in atomic bomb survivors and reported significant associations for glioma (ERR/100 mGy = 0.167; 95% CI: 0.012, 0.526; 67 cases) and meningioma (ERR/100 mGy = 0.182; 95% CI: 0.051 to 0.430; 107 cases), with no clear dose-risk modifying effect for age at exposure or attained age. Non-CNS cancers may also result from irradiating the brain, including basal cell carcinoma and leukemia, whose risk is

elevated in groups of nuclear workers (Muirhead et al. 2009; Haylock et al. 2018): 8% of active bone marrow in adults is in the cranium (ICRP 2002).

Evidence of increased risk of neurocognitive effects after RT also comes from studies of cranial RT in children who have been shown to have increased risks of neurocognitive impairment (Krull et al. 2018). Neurocognitive impairments seem to occur independently of whether patients receive concomitant neurotoxic chemotherapies. The extent of impairments in long-term childhood cancer survivors depends on the original cancer site, dose of cranial RT, medical complications during treatment and genetic predisposition (Krull et al. 2018). Some genetic variants have been associated with higher frequency of cognitive dysfunction in survivors by accelerating its onset (Howarth et al. 2014). Neurocognitive effects are modified by age at diagnosis (with higher risks for younger age at exposure) and brain volume irradiated, and seem to increase with longer time since treatment (Duffner 2010).

The eye receives radiation during WBRT. Even with hippocampal sparing WBRT by volumetric modulated arc therapy (VMAT) or tomotherapy, the ocular lens receives 6–27% of the dose to the whole brain (i.e., 1–5 Gy to the lens vs 20 Gy to the whole brain) (Kim et al. 2016; Oh et al. 2020; Miura et al. 2021). Using radiation cataract incidence risk estimated in the US Radiologic Technologists cohort (Little et al. 2018), baseline cataract incidence risk and mortality risk for the US population (CDC 2020; NEI 2023), lifetime radiation risk of 21.9–81.3% and excess lifetime radiation risk of 12.9–44.4% can be estimated for cataract incidence following exposure of the lens to 1–30 Gy (Table 3). It should be borne in mind that there is a high baseline prevalence of cataract, so that even in the absence of radiation exposure ~45% of the US population will eventually develop cataract (Table 3). Depending on the level of sparing, radiation risk of glaucoma (neovascular glaucoma and normal-tension glaucoma in particular) is also of concern (Hamada et al. 2019; Kiuchi et al. 2019; Azizova et al. 2022), as well as damage to the retina and optic nerve.

In summary, studies published in the last decade point towards an association between radiation exposure and outcomes such as dementia, AD, PD, CeVD, cataracts, brain/CNS cancer and possibly glaucoma. The majority of epidemiological studies included in both meta-analyses (Lopes et al. 2022a; Srivastava et al. 2023) examined the effects of low-dose radiation exposures. Further investigations are necessary to better understand the nature of this association, particularly because the underlying biological mechanisms remain incompletely understood.

Radiotherapy for COVID-19 pneumonia

Since the early part of the last century, before the advent of antibiotics in the 1940s, LDRT was used to treat pneumonia resulting from bacterial or viral infection (Calabrese and Dhawan 2013), and about the same time various radiobiological animal experiments were conducted to investigate radiation-modification of infectious pathology (Little et al. 2021). This old clinical and experimental data was the basis of proposals to use of LDRT for treatment of COVID-19-associated pneumonia (Ghadimi-Moghadam et al. 2020; Kirkby and Mackenzie 2020).

High dose radiation exposure causes a number of adverse health effects, specifically CVD and cancer. At low doses (<0.1 Gy) deleterious effects are more controversial, with much data suggesting increased risks of cancer (Wakeford and Bithell 2021; Little et al. 2022a, 2022b), although there is some experimental data suggesting the reverse (Guéguen et al. 2019) (Yang et al. 2016; Vaiserman et al. 2018), in particular via effects on the innate and adaptive immune system (Cui et al. 2017). A recent review of the biological mechanisms of low dose and low dose-rate radiation effects concluded that the impact of such beneficial effects would not affect the magnitude of cancer risk posed by such exposures (UNSCEAR 2022). Overall, the health risks and benefits associated with low dose radiation remain a subject of debate.

Relevant clinical data

The conclusions of the review paper of Calabrese and Dhawan (Calabrese and Dhawan 2013) underlay many proposals to treat COVID-19 pneumonia with LDRT (Ghadimi-Moghadam et al. 2020; Kirkby and Mackenzie 2020). Little et al. (Little et al. 2021, 2023b) highlighted the problems with the selection of data and the sampling framework of the human case series data assembled by Calabrese and Dhawan (Calabrese and Dhawan 2013), which rendered it largely uninterpretable. As of November 2023, there were 35 registered clinical trials in 17 countries on LDRT for COVID-19 pneumonia (ClinicalTrials.gov. 2023), although many of these trials appear to be suspended or stopped. All of these trials were based on chest doses of 0.5–1.5 Gy in one or two fractions, which was assumed to be effective in treating viral pneumonia. Irradiation to the lungs was generally given via anteroposterior, but sometimes anteroposterior and posteroanterior irradiation. In most cases this was from a LINAC with energy 5–15 MV, giving a mean lung dose of 0.5–1.5 Gy. The literature in this area has been subject to several systematic reviews (Little et al. 2021; Pandey et al. 2022; Piras et al. 2022; Kolahdouzan et al. 2022).

The 17 reports from 10 clinical trials of LDRT for COVID-19 are summarized in Table 4 (Ameri et al. 2020, 2021; Hess et al. 2020, 2021a, 2021b; Del Castillo et al. 2020; Sanmamed et al. 2021; Papachristofilou et al. 2021; Ganesan et al. 2021, 2022; Mousavi Darzikolaee et al. 2021; Sharma et al. 2021; Arenas et al. 2021, 2023; Moreno-Olmedo et al. 2021; Ortiz et al. 2022; Magrini et al. 2022). Of these, the only double blind randomized trial, in severe acute respiratory distress syndrome (ARDS)/intubated patients, is that of Papachristofilou et al. (Papachristofilou et al. 2021), which was null. All of the other trials, which were either not randomized or not double blinded, are very difficult to interpret. This remains the case even when, as there were for six studies, control groups (Hess et al. 2021a, 2021b; Ganesan et al. 2022; Mousavi Darzikolaee et al. 2021; Ortiz et al. 2022; Arenas et al. 2023); in some cases the presence of other therapies unequally in control and treatment groups (Hess et al. 2021a, 2021b) implies that the control group may not be adequate as a contrast to the treatment group.

Relevant radiobiological data

Calabrese and Dhawan (Calabrese and Dhawan 2013) identified four animal studies in which LDRT was given after the inoculation with the infective agent (Fried 1941)

(Lieberman et al. 1941) (Baylin et al. 1946) (Dubin et al. 1946), but based on a partial survey of the literature. Little et al. (Little et al. 2021) systematically reviewed the publicly available radiobiological data, discovering 13 datasets published in the period 1937–1973. The age of literature entailed a complete reanalysis of the data using state of the art survival models (Cox proportional hazards and logistic models). Absorbed doses were generally under 7 Gy, and for six of the datasets radiation was given after the infective (bacterial or viral) agent, the scenario of most relevance to LDRT treatment for COVID-19 pneumonia. Four out of these six studies showed no significant change ($p>0.05$) in mortality after radiation exposure, with one study exhibiting an increase ($p<0.001$) and another decrease ($p<0.001$) (Little et al. 2021). These data do not suggest a protective effect of radiation exposure after infection, but they are very heterogeneous, with different animal models, infectious agents and radiation doses. Ascertainment bias cannot be discounted in all these studies, as it is quite possible that investigators were not blinded to the animals' exposure status (Little et al. 2021).

To the best of our knowledge the study by Meziani et al. (Meziani et al. 2021) is the only one using viral infection and that appeared after the above review (Little et al. 2021). They used airways-instilled lipopolysaccharide (LPS) in a murine model with a mouse-adapted strain of influenza virus; the experiment also assessed toll-like receptor (TLR)-3 stimulation in human lung macrophages in tissue of patients with lung cancer or benign lung disease. They showed that LDRT (0.5–1 Gy) decreased LPS-induced pneumonia and increased the prevalence macrophages producing interleukin 10 (IL-10).

The inflammation caused by SARS-CoV-2 infection has been attributed to increases in cellular senescence, DNA damage (assessed by phosphorylated histone H2AX (γH2AX) foci) and pro-inflammatory cytokines (e.g., IL-1β, -6 and -8) (Evangelou et al. 2022). DNA damage response (DDR) has been proposed as one of the factors underlying the age-dependent severity of SARS-CoV-2 infection. Angiotensin-converting enzyme 2 (ACE2) is the cell surface protein to which the virus binds to enter the host cells. In cultured mammalian cells and in mice, ACE2 expression was shown to increase with telomere shortening or dysfunction, and inhibition of global DDR and telomeric DDR was found to prevent ACE2 upregulation following telomere damage (Sepe et al. 2022). Similarly, DNA damage caused by exposure to high dose (1–10 Gy) γ-rays or ultraviolet light, treatment with etoposide (topoisomerase II inhibitor), restriction endonuclease or telomere dysfunction was demonstrated to facilitate entry of SARS-CoV-2 into cells, and DDR inhibition hampered such entry: irradiation was also found to increase ACE2 expression (Jin et al. 2022).

SARS-CoV-2 infection itself led to elevation of DNA damage as assessed by γH2AX, pRPAS4/8 and pKAP1S824 foci, and the SARS-CoV-2 proteins ORF6 and NSP13 caused proteasomal and autophagic degradation of CHK1 (DDR kinase), respectively (Gioia et al. 2023). The reduction in CHK1 protein levels resulted in deoxynucleoside triphosphate (dNTP) shortage, causing impaired S-phase progression, DNA damage, pro-inflammatory pathways activation and cellular senescence (Gioia et al. 2023). Furthermore, SARS-CoV-2 N-protein impaired p53-binding protein 1 (53BP1) focus formation through interfering with damage-induced long non-coding RNAs, thus reducing DNA repair activity. Additionally,

the SARS-CoV-2 spike protein s-subunit was suggested to bind to key DDR proteins (BRCA1, BRCA2, p53, BRD4 and DNMT1 methyltransferase) (Mekawy et al. 2022).

Peripheral lymphocytes from COVID-19 patients were found to have lower mRNA levels of p53, ATM and CHK2. Numerous p53 target genes involved in cell cycle arrest, apoptosis and p53 feedback inhibition were up-regulated, while other p53 target genes were downregulated (Polozov et al. 2023). The dysregulation of p53 signaling pathway had functional consequences in that the transcription of p53-dependant genes (CCNG1, GADD45A, DDB2, SESN1, FDXR, APOBEC) was reduced 24 h after X-ray exposure ex-vivo to both low (0.1 Gy) or high (2 Gy) doses (Polozov et al. 2023), suggesting significant disruption of the transcription of DDR genes.

Altogether, SARS-CoV-2 infection causes DNA damage and inhibits DNA repair activities through a range of interactions and mechanisms. These recent findings indicate that LDRT for COVID-19 pneumonia should be used with considerable caution.

Potential long-term risk

Set against these possible beneficial effects of LDRT, there is abundant epidemiological evidence that radiation causes lung cancer. According to risk factors evaluated by the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) (UNSCEAR 2008) based on the atomic bomb survivor data, the acutely delivered lung doses of 0.5–1.5 Gy used in various clinical trials reported in Table 4 would nominally induce 1–6.5 excess lung cancers in 100 persons exposed. There is also accumulating evidence of association between low and moderate dose of radiation and most types of CVD (Little et al. 2012, 2023a; Little 2016). Taken at face value, a single 0.5–1.5 Gy lung dose (which the heart and aorta would also receive) would be associated with 1.3–3.8 excess deaths from CVD in 100 persons exposed (Little et al. 2023a). These substantial adverse effects, which derive from populations exposed at these (or slightly lower) levels of dose, would have to be carefully weighed against any potential benefits.

Radiotherapy for other non-cancer diseases

In addition to VT, AD, dementia and COVID-19 pneumonia, RT has been used for a wide variety of other benign conditions, based on its presumed anti-inflammatory immunosuppressive or anti-proliferative effects. RT for such benign conditions has generally been used to alleviate conditions, in contrast to the case for VT and severe COVID-19 pneumonia that are immediate life-threatening conditions.

The doses utilized range from 3 Gy delivered in 0.5 Gy fractions (e.g., for osteoarthritis) to >70 Gy in a single fraction (e.g., for trigeminal neuralgia) (Wilson et al. 2020), but dose regimens vary widely among geographic regions and institutions. In the 1990’s, orthovoltage (50–120 kV) photons have been replaced with megavoltage (4–6 MV) photons using LINACs in most deep-seated lesions (i.e., not limited to the skin and subcutaneous tissues).

Most studies of RT for non-cancer diseases are of retrospective type, with the level 4 evidence (evidence from case series, low-quality cohort or case-control studies). Dose-response assessments were performed using randomized trials for a few diseases (Seegenschmiedt et al. 2001; Ott et al. 2015; Niewald et al. 2015). As yet, there are few randomized studies and no double-blind randomized studies to assess the risks of RT (Sclafani et al. 1996). Among various non-cancer diseases where RT has been employed for treatment, the following subsections focus on vascular disorders, skeletal disorders, hyperproliferative disorders, metabolic disorders and autoimmune disorders.

Vascular disorders

Vascular disorders may be due either to malformations or to degenerative diseases, and may result in abnormal vessels that are at risk for hemorrhage and dysfunctional outcomes. Vascular disorders include arteriovenous malformations (AVM, vascular lesions in the brain where feeding arteries drain directly into veins without passing capillaries) and cavernomas (i.e., clusters of dilated vessels). RT is expected to induce vessel wall injury, with subsequent sclerosis and obliteration to reduce the risk of hemorrhage, stroke or death. A typical dose prescribed to symptomatic medically refractory patients is a single fraction of 20 Gy by stereotactic irradiation. Obliteration is achieved in 85% of cases. Its effect reaches a maximum at two years post-RT, but with a possible early increase in the risk of hemorrhage (Lucas et al. 2014; Okunlola et al. 2023). However, a recent non-blinded randomized trial demonstrated that medical management alone remained superior to interventional therapy to prevent death or symptomatic stroke in patients with an unruptured AVM (Mohr et al. 2020).

Trigeminal neuralgia is a neurological disorder that most commonly occurs due to nerve compression by an aberrant vascular loop with pain and facial dysesthesia. RT may be advocated in medically refractory patients for whom surgery is contraindicated. RT aims at axonal degeneration and necrosis by targeting the trigeminal nerve root by stereotactic irradiation with a single fraction of 70–90 Gy. Pain relief is observed in >70% of cases at one year (with lower rates in the longer term) based on >70 retrospective studies (>2500 patients) and a randomized trial (Régis et al. 2006).

Hemangiomas of the choroid or retina are leaking vessels responsible for visual dysfunction. Sporadic cases are the most common, but familial or genetic syndromes (e.g., Sturge-Weber syndrome, Kasabach-Merritt syndrome) are possible. Choroidal hemangiomas are at risk for bleeding, exudates or adverse functional loss. RT (typically prescribing 20 Gy of photons in 4 or 8 fractions) is generally used in patients refractory to photodynamic therapy. Response rates of 90% and symptomatic improvements of 80% have been reported (Mathis et al. 2021). Cataract may typically occur, treatable by lens replacement.

Vertebral hemangiomas are relatively frequent vascular benign tumors of the vertebral bodies causing pain. A clinical trial used RT with conventional fractionation of ~40 Gy in 2 Gy fractions or stereotactic irradiation with 25 Gy in 5 fractions (Miszczyk et al. 2022). A systematic review reported pain relief in 87.5% of cases (Conti et al. 2022).

Wet age-related macular degeneration (AMD) consists of retinal endothelial dysfunction with neovascular leakage/bleeding, and represents 10% of AMD but is the most severe form.

RT aims to prevent neovascularization and inhibit inflammation and fibrosis. RT with a single fraction has been used for wet AMD in the 1990's, then abandoned with the advent of inhibitors of vascular endothelial growth factor (VEGF), but recently reintroduced to treat AMD refractory to VEGF inhibitors. Wet AMD may also be associated with cataracts, as in the case of choroidal melanomas.

Skeletal disorders

Skeletal disorders include a variety of conditions, which may be classified as degenerative with an inflammatory component of the joints and bones (e.g., degenerative osteoarthritis) or as traumatic disorders triggering aberrant inflammatory processes (e.g., plantar enthesopathy/dorsal heel spur, heterotopic ossification). RT has been used mostly as cure, but also as prophylaxis of heterotopic ossification following trauma or surgery involving bone to restore or prevent functional deterioration (stiffness, pain).

Arthritis of various joints or muscle insertions include ankylosing spondylitis, rheumatoid arthritis, epicondylitis and any joint inflammatory symptoms. Similarly, RT for heel spur tarsal enthesopathies has achieved excellent pain relief. Doses are usually on the order of 3–6 Gy in 0.5–1 Gy fractions, but the 3 Gy in 0.5 Gy fraction regimen predominates based on dose finding trials. A single fraction of 7 Gy is used in RT for heterotopic ossification immediately following trauma or hip surgery. In a randomized trial among patients with an acetabular fracture (in the socket part of the joint) of a particular non-steroidal anti-inflammatory drug (NSAID), indomethacin, compared with RT, a significant difference was found in the rate of fracture nonunion among those receiving indomethacin vs those receiving RT or prophylaxis (26% vs 7%; p=0.004) (Burd et al. 2003). RT has been widely used because of its assumed anti-inflammatory effects, but its use has dramatically declined in favor of NSAIDs given orally or as infiltration in most countries apart from Germany (Seegenschmiedt et al. 2015). Use of RT should ideally be based on the results of prospective randomized clinical trials against non-radiation treatments.

Hyperproliferative disorders

Keloids are common hypertrophic scars of the skin and are treated by RT to induce an atrophic scar, although randomized trial suggested no difference in efficacy of RT and steroids (Sclafani et al. 1996). Studies showed recurrence rates of 15% following brachytherapy (showing lowest recurrence rates in a meta-analysis (Mankowski et al. 2017)) or external beam RT (15–20 Gy in 3–5 fractions). However, follow up was usually less than one year in many studies, making efficacy in preventing relapses inconclusive. Case reports suggest that patients with Kasabach-Merritt syndrome (characterized by fast growing vascular tumors) can be irradiated successfully to avoid bleeding (see Schild et al. (Schild et al. 1991) and other case reports cited therein).

RT has also been used for hyperproliferative diseases from abnormal formation of connective tissues (e.g., Dupuytren's disease, Lapeyronie's disease) to inhibit cellular proliferation, overcome contractures and joint limitations, and resolve associated pain (Pietsch et al. 2018; Kemler et al. 2022). RT (typically 30 Gy in 10 fractions) has

shown relatively good short-term efficacy, but the long-term side effects (fibrosis) make it controversial.

Desmoid tumors are forms of aggressive fibrosis, considered as benign tumors of malignant potential. Postoperative RT or definitive RT has been performed for desmoid tumors with conventional RT of 56–60 Gy in 2 Gy fractions (Mikhael et al. 2022). Such RT has been controversial due to several cases of severe toxicity or second primary cancers. Similarly, pigmented villonodular tenosynovitis (or diffuse-type giant cell tumor of soft tissues) (van der Heijden et al. 2012) and hemangioendotheliomas (Go et al. 2023) are borderline indications of RT and should be considered separately from strictly non-tumoral lesions. RT are also used for many other conditions (e.g., histiocytosis, pterygium) depicted in Table 5, with overall low supportive evidence.

Metabolic and autoimmune disorders

Radioiodine (^{131}I) has been commonly used to treat hyperthyroidism and toxic nodular goiter for the last 80 years (Holm et al. 1991; Ron et al. 1998). However, more recently antithyroid drugs have become the preferred type of treatment for Graves disease, because of increased awareness of association between ^{131}I and Graves ophthalmopathy, also a more general awareness of radiation-induced cancer (Ron et al. 1998; Kitahara et al. 2019). Excess mortality of all solid cancer and breast cancer, but not of leukemia, have been reported in the US Cooperative Thyrotoxicosis Therapy follow-up study (Kitahara et al. 2019).

Graves's orbitopathy is an autoimmune disorder, often encountered in hyperthyroidism, and consists of inflammatory infiltration of extraocular muscles that may cause optic nerve compression and glaucoma. Medically refractory Grave's orbitopathy has been treated with RT (20 Gy in 10 fractions) if steroid and hyperthyroidism treatment are not effective. Cataract is a common but treatable complication while trophic corneal effects may be noted.

Gynecomastia is a rare condition, resulting from hormonal disorders or therapy for prostate cancer. Gynecomastia has historically been treated with RT, but there are long-term thoracic normal tissue complications.

The use of RT for diabetes mellitus has been proposed based on some preclinical studies (Paithankar et al. 2023). There is only a single report of two cases being treated with radon therapy (Kojima et al. 2019). However, an increased radiation risk of diabetes has been reported in patients receiving RT for cancer and in atomic bomb survivors (Hayashi et al. 2003; de Vathaire et al. 2012), although this is uncertain at lower dose (Tatsukawa et al. 2022).

Altogether, for many of the non-cancer disease endpoints there is little evidence of RT being an effective treatment, with such evidence as there is coming from retrospective studies. For many (but perhaps not all) endpoints there are few prospective studies or randomized trials; most trials investigate dose and field issues, but not the use of RT itself, and are not blinded, as sham RT may be difficult to administer. There is highly variable practice across countries and across non-cancer diseases. Therefore, for many endpoints alternative

medical treatments are generally preferred unless there are severe symptoms resistant to several therapeutic modalities, to avoid long-term normal tissue complications and second cancers, which are particularly relevant if RT is used for young patients. However, RT might be an option for elderly patients with refractory disease. Inflammatory diseases are increasingly treated with relatively low doses (total fractionated dose of <3 Gy), vascular diseases with moderate single or fractionated doses and hyperproliferative diseases with moderate conventionally fractionated doses of up to 50 Gy in 2 Gy fractions.

Perspectives

To justify the use of RT for treatment of non-cancer diseases, it is critical to understand the mechanisms behind the potential efficacy of RT, the specific tissue targets and to identify potential alternative treatments as well as weigh the risks and benefits associated with the proposed therapy. Further mechanistic studies are needed, and one must demonstrate that QOL weighted benefits outweigh risks. To this end, continued preclinical studies, also epidemiologic studies of various types of adverse effects in follow-up of treated patients (in particular those aged <60 years at RT) could be informative. In tuberculosis patients exposed to repeated chest X-ray fluoroscopies, there was significantly increased breast cancer mortality and incidence (Boice et al. 1991; Howe and McLaughlin 1996), mortality of IHD with inverse dose fractionation effects (i.e., higher effectiveness of multiple fractions than that of single fraction, in contrast to sparing dose fractionation effects) (Zablotska et al. 2014) and increased mortality of IHD and overall CVD (below 0.5 Gy) (Tran et al. 2017), but not lung cancer (Howe 1995; Boice et al. 2022). It remains unclear whether responses to fractionated exposures vary among tissues of different anatomical sites (e.g., heart, brain, lung), whether such responses differ between healthy and diseased tissues of the same anatomical site (e.g., healthy heart vs heart with VT), and what mechanisms underlie detrimental radiation effects to healthy tissues vs therapeutic effects to diseased tissues. Further studies are required to address these questions.

The limitations of this narrative review of the literature must be acknowledged. The review does not pretend to be systematic, although most of the studies of LDRT for VT, AD and COVID-19 pneumonia are likely to be included.

More studies are also needed on dose optimization schemes (balancing therapeutic effects vs normal tissue complications). Fractionated doses have been used in some clinical trials of RT for AD and COVID-19 pneumonia. One of the aims of such schemes is to reduce normal tissue complications, but fractionation may result in an inverse dose fractionation effect in some tissues (e.g., the brain (Begolly et al. 2018) and the circulatory system (Little et al. 2023a; Zablotska et al. 2014; Hamada et al. 2022, 2024)), thereby increasing normal tissue complications. Attempts to reduce dose while maintaining therapeutic potential are important for dose optimization. For example, in a murine model of bleomycin-induced pneumonitis, whole lung irradiation at 1 Gy suppressed accumulation of pulmonary interstitial macrophages, $CD103^{+}$ dendritic cells and neutrophil-dendritic cell hybrids, thereby improving pneumonitis (Jackson et al. 2022); however, such effects were not observed at 0.5 and 1.5 Gy (Jackson et al. 2022), suggesting a very narrow window for effectiveness of RT for COVID-19 pneumonia.

Conclusions

There has been a recent upsurge of interest in RT for various non-cancer diseases and benign conditions (Table 5). A growing body of evidence has suggested that radiation represents a double-edged sword, not only for cancer, but also for non-cancer diseases. At present, clinical evidence has shown some beneficial effects of RT for VT, but there is little or no such evidence of RT for other newly proposed non-cancer diseases (e.g., AD, COVID-19 pneumonia). Patients with VT and COVID-19 pneumonia have thus far been treated with RT when they are an urgent life threat with no efficient alternative treatment, but some survivors may encounter a paradoxical situation where patients were rescued by RT but then get harmed by RT. Further studies are needed to justify clinical use of RT for non-cancer diseases, and optimize dose to diseased tissue while minimizing dose to healthy tissue.

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Table 1.

Results of radiotherapy for refractory ventricular arrhythmia.

Reference	Number of patients	Duration to deliver radiation dose in a single fraction (25 Gy unless otherwise stated)	Follow-up duration	Outcome	Notes
Cuculich et al. (Cuculich et al. 2017)	5	Mean 14 min (range 11–18)	46 person months after 6 week blanking period	99.9% reduction in incidence of episodes of VT after 6-week post-ablation blanking period. One patient died from stroke 3 weeks after treatment. Mean LVEF did not decrease with treatment.	All patients on anti-arrhythmic drugs (amiodarone, mexiletine); for 3 patients this was stopped 2 months after treatment.
Jumeau et al. (Jumeau et al. 2018)	1	45 min	4 months, no blanking period	Immediate and durable (up to 4 months) reduction in VT in a single patient.	Difficult to attach weight to this small study, which also lacks a blanking period.
Robinson et al. (Robinson et al. 2019)	19	Mean 15.3 min (range 5.4–32.3)	Up to 12 months; 89% survived ≥6 months, after 6 week blanking period	Significant (p<0.001) reduction in incidence of episodes of VT.	More than half of patients on >1 anti-arrhythmic drugs.
Neuwirth et al. (Neuwirth et al. 2019	10	Mean 68 min	Median 28 months (range 16–54), after 90 day blanking period	Significant (p=0.012) reduction by 87.5% in incidence of episodes of VT, although after the blanking period VT recurred in 8/10 patients, and electrical storm reoccurred in 3/10. Three patients died 18, 43, and 54 months after treatment, two from heart failure.	
Gianni et al. (Gianni et al. 2020)	5	82 min ± 11	12 months (range 10–14), no blanking period	Despite some initial improvement, VT recurred in all patients. 2 patients died of complications of heart failure.	
Lloyd et al. (Lloyd et al. 2020)	8	Unspecified	Mean 176 days (range 118–273) after exclusion of 2 patients who died within days of SBRT, no blanking period	Borderline significant reduction in seconds of VT (p=0.04) and ICD shock (p=0.07) post-ablation. Three patients received transplants post-ablation, and two moved to hospice care. Two patients developed pneumonitis.	All patients on anti-arrhythmic drugs, all but two on >1 drugs.
Chin et al. (Chin et al. 2021)	8	18.2 ± 6.0 min	Median 7.8 months (IQR 4.8–9.9). No blanking period	ICD therapies decreased from median 69.5 (IQR 43.5–115.8) pre-SBRT to 13.3 (IQR 7.7–35.8) post-SBRT (p=0.036). There were three patient deaths in the follow-up period, unrelated to SBRT. Apparent clinical benefit occurred 33% of the time after SBRT.	All patients were male, mean age 75 ± 7.3 years.
Lee et al. (Lee et al. 2021)	7	5–12 min	5 patients had at least 6 month follow-up after SBRT. No blanking period	Acute suppression of VT was seen in all 7 patients. For 5 patients with at least 6 months follow-up, overall reduction in VT burden was 85%. No high-grade radiotherapy treatment-related side effects were documented. 3 deaths (two within 4 weeks of SBRT, one 9 months after SBRT) occurred, all due to heart failure.	All patients in 60s or 70s.
Carbucicchio et al. (Carbucicchio et al. 2021)	7	Unspecified	Median 8 months, 4/7 patients with ≥6 months follow-	Three patients died (one from heart failure). Among four patients that completed 6-month follow-up, there was	

Reference	Number of patients	Duration to deliver radiation dose in a single fraction (25 Gy unless otherwise stated)	Follow-up duration	Outcome	Notes
			up, after 6 week blanking period	borderline significant (p=0.08) reduction in number of episodes of VT.	
Qian et al. (Qian et al. 2022)	6	Unspecified	Median 231 days, up to 18 months, no blanking period	Radioablation did not significantly reduce device treated or sustained VT episodes (p=0.438); however, a borderline significant (p=0.046) reduction in ICD shocks was observed. Three patients died of heart failure (136, 215, 264 days after SBRT), and another developed left ventricular dysfunction (104 days after SBRT).	
Ninni et al. (Ninni et al. 2022)	17	Unspecified	Median 12.5 months (range 10.5–17.8) after 6 week blanking period	91% reduction in VT episodes after radioablation (p<0.0001).	All patients received anti-arrhythmic drugs.
van der Ree et al. (van der Ree et al. 2023a)	20	Unspecified (20–25 Gy prescribed to the PTV)	Median 1.7 years (range 0.9–3.9), no blanking period	Radioablation did not significantly change LVEF. Worsening of valve function after radioablation occurred in 6 patients (4 in the aortic valve), and there was a significant difference in dose to the aortic valve in the group with or without aortic valve worsening (p=0.03).	
van der Ree et al. (van der Ree et al. 2023b)	6	Unspecified (20–25 Gy prescribed to the PTV)	Follow-up to a year after treatment compared with 12 months before treatment. A blanking period of 6 weeks.	Reduction of episodes of VT after irradiation by >50% in 4/6 (67%) patients. Mean number of episodes of VT after blanking period reduced by 87% (p=0.075). 2/6 (33%) patients died during follow-up, from non-cardiac causes. 3/6 (50%) patients experienced fatigue. During follow-up, no reduction in cardiac and pulmonary function or treatment-related serious adverse events were observed.	All male patients.

ICD, implantable cardioverter-defibrillator. IQR, interquartile range. LVEF, left ventricular ejection fraction. PTV, planning target volume. SBRT, stereotactic body radiation therapy. VT, ventricular tachycardia.

Table 2.

Results of meta-analyses of the risk of dementia, cerebrovascular diseases, or brain cancer, after adulthood exposure of the brain to low to moderate doses of ionizing radiation.

Reference	Type of exposure	ERR at 100 mGy (95% confidence intervals)			
		Dementia	Parkinson's disease	Cerebrovascular disease	Brain cancer
Lopes et al. (Lopes et al. 2022a)	Occupational		0.11 (0.06, 0.16)[a]	0.01 (−0.00, 0.02)[b] 0.04 (0.03, 0.05)[c]	
Lopes et al. (Lopes et al. 2022b)	Occupational, environmental				−0.01 (−0.05, 0.04)
Srivastava et al. (Srivastava et al. 2023)	Occupational	0.11 (0.04, 0.18)	0.12 (0.07, 0.17)[a]		
Dauer et al. (Dauer et al. 2023)	Occupational		0.17 (0.05; 0.29)[b]		

ERR, excess relative risk.

[a]Based on the same studies.

[b]Mortality only.

[c]Morbidity only.

Table 3.

Lifetime risk of radiation exposure-induced cataract incidence.

Dose to the lens (Gy)	Lifetime risk in % (95% CI)	Excess lifetime risk in % (95% CI)[a]
1	21.9 (9.9, 31.9)	12.9 (5.9, 18.6)
5	56.5 (35.2, 66.5)	32.0 (20.5, 37.2)
10	69.3 (51.1, 76.1)	38.6 (29.2, 41.9)
15	74.8 (59.8, 79.9)	41.3 (33.8, 43.8)
20	77.9 (65.3, 82.0)	42.8 (36.6, 44.8)
30	81.3 (71.7, 84.3)	44.4 (39.8, 45.9)

CI, confidence intervals.

[a]Baseline cataract risk = 45.4%.

Table 4.

Results of clinical trials of LDRT for COVID-19 pneumonia.

Reference	Numbers of subjects	Randomized/ non-randomized	Doses	Follow-up	Results	Comments
Ameri et al. (Ameri et al. 2020)	5	Unrandomized single arm study	Single fraction 0.5 Gy to lungs	5–7 days	3/5 improved, 1/5 dropped out, 1/5 died	All patients on oxygen supplementation
Ameri et al. (Ameri et al. 2021)	10	Unrandomized single arm study	Single fraction 0.5 or 1 Gy to lungs, or split dose of 1 Gy to lungs	3–10 days	3/10 improved, 1/10 dropped out, 6/10 died	The full study of the pilot part (Ameri et al. 2020); two of deaths were at home within 3 days of discharge from hospital
Hess et al. (Hess et al. 2020)	5	Unrandomized single arm study	Single fraction 1.5 Gy to lungs	14 days	4/5 recovered	Of planned enrollment of 9, only five were given LDRT due to rapid clinical decline of enrolling patients
Hess et al. (Hess et al. 2021a)	20 (10 irradiated + 10 controls)	Unrandomized, with prospective individual matching of unirradiated control group; antipyretic medication was suspended for irradiated group but not controls	Single fraction 1.5 Gy to lungs	28 days	Median time to clinical recovery 3 days in LDRT group vs 12 days in control group (p=0.05), 1 death in LDRT group	The full study of the pilot part (Hess et al. 2020); controls were treated with mixture of remdesivir, hydroxychloroquine, ACTT-1 and steroids. LDRT was delivered without any concurrent systemic therapy, whereas controls received “best supportive care with or without drug therapies for COVID-19 (i.e, remdesevir, hydroxychloroquine, glucocorticosteroids, or azithromycin) per protocol or physician discretion.”.
Hess et al. (Hess et al. 2021b)	40 (20 irradiated + 20 controls)	Unrandomized, with retrospective individual matching of unirradiated control group; unlike intervention group controls were not oxygen weaned	Single fraction 1.5 Gy to lungs	28 days	Intubation rates were 14% with LDRT compared to 32% without (p=0.09). Biomarkers of inflammation (C-reactive protein, p=0.02) and cardiac injury (creatine kinase, p<0.01) declined following LDRT compared to controls. Mean time febrile was 1.4 vs 3.3 days, respectively (p=0.14).	Some patients received glucocorticosteroids, remdesevir etc before intervention, and this carried on for some in control group.
Del Castillo et al. (Del Castillo et al. 2020)	1	Unrandomized single arm study	Single fraction 1 Gy to lungs	8 days	Recovered	Patient given adjuvant hydroxychloroquine, ceftriaxone, azithromycin and enoxoparin
Sanmamed et al. (Sanmamed et al. 2021)	9	Unrandomized single arm study	Single fraction 1 Gy to lungs	7 days	1 patient died, 1 dropped out (could not be given second CT exam), no significant difference (p=0.32) in lung abnormalities between first and second CT, but significant difference (p=0.03) between first and third CT. 2 patients died 13 and 34 days after LDRT	Patients assayed via lung CT given at baseline (before LDRT) and 3 and 7 days after LDRT to determine change in state of lungs (e.g., ground glass opacities); all patients age >50 years and all were administered hydroxychloroquine, antithrombotic drugs and steroids

Reference	Numbers of subjects	Randomized/ non-randomized	Doses	Follow-up	Results	Comments
Papachristofilou et al. (Papachristofilou et al. 2021)	22	Randomized double blind	Single fraction 1 Gy to lungs or sham irradiation	28 days	Overall survival was identical at 28 days (p=0.69) in both arms of the study, lymphocyte counts significantly reduced (p<0.01) in LDRT groups	All patients received dexamethasone, 50% of patients received remdesivir, 3 patients received experimental drugs (canakinumab, conestat alfa) as part of ongoing clinical trial
Ganesan et al. (Ganesan et al. 2021)	25	Unrandomized single arm study	Single fraction 0.5 Gy to lungs	14 days	Significant improvement in oxygenation pre-LDRT to days 2 (p<0.05), 3 (p<0.001) and 7 (p<0.001) after LDRT, 88% attained clinical recovery, 3 patients died	Patients assayed via lung CT given at baseline (before LDRT) and 1, 3, 7 and 14 days after LDRT to determine change in lymphocyte count, oxygenation, requirement for supplemental oxygen, also radiological changes; all patients age >40 years
Ganesan et al. (Ganesan et al. 2022)	34 irradiated + 17 unirradiated	Randomized non-blinded trial	Bilateral whole lung 0.5 Gy, single fraction	28 days	Improvement in oxygenation (SpO_2/FiO_2) in LDRT vs control on days 2, 3 and 7 after LDRT (p<0.001). Significantly shorter time to clinical recovery in treatment group.	Five patients in LDRT group and 4 in control group eventually succumbed. No significant survival between the two groups (p=0.460).
Mousavi Darzikolaee et al. (Mousavi Darzikolaee et al. 2021)	11 irradiated + 12 controls	Unrandomized with unirradiated control group	Single fraction 1 Gy to both lungs	28 days	Overall survival in LDRT vs controls was 91% vs 64% at 7 days after allocation, 43% vs 34% at 14 days since allocation, and 32% vs 11% at 28 days after allocation. Two patients from each group survived to 28 days. There was borderline significant improvement in change in X-ray severity score (post-treatment – pre-treatment) for the irradiated vs control groups (p=0.085). There was no significant difference in O_2 saturation in the two groups.	Patients in LDRT and control groups were given oxygen and intubation as necessary. 54.5% of patients were administered dexamethasone, 100% were given remdesivir and methylprednisolone, 68.2% were given atazanavir, 90.9% were given interferon β1-a.
Sharma et al. (Sharma et al. 2021)	10	Unrandomized single arm study	Single fraction of 0.7 Gy	14 days	9 out of 10 recovered (with improved NEWS score), one death	All male patients, aged 38–63 years at admission, all with moderate to severe NEWS score (≥5). Other forms of treatment are not mentioned.
Arenas et al. (Arenas et al. 2021)	36	Unrandomized single arm study	Single fraction of 0.5 Gy to both lungs	1 month	8 deaths from COVID-19 and 5 other deaths during follow-up. 21 of 25 evaluated at 1 week had improvement in oxygenation (SpO_2/FiO_2), and among 13 evaluated at 1 month all showed improvement in this ratio.	Mean age 84, all given dexamethasone; one patient also received tocilizumab, one received remdesivir, and one received both tocilizumab and remdesivir.

Reference	Numbers of subjects	Randomized/ non-randomized	Doses	Follow-up	Results	Comments
Arenas et al. (Arenas et al. 2023)	50 irradiated and 50 control	Unrandomized with controls selected to match by age, sex, comorbidities and rate of pulse oxymetric saturation	Single fraction of 0.5 Gy to both lungs.	1 month	7 days after treatment LDRT patients reported significant increase in SpO_2 (p=0.0052) and a significant reduction in amount of FiO_2 needed (p=0.038) and this remained the case after 1 month also (p<0.0051, p=0.0002 respectively) with significant improvements also in SAFI (p<0.0001) and PAFI (p<0.0001). The length of hospitalization was significantly shorter in the LDRT group (p=0.01). Overall mortality did not differ (p=0.158), although when adjusted for comorbidities, sex, age, number of days with symptoms there was a significant reduction in mortality in the LDRT group (p=0.025)	Dexamethasone was used in both treated and control groups.
Moreno-Olmedo et al. (Moreno-Olmedo et al. 2021)	2	Unrandomised single arm study	Single fraction of 0.8 Gy to both lungs	4 weeks	Both patients showed an improvement in oxygenation, although only one had supplemental oxygen removed during follow-up, although other patient had supplemental oxygen discontinued 2 months after treatment.	Patients aged 65 and 80 years at admission. Both administered lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperazillin/ tazobactam, corticosteroids and tocilizumab.
Ortiz et al. (Ortiz et al. 2022)	30 irradiated + 29 controls	Unrandomized with unirradiated age/sex matched control group	Single fraction 1 Gy to both lungs	>40 days	Mortality in the irradiated group was 27.5% vs 58.6% in the control group (p=0.05). Among patients with moderate ARDS survival was significantly better for irradiated vs control (100% vs 40%, p=0.01); among patients with severe ARDS survival was no better for irradiated vs control (22% vs 0%, p=0.90). Length of hospital stay was similar between irradiated and control groups (p=0.4)	
Magrini et al. (Magrini et al. 2022)	3 irradiated patients	Single arm study	Single fraction of 0.7 Gy to both lungs.	25 days	The two male patients at age 81 years, 79 years died soon (16 days, 3 days respectively) after LDRT, the single female patient (age 61 years) survived ≥25 days after treatment	Both male patients received dexamethasone, one also enoxaparin, the female patient both dexamethasone and enoxaparin

ACTT-1, Adaptive COVID-19 Treatment Trial (NCT04280705). ARDS, acute respiratory distress syndrome. COVID-19, Coronavirus Disease 2019. CT, computed tomography. FiO_2, fractional inspired oxygen. LDRT, low dose radiotherapy. NEWS, National Early Warning Score. PAFI,

arterial oxygen partial pressure/fraction of inspired oxygen. SAFI, pulse oxymetric saturation/fraction of inspired oxygen. SpO_2, pulse oximetric saturation.

Table 5.

Non-cancer diseases or benign conditions for which radiotherapy has been used or newly proposed.

Newly proposed radiotherapy
Cardiovascular diseases
Ventricular tachycardia, heart failure
Neurodegenerative diseases
Alzheimer's disease, dementia
Infectious diseases
COVID-19 pneumonia
Metabolic disorders
Diabetes
Existing radiotherapy
Vascular disorders
Arteriovenous malformation, wet age-related macular degeneration, hemangioma (uveal, vertebral), trigeminal neuralgia
Skeletal disorders
Osteoarthritis, tarsal entesopathy, heterotopic ossification
Hyperproliferative disorders
Keloids, Kasabach-Merritt syndrome, Dupuytren's disease, Lapeyronie's disease, pigmented villonodular tenosynovitis, hemangioendothelioma, desmoid tumors, pterygium, pseudo tumors, Langerhans cell histiocytosis
Metabolic or autoimmune disorders
Grave's disease, gynecomastia

COVID-19, Coronavirus Disease 2019.