Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes

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In recent years the use of radiation treatment for benign tumours has increased with the advent of stereotactic delivery and, in particular, single high dose gamma knife therapy. This has been particularly true for benign CNS (central nervous system) tumours such as vestibular schwannoma, meningioma, pituitary adenoma, and haemangioblastoma. While short term follow up in patients with isolated tumours suggests this treatment is safe, there are particular concerns regarding its use in childhood and in tumour predisposing syndromes. We have reviewed the use of radiation treatment in these contexts with particular regard to malignant transformation and new tumour induction. This review indicates that much more caution is warranted regarding the use of radiation treatment for benign tumours in childhood and in tumour prone conditions such as the neurofibromatoses.

Clinical geneticists are increasingly involved in the management of inherited tumour prone disorders through genetic registers and other active management strategies; this is particularly true for the neurofibromatoses and von Hippel-Lindau disease. Therefore, knowledge of treatment strategies and their potential pitfalls in genetic disease is increasingly becoming a necessity; genetic susceptibility to radiation damage has been investigated over the past few years. Certain disorders such as ataxia telangiectasia leave cells exquisitely sensitive to radiation damage. This damage can affect the integrity of the chromosome by causing double strand breaks and can have effects at the nucleotide level. Thus damage to any genes intimately involved in DNA repair and chromosome integrity could theoretically leave a patient with a deleterious mutation susceptible to radiation induced tumours. That this could be a widespread phenomenon is demonstrated by the fact that 40% of breast cancer patients and 10% of controls show increased chromosome damage when lymphocytes are irradiated in G2.

Radiation has been used in medical diagnosis and therapy for over a century. There have been enormous benefits in terms of improved diagnosis and outcomes, particularly for cancer. About 15% of annual exposure to ionising radiation comes from medical irradiation, although diagnostic radiation accounts for only 0.6–3% of the entire cancer burden. Radiation treatment for benign diseases such as tonsillitis, tinea capitis, and capillary haemangiomas was common from the 1940s to the 1960s, but it was used less as the causal role of radiation in cancer induction became clear from studies of radiation exposure from the atomic bomb and studies of occupational radiation exposure of workers in radium dial factories. The reduced use of radiation therapy proved to be well founded when long term follow-up studies of patients with radiation treatment in childhood for tonsillitis and tinea capitis showed significant excess risk for tumours in the radiation field.

Nonetheless, in the last few decades there has been an increase in the use of several types of radiation treatment for benign tumours (particularly vestibular schwannomas, pituitary adenomas, and meningiomas) as an alternative to surgical excision. Radiation therapy may well be beneficial for treating benign sporadic tumours, but this is less clear for tumour predisposing conditions because the rate of radiation induced tumours is far higher. We have reviewed the available literature to determine whether radiation therapy should be used for the treatment of benign tumours in tumour predisposing syndromes. There are two main issues: (i) malignant transformation of a benign tumour and (ii) development of new primary tumours in the radiation field.

REVIEW PROCESS

The literature was searched through PubMed using the following terms: radiation, radiotherapy, tumour induction, second primary, malignant transformation, neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), Gorlin syndrome, von Hippel-Lindau, atomic bomb, schwannoma, meningioma, pituitary adenoma, and combinations thereof. In addition, articles were sought from the references of publications that were identified using the above terms.

MALIGNANT TRANSFORMATION IN PATIENTS WITHOUT TUMOUR PRONE CONDITIONS

Malignant transformation can occur after radiation treatment for vestibular schwannoma and cranial nerve sheath tumours. However, this is rare. The risk of malignant transformation of a benign tumour after radiation treatment is difficult to quantify and is influenced by many factors, including age at treatment, type of tumour, and dose of radiation.

**Abbreviations:** BCC, basal cell carcinomas; CI, confidence interval; CNS, central nervous system; LFS, Li-Fraumeni syndrome; MNPP, malignant peripheral nerve sheath tumours; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2; RR, relative risk
pituitary adenoma, probably because insufficient cells are killed in the tumour and some of the surviving cells acquire mutations in genes, such as TP53, that can transform a benign tumour into a malignant one. Malignant transformation of vestibular schwannoma has been reported from 6 months to 7 years after therapy, and most tumours appear to be sarcomatous. In one particular case the excised tumour was available for histological and molecular analysis before and after radiation: the tumour gained a TP53 mutation and became malignant after radiation. Thus far, there are at least seven cases in the literature in which malignant transformation occurred after radiation treatment of vestibular schwannoma, and 21 cases where sarcomatous change occurred in the sella after radiotherapy for pituitary tumour.

### NEW PRIMARY TUMOURS IN PATIENTS WITHOUT TUMOUR PRONE CONDITIONS

It is well known that new primary tumours can occur in the therapeutic radiation field. The tissues at highest risk are haematopoietic, thyroid, salivary gland, central nervous system (CNS), skin, and breast. New primary tumours usually occur 7–30 years post-irradiation, with a peak latent period of around 15 years. One of the first studies to establish an increased risk noted the occurrence of salivary tumours in patients who had received radiation to the tonsils and nasopharynx. Twenty seven tumours were found, with an observed to expected ratio of 19 for benign tumours and 40 for malignant tumours. The latent period between the initial radiation treatment and tumour diagnosis ranged from 7 to 32 years.

The relationship between radiotherapy in childhood for tinea capitis and the development of brain and nervous system tumours was investigated in 10 834 patients treated between 1948 and 1960. The 30 year cumulative risk for neural tumours was 0.8% and the incidence was 1.8 tumours per 10 000 persons per year. The estimated relative risk (RR) was 6.9 for all tumours and 8.4 for neural tumours of the head and neck. There were significantly increased RR for meningiomas (RR = 9.5, 95% confidence interval (CI) 3.5 to 25.7), nerve sheath tumours (RR = 18.8, 95% CI 6.7 to 52.5), and other neural tumours (RR = 3.4, 95% CI 1.1 to 10.2). There was a strong dose-response relationship, with an RR of almost 20 after estimated doses of about 2.5 Gy.

Another study found an increased incidence of meningiomas and schwannomas in 2013 patients treated with radiotherapy before the age of 16, mostly for enlarged tonsils. Seventy (2.3%) of the patients developed neural tumours, with seven developing multiple schwannomas or meningiomas. The higher incidence of secondary tumours than in the study of tinea capitis reflects the higher doses, which averaged 7.5 Gy.

Long term studies of secondary tumours occurring after therapeutic treatment of benign tumours mainly concern pituitary tumours. A total of 334 patients with pituitary adenoma who were treated with conservative surgery and radiotherapy (median dose: 45 Gy) were followed for an average of 11 years. The cumulative risk of developing a secondary brain tumour within 10 years of radiotherapy was 1.3% (95% CI 0.4 to 3.9%), and within 20 years, 1.9% (95% CI 0.7 to 5.0%). The RR of a secondary brain tumour was 9.4 (95% CI 3.0 to 21.9).

Another study reviewed 134 pituitary adenoma patients who underwent radiation therapy from 1970 to 1988 with doses of 45–50 Gy over 25 fractions. The mean follow-up period was 8.4 years and there were two secondary malignancies. The most recent long term study assessed the incidence of secondary brain tumours in 325 patients operated on and irradiated for pituitary tumours. The observed to expected ratio of secondary brain tumours was 2.7 (95% CI 0.6 to 7.8), but a meta-analysis of published cohort studies of patients with irradiated pituitary tumours indicated that there was a significantly increased incidence ratio (95% CI 3.2 to 10.7).

In these three studies of adult irradiated patients who received large doses of radiation, there was a smaller overall RR of radiation induced tumours than in the childhood studies. This is consistent with breast cancer incidence after irradiation for Hodgkin’s disease, where the increased risk appears confined to women who were irradiated below the age of 30.

Overall, these studies indicate that the risk of radiation induced tumours after radiotherapy for benign disease is 0.3–3% after 30 years. The lifetime risk of malignancy in the general population is 33–40%. The relatively small risks of malignant transformation and new primary tumours, when compared to the benefits of radiation treatment for benign CNS tumours, justifies the use of radiation in certain circumstances, for example when surgery is refused for a growing tumour or in an elderly or infirm patient. Nonetheless, people who have such treatment should be made aware of the potential risks of tumour induction.

### TUMOUR PRONE CONDITIONS

The overall risks of tumour induction from radiotherapy in people without tumour prone conditions appear to be quite small, but this is not the case for people with tumour predisposing conditions. The sensitivity to radiation is well established for certain autosomal recessive conditions such as ataxia telangiectasia. Indeed, heterozygote carriers may be at risk of radiation induced tumours. However, this part of the review will concentrate on the treatment of CNS tumours in autosomal dominant conditions such as the neurofibromatoses (table 1). Recent reports continue to advocate the use of radiation treatment in these conditions without the necessary long term follow up, and in some cases, ignoring the existing evidence of substantial problems. While it is not always possible to determine the difference between tumours that would and would not have occurred without radiation, case control studies now confirm the risk of tumour induction.

#### Neurofibromatosis 1

The risk of radiation induced malignant peripheral nerve sheath tumours (MPNST) in people with NF1 has been largely overlooked in recent years, but there are many such cases in the literature. In a series of 12 patients with MPNST after radiation, seven had NF1, of whom two had received radiotherapy for optic glioma 5 and 17 years previously. In another report, two of four patients with head and neck MPNST after radiotherapy had NF1.

We reported four MPNSTs that occurred in the radiation field of optic gliomas in three NF1 patients. We have recently shown that there is a significantly increased risk of new glioma and MPNST in NF1 patients who were irradiated for optic glioma. Of 19 irradiated patients, seven developed a new glioma and there were four MPNSTs. Only six patients who survived more than 15 years did not have a secondary tumour. There was a threefold increased significant risk of a malignant tumour in the radiation field compared to optic glioma patients who had not undergone radiotherapy.

In addition to the well established risk of secondary tumours, there is evidence of a substantial risk of cardiovascular complications, such as cerebrovascular accident from Moyamoya disease. The risk of growth hormone deficiency is also greatly increased, with 46% of 84 children developing this complication.
These substantial risks mean that radiotherapy should be used only when absolutely necessary in NF1 patients, which excludes treatment for optic glioma. In general, optic glioma in NF1 patients has a more indolent course than in those with sporadic optic glioma. However, the better prognosis should not be confused with reports of improved outcomes with radiotherapy since the improved survival in NF1 patients is independent of such treatment.

**Neurofibromatosis 2**

Many recent reports have advocated the use of radiation treatment for vestibular schwannomas in NF2, but the median follow-up period is as little as 36 months for stereotactic radiosurgery and 42 months for fractionated radiotherapy. There appears to be little concern about the 18.8-fold increased relative risk of schwannoma induction and 9.5-fold increased RR of meningioma following radiation doses of 2.5 Gy. A patient with NF2 who is already likely to develop multiple tumours of both types may not be able to survive such an increase in tumour burden, even if they are confined to part of the brain. The possibility of increased risk of meningioma or schwannoma in the radiation field of NF2 patients has not been satisfactorily addressed, and it is likely that radiation induced tumours have been overlooked as being part of the normal NF2 condition.

It is harder to ignore the increasing number of reports of malignant transformation in irradiated NF2 patients. At least a 10-fold increased risk of malignancy may exist for irradiated as compared to unirradiated NF2 patients. Approximately 5% of all vestibular schwannomas occur in NF2 patients, but half the reported malignant transformations occur in NF2 patients. The number of these reports is small, but it is alarming that they refer disproportionately to NF2 patients. The largest radiosurgery series from the United States, which summarises the experience of gamma knife surgery for 829 vestibular schwannomas, contained the results for 62 NF2 patients with vestibular schwannomas. Thus, although only ~7% of irradiated patients have NF2, nearly half of the reports of malignant change occur in the NF2 context. There are probably yet more of these cases because NF2 patients whose tumours grow rapidly after radiosurgery may not undergo post mortem examination. Spontaneous malignant transformation of vestibular schwannoma is exceedingly rare, and to our knowledge has never been reported in NF2 patients.

MPNSTs have been reported at other sites in the absence of radiation treatment, but MPNSTs are unlikely to occur spontaneously in the cerebellopontine angle. Reports that these tumours were probably malignant before radiation treatment are therefore suspect. A likely reason for the increased risk of malignant transformation of NF2 tumours is their multifocal nature. The reduction in peripheral doses may allow small tumours on the outside of a tumour mass to survive treatment and gain the necessary extra genetic events that are necessary for malignant transformation. In this context, gain of a TP53 mutation after radiation treatment has been described in a sporadic vestibular schwannoma, and tumours removed from NF2 patients after radiotherapy have more chromosomal changes than non-irradiated vestibular schwannomas.

Therefore, physicians should exercise far more caution before advocating radiation treatment for benign tumours in NF2. A long term study of irradiated tumours is necessary to properly assess the risks of radiation induced tumours in NF2, with evaluation of the incidence of new tumours in areas of the brain exposed and not exposed to radiation.

**von Hippel-Lindau disease**

von Hippel-Lindau disease is an autosomal dominant condition predisposing to retinal and cerebellar haemangioblastomas, renal and pancreatic cysts, and renal cell carcinoma. Intrinsically, the vascular nature of these tumours makes radiotherapy an attractive option, and radiation treatment is now being used in von Hippel-Lindau disease. Although there are no clearly reported malignant changes and no plainly increased incidence of new primary tumours, the follow-up period for retinal angiomas has been very short and for few patients. Reports concerning irradiated von Hippel-Lindau patients include a total of 21 patients with a mean follow-up period of only 43–48 months. Tumour control rates are not as good for vestibular schwannoma, with only 75% control at 5 years and a third of patients having died. There is considerable uncertainty about the long term risks of radiation induced tumours in von Hippel-Lindau disease. Recent reports at the 12th International Meeting of the Leksell Gamma Knife Society in Vienna noted substantial tumour recurrence or new primaries around the site of irradiated haemangioblastomas in the cerebellar region. It is not clear if this would have been the pattern of disease without intervention.

**Radiotherapy for benign tumours**

While the focus of this review has been on treatment of benign tumours, radiation treatment has also been used in other genetic conditions.

**Gorlin syndrome**

Gorlin syndrome (nevus basal cell carcinoma syndrome) is an autosomal dominant condition predisposing to jaw cysts, basal cell carcinomas (BCC), and birth defects. Although radiotherapy is not used for benign tumours in Gorlin syndrome, the condition exemplifies why radiation treatment should be used sparingly (if at all) in tumour prone conditions. Almost 30 years ago, Strong reported multiple BCC in the cranio-spinal radiation field for a Gorlin syndrome related medulloblastoma. The extent and number of BCC can be so devastating as to cause death. The usual latent period for radiation induced tumours in Gorlin syndrome is 3–10 years after treatment, and radiotherapy is now
contraindicated in medulloblastomas that occur in Gorlin syndrome or in desmoplastic medulloblastomas (the histological type that occurs in Gorlin syndrome) in patients younger than 5 years of age. Rainbow Radiotherapy has been used in the past for the treatment of BCC in Gorlin syndrome, but this is no longer tenable; indeed, multiple BCC of the palm have been reported after radiotherapy for a benign palmar condition.

Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is perhaps the most devastating tumour predisposing syndrome. The condition is predominantly caused by mutations in the TP53 gene and leads to the development of multiple malignant tumours, including sarcomas and breast cancer. There are many reports of radiation induced malignancies, including five malignancies that occurred in the radiation field of three children who survived more than 3 years after treatment for adrenocortical tumours. Our own series of LFS families with germline TP53 mutations includes at least nine examples of second and subsequent primary cancers occurring in previous radiotherapy fields. Among these are three cases where radiotherapy for a benign haemangioma, radiation induced menopause in a patient with breast cancer, and radiotherapy for ductal carcinoma in situ of the breast were followed by fibrosarcoma, pelvic leiomyosarcoma, and grade III infiltrating ductal carcinoma, respectively.

The importance of recognising the possibility of a germline TP53 mutation is more relevant to malignant disease when there are choices between surgery and radiotherapy. We recently reported a change in treatment option from radiotherapy to mastectomy in a 20 year old woman with breast cancer when a TP53 mutation was identified.

The cause of the particularly high risk of second tumours in TP53 mutation positive patients appears to be because cells are unable to recognise and repair DNA and chromosomal damage, and because cells enter programmed cell death (apoptosis).

This is often termed radiation resistance.

Childhood cancers

The excess risks of developing second primary cancers following treatment for childhood malignancies have been well documented in several large studies. Radiotherapy has emerged as a consistent and important risk factor for developing second malignancies. A recent study in the Nordic countries included 234 cases of second malignancies following childhood cancers with follow-up periods of up to 30 years. Radiation was found to be the most important treatment related risk factor for the development of second malignancies with an overall RR of 4.3 (95% CI 3.0 to 6.2) within the irradiated volume. Highest risks were seen in children diagnosed below 5 years of age and risks increased with increasing radiation dose and with increasing follow-up time. The study reported by de Vathaire et al, based on large patient cohorts from France and the UK, found that the absolute excess risk of second malignancies following cancer in childhood increased during a period of at least 30 years after initial diagnosis. Given the very early age of onset and embryonal nature of many childhood cancers, it is likely that genetic factors are important in aetiology.

Retinoblastoma

The archetypal hereditary childhood cancer is retinoblastoma and there is strong evidence of substantially increased risks of second malignancies following radiotherapy for genetic retinoblastoma compared with sporadic cases. Thus Draper et al found that the RR for osteosarcoma of the orbit in patients who had received radiotherapy for hereditary retinoblastoma was of the order of 4000 based on eight cases. There were no comparable cases among sporadic retinoblastoma patients. The overall rate for second malignancies in the radiation field in the 314 genetic cases who received radiotherapy was 6.6% by 18 years of age. In contrast, only one patient with sporadic retinoblastoma among 100 irradiated cases developed a second malignancy, a meningioma diagnosed 31 years after treatment. It would appear that patients with genetic disease are particularly sensitive to radiation carcinogenesis.

CONCLUSIONS

In the past few years, there has been a dramatic increase in the use of radiation treatment for benign tumours, particularly those affecting the cranial cavity. It is most worrying that this is being offered as a first line treatment in tumour prone conditions without any reference to the age of the patient. The typical statement that radiation treatment is safe, coming as it does from studies with as little as 3–4 years of follow up, ignores the chequered history of radiotherapy for benign diseases of the skin (acne, tinea capitis, haemangiomas) and for tonsillitis, which led to substantially increased risks of thyroid cancer, parotid, parathyroid and CNS tumours. The typical latent period for these tumours is about 15 years. Similar statements about the safety of radiotherapy were made by its early advocates before radiation induced tumours appeared. Do we want to repeat this experience, and wait for radiation induced tumours to start occurring in people with tumour prone conditions and in children with benign tumours?

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