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REVIEW ARTICLE

Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation

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ABSTRACT

Most radiotherapy (RT) involves the use of high doses (>50 Gy) to treat malignant disease. However, low to intermediate doses (approximately 3–50 Gy) can provide effective control of a number of benign conditions, ranging from inflammatory/proliferative disorders (*e.g.* Dupuytren's disease, heterotopic ossification, keloid scarring, pigmented villonodular synovitis) to benign tumours (*e.g.* glomus tumours or juvenile nasopharyngeal angiofibromas). Current use in UK RT departments is very variable. This review identifies those benign diseases for which RT provides good control of symptoms with, for the most part, minimal side effects. However, exposure to radiation has the potential to cause a radiation-induced cancer (RIC) many years after treatment. The evidence for the magnitude of this risk comes from many disparate sources and is constrained by the small number of long-term studies in relevant clinical cohorts. This review considers the types of evidence available, *i.e.* theoretical models, phantom studies, epidemiological studies, long-term follow-up of cancer patients and those treated for benign disease, although many of the latter data pertain to treatments that are no longer used. Informative studies are summarized and considered in relation to the potential for development of a RIC in a range of key tissues (skin, brain etc.). Overall, the evidence suggests that the risks of cancer following RT for benign disease for currently advised protocols are small, especially in older patients. However, the balance of risk *vs* benefit needs to be considered in younger adults and especially if RT is being considered in adolescents or children.

INTRODUCTION

In the past, low to intermediate dose radiotherapy (RT) has been used to treat a range of benign diseases including peptic ulcers, tinea capitis (ringworm) and excessive uterine bleeding. RT for many of these indications has been discontinued because of the availability of other treatments and the associated small (subsequently identified) risk of radiation-induced cancer (RIC), a contraindication that is particularly pertinent for RT exposure of children and adolescents. Currently, the use of RT for benign disease is confined to a limited range of predominantly hyperproliferative and inflammatory benign diseases for which there is good evidence for RT as a first or second line of treatment (Table 1). However, in many RT centres within the UK, it is rarely used;[10] a situation that also pertains across much of Europe and North America.[27] By contrast, RT departments in Germany have a long tradition of using RT for benign indications and a significant proportion of relevant publications come from this country.[28–30]

We have recently reviewed the evidence for the effectiveness of RT for benign disease and provided, where appropriate, recommended treatment protocols.[10] It is hoped that clinical oncologists will now reconsider the use of the protocols for these specific conditions, although in many cases, their use is predicated on referral from other consultants (*e.g.* ophthalmologists, dermatologists etc.) who are responsible for the initial diagnosis and management of the benign diseases. The most important deterrent to the use of RT for benign disease is the putative risk of RIC; the following review discusses the available evidence that informs identification of this risk following exposure to

Table 1. Benign diseases for which intermediate dose radiotherapy has utility

Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Ocular disease						
Pterygium	Fibrovascular proliferating tissue	Early 20s to old age	20–50	Lens, sclera, anterior brain structures	Surgery is preferred option; adjuvant RT can improve outcome	Ali et al[1]
Choroidal haemangioma	Proliferation of normal vasculature	30–50	20	Lens, anterior brain structures	Rarely used; would require discussion in specialist centre	Frau et al[2]
Age-related macular degeneration	Neovascularization	>65	20	Lens, anterior brain structures	No longer routinely used, but subject to ongoing research	Evans et al[3]
Reactive lymphoid hyperplasia/orbital pseudotumour	Idiopathic orbital inflammation	Median 40–50	20	Orbit, anterior brain structures	Steroids are first line treatment. RT effective if inadequate response to steroids	Mendenhall and Lessner[4]
Thyroid eye disease	Autoimmune	20–40	20	Orbit, anterior brain structures	Steroids are first line treatment. RT considered if impaired mobility/ diplopia	Bartalena et al[5]
Orthopaedic/musculoskeletal disease						
Heterotopic ossification of the hip	Extraskeletal new bone formation	50–80	7	Pelvic bones and muscles	Adjuvant post-surgery	Lo et al[6]
Plantar fasciitis	Inflammation and degeneration	40–60	3–6	Tissues of foot (skin, muscle)	RT indicated if failed conservative management for 6–12 months	Heyd et al[7] and Niewald et al[8]
Aneurysmal bone cyst	Benign osteolytic bone lesion	Children and young adults	30	Bone, other tissues depending on site	Rarely used; useful for cysts in anatomically difficult locations and for recurrence following surgery	Heyd and Seegenschmiedt[9]
Vertebral haemangiomas	Benign vascular proliferation	All ages	36–40	Bone, soft tissue, spinal cord	Rarely used; evidence suggests useful for control of pain relief	Taylor et al[10] and Heyd et al[11]
Keloid	Abnormal fibroblasts, reduced apoptosis, increased collagen and cytokines	10–30	5–12	Depends on site of keloid	Adjuvant post-surgery	Ragoowansi et al[12]
Dupuytren's disease	Benign fibroblastic proliferation of the palmar fascia	50–70	30	Tissues of hand (skin, muscle)	In early progressive disease, prevents progression and need for surgery	Seegenschmiedt et al[13]
Ledderhose disease (plantar fibromatosis)	Benign fibroblastic proliferation of the plantar fascia	20–40	30	Tissues of foot	RT reduces pain and improves function	Seegenschmiedt et al[14]
Pigmented nodular synovitis	Proliferation of synovial membranes	20–40	35–40	Depends on site	May also be suitable for instillation of radionuclide	O'Sullivan et al[15]

(Continued)

Table 1. (Continued)

Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Peyronie's disease	Wound healing disorder of tunica albuginea of the penis	30–70	9–30	Lower pelvis	Currently rarely used; can be useful for pain relief in intractable case	Taylor et al[10] and Niewald et al[16]
Chronic eczema	Pruritic chronic inflammatory skin disease	All	4–5	Various; depends on site of lesions	Only very rarely recommended for intractable condition in adults	Taylor et al[10] and Sumila et al[17]
Lentigo maligna	Atypical melanocyte proliferation	>60	45–50	Various; depends on site of lesion	Surgery preferred option; when contraindicated RT can provide good outcome	Tsang et al[18]
Psoriasis	Autoimmune T-cell-mediated disorder	All ages from young adult	6–8	Various; depends on site of lesions	Rarely used; some evidence for utility in recalcitrant disease particularly involving nail beds	De Vries et al[19]
Trigeminal neuralgia (SRS)	Uncertain	Peak 60–70 (>90% over age 40 years)	Max. point dose 80–90	Brainstem	Very small treatment field, usually carried out with Gamma Knife	Taylor et al[10]
Meningioma	Benign tumour	Wide age range; incidence increases with age	50–55 (or 14 Gy for SRS)	Various; depends on site of lesion	SRS tends to be for smaller lesions, particularly in base of skull	Taylor et al[10]
Arteriovenous malformation in brain (SRS)	Vascular anomaly	10–40	Ideally >20 for SRS	Various; depends on site of lesion	Can occur throughout brain and vary in size. Treatment more effective and safer with smaller lesions	Taylor et al[10]
Acoustic schwannoma	Benign tumour	Majority over 40	12 (SRS) 45–56	Brainstem, facial nerve, cochlea	Other options include surgery or surveillance depending on size, hearing and rate of growth	Combs et al[20]
Head and neck						
Sialorrhoea	Excessive drooling often because of severe neurological disorder	Elderly	10–20	Oral cavity/oropharynx, parotid	RT is effective at reducing saliva flow. RT can be used if anti-cholinergics and/or botulinum toxin ineffective	Assouline et al[21]
Salivary pleomorphic adenoma	Benign tumour of the salivary gland	30–60	50	Adjacent head and neck structures, *e.g.* oropharynx	Surgery with clear margins offers high local control. Adjuvant RT improves local control in high-risk patients (with positive margins/recurrent disease)	Mendenhall et al[22]
Glomus tumour	Paraganglioma, benign vascular tumour	Median 50	45	Adjacent head and neck structures, *e.g.* nasopharynx, oropharynx	Surgery or RT offer high rates of local control	Mendenhall et al[23]

(Continued)

Table 1. (Continued)

Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Juvenile nasopharyngeal angiofibroma	Rare benign vascular tumour	Median 14	35–45	Adjacent head and neck structures, *e.g.* nasopharynx, oropharynx	Surgery is treatment of choice. RT effective if unresectable. Surgery or RT considered for recurrence	Chakraborty et al[24]
Miscellaneous						
Hidradenitis suppurativa	Chronic inflammatory/ infective	Young adult	10	Depends on site	Only to be considered in refractory cases	Fronlich et al[25]
Gynaecomastia	Breast tissue hyperplasia	>60	10	Breast tissue, skin, lungs	Occurs in males on hormonal therapy for prostate cancer	Viani et al[26]

RT, radiotherapy; SRS, stereotactic radiosurgery.
This provides a summary of benign diseases for which intermediate dose RT has utility. Benign diseases that are no longer treated with RT are not included but are discussed elsewhere in the text.
[a]The total dose is only indicative and can vary considerably between centres and in different countries.
[b]It is assumed that skin is normally at risk; any other "at-risk" normal tissues are indicated, although these can vary in some situations. For detailed discussion of RT regimens, risks of RT and comparisons with other treatment options, see Taylor et al.[10]

low to intermediate dose RT, in order to assist the clinician and patient to make a balanced judgement as to the benefits and risks of RT for a benign condition.

EVIDENCE THAT MAY INFORM THE RISK OF RADIATION-INDUCED CANCER FROM EXPOSURE TO INTERMEDIATE DOSE RADIOTHERAPY

The many sequelae of normal tissue exposure to high dose RT during treatment of malignant tumours have been well documented and, indeed, they define the dose limits for RT exposure of specific organs.[31,32] In cancer survivors, an important consequence of RT is the risk of a subsequent RIC. Although this risk is small, for cancer patients, it is accepted because of the greater threat from poor control of their presenting pathology. For patients treated for benign disease with intermediate dose RT (range approximately 3–50 Gy; mean approximately 20 Gy) most normal tissue side effects are rare or minimal. However, there is an acknowledged, if normally very small, risk of RIC which may be important in a few situations. This requires that a risk verses benefit evaluation be made to assess the likelihood of the development of a RIC against the frequently observed good control with RT for specific benign diseases which, if untreated, may affect the quality of life but are unlikely to be life threatening.

This poses a problem since the number of patients required to detect a small increase in RIC incidence, occurring many years after exposure to intermediate RT doses to a confined radiation field, is large; yet, with a few exceptions, the number treated for these specific indications is relatively small. Consequently, there have been few closely comparable trials to assess this. Indeed, owing to the long latency time (LT) required, most of the studies discussed in this review relate to patients treated >25 years ago when treatment planning was less accurate and consequently more generous margins were often used. The equipment used for delivering RT was also much less sophisticated, limiting the more accurate targeting that is possible with current technology. However, with the advent of modern techniques, it is unclear how they will modify the risks of RIC. For example, intensity-modulated RT often results in a greater volume of normal tissue being exposed to a lower dose with a consequent potential for increasing the risk of RIC, although this can be mitigated using a variety of means.[33]

These studies must therefore be viewed with caution when extrapolating to the risks of current treatment protocols. The risk of RIC following RT for benign diseases has therefore been informed using data from a range of methodologies (see next section). Only a proportion are directly related to current RT practice so that any risk assessments provided are based on statistical probability and are subject to a number of important variables; frequently, they require extrapolation from a different scenario than that which pertains directly to RT for the specific benign disease.

STUDIES PROVIDING INDIRECT EVIDENCE OF THE EXCESS RISK OF RADIATION-INDUCED CANCERS

In order to predict future risk, it is necessary to use theoretical models or phantom studies. The disadvantage of mathematical

models is that they are based on a series of assumptions that are subject to differing interpretation. For example, for many years, it was thought that as the radiation dose increases above a poorly defined threshold, the risk of a RIC decreased owing to the effective sterilization of clonogens.[34] However, it is now thought that cells in the periphery of heavily irradiated tissue will proliferate rapidly for a few months following radiation exposure and that repopulation of the sterilized tissue will derive from these "normal" cells. Importantly, these are likely to include radiation-induced premalignant cells that have survived the lower dose exposures of the peripheral radiation dose field.[35,36] It is therefore proposed that, in some situations, this accelerated proliferation of premalignant cells will approximately cancel out the radiation-induced cell killing. This theory is consistent with many studies which show an approximately linear increase in risk of RIC with dose, although this may be modified depending on the radiation type.[37] For example, analysis of patients treated with RT for Hodgkin lymphoma has shown an approximately linear dose-dependent increase in cancers arising in the breast and lung.[38–42] This was confirmed for the risk of developing lung cancer following RT for peptic ulcers, although there was more variation from linearity for tumours arising at other sites.[43] Survivors of the atomic bomb in Japan also show an approximately linear response for an excess risk of solid tumours, although, as expected, this varies for different sites and shows significant variation with gender, attained age and age at exposure (see below).[44] In some situations, a lower risk is found with higher dose exposures. For example, children treated for a range of cancers show a non-linear dose-dependent increase in risk for subsequent development of thyroid cancer.[45]

Few relevant phantom studies have been described. However, a useful recent study of both male and female anthropomorphic phantoms has demonstrated the long-term risks of RIC in patients treated with modern RT protocols for a range of benign diseases (heterotopic ossification, arthritis of the shoulder or knee joints, heel spurs and hidradenitis suppurativa).[46] The risk of RIC was calculated using the International Commission on Radiological Protection recommendation of the average carcinogenic risk resulting from radiation exposure, which was estimated to be 10%/Sv for high dose and high-dose rate exposure to ionizing radiation (IR).[47] The authors discussed in some detail the basis of the assumptions which indicated that when using RT to treat these conditions, the effective dose range was 5–400 mSv, providing a prediction of an increase in RICs of 0.5–40/1000 patients treated. They acknowledged that this is a wide range, with age at exposure being a key risk modifier; body size and the site of irradiation also influenced the risk. Consequently, it was advised that careful body positioning and shielding should be employed to optimize target volume coverage and reduce the effective dose to normal tissues, in order to minimize the risk of RIC.

Epidemiological studies of cohorts exposed to low or very low doses of environmental, industrial or medical irradiation also provide an indication of RIC risk. However, the dose range is very much lower than that used for benign disease; in many cohorts, exposure is to the whole body and frequently the dose estimates are ill defined. By contrast, the numbers affected are often large improving reliability of the estimates. The largest group, which has been continuously monitored for more than 60 years, are the atomic bomb survivors in Japan; updates of the Lifespan Study (LSS) have been regularly published. As mentioned above, these data confirmed that the incidence of most solid tumours showed an approximately linear increase after a LT of about 10 years.[44,48] Not unsurprisingly, a big difference in risk is found depending on the age at exposure, with a ten-fold difference between children and adults. However, on current evidence, *in utero* exposure has a somewhat lower risk in comparison to the relatively high risk observed for individuals exposed in infancy, although this finding will need further follow-up.[44,49] The incidence of RIC decreases from about 15%/Sv of uniform whole-body irradiation for children less than 10 years to about 1%/Sv for adults exposed at more than 60 years.[34,50]

The data on haematological malignancies are more varied, and the effects occur earlier. In a recent analysis of the leukaemia risks in the LSS cohort, most leukaemias showed a non-linear dose response (data excluded chronic lymphocytic leukaemia and adult T-cell leukaemia since most evidence suggests they are not induced by IR). The effects were very dependent on time and age at exposure, with much of the evidence for non-linearity associated with the risks of acute myeloid leukaemia. The study confirmed previous analyses of a shorter LT than solid cancers and a decline in the excess risks of leukaemia with attained age or time since exposure; however, the excess leukaemia risks, especially for acute myeloid leukaemia, are still apparent after 55 years of follow-up. Non-Hodgkin lymphoma among males, although not in females, showed a weak link, and there was no evidence of an excess risk for either Hodgkin lymphoma or multiple myeloma.[51]

Patients exposed to high-dose RT for cancer also provide risk estimates of RIC, albeit for differing protocols and at higher doses (Table 2; also reviewed by Kumar[50]). A recent meta-analysis of >640,000 patients identified from cancer registries in the USA has shown that, within 15 years of high-dose RT, there are 5 excess cancers/1000 individuals; these data were acquired from 15 solid tumour types.[80] In a further systematic review of 28 eligible studies, they identified 3434 patients who developed second cancers in 11 different organs known to receive >5 Gy. The majority of the studies confirmed linear dose–response curves even up to ≥60 Gy; the main exception was thyroid cancer, which showed a downturn >20 Gy. They also confirmed that the risk varied according to the tissue of origin of the second cancer.[81] Since the evidence mostly confirms an approximately linear risk of RIC, the data obtained from patients with cancer treated with high doses can be used to give some guidance as to the lesser risks of RIC after exposure to intermediate doses. However, treatment protocols/fractionation regimens will often be different, so any extrapolation from high-dose studies must be interpreted with caution.

Often several tissues, with different risks of developing RIC, are exposed to radiation during RT. In a study of 104,760 females treated with RT for cervical cancer, an increased risk for all second cancers was found that was particularly evident at heavily

irradiated sites (colon, rectum/anus, urinary bladder, ovary and genital sites) as compared with females in the general population. This persisted beyond 40 years of follow-up and was modified by age at treatment.[82] In a large study of second malignancies following treatment for prostate cancer >50,000 males receiving RT were compared with >70,000 who underwent prostatectomy. Most second cancers occurred in organs close to the treatment field, *e.g.* the bladder and rectum, however, 30% were induced in the lung which would have only received a scatter dose of about 0.6 Gy. Overall, the risk for a RIC was small but significant, with an increase in relative risk (RR) for the RT *vs* surgery group of 6%, which was greater for males surviving ≥5 years (15%) and >10 years (>34%).[72]

High-dose RT for cancer in childhood carries the greatest risk of a subsequent RIC. Consequently, current childhood cancer treatment protocols incorporate a specific aim to minimize the risk of RIC, by avoiding RT whenever possible, or alternatively minimizing dose. However, since some childhood cancers involve an underlying germline mutation, this may also contribute to the observed increase in the susceptibility to second malignancies.[62,83,84] The small size of paediatric patients further increases risk, since scatter radiation will affect more tissues.[33]

STUDIES PROVIDING MORE DIRECT EVIDENCE OF THE EXCESS RISK OF RADIATION-INDUCED CANCERS FOR RADIOTHERAPY OF BENIGN DISEASE

There are a very limited number of directly relevant studies that report the risks of RIC in patients with benign disease treated using modern techniques and equipment. To some extent, doses and treatment protocols in historical cohorts are similar, but in many situations, there are key differences, adding to the uncertainty of risk estimates for current protocols. In addition, many of the previous studies have limitations, *e.g.* there is marked variance in estimates of the received dose, dose exposure between individuals, age on irradiation and age at follow-up, and often cohorts are small.

Benign diseases that may be treated with RT are very varied and involve many disparate parts of the body, varying doses and patients of all ages (Table 1). Currently, the majority of patients with benign diseases, who might be considered for RT, are in the older age groups although much of the evidence on the risks has come from children irradiated in procedures no longer in use, *e.g.* tinea capitis. Clearly, individual indications treated with RT have very different normal tissue exposure profiles. For this reason, the different tissue types are considered in relation to the evidence available; this can then be used to consider the risks of RT treatment for individual patients with specific benign diseases. A selection of some of the more relevant studies that inform as to this risk assessment are summarized in Table 2.

Skin cancer

Skin cancer is a potential risk for all patients receiving RT since there is, of necessity, almost always a concomitant skin exposure; when it occurs, there is a minimum LT of about 10 years. Several studies show an increase in non-melanoma skin cancer (NMSC) caused by occupational exposure to IR[85] and during RT for a range of benign indications, *e.g.* tinea capitis,[52,53,86] acne and other skin disorders.[54,55] Other reports have failed to confirm this. For example, individuals receiving RT for ankylosing spondylitis showed no increase in mortality from skin cancer[87] and females treated with RT for cervical cancer showed no increase in risk of NMSC.[88] Since NMSCs are rarely fatal, the conflicting data may result from the use of skin cancer mortality data as the identification criterion in a proportion of the studies. In addition, most of the data supporting an increased incidence of skin cancer following RT at low to intermediate doses relates to individuals irradiated as children. One concerning statistic is the increased incidence of NMSC in children treated with a wide range of doses for a variety of cancers. A recent study from the Childhood Cancer Survivor Study (CCSS) has shown that it presages development of subsequent malignant neoplasms in a small but significant number of patients, which may be associated with their exposure to RT and/or linked to a genetic predisposition.[62] An approximate 2.5-fold increase in risk of melanoma has also been found in this cohort, suggesting that they should be subject to long-term surveillance.[89]

Studies of adults with benign conditions exposed to IR slightly above background levels, such as patients with tuberculosis exposed to multiple fluoroscopies (average 77) during treatment, have shown no marked increase in skin cancer risk.[71] One factor known to increase the RIC risk is the extent of sun exposure to the skin, suggesting synergism between the carcinogenic effects of IR and ultraviolet radiation.[90,91] The lifetime risk of development of a radiation-induced basal cell carcinoma (BCC) has been estimated to be approximately 0.006% based on 100 cm^2 of skin treated to a mean dose of 3 Gy.[92] Another report has suggested this risk to be ≤0.1% in a sun-exposed field and an order of magnitude lower in skin not exposed to the sun.[90] It should be noted that all these figures are very much smaller than the spontaneous lifetime risk which is >20%.[92] Overall, the data suggest there is a dose-dependent increase in the risk of NMSC. Most of these are BCCs that can usually be treated successfully (Table 2), although some studies suggest that BCCs resulting from IR exposure are more aggressive and should ideally be excised with wider margins.[93] Long-term surveillance and reporting of suspicious changes in irradiated skin is advised, especially in individuals treated as children.

Brain cancer

The risk of tumours arising in the brain can be estimated from a wide variety of sources. Cohorts exposed to low-dose RT have shown that there is a linear, dose-dependent increase in the risk of RIC in the brain which is inversely related to age.[44,94,95] Meningiomas are the most frequently reported RIC following exposure to intermediate- or high-dose RT.[58,59] In a recent meta-analysis of 66 studies of RT for a wide range of conditions (mostly tumours), only 143 patients were found to have developed meningiomas attributable to the RT (median age when receiving RT was 12 years). It was notable that this group presented with meningioma at a younger age (80% at less than 22 years) compared with spontaneous tumours which peak in adults aged 50–70 years. In addition, atypical or malignant meningiomas were more prevalent in the study cohort than is usual in spontaneous meningioma cohorts. The median LT was

Table 2. The risk of radiation-induced cancer (RIC): evidence from selected studies pertinent to the risks of intermediate dose exposure

Tissue(s) at risk	Original indication	RIC type[a]	Number in cohorts	Dose (Gy); mean/ median (range)	LT (years)	Follow-up (years)	Comments	Study
Skin	Tinea capitis	Predominantly BCC (42 of 80)	>10,000, controls: 16,000	Mean dose: 6.8 (5.5–24.4), 9% treated with >1 dose	~ 22	24.5 (11–41)	Risk of skin Ca increased ×4; no increase in MM; ERR: 0.7 Gy^{-1}	Ron et al[52]
Skin	Tinea capitis	Most BCC, single: 8%, multiple: 2.4%	5356	2 dose groups: 3.25–4 or ≥6.3	47.2 ± 7.3	>40	Dose-dependent response found; shorter LT in higher dose group. LT measured from time of lesion excision	Boaventura et al[53]
Skin	Skin disorders: eczema, warts, psoriasis etc.	NMSC, MM, BCC not recorded	14,140	Grenz rays: 1–290 (25.0 ± 39.8 SD); 481 pts received >100	6 to >25	>5; mean 15	58 Ca: 39 NMSC; 27 expected; 19 MM *vs* 17.8 expected. No pts with MM and only 8 with NMSC received RT to site of new Ca; 6 of 8 had exposure to other carcinogens	Lindelöf and Eklund[54]
Skin	Acne (114), other BD of skin (65), Ca (24), other (50)	BCC or SCC (selected when NMSC presented)	1690	NA	NA	<20 to >40	Increased risk of BCC not SCC. Increased with time since exposure and younger age. Acne pts particularly susceptible (RR 3.3)	Karagas et al[55]
Head	Tinea capitis	Majority benign	10,834, controls: matched population +5392 siblings	Mean 1.5 (1–6); 9% received 2+ doses	17.6 (6 to 29+)	>30	Overall RR for neural Ca: 6.9. Number (RR): MG, 19 (9.5); glioma, 2.6 (7); nerve sheath Ca, 18.8 (25); others, 3.4 (9)	Ron et al[56]
Head	Childhood Ca (age <21 years; 53% <5); *e.g.* CNS Ca, lymphoma, LK, kidney Ca, SCa, neuroblastoma	CNS Ca: MG (66), glioma (40), other (10)	14,361; 116 CNS Ca compared with 464 matched controls	Median ~ 25 (1 to >45)	9 (glioma), 17 (MG)	Median 14 (5–28)	Incidence of second Ca, small but significant. Gliomas present earlier than MGs. ERR highest when RT at <5 years. Original Ca and CT not associated with risk. Second Ca has significant dose response ($p < 0.001$)	Neglia et al[57]

(Continued)

Table 2. (Continued)

Tissue(s) at risk	Original indication	RIC type[a]	Number in cohorts	Dose (Gy); mean/ median (range)	LT (years)	Follow-up (years)	Comments	Study
Head	Various; most had primary Ca	MG (14), SCa (7), astrocytoma (4), medulloblastoma (2)	27 brain Ca (10 years cohort); pts exposed to cranial RT	46 (18–65); mean dose to head: MG, 41.3; SCa, 56.3	18.8 (4–47); benign 8.5 *vs* malignant 20.3	NA	Most RIC in high-dose region. RT at young age: longer LT and lower-grade RICs (*e.g.* MGs). Older: shorter LT and increased chance of higher-grade RIC (*e.g.* SCa)	Chowdhary et al[58]
Head	Most childhood brain Ca	Study of MGs presenting in 5 years period as: (i) RIC, (ii) SM	(i) 26 RIC, (ii) 364 SM	>18	26.5 (4–47)	NA	Comparing (i) to (ii): mean age, 38.5–60.1 years. Female-to-male: 1.88 : 1 *vs* 2.37 : 1. MGs (i) 86.5% gd I; 11.5% gd II (atypical); (ii) 91.5% gd I, 7.1% gd II, 1.4% gd III	Godlewski et al[59]
Head	AVM (2615); VS (856); other Ca (1065); other pathology (347)	Astrocytoma	4877	50 (single exposure to small volume)	NA	2296 >10 years; 993 >15 years	SRS treatment caused no increase in incidence of RIC compared with age, sex and time-matched control (reanalysis due shortly; Jeremy Rowe, 2014, personal communication)	Rowe et al[60]
Head	Cranial RT, *e.g.* Brain Ca (66), LK (20), tinea capitis (14)	MG	66 studies. Total of 143 MG found	Low to high (<10 to >50)	19 (1–63)	>30	Meta-analysis of MG caused by RT confirms low risk of RIC. Age of initial RT was major influence; LTs varied	Paulino et al[61]
Head and other sites	Various, including LK, CNS Ca, HL, NHL, Wilms Ca, neuroblastoma, SCa	Various Ca	14,358 (67.8% treated with RT)	Wide range; details NA	>5	23.6 (5–37.5)	Retrospective study of survivors of childhood Ca. Evidence of multiple subsequent neoplasms, partially related to RT exposure	Armstrong et al[62]
Head	VS	Malignant Ca	440	Median dose, 25 (13–36); marginal dose, 12.8 (10–18)	12.5	12.5	1 patient had malignant Ca; 10 developed cysts	Hasegawa et al[63]
Thyroid	Tinea capitis	Papillary Ca	>10,000, controls: sibling and general	Est. dose to thyroid gland: 0.09 (0.45–0.50)	Most 10–39; few >40	>40	ERR Gy^{-1}: 20.2 (95% CI 11.8–32.3). Positive link to dose, negative with age at RT. ERR Gy^{-1} significant after RT at: 10–19 years, peak at 20–30 years, decreased (but significant) >40 years	Sadetski et al[64]

(Continued)

Table 2. (Continued)

Tissue(s) at risk	Original indication	RIC type[a]	Number in cohorts	Dose (Gy); mean/ median (range)	LT (years)	Follow-up (years)	Comments	Study
Thyroid	Children with wide range of BD and Ca; atomic bomb survivors; women with cervical Ca	Thyroid Ca	Exposed group ~58,000; controls 61,000; ~700 thyroid Ca	Low ~ 1 (0.01–11) to thyroid gland; pts with Ca 12.5 (1–76)	Wide range of LTs; almost all >5	5 to >40	BD treated: cervical adenopathy, tinea capitis, tonsillitis, enlarged thymus. Thyroid in young very radiosensitive. Age <5 years, RR ~20; adolescents, RR ~4; >40 years, no evidence	Ron et al[65]
Thyroid	Childhood Ca, including LK, CNS and lymphoma. Meta-analysis of four studies	Thyroid Ca	16,757 treated; 187 primary thyroid Ca	11.3 (0–67)	NA	5 to >25	RR increased linearly up to 10 Gy, levelled off at 10–15 fold for 10–30 Gy, then declined although still increased at >50 Gy. CT showed a small NS elevation in two studies	Veiga et al[45]
Breast	Acute postpartum mastitis	BCa	Treated, 601; controls, 1239	0.6–11.5 (median 3.5)		Median 29, up to 45	56 cases (32 expected). Risk linear increase with dose; may flatten at >7 Gy	Shore et al[66]
Breast	Acute or chronic mastitis or fibroadenomatosis	BCa	Treated, 1216; controls, 1874; cases, 278 (95 in unexposed cohort)	5.8 (<0.1 to 50)	Wide range of LT with excess risk apparent for >60 years	>60	Lowest dose relate to the contralateral breast in pts receiving RT to axilla. Risk higher in younger pts but apparent at all ages and for life	Mattsson et al[67]
Chest	Haemangioma in infancy; mean age at first RT: 6 months	BCa	9675	0.39 (<0.01–35.8)	Attained age at diagnosis: 44 (25–63)	39 (1–67)	75 BCa found; 60.5 expected. Risk increased linearly with dose. ERR at 1 Gy was 2.25. Those receiving >1 Gy most at risk	Lundell et al[68]
Chest	HL	BCa	48 BCa in 650 >5 years survivors after RT for HL; 175 controls	Average breast dose: pts: 38.5, controls: 37.6 (range ~0.26–56)	Median 18.7	Up to 39	BCa risk increased ~linearly with increasing dose. Adjuvant CT reduced the risk; linked to CT-induced early menopause	van Leeuwen et al[40]

(Continued)

Table 2. (Continued)

Tissue(s) at risk	Original indication	RIC type[a]	Number in cohorts	Dose (Gy); mean/ median (range)	LT (years)	Follow-up (years)	Comments	Study
Chest	HL	LCa	179 LCa; 356 controls	Average/median dose to tumour area: pts 27.2/33.8, controls 21.8/29.4	Mean (age of HL RT): 17 (<40 years), 10.6 (40–54 years), 6.7 (>55 years)	>20	LCa showed RT dose-dependent increase; additive with CT and multiplicative influence of smoking. Mean LT for LCa varied with pts' age at time of RT for HL	Travis et al[69]
Chest	Childhood Ca	BCa	1230 females receiving chest dose	2–60; depending on treatment	NA	24.1 (10.7–40.6)	Highlights enhanced risk of BCa in this cohort even with intermediate-dose RT (10–19)	Maskowitz et al[70]
Lung (repeat fluoroscopy)	Tuberculosis	BCa, LCa, OCa, LK	13,385; 6285 fluoroscopy (average 77); 7100 other treatments	Est. mean dose: lung (0.84), breast (0.75), oesophagus (0.80), bone marrow (0.09), Max. ~8	NA	Mean 25 (up to 50)	BCa (RR 1.4, $n = 62$), OCa (RR = 2.1, $n = 14$). Risk of OCa decreased with time since exposure. LCa and LK not increased	Davis et al[71]
Prostate	PCa	Bladder, rectum, LCa, SCa	3549 second Ca in 51,584 RT pts *vs* 5055 in 70,539 surgery pts	Pelvic dose NA. Most had whole pelvic ^{60}Co-RT. Est. dose to the lung ~0.6; bladder and rectum ~2.4	NA (est. 5–6)	4 (up to >10)	Risk of RIC was ~1 in 290 for all PCa pts treated with RT, increasing to 1 in 70 at (≥10 years). No increase in LK was noted	Brenner et al[72]
Soft tissue and bone	Various, including BD; largest groups Rb early onset BCa	(i) Soft-tissue SCa, (ii) osteo-SCa	(i) 20, (ii) 27	Moderate to high dose	Means: (i) 11, (ii) 12	12 (3–40)	Survey of SCa over 50 years. 47 found. LT longer with larger RT doses; children more susceptible to RIC. No osteo-SCa at <30 Gy	Kim et al[73]
Various	Childhood Ca	SCa	14,372 Ca survivors. 105 SCa; 422 matched controls	<10–76; mean NA	11.8 (5.3–31.3)	>31	Dose-related increased risk at >10 Gy, more marked >50 Gy. Children with HL or primary SCa more likely to develop second SCa. CT also increased risk	Henderson et al[74]
Various	Childhood Ca	SCa (osteo-SCa, 30; chondro-SCa, 5; others, 4)	4171 survivors; 39 SCa	Median dose to bone 0.48 (0.00–179.83)	NA	Median 26	Children treated for Rb, Ewing's, soft-tissue SCa and HL had highest risk of second Ca. Risk linear with RT dose. ERR Gy^{-1} = 1.78	Schwartz et al[75]

(Continued)

Table 2. (Continued)

Tissue(s) at risk	Original indication	RIC type[a]	Number in cohorts	Dose (Gy); mean/ median (range)	LT (years)	Follow-up (years)	Comments	Study
Uterus	Benign gynaecologic disorders, most uterine bleeding	LK and lymphomas; solid Ca in pelvic area	12,955: 9770 RT; 3186 other treatments	Median dose to cervix, 120; uterine corpus, 34; bladder, rectum and colon 1.7–7.2	Varied; earlier for LKs but still evident at >30	30.1 (1–69.9)	Pts received external beam or brachy-RT or both. Total dose very variable and across different tissues. Increase in Ca of uterine corpus, ovary, bladder, rectum, colon and brain, and LK (not CLL). No effect on cervical Ca, HL/ NHL, multiple myeloma	Sakata et al[76]
Spine and pelvic region	Ankylosing spondylitis	LK, wide range of other Ca	14,554	NA (low to moderate to "large" to spine area)	Few, 15	5–25	Mortality study. 52/1582 deaths attributed to LK; 5 expected. Most in first 15 years after RT. Other Ca showed increase in "heavily" irradiated area; no increase in areas receiving lower doses	Brown and Doll[77]
Spine and pelvic region	Ankylosing spondylitis	LKs, most solid Ca	>14,000 treated, 3175 were dead	Dose variable to wide area, est. total body ~2, mediastinal ~5	Peak of LKs ~4; solid Ca ~11	~30–50	Mortality study. RR 1.26 of death from all solid Ca (LCa ~40%). Colon Ca was excluded because of disease-associated increase. RR of 3.3 for death from LK. Although RRs decline, they are still apparent at >35 years	Darby et al[78]
Stomach	Peptic ulcer	Most solid Ca and LK	3719: 1859 exposed to RT; 1860 unexposed	Mean 14.8 (1.0–42.0)	Variable LTs. LK early than other solid Ca	Mean, 25; maximum, 62	125 *vs* 84 expected. RR 1.24 at 1 Gy mean lung dose. RT group had more smokers. Later reanalysis confirmed RRs: lung ($p < 0.05$), stomach (0.07), LK ($p = 0.06$); pancreas ($p = 0.007$). RR falls with increasing age of RT for all sites	Little et al[43] and Carr et al[79]

~, approximately; AVM, arteriovenous malformation; BCa, breast cancer; BCC, basal cell carcinoma; BD, benign disease; Ca, cancer; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; Co, cobalt; CT, chemotherapy; ERR, excess relative risk; est., estimated; gd, grade; HL, Hodgkin lymphoma; LCa, lung cancer; LK, leukaemia; LT, latency time; MG, meningioma; MM, malignant melanoma; NA, not available; NHL, non-Hodgkin lymphoma; NMSC, non-melanoma skin cancer; NS, not significant; OCa, oesophageal cancer; PCa, prostate cancer; pts, patients; Rb, retinoblastoma; RR, relative risk; RT, radiotherapy; SCa, sarcoma; SCC, squamous cell carcinoma; SM, spontaneous malignancy; SRS, stereotactic radiosurgery; VS, vestibular schwannoma.
Summarized information is from a disparate range of studies and is provided to help inform as to the ERR of developing a tumour after exposure to intermediate dose radiation. For a variety of reasons, not all studies provide a full description of the doses etc. (indicated as NA). The studies selected are mostly of two types, involving (i) cohorts that have been treated with low- to intermediate-dose RT for BD most of which are not used currently and (ii) cohorts treated with high-dose RT for a primary tumour, often in childhood.
[a]Tumour types that might result from previous radiation exposure.

19 years, and no explanation was found for the slightly shorter LTs in males (18 years) *vs* females (24.7 years). The LTs also varied with a number of other factors. For example, LTs were shorter for patients presenting with leukaemia compared with benign conditions (14.9 *vs* 32.1 years); although not proved, it was suggested that this might have been influenced by the adjunct chemotherapy used for treating leukaemia. Patients receiving higher dose RT had intermediate LTs (20.2 and 18.5 years). Those receiving the lowest doses, *e.g.* for tinea capitis had long LTs. Patients exposed to partial brain RT as compared with craniospinal or cranial RT had longer LTs, confirming that the larger the exposed volume, the greater the risk of earlier development of a RIC.[61] However, for children receiving RT to the head, the risk of RIC is significantly higher than background, especially when treated at age less than 5 years.[57] In a cohort of 10,834 children treated with low-dose RT (mean 1.5 Gy) for tinea capitis, there were 73 neural tumours which gave an overall RR of 6.9 for development of RIC of the brain. Tumours in areas below the neck did not show an increased risk.[56] A recent systematic review of 18 studies investigating the risk of RIC following RT for childhood cancer confirmed the enhanced risk for this cohort.[96]

Intracranial stereotactic radiosurgery (SRS) is a form of RT that exposes the brain to high radiation doses/fraction, albeit to very small volumes. Most follow-up studies show no increase in brain tumours (Jeremy Rowe, 2014, personal communication).[60,63,97] Six case reports have suggested a potential link between SRS and risk of malignant transformation of benign tumours; however, it is difficult to be certain that cells with an increased malignancy were not already present.[98] An earlier report has suggested that progression of benign cerebral tumours may be related to the presence of malignant foci on first presentation.[99] These authors advise that, prior to SRS, benign neoplasms should be evaluated for their proliferative potential, either by biopsy or the use of metabolic imaging to identify aggressive subtypes. However, this is not always realistic or practical. Since SRS is a relatively new modality, the follow-up is predominantly less than 15 years, therefore none of the completed studies can definitively prove the safety of SRS over a lifetime, although for older patients, the data show the risk is negligible. However, the data are still being accrued; consequently, the potential risk of a RIC should be considered when treating younger individuals with SRS for benign disease in the head and neck area.

RT can be used for the treatment of a number of eye conditions with good effect (Table 1). There is a recognized risk of radiation-induced cataract.[10,100–102] However, since cataracts are treatable, it is not normally considered a major contraindication. The radiation dose to the orbit and surrounding brain tissue during RT of eye conditions is often in the order of 20 Gy. Based on a number of approximations, the risk of a RIC arising in the brain as a result of the IR exposure has been estimated to be approximately 0.2% above that expected.[92] Overall, there is now considerable evidence that, although there is a measurable increase in brain tumours following an initial RT treatment, the risk is very small although age dependent, a factor clearly of importance when children and adolescents are being treated.

Thyroid cancer

Current RT protocols for treating benign disease rarely expose the thyroid to significant doses of IR. However, previously, a number of benign diseases were treated with RT that resulted in significant exposure of the thyroid with increased levels of thyroid cancer found for children treated for benign diseases such as tinea capitis, cervical adenopathy or tonsillitis.[64,65] Follow-up of these cohorts has led to identification of the lifetime risk of a RIC in the thyroid for children exposed before the age of 10 years to be approximately 1% Gy^{-1}, although in very young children this may be higher.[64,92] A recent systematic review of four studies meeting the selection criteria, showed a significant increase in thyroid cancer in individuals ($n = 16{,}757$) receiving RT for a wide range of primary childhood cancers. In total, 187 RICs were identified; a linear dose response was identified up to 10 Gy which then plateaued to 30 Gy, beyond this the risk reduced. This study also confirmed that the excess RR Gy^{-1} increased significantly with decreasing age at exposure ($p < 0.01$).[45]

Haematological malignancies

It is well recognized that there is a shorter LT for leukaemias induced by RT. The risk is dose-dependent peaking about 15 years after exposure although it is still apparent for more than 25 years and is likely to be slightly elevated for life. These findings have been confirmed in the treatment of a number of benign diseases although none of these protocols has been used for many years, *e.g.* ankylosing spondylitis,[77,78] benign gynaecological disorders[76,103] and peptic ulcers.[43] Chronic myelocytic leukaemia has the shortest LT compared with other leukaemias (mean approximately 5 years),[43,51,104] whereas there is little evidence linking chronic lymphocytic leukaemia or adult T-cell leukaemia to IR exposure.[51] These authors also found a weak link for non-Hodgkin lymphoma among males although not in females, and no evidence of radiation-associated excess risks for either Hodgkin lymphoma or multiple myeloma. From the LSS data, an adult irradiated with 1 Gy is calculated to have an increased lifetime risk of approximately 1%. For RT at the intermediate doses used in benign disease and with the much reduced bone marrow exposure, this will be much less. For example, patients with ankylosing spondylitis exposed to a mean bone marrow dose of 1 Gy will have an increase in leukaemia risk of approximately 0.2%.[92]

Soft-tissue and bone cancer

Sarcoma is known to occur following RT for a range of malignant and non-malignant diseases but only at very low frequency (0.05%), and rarely if the dose is <10 Gy.[73] In the LSS cohort, five excess cases have been reported following exposure to a mean total-body dose of 0.23 Gy. This equates to a lifetime risk of osteosarcoma after exposure to low-dose IR of <0.1% for 1 Gy total-body dose.[105] Correcting for a typical small RT field of 100 cm^2 would indicate an increased risk of sarcoma after intermediate dose RT to be <1 in 100,000.[92] However, in patients treated for inherited retinoblastoma, there is a significant increase in the risk of developing a sarcoma within the radiation field (approximately 6% over 18 years); this suggests that individuals with a retinoblastoma gene defect have enhanced sensitivity to RT.[106] In a recent report from the CCSS,

an elevated risk of the development of a radiation-induced sarcoma was found in children treated for childhood cancer with a median LT of 11.8 years. The risk was further increased by exposure to anthracyclines and was more likely if the initial treatment was for Hodgkin lymphoma or a primary sarcoma.[74] Data from a European study have confirmed this finding. In a study of 4171 survivors of childhood cancer treated with RT, an excess RR of secondary sarcoma has been calculated to be 1.77 Gy^{-1}.[75]

In a recent study of 34 patients (mean age 44 years) who were treated with RT (8-Gy single dose) 1 day after surgical reconstruction for acetabular fractures, there was a much decreased incidence of subsequent heterotopic ossification of the hip. This study showed that the risks from RT prophylaxis were small and that RT was safer than indometacin and substantially overlapped with the range for no prophylaxis.[107] Clearly RT offers a good control, although the risk of a RIC will be unknown for many years; in these older patients, it is likely to be very small.

Irradiation of the chest area

Previously, RT was used in females to treat benign disease of the breast, *e.g.* for acute mastitis. Study of females (the majority were between 20 and 40 years at the time of RT) showed that this exposure increased the risk of a subsequent cancer.[66,67] In a recent review of three eligible studies, the evidence shows that there is a linear increase in excess risk for breast tissue as for other solid tumours,[81] although in the earlier studies, there was evidence of a flattening of the risk above approximately 5 Gy.[66,67] The dose– response relationship was also found in female infants whose chest area was exposed to low-dose RT for haemangioma with those receiving >1 Gy being mainly responsible for the increased risk.[68] This underlines the necessity to keep as low as is possible the chest wall/breast dose for young girls. A later analysis has shown that description of the radiation risk was significantly improved when a model of genomic instability was included at the earliest stages of carcinogenesis.[108] In studies of females treated for Hodgkin lymphoma, an approximately linear increase in risk was identified, which was radiation dose and time related; a further analysis showed that the risk was reduced by adjuvant chemotherapy probably through initiation of early menopause.[39,40] A significantly increased risk of breast cancer has been reported in females treated with mediastinal RT for Hodgkin lymphoma in childhood.[109] This increase was confirmed in a recent analysis of 1230 females treated for childhood cancer (CCSS cohort) which involved chest irradiation. This showed that survivors treated with lower dose RT (median, 14 Gy; range, 2–20 Gy) to a large volume (whole-lung field) had a similarly high risk of breast cancer as survivors treated with high doses (median, 40 Gy) to the mantle (extended) field. The cumulative incidence of breast cancer by age 50 years was 30% with a 35% incidence among Hodgkin lymphoma survivors. Breast cancer associated mortality at 5 and 10 years was also substantial (12% and 19%, respectively). This study has highlighted the importance of close monitoring of this cohort and demonstrates that, where possible, the dose to the chest wall/breast should be minimized.[70]

In a modeling study of the risk of RIC following intermediate dose RT (20–35 Gy) for mediastinal Hodgkin lymphoma, a marked reduction in the risk of subsequent breast and lung cancer was calculated when involved field RT was compared with mantle/extended field RT. This study demonstrated that care in reducing the field size to a minimum, use of modern RT techniques and dose reduction (where justified) will significantly reduce the subsequent risk of a RIC.[110] A cautious estimate of the increased lifetime risk of breast cancer for a breast exposed to 1 Gy has been made for different age groups: approximately 5% (less than 35 years), <3% (35–45 years), and much less, or possibly zero (more than 45 years).[92]

As can been seen from Table 2, there is evidence that lung cancer incidence shows a small, but quantifiable, increase following RT to the chest area. The absolute risk of a RIC has been estimated to be approximately 1% within 25 years of a 1-Gy exposure to the lung.[92] In a study of lung cancer in patients treated for Hodgkin lymphoma, there was clear evidence of a dose-dependent increase in risk up to at least 30 Gy.[38,69] This showed an additive increase with adjuvant chemotherapy and a multiplicative effect of smoking. The influence of smoking when analysing RIC in the lung is difficult to analyse as its prevalence is wide spread and notoriously difficult to quantify. This was also observed in a study of individuals irradiated for peptic ulcers, a treatment which is no longer in use.[79] In a reanalysis of this cohort, there was confirmation of a statistically significant ($p < 0.05$) excess risk for all cancers and lung cancer, with a borderline increase in risk for stomach cancer ($p = 0.07$) and leukaemia ($p = 0.06$). For all tumour types, age at exposure is inversely related to RR.[43] Evidence from the LSS cohort also confirms that smoking significantly increases the excess risk of lung cancer.[111]

CONCLUSIONS

Assessing the risk of RT for benign disease has many challenges as the evidence base is limited, and consequently, it has to be assembled from a wide range of different sources that are rarely directly comparable. Overall, for older adults treated with RT for benign disease, especially located in peripheral tissues, the risk of a RIC is very small and reduces further with increasing age. Skin cancer is clearly a potential risk, but for most patients, this risk is low and the tumour types arising are likely to be treatable (predominantly BCC). Where possible, the volume of red bone marrow exposed to radiation should be kept to a minimum to minimize the slightly increased risk of leukaemia. The risk of other solid tumours will also depend on the tissue within, or close to, the radiation field and the volume exposed.

RT for non-malignant indications certainly has a place in modern medicine, and there is considerable evidence for the utility of low- to intermediate-dose RT for treating a range of specific indications. RT at these doses is relatively easy to administer, has few symptomatic side effects and often provides good long-term control and improved quality of life.[10] The current limited use of RT for treating benign disease can partly be ascribed to anxiety over the subsequent presentation of a RIC. However, many of the alternative treatments also have side effects that need to be compared against the, often very small, risk of RIC. This is especially relevant when considering older

age groups since their excess RR for RIC is likely to be small. However, it cannot be completely ruled out, and clinicians must weigh up carefully all of the risks and quality of life issues. Where treatment is for benign disease of peripheral tissues, the risk is smaller as there is less likelihood of scatter radiation to critical organs. However, caution must be exercised when considering RT for younger adults and, especially, children since they have enhanced radiosensitivity and expected longevity. For children treated with intermediate- to high-dose RT for childhood cancers, the risk of second and subsequent cancers is clinically significant, an outcome that is becoming more apparent as survival rates improve. Consequently, although the doses required to treat benign disease are generally lower than those used to treat cancer, caution is advised when considering RT for these conditions in children and young adults.

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