REVIEW

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

D G R Evans, J M Birch, R T Ramsden, S Sharif, M E Baser

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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.

See end of article for authors' affiliations

Correspondence to: Dr D Gareth R Evans, Academic Unit of Medical Genetics and Regional Genetic Service, St Mary's Hospital (SM2), Hathersage Road, Manchester, M13 OJH, UK; Gareth.evans@cmmc.nhs.uk

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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.[1–3] 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 telangectasia leave cells exquisitely sensitive to radiation damage.[4] 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.[5]

Radiation has been used in medical diagnosis and therapy for over a century.[6] 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,[6 7] although diagnostic radiation accounts for only 0.6–3% of the entire cancer burden.[7] 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[8] 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[9] and tinea capitis[10] 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[11] and

Abbreviations: BCC, basal cell carcinomas; CI, confidence interval; CNS, central nervous system; LFS, Li-Fraumeni syndrome; MPNST, malignant peripheral nerve sheath tumours; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2; RR, relative risk

pituitary adenoma,[12] 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[13] to 7 years after therapy,[11 14–17] 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.[13] Thus far, there are at least seven cases in the literature in which malignant transformation occurred after radiation treatment of vestibular schwannoma,[11 13–17] and 21 cases where sarcomatous change occurred in the sella after radiotherapy for pituitary tumour.[12]

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.[6] 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.[9] 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.[10] 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.[10]

Another study found an increased incidence of meningiomas and schwannomas in 3013 patients treated with radiotherapy before the age of 16, mostly for enlarged tonsils.[18] 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[10] 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.[19] 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.[20] 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).[21]

In these three studies of adult irradiated patients who received large doses of radiation,[19–21] there was a smaller overall RR of radiation induced tumours than in the childhood studies.[9 10] 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.[22]

Overall, these studies indicate that the risk of radiation induced tumours after radiotherapy for benign disease is 0.5–3% 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 telangectasia.[23] Indeed, heterozygote carriers may be at risk of radiation induced tumours.[23] 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,[24 25] and in some cases,[26] ignoring the existing evidence of substantial problems.[27–30] 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.[29–32] In a series of 12 patients with MPNST after radiation,[30] 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 radiation had NF1.[31]

We reported four MPNSTs that occurred in the radiation field of optic gliomas in three NF1 patients.[32] 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.[33] 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.[33]

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.[27 28] The risk of growth hormone deficiency is also greatly increased, with 46% of 84 children developing this complication.[27]

Table 1 Tumours in autosomal dominant conditions

Condition	Inheritance	Main tumours	Malignancies occurring post radiotherapy	Gene and chromosomal location
NF1	AD	Neurofibroma, glioma, and MPNST	MPNST, glioma	NF1 -17q
NF2	AD	Schwannoma, meningioma, ependymoma	MPNST	*NF2* -22q
Gorlin	AD	BCC, medulloblastoma	BCC	*PTCH* -9q
VHL	AD	Renal cell carcinoma, retinal and cerebellar haemangioblastoma	?	*VHL* -3p
Li-Fraumeni syndrome	AD	Sarcoma, breast cancer, glioma, lung cancer, adreno-cortical tumours	Sarcoma	*TP53* -17p

AD, autosomal dominant; BCC, basal cell carcinomas; MPNST, malignant peripheral nerve sheath tumours; VHL, von Hippel-Lindau disease.

These substantial risks mean that radiotherapy should be used only when absolutely necessary in NF1 patients, which excludes treatment for optic glioma.[27 34] 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[26 35] since the improved survival in NF1 patients is independent of such treatment.[34–36]

Neurofibromatosis 2

Many recent reports have advocated the use of radiation treatment for vestibular schwannomas in NF2,[24 25 37] but the median follow-up period is as little as 36 months for stereotactic radiosurgery[24] and 42 months for fractionated radiotherapy.[37] 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.[10] 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.[38] Approximately 5% of all vestibular schwannomas occur in NF2 patients, but half the reported malignant transformations occur in NF2 patients.[14–16] 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.[39] 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.[40] Spontaneous malignant transformation of vestibular schwannoma is exceedingly rare,[41] and to our knowledge has never been reported in NF2 patients.

MPNSTs have been reported at other sites in the absence of radiation treatment,[42] but MPNSTs are unlikely to occur spontaneously in the cerebellopontine angle. Reports that these tumours were probably malignant before radiation treatment are therefore suspect.[15] A likely reason for the increased risk of malignant transformation of NF2 tumours is their multifocal nature.[43] 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.[44] In this context, gain of a *TP53* mutation after radiation treatment has been described in a sporadic vestibular schwannoma,[14] and tumours removed from NF2 patients after radiotherapy have more chromosomal changes than non-irradiated vestibular schwannomas.[44]

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.[45–48] 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.[48] Reports concerning irradiated von Hippel-Lindau patients include a total of 21 patients with a mean follow-up period of only 43–48 months.[45–47] Tumour control rates are not as good as for vestibular schwannoma, with only 75% control at 5 years[47] 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[49 50] noted substantial tumour recurrence or new primaries around the site of irradiated haemangioblastomas in the cerebellar region.[49 50] It is not clear if this would have been the pattern of disease without intervention.[50]

RADIOTHERAPY FOR MALIGNANCY IN OTHER TUMOUR PRONE DISORDERS

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 (nevoid 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.[51] The extent and number of BCC can be so devastating as to cause death.[52] The usual latent period for radiation induced tumours in Gorlin syndrome is 3–10 years after treatment,[51–53] 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.[54] 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.[55]

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,[56–61] including five malignancies that occurred in the radiation field of three children who survived more than 3 years after treatment for adrenocortical tumours.[56] Our own series of LFS families with germline TP53 mutations[62] 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.[62] 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).[63–68] This is often termed radiation resistance.[4]

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.[69–74] A recent study in the Nordic countries[69] 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*,[70] 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.[75]

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*[76] 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.[77] 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)[10 78–80] and for tonsillitis,[9] 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?

Authors' affiliations

D G R Evans, S Sharif, Academic Unit of Medical Genetics and Regional Genetic Service, St Mary's Hospital (SM2), Hathersage Road, Manchester, M13 OJH, UK
J M Birch, CRUK Paediatric and Familial Cancer Research Group, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester, M27 4HA, UK
R T Ramsden, Department of Otolaryngology, Manchester Royal Infirmary, Manchester, M13 9WL, UK
M E Baser, Los Angeles, CA, USA

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REFERENCES

1 **Maddock I**, Moran A, Teare D, Norman A, Lavin M, Dodd C, Whitehouse R, Super M, Harris R, Evans DGR. A genetic register for von Hippel Lindau disease. *J Med Genet* 1996;**33**:120–7.
2 **McGaughran J**, Harris DI, Donnai D, Teare D, McLeod R, Kingston H, Super M, Harris R, Evans DGR. A clinical study of type 1 neurofibromatosis in North West England. *J Med Genet* 1999;**36**:197–203.
3 **Evans DGR**, Baser ME, O'Reilly B, Rowe J, Gleeson M, Saeed S, King A, Huson S, Kerr R, Thomas N, Irving R, MacFarlane R, Ferner R, McLeod R, Moffat D, Ramsden R. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *Br J Neurosurg* 2005;**19**:5–12.
4 **Scott D**, Roberts SA, Spreadborough AR, Bulman B, Barber JBP, Evans DGR. Chromosomal radiosensitivity and cancer predisposition. *Cancer Res* 2000;**2**:470–1.
5 **Roberts SA**, Spreadborough AR, Bulman B, Barber JBP, Evans DGR, Scott D. Heritability of cellular radiosensitivity: a marker of low penetrance predisposition genes in breast cancer. *Am J Hum Genet* 1999;**65**:784–94.
6 **Ron E**. Cancer risks from medical radiation. *Health Phys* 2003;**85**:47–59.
7 **Berrington de Gonzalez A**, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004;**363**:345–51.
8 **Tokunaga M**, Norman JE Jr, Asano M, Tokuoka S, Ezaki H, Nishimori I, Tsuji Y. Malignant breast tumors among atomic bomb survivors, Hiroshima and Nagasaki, 1950–74. *J Natl Cancer Inst* 1979;**62**:1347–59.
9 **Schneider AB**, Favus MJ, Stachura ME, Arnold MJ, Frohman LA. Salivary gland neoplasms as a late consequence of head and neck irradiation. *Ann Intern Med* 1977;**87**:160–4.
10 **Ron E**, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, Katz L. Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med* 1988;**319**:1033–9.
11 **Shin M**, Ueki K, Kurita H, Kirino T. Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. *Lancet* 2002;**360**:309–10.

12 **Prabhu SS**, Aldape KD, Gagel RF, Benjamin RS, Trent JC, McCutcheon IE. Sarcomatous change after sellar irradiation in a growth hormone-secreting pituitary adenoma. *Can J Neurol Sci* 2003;**30**:378–83.
13 **Hanabusa K**, Morikawa A, Murata T, Taki W. Acoustic neuroma with malignant transformation. Case report. *J Neurosurg* 2001;**95**:518–21.
14 **Thomsen J**, Mirz F, Wetke R, Astrup J, Bojsen-Moller M, Nielsen E. Intracranial sarcoma in a patient with neurofibromatosis type 2 treated with gamma knife radiosurgery for vestibular schwannoma. *Am J Otol* 2000;**21**:364–70.
15 **Bari ME**, Forster DM, Kemeny AA, Walton L, Hardy D, Anderson JR. Malignancy in a vestibular schwannoma. Report of a case with central neurofibromatosis, treated by both stereotactic radiosurgery and surgical excision, with a review of the literature. *Br J Neurosurg* 2002;**16**:284–9.
16 **Noren G**. Long-term complications following gamma knife radiosurgery of vestibular schwannomas. *Stereotact Funct Neurosurg* 1998;**70**(Suppl 1):65–73.
17 **Wilkinson JS**, Reid H, Armstrong GR. Malignant transformation of a recurrent vestibular schwannoma. *J Clin Pathol* 2004;**57**:109–10.
18 **Sznajder L**, Abrahams C, Parry DM, Gierlowski TC, Shore-Freedman E, Schneider AB. Multiple schwannomas and meningiomas associated with irradiation in childhood. *Arch Intern Med* 1996;**156**:1873–8.
19 **Brada M**, Ford D, Ashley S, Bliss JM, Crowley S, Mason M, Rajan B, Traish D. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *Br Med J* 1992;**304**:1343–6.
20 **Fisher BJ**, Gaspar LE, Noone B. Radiation therapy of pituitary adenoma: delayed sequelae. *Radiology* 1993;**187**:843–6.
21 **Erfurth EM**, Bulow B, Mikoczy Z, Svahn-Tapper G, Hagmar L. Is there an increase in second brain tumours after surgery and irradiation for a pituitary tumour? *Clin Endocrinol (Oxf)* 2001;**55**:613–6.
22 **Wahner-Roedler DL**, Nelson DF, Croghan IT, Achenbach SJ, Crowson CS, Hartmann LC, O'Fallon WM. Risk of breast cancer and breast cancer characteristics in women treated with supradiaphragmatic radiation for Hodgkin lymphoma: Mayo Clinic experience. *Mayo Clin Proc* 2003;**78**:708–15.
23 **Swift ML**, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia telangectasia. *N Engl J Med* 1987;**316**:1289–94.
24 **Subach BR**, Kondziolka D, Lunsford LD, Bissonette DJ, Flickinger JC, Maitz AH. Stereotactic radiosurgery in the management of acoustic neuromas associated with neurofibromatosis type 2. *J Neurosurg* 1999;**90**:815–22.
25 **Kida Y**, Kobayashi T, Tanaka T, Mori Y. Radiosurgery for bilateral neurinomas associated with neurofibromatosis type 2. *Surg Neurol* 2000;**53**:383–9.
26 **Fouladi M**, Wallace D, Langston JW, Mulhern R, Rose SR, Gajjar A, Sanford RA, Merchant TE, Jenkins JJ, Kun LE, Heideman RL. Survival and functional outcome of children with hypothalamic/chiasmatic tumors. *Cancer* 2003;**97**:1084–92.
27 **Guillamo JS**, Creange A, Kalifa C, Grill J, Rodriguez D, Doz F, Barbarot S, Zerah M, Sanson M, Bastuji-Garin S, Wolkenstein P, Reseau NF. Prognostic factors of CNS tumours in neurofibromatosis 1 (NF1): a retrospective study of 104 patients. *Brain* 2003;**126**:152–60.
28 **Grill J**, Couanet D, Cappelli C, Habrand JL, Rodriguez D, Sainte-Rose C, Kalifa C. Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. *Ann Neurol* 1999;**45**:393–6.
29 **D'Agostino AN**, Soule EH, Miller RH. Primary malignant neoplasms of nerves (malignant neurolemmomas) in patients without multiple neurofibromatosis (Von Recklinghausen disease). *Cancer* 1963;**16**:1003–14.
30 **Ducatman B**, Scheithauer B, Piepgras D, Reiman H, Istrup D. Malignant peripheral nerve sheath tumors: a clinicopathological study of 120 patients. *Cancer* 1986;**57**:2006–21.
31 **Loree TR**, North JH, Werness BA, Nangia R, Mullins AP, Hicks WL. Malignant peripheral nerve sheath tumors of the head and neck: analysis of prognostic factors. *Otolaryngol Head Neck Surg* 2000;**122**:667–72.
32 **Evans DGR**, Baser ME, McGaughran J, Sharif S, Donnelly B, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. *J Med Genet* 2002;**39**:311–14.
33 **Sharif S**, Ferner R, Birch J, Gattamaneni R, Gillespie J, Evans DGR. Second primary tumours in NF1 patients treated for optic glioma: substantial risks post radiotherapy. *J Clin Oncol* 2005 (submitted for publication).
34 **Listernick R**, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. *J Pediatr* 1989;**114**:788–92.
35 **Hoyt WF**, Baghdassarian SA. Optic glioma of childhood natural history and rationale for conservative management. *Br J Ophthalmol* 1969;**53**:793–8.
36 **Singhal S**, Kerr B, Birch J, Lashford L, Evans DGR. Clinical characteristics of symptomatic sporadic and NF1 related optic gliomata: implications for management. *Arch Dis Child* 2002;**87**:65–70.
37 **Fuss M**, Debus J, Lohr F, Huber P, Rhein B, Engenhart-Cabillic R, Wannenmacher M. Conventionally fractionated stereotactic radiotherapy (FSRT) for acoustic neuromas. *Int J Radiat Oncol Biol Phys* 2000;**48**:1381–7.
38 **Baser ME**, Evans DGR, Jackler RK, Sujansky E, Rubinstein A. Malignant peripheral nerve sheath tumours, radiotherapy and neurofibromatosis 2. *Br J Cancer* 2000;**82**:998.
39 **Lunsford LD**, Niranjan A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. *J Neurosurg* 2005;**102**(Suppl):195–9.
40 **McEvoy AW**, Kitchen ND. Rapid enlargement of a vestibular schwannoma following gamma knife treatment. *Minim Invasive Neurosurg* 2003;**46**:254–6.
41 **Kudo M**, Matsumoto M, Terao H. Malignant nerve sheath tumour of acoustic nerve. *Arch Pathol Lab Med* 1983;**107**:293–7.
42 **Mohyuddin A**, Neary WJ, Wallace AJ, Purcell S, Wu C-L, Reid H, Ramsden RT, Read AP, Evans DGR. Molecular genetic exclusion of NF2 in young patients diagnosed with a unilateral vestibular schwannoma. *J Med Genet* 2002;**39**:315–22.
43 **Plowman N**, Evans DGR. Stereotactic radiosurgery, acoustic neuroma therapy and radiation oncogenesis. *Br J Neurosurg* 2000;**14**:93–5.
44 **Warren C**, James LA, Ramsden RT, Wallace A, Baser ME, Varley JM, Evans DG. Identification of recurrent regions of chromosome loss and gain in vestibular schwannomas using comparative genomic hybridisation. *J Med Genet* 2003;**40**:802–6.
45 **Pan L**, Wang EM, Wang BJ, Zhou LF, Zhang N, Cai PW, Da JZ. Gamma knife radiosurgery for hemangioblastomas. *Stereotact Funct Neurosurg* 1998;**70**(Suppl 1):179–86.
46 **Chang SD**, Meisel JA, Hancock SL, Martin DP, McManus M, Adler JR Jr. Treatment of hemangioblastomas in von Hippel-Lindau disease with linear accelerator-based radiosurgery. *Neurosurgery* 1998;**43**:28–34.
47 **Jawahar A**, Kondziolka D, Garces YI, Flickinger JC, Pollock BE, Lunsford LD. Stereotactic radiosurgery for hemangioblastomas of the brain. *Acta Neurochir (Wien)* 2000;**142**:641–4.
48 **Raja D**, Benz MS, Murray TG, Escalona-Benz EM, Markoe A. Salvage external beam radiotherapy of retinal capillary hemangiomas secondary to von Hippel-Lindau disease: visual and anatomic outcomes. *Ophthalmology* 2004;**111**:150–3.
49 **Park YG**, Park YS, Kim GH, Chang JH, Chang JW. The role of gamma knife radiosurgery for the treatment of multiple hemangioblastomas (abstract). In:Proceedings of the 12th International Meeting of the Leksell Gamma Knife Society, Vienna, 2004.
50 **Rajaraman C**, Rowe J, Walton L, Malik I, Rdatz M, Kemeny A. Treatment options for von Hippel-Lindau's haemangioblastomatosis: the role of gamma knife stereotactic radiosurgery. *Br J Neurosurg* 2004;**18**(4):338–42.
51 **Strong L**. Genetic and environmental interactions. *Cancer* 1977;**40**(Suppl 4):S1861–6.
52 **Evans DG**, Birch JM, Orton CI. Brain tumours and the occurrence of severe invasive basal cell carcinoma in first degree relatives with Gorlin syndrome. *Br J Neurosurg* 1991;**5**:643–6.
53 **Evans DGR**, Farndon PA, Burnell LD, Gattameneni R, Birch J. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. *Br J Cancer* 1991;**64**:959–61.
54 **Amlashi SF**, Riffaud L, Brassier G, Morandi X. Nevoid basal cell carcinoma syndrome: relation with desmoplastic medulloblastoma in infancy. A population-based study and review of the literature. *Cancer* 2003;**98**:618–24.
55 **Golitz LE**, Norris DA, Luekens CA Jr, Charles DM. Nevoid basal cell carcinoma syndrome. Multiple basal cell carcinomas of the palms after radiation therapy. *Arch Dermatol* 1980;**116**:1159–63.
56 **Varley JM**, McGown G, Thorncroft M, Evans DGR, Kelsey AM, Birch JM. Analysis of a panel of patients with childhood adrenocortical tumors for germline TP53 mutations. *Am J Hum Genet* 1999;**65**:995–1006.
57 **Broniscer A**, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE. Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. *Cancer* 2004;**100**:2246–52.
58 **Limacher JM**, Frebourg T, Natarajan-Ame S, Bergerat JP. Two metachronous tumours in the radiotherapy fields of a patient with Li-Fraumeni syndrome. *Int J Cancer* 2001;**96**:238–42.
59 **Nutting C**, Camplejohn RS, Gilchrist R, Tait D, Blake P, Knee G, Yao WQ, Ross G, Fisher C, Eeles R. A patient with 17 primary tumours and a germ line mutation in TP53: tumour induction by adjuvant therapy? *Clin Oncol (R Coll Radiol)* 2000;**12**:300–4.
60 **Heyn R**, Haeberlen V, Newton WA, Ragab AH, Raney RB, Tefft M, Wharam M, Ensign LG, Maurer HM. Second malignant neoplasms in children treated for rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol* 1993;**11**:262–70.
61 **Lalloo F**, Varley J, Ellis D, O'Dair L, Pharoah P, Evans DGR, and The Early Onset Breast Cancer Study Group. Family history is predictive of pathogenic mutations in BRCA1, BRCA2 and TP53 with high penetrance in a population based study of very early onset breast cancer. *Lancet* 2003;**361**:1101–2.
62 **Birch JM**, Alston RD, McNally RJQ, Evans DGR, Kelsey AM, Harris M, Eden OB, Varley JM. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. *Oncogene* 2001;**20**:4621–8.
63 **Ricevuto E**, Marchetti P, Cannita K, De Galitiis F, Di Rocco ZC, Tessitore A, Martella F, Bisegna R, Porzio G, Bafile A, Vicentini R, Resta V, Mattucci S, Ventura T, Martinotti S, de Rubeis GP, Ficorella C. Can analysis of the molecular status of the p53 gene contribute to improving the therapeutic strategy for breast carcinoma? *Tumori* 2003;**89**(Suppl 4):S197–9.
64 **Fei P**, El-Deiry WS. P53 and radiation responses. *Oncogene* 2003;**22**:5774–83.
65 **Rosen EM**, Fan S, Rockwell S, Goldberg ID. The molecular and cellular basis of radiosensitivity: implications for understanding how normal tissues and tumours respond to therapeutic radiation. *Cancer Invest* 1999;**17**:56–72.
66 **Boyle JM**, Spreadborough AR, Greaves MJ, Birch JM, Varley JM, Scott D. Delayed chromosome changes in gamma-irradiated normal and Li-Fraumeni fibroblasts. *Radiat Res* 2002;**157**:158–65.
67 **Boyle JM**, Mitchell EL, Greaves MJ, Roberts SA, Tricker K, Burt E, Varley JM, Birch JM, Scott D. Chromosome instability is a predominant trait of fibroblasts from Li-Fraumeni families. *Br J Cancer* 1998;**77**:2181–92.
68 **Sproston AR**, Boyle JM, Heighway J, Birch JM, Scott D. Fibroblasts from Li-Fraumeni patients are resistant to low dose-rate irradiation. *Int J Radiat Biol* 1996;**70**:145–50.
69 **Garwicz S**, Anderson H, Olsen JH, Dollner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Moller T, Sankila R, Tulinius H. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric

Hematology and Oncology. The Association of the Nordic Cancer Registries. *Int J Cancer* 2000;**88**(4):672–8.
70 **De Vathaire F**, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, Shamsaldin A, Diallo I, Bell J, Grimaud E, Hardiman C, Lagrange JL, Daly-Schveitzer N, Panis X, Zucker JM, Sancho-Garnier H, Eschwege F, Chavaudra J, Lemerle J. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br J Cancer* 1999;**79**(11–12):1884–93.
71 **Hawkins MM**, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. *Int J Cancer* 1987;**56**:339–47.
72 **Klein G**, Michaelis J, Spix C, Wibbing R, Eggers G, Ritter J, Kaatsch P. Second malignant neoplasms after treatment of childhood cancer. *Eur J Cancer* 2003;**39**:808–17.
73 **Neglia JP**, Friedman DL, Yasuo Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst* 2001;**93**(8):618–29.
74 **Rubino C**, Adjadj E, Guerin S, Guibout C, Shamsaldin A, Dondon MG, Valteau-Couanet D, Hartmann O, Hawkins M, de Vathaire F. Long-term risk of second malignant neoplasms after neuroblastoma in childhood: role of treatment. *Int J Cancer* 2003;**107**(5):791–6.
75 **Birch JM**. Genes and cancer. *Arch Dis Child* 1999;**80**(1):1–3.
76 **Draper GJ**, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. *Br J Cancer* 1986;**53**:661–71.
77 **Roche PH**, Robitail S, Thomassin JM, Pellet W, Regis J. [Surgical management of vestibular schwannomas secondary to type 2 neurofibromatosis]. *Neurochirurgie* 2004;**50**(2–3 Pt 2):367–76.
78 **Albright EC**, Allday RW. Thyroid carcinoma after radiation therapy for adolescent acne vulgaris. *JAMA* 1967;**199**:280–1.
79 **Ju DM**. Salivary gland tumors occurring after radiation of the head and neck area. *Am J Surg* 1968;**116**:518–23.
80 **De Jong SA**, Demeter JG, Jarosz H, Lawrence AM, Paloyan E. Thyroid carcinoma and hyperparathyroidism after radiation therapy for adolescent acne vulgaris. *Surgery* 1991;**110**:691–5.