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## Original Paper

# Second Cancers in Patients with Brain Tumours—Impact of Treatment

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**The records of the Finnish Cancer Registry from 1953 to 1994 were used to assess the risk of subsequent primary cancer among 14 493 brain tumour patients. They had been treated with surgery only ($n = 9804$), radiotherapy ($n = 4099$), chemotherapy and radiotherapy ($n = 493$) or chemotherapy alone ($n = 97$). By the end of 1994, 403 subsequent primary cancers were registered in these patients, whilst the expected number based on national incidence was 332. The standardised incidence ratio (SIR) was 1.2 (95% confidence interval (CI) 1.1–1.3). A significant excess risk of tumours in the central nervous system (CNS) including meningeomas (SIR 2.6, 95% CI 1.7–3.8), non-Hodgkin's lymphoma (SIR 2.6, 95% CI 1.6–4.1) and skin melanoma (SIR 1.9, 95% CI 1.0–3.1) was observed. CNS tumours were observed in excess among patients treated with surgery alone (SIR 2.0, 95% CI 1.2–3.2) and with radiotherapy (SIR 5.1, 95% CI 2.5–9.4). In conclusion, brain tumours are associated with an increased risk of both CNS second tumours and non-CNS second cancers, especially non-Hodgkin's lymphoma and melanoma. A moderately increased risk of second tumours in the CNS was observed among brain tumour patients treated with surgery only and a larger excess among those treated with radiotherapy.**


**Key words: brain tumours, glioma, meningeoma, radiotherapy, second cancer**
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## INTRODUCTION

TUMOURS OF the central nervous system (CNS) comprised 3.2% of all cancers among men and 3.6% among women in Finland in 1995 [1]. The age-standardised incidence and mortality rates of brain tumours have increased during recent decades [1–4]. Brain tumours are relatively common in children, although the highest incidence occurs between the ages of 50 and 70 [1].

The major goal in the treatment of brain cancer is local tumour control, which is difficult to obtain with surgery alone, especially in high-grade tumours. External radiotherapy is the treatment of choice if surgery is not possible and as an adjuvant treatment to surgery [5].

Unfortunately, an increased risk of second cancer and meningeoma has been suggested for patients whose brain tumours have been treated with radiation [7, 9]. An increased risk of second cancers and meningeomas has also been observed among children treated with prophylactic cranial irradiation for leukaemia or for benign conditions [10, 11]. The occurrence of a second brain tumour after radiotherapy has been associated with both low- and high-doses of radiation [12]. Radiation can induce changes similar to those seen in tumorigenesis and the genetic changes are qualitatively and quantitatively similar to those which occur spontaneously [8].

Second cancer is an independent new primary cancer arising after the diagnosis of the first cancer. The possible explanations for the occurrence of multiple cancers include simultaneous carcinogenic exposures to different organs and genetic predisposition. Cancer treatment may contribute to the risk of a second cancer. The relative risk of a second cancer in patients who have survived one cancer depends on the site of the first cancer, its treatment and age and sex of the patient [6].

In Finland, all cancer patients have been registered and also followed-up for new cancers by the Finnish Cancer Registry (FCR) since 1953. The aim of this study was to assess the risk of second primary cancers after different modalities used to treat brain tumours and especially to estimate the risk of new tumours in the CNS after radiation treatment.

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## PATIENTS AND METHODS

The records of the population-based, nationwide Finnish Cancer Registry (FCR) cover almost completely all cancer cases diagnosed in Finland since 1953 [1]. Hospitals, practising physicians and pathological and haematological laboratories are requested to report to the FCR all cases of cancer that come to their attention. In addition, all death certificates with a mention of cancer are annually transferred from the files of the Statistics Finland to the FCR. Benign intracranial and spinal neoplasms are also registered at the FCR. In approximately 1% of cases the information received by the FCR is based on death certificates alone. The study population constituted all registered brain tumour patients diagnosed between 1953 and 1994 in Finland. The follow-up started at the time of diagnosis and ended at death, emigration or on 31 December 1994, whichever occurred first. The follow-up yielded 67 709 person-years at risk.

At the FCR, each independent primary cancer has always been coded as a new entity. This means that for a brain tumour patient, a second intracranial primary neoplasm (synchronous or metachronous) may be coded at another site of the brain, even if the histologies are the same. For example, a meningioma patient may have another meningeoma and a glioma patient may later have a meningioma in the FCR file.

The distribution of the patients according to treatment is shown in Table 1. The treatment groups considered separately were: surgery alone (surgery only, no radiotherapy or chemotherapy); radiotherapy (radiotherapy with or without surgery, but no chemotherapy); chemotherapy (with or without surgery but no radiotherapy); and combined radiotherapy and chemotherapy (with or without surgery).

The observed numbers of subsequent cancers were obtained by follow-up of the patients up to the end of 1994 through the files of the FCR. The expected numbers were calculated by multiplying the 5-year age-group, calendar period and gender-specific numbers of person-years by the respective national incidence rates. The risk of contracting a new primary cancer was estimated as a standardised incidence ratio (SIR), defined as the ratio of the observed and expected numbers of cases. A SIR of 1.0 indicates that there is no excess risk or risk deficit of contracting a new primary cancer. The 95% confidence intervals (CI) were estimated under the assumption that the observed number followed a Poisson distribution.

*Table* 1. *Distribution of the study group of* 14 493 *brain tumour patients by treatment for the brain tumour*

| Treatment | Men | Women | Total | Person-years at risk |
|---|---|---|---|---|
| Surgery alone | 4155 | 5649 | 9804 | 50 598 |
| Radiotherapy* | 2190 | 1909 | 4099 | 15 433 |
| Chemotherapy* | 49 | 48 | 97 | 198 |
| Radiotherapy and chemotherapy* | 279 | 214 | 493 | 1480 |
| Total | 6673 | 7820 | 14 493 | 67 709 |

*With or without surgery.

*Table* 2. *Observed and expected numbers of second cancers and standardised incidence ratios (SIR) with their* 95% *CI in a cohort of brain tumour patients, by site of the second cancer, Finland* 1953–1994

| Site of second cancer | Obs. | Exp. | SIR | 95% CI |
|---|---|---|---|---|
| CNS | 28 | 10.8 | 2.6 | 1.7–3.8 |
| NHL | 19 | 7.2 | 2.6 | 1.6–4.1 |
| Hodgkin's disease | 1 | 1.9 | 0.5 | 0.01–2.9 |
| Leukaemia | 12 | 7.7 | 1.6 | 0.8–2.7 |
| Skin, melanoma | 14 | 7.5 | 1.9 | 1.0–3.1 |
| Skin, non-melanoma* | 8 | 8.8 | 0.9 | 0.4–1.8 |
| Mouth, pharynx | 11 | 7.6 | 1.5 | 0.7–2.6 |
| Thyroid gland | 8 | 4.9 | 1.6 | 0.7–3.2 |
| Breast | 60 | 54 | 1.1 | 0.9–1.4 |
| Endometrium | 21 | 14 | 1.5 | 0.9–2.4 |
| All | 403 | 332 | 1.2 | 1.1–1.3 |

*Excludes basal cell carcinoma. Obs, observed; Exp., expected; CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin's lymphoma.

## RESULTS

During 1953–1994, 14 493 patients with brain tumours were registered. Among them, 403 subsequent primary cancers were recorded during follow-up. This was significantly more than expected (332, SIR 1.2, 95% CI 1.1–1.3). A significant excess risk of CNS tumours, non-Hodgkin's lymphoma (NHL) and skin melanoma (borderline significance) was observed (Table 2).

Among the 9804 patients treated with *surgery only*, 340 second tumours were observed versus 287 expected (SIR 1.2) (Table 3). The overall risk of second cancer was increased during the first year of follow-up mainly attributable to tumours of the CNS and NHL (Table 4). An excess risk was also observed after follow-up of 15 years among both men (SIR 1.5, 95% CI 1.0–2.1) and women (SIR 1.3, 95% CI 1.0–1.7). In total, a significantly increased number of CNS tumours, NHL and skin melanoma (borderline) was observed (Table 4).

Among the 4099 patients treated with *radiotherapy*, 56 new tumours were observed versus 41 expected (SIR 1.4)

*Table* 3. *Observed numbers of second cancers and standardised incidence ratios (SIR) with their* 95% *CI among brain tumour patients, by treatment mortality and follow-up time*

| | Total | | | < 1 year | | | 1–4 years | | | 5–14 years | | | 15+ years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI |
| Surgery | 340 | 1.2 | 1.1–1.3 | 44 | 1.6 | 1.2–2.2 | 67 | 0.9 | 0.7–1.1 | 135 | 1.2 | 1.0–1.4 | 94 | 1.4 | 1.1–1.7 |
| Radiotherapy* | 56 | 1.4 | 1.0–1.8 | 12 | 1.0 | 0.5–1.8 | 23 | 1.9 | 1.2–2.8 | 15 | 1.4 | 0.8–2.2 | 6 | 1.1 | 0.4–24 |
| Chemotherapy* | 1 | 1.2 | 0.0–6.7 | 1 | 6.5 | 0.2–36 | – | – | 0–16 | – | – | 0–11 | – | – | 0–28 |
| Radiotherapy and chemotherapy* | 6 | 1.7 | 0.6–3.7 | – | – | 0–2.8 | 4 | 3.1 | 0.9–8.0 | 1 | 1.3 | 0–7.2 | 1 | 5.2 | 0.1–29 |

*With or without surgery. See Table 2 legend for abbreviations.

*Table* 4. *Observed numbers of selected second cancers and standardised incidence ratios (SIR) with their* 95% *CI among brain tumour patients, by follow-up time*

| Therapy second cancer | Total | | | < 1 year | | | 1–4 years | | | 5–14 years | | | > 15 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI | Obs. | SIR | 95% CI |
| Surgery only | | | | | | | | | | | | | | | |
| CNS | 18 | 2.0 | 1.2–3.2 | 9 | 10.6 | 4.9–20 | 1 | 0.4 | 0.0–2.3 | 3 | 0.8 | 0.2–2.4 | 5 | 2.6 | 0.8–6.0 |
| NHL | 16 | 2.6 | 1.5–4.2 | 4 | 7.3 | 2.0–19 | 3 | 1.9 | 0.4–5.6 | 6 | 2.4 | 0.9–5.2 | 3 | 1.8 | 0.4–5.7 |
| Leukaemia | 8 | 1.2 | 0.5–2.4 | – | – | | 3 | 1.7 | 0.4–5.1 | 1 | 0.4 | 0.01–2.1 | 4 | 2.6 | 0.7–6.6 |
| Melanoma | 12 | 2.9 | 1.0–3.4 | 1 | 1.8 | 0.0–9.8 | 3 | 1.8 | 0.4–5.3 | 6 | 2.4 | 0.9–5.2 | 2 | 1.4 | 0.2–5.1 |
| Thyroid | 6 | 1.5 | 0.5–3.2 | 1 | 2.7 | 0.1–15 | – | – | | 5 | 3.0 | 0.9–7.0 | – | – | |
| All sites | 340 | 1.2 | 1.1–1.3 | 44 | 1.6 | 1.2–2.2 | 67 | 0.9 | 0.7–1.1 | 135 | 1.2 | 1.0–1.4 | 94 | 1.4 | 1.1–1.7 |
| Radiotherapy* | | | | | | | | | | | | | | | |
| CNS | 10 | 5.1 | 2.5–9.4 | 3 | 7.2 | 1.5–21 | 2 | 3.1 | 0.4–11.1 | 2 | 3.6 | 0.4–13 | 3 | 11.1 | 2.3–32 |
| NHL | 3 | 2.9 | 0.6–8.4 | 1 | 3.6 | 0.1–20 | 1 | 3.1 | 0.1–17 | 1 | 34 | 0.1–19 | – | – | 0–25 |
| Leukaemia | 4 | 3.6 | 1.0–9.1 | 1 | 3.0 | 0.1–17 | 2 | 5.2 | 0.6–19 | 1 | 3.6 | 0.1–20 | – | – | 0–31 |
| Melanoma | 2 | 1.5 | 0.2–5.4 | – | – | 0–12 | 1 | 2.3 | 0.1–13 | – | – | 0–9.5 | 1 | 5.3 | 0.1–29 |
| Thyroid | 2 | 2.4 | 0.3–8.6 | – | – | 0–20 | 2 | 7.1 | 0.9–26 | – | – | 0–15 | – | – | 0–29 |
| All sites | 62 | 1.4 | 1.1–1.8 | 12 | 0.9 | 0.5–1.6 | 27 | 2.0 | 1.3–2.9 | 16 | 1.4 | 0.8–2.2 | 7 | 1.2 | 0.5–2.5 |
| Chemotherapy† | | | | | | | | | | | | | | | |
| All sites | 1 | 1.2 | 0.03–6.7 | 1 | 6.5 | 0.2–36 | – | – | 0–16 | – | – | 0–11 | – | – | 0–28 |

*With or without surgery or chemotherapy. †With or without surgery. See Table 2 legend for abbreviations.

(Table 3). The small excess risk of a second cancer in 493 patients treated with *combined radiotherapy and chemotherapy* (SIR 1.7) was not statistically significant (Table 3). Among the 97 patients treated with *chemotherapy*, only one second cancer was observed versus 0.8 expected.

In further analyses all patients subjected to radiotherapy were combined. In this group, an increased risk of CNS tumours was found (SIR 5.1) which persisted throughout the whole follow-up period (Table 4). The risk of leukaemia was also somewhat increased although no clear follow-up time-dependent pattern emerged (Table 4).

28 out of 14 493 brain tumour patients had a second CNS tumour during follow-up. 17 of these were meningeomas. Of the 18 CNS tumours observed among cases treated with surgery only, 9 were meningeomas and 4 of these were diagnosed at the time of or soon after the diagnosis of the first tumour. There were 8 meningeomas among the 10 second CNS tumours in radiotherapy-treated patients, 2 of these diagnosed at the time of diagnosis of the first primary.

## DISCUSSION

Since the 1950s, an increase in the age-standardised incidence of malignant gliomas has been reported by a number of population-based cancer registries [1, 2, 4]. In Finland, the incidence of glioma and meningeoma has particularly increased during recent years [13]. An association between exposure to radiation, viruses, chemicals and nutritional factors and brain tumours has been suggested [14, 15]. Part of the increase in the incidence among the elderly may be due to an increased detection rate through improved diagnostic facilities. However, an overall increase in the incidence occurred well before the introduction of computer tomography (CT) scanning and rates have continued to rise steadily [13, 15].

Brain tumours are usually primarily treated with surgery, aiming at complete resection of the tumour. Standard treatment for malignant astrocytomas is surgical debulking, when possible, followed by postoperative radiotherapy. Among children, chemotherapy is predominantly used. During recent years, the combination of radiotherapy and chemotherapy or the use of chemotherapy in tumours which have recurred after radiotherapy has become common in the treatment of brain tumours in adults.

Since the 1950s, reports of induction of CNS tumours by radiation have been published [7, 8, 12]. There is evidence of irradiation-induced brain tumours from animal experiments, after prophylactic brain irradiation for childhood acute leukaemia and after irradiation for benign diseases in children [12]. The observations of CNS tumour induction after curative treatment of brain tumours are sporadic [7, 8]. In addition to case reports, the series have mainly consisted of patients radiated because of benign diseases in children (tinea) or those with prophylactic irradiation (leukaemia) [12]. In our series an excess risk of non-CNS tumours was observed among brain tumour survivors. A significant excess risk of non-CNS tumours has been reported after pituitary irradiation in Edinburgh [16]. In other reports, the risk for a second malignancy of the brain was 2.7% at 15 years (RR 16.9, 95% CI 4.4–44) after pituitary irradiation [17, 18]. The age at first exposure is important: children with leukaemia undergoing prophylactic CNS irradiation under the age of 5 years have a higher relative risk (RR) of second CNS tumours than those irradiated at a later age [19, 20].

It is almost impossible to evaluate causation in an individual cancer case. The second neoplasm may have occurred just by coincidence, through joint aetiology or as a part of an underlying susceptibility of developing neoplastic illnesses. The causes of brain tumours are largely unknown and common aetiological factors cannot be identified. Treatment of brain tumour is a plausible candidate for being the cause of the observed excess risks of second cancer. The criteria for the attribution of a CNS tumour to radiation have been defined [9, 10] as follows: the lesion must arise in the field of previous radiation treatment, it must be histologically different from the first cancer, a sufficient latency period must elapse between the commencement of irradiation and the clinical onset of the tumour and conditions that facilitate neoplastic growth such as von Recklinghausen's disease,

xeroderma pigmentosum, retinoblastoma and immunodeficiency syndromes must be excluded [9]. These criteria were fulfilled by only a few of the tumours observed after radiation among our patients.

There have been some problems in the reporting of benign tumours of the CNS to the FCR [21]. However, underreporting or delayed reporting of some 10–20% is not a major issue in the analyses because both the observed numbers of new cases and the calculation of the expected numbers are based on the same data set, in other words, both the observed and expected numbers are affected in the same way. A very good coverage is obtained for malignant tumours of the CNS (as for all malignant solid tumours).

Diagnosis of one cancer may lead to detection of a second primary tumour earlier than would be the case otherwise. However, if two tumours are diagnosed approximately at the same time, it is arbitrary which of them is coded to be the first one. Consequently, the results for the first year after diagnosis of brain tumour are subject to some uncertainty. Also, the possible effect of radiotherapy or chemotherapy would not be apparent that soon.

The coding practices at the FCR for patients with multiple primary cancers have always been of primary concern and all these cases have been evaluated by a physician. Strict criteria have been followed in coding a second tumour of a patient as a new malignant entity. In this evaluation, all the information available for the patient and the tumour as well as knowledge of the clinical behaviour of cancer in general were utilised.

A centralised cancer registry is not always in a position to record all details of cancer treatment, but for the FCR, information of the treatment has been shown to be, in most instances, correct. However, there may be cases who have been treated with surgery and radiotherapy and for whom only surgery is known to the FCR. This kind of misclassification of treatment would result in diminishing the relative risk of differences observed between treatment groups. If exact information of treatment were available for every single patient, the observed relative risk differences would be accentuated.

International comparisons have revealed that the coding principles in Finland are more strict (conservative) than in most countries, i.e. in uncertain cases a new cancer is not easily accepted as a new primary. Therefore, the SIR estimates of subsequent cancers are in Finland usually somewhat lower than those obtained in similar settings elsewhere [22, 23].

During more than 30 years of registration, the diagnostic methods and classification criteria may have gradually changed. However, a cancer registry database is considered to be useful in the assessment of the risks and risk determinants of subsequent new malignancies among cancer patients [6, 24]. A Swedish study on the quality of recording multiple cancers over 25 years showed that 94% of all second cancers were correctly reported and registered [24].

The clinical implication of our registry study is that brain tumour patients should have a prolonged active follow-up with a short interval for neuro-imaging with CT or preferably magnetic resonance imaging (MRI) or positron emission tomography (PET). We conclude that patients with gliomas have an increased risk of second non-CNS and CNS cancers.


1. *Cancer Incidence in Finland* 1995. Cancer Society of Finland Publication No. 58. Finnish Cancer Registry, Helsinki 1997.
2. Davis L, Ahlbom A, Hohl D, Percy C. Is brain cancer mortality increasing in industrialised countries? *Am J Industr Med* 1991, **19**, 423–431.
3. Helseth A, Langmark F, Mork S. Neoplasms of the central nervous system in Norway. *Acta Path Microbiol Immunol Scand* 1988, **96**, 1066–1074.
4. Shugg D, Allen B, Blizzard L, Dwyer T, Roder D. Brain cancer incidence, mortality and case survival: observations from two Australian cancer registries. *Int J Cancer* 1994, **59**, 765–770.
5. Walker M, Green S, Byar D, *et al*. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980, **303**, 1323–1329.
6. Teppo L, Pukkala E, Saxen E. Multiple cancer—an epidemiological exercise in Finland. *JNCI* 1985, **75**, 207–217.
7. Shapiro S, Mealey J, Sartorius C. Radiation-induced intracranial malignant gliomas. *J Neurosurg* 1989, **71**, 77–82.
8. Salvati M, Artico M, Caruso R, Rocci G, Orlando E, Nucci F. A report of radiation induced gliomas. *Cancer* 1991, **67**, 392–397.
9. Liwnicz B, Berger T, Liwnicz R, Aron B. Radiation associated gliomas. A report of four cases and analysis of postradiation tumours of the central nervous system. *Neurosurgery* 1985, **17**, 436–445.
10. Leung J, Guiney M. Secondary tumours after prophylactic cranial irradiation. *Australasian Radiol* 1996, **40**, 43–44.
11. Lindberg S, Karlsson P, Arvidsson B, Holmberg E, Lundberg LM, Wallgren A. Cancer incidence after radiotherapy for skin haemangioma during infancy. *Acta Oncol* 1995, **34**, 735–740.
12. Cavin W, Dalrymple G, McGuire E, Maners A, Broadwater J. CNS tumours induction by radiotherapy: a report of four new cases and estimate of dose required. *Int J Rad Oncol Biol Phys* 1990, **18**, 399–406.
13. Salminen E, Nuutinen JM, Huhtala S. Multivariate analysis of prognostic factors in 106 patients with malignant glioma treated with external radiotherapy. *Eur J Cancer* 1996, **32A**, 1918–1923.
14. Giles G, McNeil J, Donnan G, *et al*. Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. *Int J Cancer* 1994, **59**, 357–362.
15. Greig N, Ries L, Yancik R, Rapoport S. Increasing annual incidence of primary malignant brain tumors in the elderly. *JNCI* 1990, **82**, 1621–1624.
16. Bliss P, Kerr G, Gregor A. Incidence of second brain tumours after pituitary irradiation in Edinburgh 1962–1990. *Clin Oncol R Coll Radiol* 1994, **6**, 361–363.
17. Tsang R, Laperrierre N, Simpson W, Brierley J, Panzarella T, Smyth H. Glioma arising after radiation therapy for pituitary adenoma: a report of four patients and estimation of risk. *Cancer* 1993, **72**, 2227–2233.
18. Brada M, Ford D, Ashley S, Holmes-Sellors P, Nussey S, Uttley D. Risk of second brain tumours after conservative surgery and radiotherapy for pituitary adenoma. *Br Med J* 1992, **304**, 1343–1346.
19. Bernstein M, Laperriere N. Radiation induced tumours of the nervous system. In Gutin P, Leihel S, Sheline G, eds. *Radiation Injury to the Nervous System*. New York, Raven Press, 1991, 455–472.
20. Musa B, Pople I, Cummins B. Intracranial meningeomas following irradiation—a growing problem? *Br J Neurosurg* 1995, **9**, 629–637.
21. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. *Acta Oncol* 1994, **33**, 365–369.
22. Kleinerman R, Boice J, Storm H, *et al*. Second cancers following treatment for cervical cancer: an international cancer registries study. *Cancer* 1995, **76**, 442–452.
23. Travis L, Curtis R, Storm H, *et al*. Risk of second malignant neoplasmas among long-term survivors of testicular cancer. *JNCI* 1997, **89**, 1429–1439.
24. Frödin J-E, Ericsson J, Barlow L. Multiple primary malignant tumours in a national cancer registry. *Acta Oncol* 1997, **36**, 465–469.