# Risk of radiation-associated intracranial malignancy after stereotactic radiosurgery: a retrospective, multicentre, cohort study

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## Summary

**Background** A major concern of patients who have stereotactic radiosurgery is the long-term risk of having a secondary intracranial malignancy or, in the case of patients with benign tumours treated with the technique, the risk of malignant transformation. The incidence of stereotactic radiosurgery-associated intracranial malignancy remains unknown; therefore, our aim was to estimate it in a population-based study to assess the long-term safety of this technique.

**Methods** We did a population-based, multicentre, cohort study at five international radiosurgery centres (Na Homolce Hospital, Prague, Czech Republic [n=2655 patients]; Ruber International Hospital, Madrid, Spain [n=1080], University of Pittsburgh Medical Center, Pittsburgh, PA, USA [n=1027]; University of Virginia, Charlottesville, VA, USA [n=80]; and NYU Langone Health System, New York, NY, USA [n=63]). Eligible patients were of any age, and had Gamma Knife radiosurgery for arteriovenous malformation, trigeminal neuralgia, or benign intracranial tumours, which included vestibular or other benign schwannomas, WHO grade 1 meningiomas, pituitary adenomas, and haemangioblastoma. Patients were excluded if they had previously had radiotherapy or did not have a minimum follow-up time of 5 years. The primary objective of the study was to estimate the incidence of stereotactic radiosurgery-associated intracranial malignancy, including malignant transformation of a benign lesion or development of radiation-associated secondary intracranial cancer, defined as within the 2 Gy isodose line. Estimates of age-adjusted incidence of primary CNS malignancies in the USA and European countries were retrieved from the Central Brain Tumor Registry of the United States (CBTRUS) and the International Agency for Research on Cancer (IARC) Global Cancer statistics.

**Findings** Of 14 168 patients who had Gamma Knife stereotactic radiosurgery between Aug 14, 1987, and Dec 31, 2011, in the five contributing centres, 4905 patients were eligible for the analysis (had a minimum follow-up of 5 years and no history of previous radiation therapy). Diagnostic entities included vestibular schwannomas (1011 [20·6%] of 4905 patients), meningiomas (1490 [30·4%]), arteriovenous malformations (1089 [22·2%]), trigeminal neuralgia (565 [11·5%]), pituitary adenomas (641 [13·1%]), haemangioblastoma (29 [0·6%]), and other schwannomas (80 [1·6%]). With a median follow-up of 8·1 years (IQR 6·0–10·6), two (0·0006%) of 3251 patients with benign tumours were diagnosed with suspected malignant transformation and one (0·0002%) of 4905 patients was considered a case of radiosurgery-associated intracranial malignancy, resulting in an incidence of 6·87 per 100 000 patient-years (95% CI 1·15–22·71) for malignant transformation and 2·26 per 100 000 patient-years (0·11–11·17) for radiosurgery-associated intracranial malignancy. Two (0·0004%) of 4905 patients developed intracranial malignancies, which were judged unrelated to the radiation field. Overall incidence of radiosurgery-associated malignancy was 6·80 per 100 000 patients-years (95% CI 1·73–18·50), or a cumulative incidence of 0·00045% over 10 years (95% CI 0·00–0·0034). The overall incidence of 6·8 per 100 000, which includes institutions from Europe and the USA, after stereotactic radiosurgery was found to be similar to the risk of developing a malignant CNS tumour in the general population of the USA and some European countries as estimated by the CBTRUS and IARC data, respectively.

**Interpretation** These data show that the estimated risk of an intracranial secondary malignancy or malignant transformation of a benign tumour in patients treated with stereotactic radiosurgery remains low at long-term follow-up, and is similar to the risk of the general population to have a primary CNS tumour. Although prospective cohort studies with longer follow-up are warranted to support the results of this study, the available evidence suggests the long-term safety of stereotactic radiosurgery and could support physicians counselling patients on Gamma Knife stereotactic radiosurgery.

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## Research in context

### Evidence before this study

We did not do a formal literature review of published work before the start of this study. Several case reports have been published reporting malignant transformation of benign tumours or the development of new intracranial malignant tumours after stereotactic radiosurgery. However, the incidence of radiosurgery-associated intracranial malignancy remains unknown.

### Added value of this study

In a population-based, retrospective, cohort study of 4905 patients who had stereotactic radiosurgery at five international centres between Aug 14, 1987, and Dec 31, 2011, we estimated the incidence of malignant transformation or development of radiation-associated secondary intracranial cancer and found it was similar to the incidence of developing a primary CNS tumour in the populations of the USA and some European countries, based on estimates from the Central Brain Tumour Registry of the United States and International Agency for Research on Cancer global cancer statistics.

### Implications of all the available evidence

Although longer follow-up and prospective validation of these results is warranted, these data suggest that the risk of intracranial malignancy after stereotactic radiosurgery remains low at long-term follow-up, with the cumulative incidence estimated at 0·00045% (95% CI 0·00–0·0034) over 10 years.

## Introduction

Stereotactic radiosurgery is a minimally invasive, widely used approach to manage patients with benign intracranial tumours, intracranial arteriovenous malformation, and functional disorders, including trigeminal neuralgia. For benign tumours including small-to-moderate sized vestibular schwannomas, radiosurgery offers high rates of tumour control of greater than 95% over 10 years, high rates of preservation of facial and trigeminal nerve function, and potentially maintains serviceable hearing for longer duration.[1–3] For benign WHO grade 1 meningiomas, radiosurgery has been used as either primary modality or adjuvant therapy for residual or recurrence of tumours after surgical resection, with high tumour control of greater than 90% also.[4,5] In arteriovenous malformations, radiosurgery results in the total obliteration of blood flow within the malformation, thereby eliminating the risk of intracranial haemorrhage, in 65% (range 50–85) of all patients at a median time of 3·5 years.[6] Younger patients, those with smaller arteriovenous malformation volumes, and delivery of higher margin doses are more likely to achieve total obliteration.[6] Radiosurgery is also a non-invasive approach to treat classical trigeminal neuralgia. By 1 year after radiosurgery, 75–90% of patients will have obtained pain relief, and by 5 years after radiosurgery, 46–65% of patients remain with well-controlled pain.[7] A main advantage of stereotactic radiosurgery is its precision with a steep dose fall-off which results in low toxicity to surrounding brain structures. It avoids the morbidity associated with surgical resection and the toxicity associated with the use of larger field, fractionated radiotherapy. Acute or delayed adverse events can occur after radiosurgery, including radiation-induced oedema. The rate of adverse radiation events will depend on the margin dose, location, and volume of the treated target.[8,9]

A major concern of patients considering stereotactic radiosurgery is the perceived risk of malignant transformation of benign tumours or the risk of developing a new and possibly malignant neoplasm of different histology as a result of the radiation. The scientific literature to date includes several single-patient case reports,[10–14] but large sample studies with long-term follow-up appear to be absent. We did a multicentre study of patients who had radiosurgery for various non-malignant neurosurgical conditions to estimate the incidence of malignant transformation and the incidence of secondary malignant tumours after Gamma Knife (Elekta AB, Stockholm, Sweden) surgery.

## Methods

### Study design and participants

We did a multicentre, population-based, retrospective, cohort study of patients who have undergone Gamma Knife radiosurgery at five international radiosurgery centres (Na Homolce Hospital, Prague, Czech Republic [n=2655 patients]; Ruber International Hospital, Madrid, Spain [n=1080]; University of Pittsburgh Medical Center, Pittsburgh, PA, USA [n=1027]; University of Virginia, Charlottesville, VA, USA [n=80]; and NYU Langone Health System, New York, NY, USA [n=63]; appendix p 1). We asked five of the 25 centres affiliated with the International Gamma Knife Research Foundation (now called the International Radiosurgery Research Foundation) to participate in the study. Eligible centres had to have a registry of all patients who received Gamma Knife surgery, including radiographical and clinical characteristics and outcomes during follow-up, and documentation of the development of any subsequent intracranial malignancy. Eligible patients were of any age who had single fraction Gamma Knife surgery for vestibular or other benign schwannomas, WHO grade 1 (or presumed) meningiomas, arteriovenous malformation, trigeminal neuralgia, pituitary adenomas, and haemangioblastoma. Patients were excluded if they had previous intracranial radiotherapy or did not have a minimum of 5 years of follow-up.

Institutional review board approval was obtained from each site to participate in multicentre retrospective data reviews. Each site has patient consent waivers.

See Online for appendix

### Procedures

A database was created and completed by each participating centre and included year of birth, sex, diagnosis, lesion location, previous resection history and associated histopathology, date of Gamma Knife surgery, margin dose and maximum dose of radiation received, date and pathology (if available) of new malignancy, or assessment of malignant transformation relationship to the radiosurgical target volume (defined as within the 2 Gy isodose line), last follow-up date, and date of death. The pooled and deidentified data were screened by the study coordinators (RL, RM-A, LDL, JSh, DK) and verified for compliance with patient privacy. Data on a total of 14168 patients were available from Aug 14, 1987, and Dec 31, 2011. Any instance of a new intracranial malignancy identified on follow-up imaging (either MRI or CT of the head) was included, irrespective of length of follow-up.

Estimates of the overall age-adjusted incidence of primary CNS malignancies within the general populations of the USA were obtained from the Central Brain Tumour Registry of the United States (CBTRUS) and of Europe from the International Agency for Research on Cancer (IARC) Cancer Incidence in Five Continents Vol XI.[15] The 6th report of the CBTRUS[16] contains data on all newly diagnosed primary malignant CNS tumours in the USA between 2010 and 2014, from the Centers for Disease Control and Prevention, National Program of Cancer Registries, and the National Cancer Institute, Surveillance, Epidemiology and End Results programme.[16] 51 population-based central cancer registries contributed to the CBTRUS between these 4 years, which includes 50 state cancer registries and the District of Columbia and represents almost 100% of the US population.[16] The IARC Cancer Incidence in Five Continents Vol XI[15] provides worldwide age-adjusted incidence of primary malignant CNS neoplasm (excluding brain lymphoma and leukaemia, tumours of the pituitary and pineal glands, and olfactory tumours of the nasal cavity). It contains information from 343 cancer registries in 65 countries for cancers diagnosed from 2008 to 2012. Age adjusted incidence of primary CNS malignancies for European countries was accessed online on Nov 12, 2018.[15]

### Statistical analysis

As this was a retrospective cohort study, we did no formal sample size or power calculations. The follow-up duration was defined as the time from Gamma Knife surgery to the time of death or last-follow up (data cutoff Dec 31, 2016). We expressed the incidence of radiosurgery-associated intracranial malignancy, including malignant transformation and separate radiation-associated intracranial malignancy, as the number of cases divided by the amount of person-time at risk (per 100 000 person-years) with 95% CIs (calculated using the Mid-P exact test), using Open Epi, V3.01. We calculated the 10-year cumulative incidence and associated 95% CIs of developing radiosurgery-associated malignancy using the cumulative incidence function to account for the competing risk of death using XLstat (version 2018.3). Use of the cumulative incidence function is recommended to avoid potentially overestimating the incidence of radiosurgery-associated malignancy in the presence of competing risks.[17] We did all other (medians, IQRs, and percentages) analyses using SPSS (version 22.0).

The CBTRUS estimates are publicly available online.[16]

### Role of the funding source

There was no funding source for this study. AW, MT, AH, JN, RL, NM-M, RM-A, JGG, JSi, HK, JSh, LDL, DK, and NS had access to all the raw data. The corresponding author had full access to all the data and had the final responsibility for the decision to submit for publication.

## Results

4905 (34·6%) of 14168 patients who had stereotactic radiosurgery at five of 25 centres affiliated with the

| | All patients (n=4905) | Vestibular schwannoma (n=1011) | Other schwannomas (n=80) | Meningioma (n=1490) | Haemangio-blastoma (n=29) | Pituitary adenoma (n=641) | Trigeminal neuralgia (n=565) | Arteriovenous malformation (n=1089) |
|---|---|---|---|---|---|---|---|---|
| Median age, years (IQR) | 52 (42–63) | 54 (44–63) | 47 (33–58) | 56 (48–65) | 27 (22–45) | 50 (39–59) | 64 (57–71) | 35 (23–48) |
| Sex | | | | | | | | |
| Male | 1878 (38%) | 408 (40%) | 38 (47%) | 352 (24%) | 15 (52%) | 293 (46%) | 210 (37%) | 562 (52%) |
| Female | 3027 (62%) | 603 (60%) | 42 (53%) | 1138 (76%) | 14 (48%) | 348 (54%) | 355 (63%) | 527 (48%) |
| Previous tumour resection | 1390 (28%) | 143 (14%) | 28 (35%) | 633 (43%) | 22 (76%) | 461 (72%) | NA | NA |
| Median stereotactic radiosurgery margin dose, in Gy* (IQR) | 15·0 (12·5–22·0) | 13·0 (12·0–13·0) | 12·5 (12·0–13·0) | 13·0 (12·0–14·0) | 17·0 (15·0–19·3) | 25·0 (18·0–30·0) | 40·0 (40·0–40·0) | 20·0 (17·0–22·0) |
| Median stereotactic radiosurgery maximum dose, in Gy* (IQR) | 28·0 (24·0–40·0) | 24·0 (24·0–26·0) | 24·0 (21·7–26·0) | 24·0 (24·0–28·0) | 32·0 (28·0–35·4) | 50·0 (36·0–70·0) | 80·0 (80·0–80·0) | 35·7 (30·1–46·0) |
| Median follow-up, years (IQR) | 8·1 (6·0–10·6) | 8·2 (6·0–10·5) | 7·2 (6·1–10·9) | 8·1 (6·0–10·3) | 8·8 (5·8–13·1) | 8·6 (6·0–10·1) | 7·2 (6·0–9·9) | 8·1 (6·1–12·5) |

Data are n (%), unless otherwise specified. Gy=Gray. *Data for margin and maximum dose not available for 52 patients.

*Table 1:* **Baseline characteristics of patients by diagnosis**

| | Initial diagnosis | Pathology at initial diagnosis | Year of stereotactic radiosurgery | Margin dose; maximum dose, Gy | Event | Time to event, years | Pathology at second diagnosis | Year of death |
|---|---|---|---|---|---|---|---|---|
| Case 1 | Vestibular schwannoma | Yes | 2003 | 12; 24·3 | Malignant transformation | 8·7 | Peripheral nerve sheath tumour | 2014 |
| Case 2 | Vestibular schwannoma | No | 2001 | 12; 24 | Malignant transformation | 11·8 | Malignant schwannoma | 2015 |
| Case 3 | Pituitary adenoma | Yes | 1998 | 20; 40 | Secondary radiation-associated tumour | 12·8 | Osteosarcoma | 2012 |

Gy=gray.

*Table 2:* **Cases of malignant transformation or radiation-related secondary intracranial malignancy**

International Gamma Knife Research Foundation (now International Radiosurgery Research Foundation) between Aug 14, 1987, and Dec 31, 2011, were included in the study. The analysis included patients with vestibular schwannoma (1011 [20·6%] of 4905 patients), meningioma (1490 [30·4%]), arteriovenous malformations (1089 [22·2%]), trigeminal neuralgia (565 [11·5%]), pituitary adenoma (641 [13·1%]), haemangioblastoma (29 [0·6%]), and other benign schwannomas (80 [1·6%]). Patient characteristics are shown in table 1. Excluded patients were similar in age, previous resection, and prescribed radiation dose, and the number of men and women were similar (data not shown). The median time of clinical follow-up after radiosurgery was 8·1 years (IQR 6·0–10·6). All patients had a minimum of 5 years of follow-up with 3233 patients (65·9%) with 5–10 years, 1256 (25·6%) patients with 10–15 years, and 416 (8·5%) patients with greater than 15 years of follow-up. 379 (7·7%) of the 4905 patients included in the study died during follow-up from causes unrelated to a secondary malignancy or malignant transformation.

Regarding the risk of malignant transformation, of the 3251 patients with benign tumours, two (0·0006%) cases of malignant transformation of vestibular schwannomas were confirmed, which were diagnosed at 8·7 years and 11·8 years after radiosurgery (table 2). Taking these two cases into account, the incidence of malignant transformation after radiosurgery of benign tumours in this population was 6·87 per 100 000 patient-years (95% CI 1·15–22·71). With respect to the risk of new radiation-associated intracranial malignancy, only one (0·0002%) of 4905 patients developed a pathologically verified osteosarcoma at 12·8 years after receiving radiosurgery to treat a pituitary adenoma. The osteosarcoma was judged as treatment-related because it developed within the irradiated field (ie, 2 Gy isodose line). No other radiation-induced malignancy were identified in this population. Taking this single event into account, the incidence of a new radiosurgery-associated malignancy was 2·26 per 100 000 patient-years (95% CI 0·11–11·17).

Two (0·0004%) of 4905 cases of new distant intracranial malignant tumours were outside of the radiation field (2 Gy isodose line) and were thus deemed not to be associated with radiosurgery. These tumours were diagnosed at 4·3 years after radiosurgery of a vestibular schwannoma and 8·7 years after radiosurgery of a WHO grade 1 meningioma. Both tumours were pathologically confirmed as malignant gliomas. The incidence of developing an intracranial malignancy unrelated to the radiation field in this cohort was 4·53 per 100 000 patient-years (95% CI 0·76–14·97).

The overall incidence of radiosurgery-associated malignancy was 6·80 per 100 000 patient-years (95% CI 1·73–18·50). The cumulative incidence of developing radiosurgery-associated malignancy, either new or a transformation of a benign tumour, is 0·00045% (95% CI 0·00–0·0034) over 10 years, accounting for the competing risk of death. No cases of a new malignancy were found in patients who had undergone stereotactic radiosurgery for non-tumour-related disorders, including arteriovenous malformation or trigeminal neuralgia.

The calculated incidence of a secondary brain malignancy after radiosurgery was similar to the age-adjusted annual incidence derived from the CBTRUS at 7·15 per 100 000 patient-years (95% CI 7·10–7·19) for all primary malignant CNS tumours in the USA population. Since regional variability exists in the incidence of CNS malignancy, we also looked at estimates of incidence of CNS malignancy for European countries derived from IARC data.[15] The age-adjusted incidence of CNS malignancy was 3·6–9·1 per 100 000 for men and 3·1–7·9 per 100 000 women across European countries (appendix pp 1–4). Incidence rates of specific European countries reported in the IARC's updated Cancer Incidence in Five Continents Vol XI[15] are available in the appendix (pp 1–4).

## Discussion

In this retrospective, multicentre, cohort study, we found that the incidence of a radiosurgery-associated intracranial malignancy is low at 6·80 per 100 000 patient-years (95% CI 1·73–18·50) or a cumulative incidence of 0·00045% (95% CI 0·00–0·0034) over 10 years, and seem to be similar to population-derived incidences of primary malignant CNS tumours within the USA and several European countries, ranging between 3·1 and 9·1 per 100 000 patient-years.[15,16,18]

Several anecdotal case reports have reported malignant transformation of vestibular schwannomas after radiosurgery,[10–12] or formation of new benign or malignant intracranial tumours after radiosurgery of arteriovenous malformations or other benign tumours, including meningiomas.[13,14] Three studies have attempted to address the issue of radiation-induced tumours after stereotactic radiosurgery, either Gamma Knife surgery or

linear accelerator stereotactic radiosurgery, by assessing a larger cohort of patients.[19–21] A case series study from the Mayo Clinic[21] looked at their 25-year experience in 1837 patients with at least 5 years of follow-up receiving single-fraction stereotactic radiosurgery for arteriovenous malformations or benign tumours. The study reported no new radiation-induced tumours and a low frequency of malignant transformation after stereotactic radiosurgery, with an increased risk of meningiomas with a 15-year risk of malignant transformation of 2·4%.[21] Yet, the dedifferentiation of benign WHO grade 1 meningioma to grade 2 and 3 meningiomas is well known to occur naturally. Malignant progression of WHO grade 1 meningiomas has been reported to occur in 0·16–5% patients[22] not previously irradiated and is associated with molecular alterations including activating TERT promoter mutations and CDKN2A/B loss, among others.[23,24]

To our knowledge, the current study provides the largest number of patient-years accumulated prospectively to estimate the incidence of malignant transformation and secondary malignancy in patients treated with Gamma Knife radiosurgery since 1987 at five major radiosurgery centres. A limitation of the current study is the inability to distinguish causality from natural history. Since meningiomas and vestibular schwannomas can dedifferentiate as part of their natural history, a study including a matched control group that has not had radiosurgery would be required to calculate the relative risk of stereotactic radiosurgery. A further limitation of this study, due to its retrospective nature, is an inability to control for many factors associated with the development of radiation-related secondary malignancies, including age, environmental factors (such as exposure to other ionising radiation or cytotoxic drugs), and the presence of a predisposition syndrome, among others. This study specifically looked at intracranial malignancies and did not address the risk of developing other non-intracranial malignancies (eg, scalp, haematological, or head and neck malignancies) or the risk of developing a benign intracranial tumour (eg, meningioma). Additionally, studies with longer follow-up time are needed. Further, given the low number of outcome events, studies with larger sample sizes are required to characterise whether or not stereotactic radiosurgery causes a small increased risk in the frequency of malignant transformation and secondary malignancies. This study did not investigate patients who had linear accelerator-based radiosurgery. The inclusion of additional patients from institutions other than the five sites participating in this study would increase the generalisability of our results. Finally, as a retrospective cohort study, differential loss to follow-up might be present. Although we think it unlikely, other cases of malignant transformation might have occurred that were not reported to the investigators.

A major concern of patients and referring physicians who are considering radiosurgery as a treatment option for intracranial conditions is the potential long-term risk of a new or secondary intracranial malignancy as the result of the radiation. Based on the results of this study, for patients who are having either primary or salvage stereotactic radiosurgery for a histologically benign brain tumour, the risk of neoplastic transformation or the risk of having a new radiation-induced intracranial malignancy after radiosurgery is low and similar to that of the annual incidence of primary CNS tumours in the general population, even at long-term follow-up (more than 10 years). Our data support physicians counselling patients on the long-term safety of Gamma Knife stereotactic radiosurgery.

**Contributors**

AW, JN, RL, NM-M, RM-A, HK, JSh, LDL, and DK participated in the study design. AW, MT, AH, JN, RL, NM-M, RM-A, NS, JGG, JSi, HK, JSh, LDL, and DK collected data. AW, MT, and DK analysed the data. AW, KN, LDL, and DK assisted with interpretation of the data. AW, KN, LDL, and DK wrote the manuscript. All authors reviewed the report and gave final approval to submit for publication.

**Declaration of interests**

HK reports grants from Elekta AB outside of the submitted work. JN reports personal fees as consultant of Elekta AB outside of the submitted work. JGG reports being a stockholder in Viewray. RL reports working as a consultant of Elekta AB. LDL reports other support from Data and Safety Monitoring Board, Insightec, and Elekta AB outside the submitted work. DK reports grants from Brainlab outside the submitted work. All other authors have no competing interests.

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