Magnetic resonance imaging has clearly revolutionized many fields of medicine, not least neurology, neuro-oncology, and neurosurgery. Today, diagnosing or ruling out intracranial disease without a cerebral MRI scan is exceedingly rare, and perhaps even no longer recommended. However, the toll for patients can be incidental findings. In asymptomatic volunteers, incidental abnormalities were seen in 18% of cerebral MRI scans, and 2.9% required further referral.\(^7\) In another study, 1.6% of healthy volunteers who underwent 1.5-T cerebral MRI scans were diagnosed with primary, most often benign tumors.\(^8\) It is often speculated that the increase in brain tumor incidence observed over recent decades may at least partially be explained by increased use of MRI.\(^2,3,5,6,14-16\) However, a direct population-based comparison of MRI use and brain tumor incidence rates is lacking.

In a population-based study we aimed to investigate whether regional cerebral MRI use correlates to regional incidence rates of intracranial tumors as reported to the Cancer Registry of Norway. We also sought to study whether a possible effect of MRI on observed brain tumor incidence has affected treatment rates or observed patient survival.

Effects of cerebral magnetic resonance imaging in outpatients on observed incidence of intracranial tumors and patient survival: a national observational study

Clinical article

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Object. It is assumed that the observed increase in brain tumor incidence may at least partially be explained by increased use of MRI. However, to date no direct estimate of this effect is available. The authors undertook this registry-based study to examine whether regional frequencies of cerebral MRI use correlate to regional incidence rates of intracranial tumors and survival of patients with these lesions.

Methods. The authors used Norwegian national population registries from January 2002 through December 2007 to conduct this observational study. They obtained information on outpatient MRI scans in Norwegian counties and examined whether the annual regional rates of cerebral MRI scans correlated to regional age- and sex-adjusted brain tumor incidence rates. They also explored whether differences in cerebral MRI use were associated with survival and examined time trends in the study period.

Results. Approximately 50,000 cerebral MRI scans are carried out annually in outpatient settings in Norway, and 6363 primary intracranial tumors were diagnosed in Norway during the study period. There was an overall positive correlation between the annual number of cerebral MRI scans per 100,000 capita and age- and sex-adjusted incidence rates of intracranial tumors in the various Norwegian counties (Spearman’s rho = 0.35, p < 0.001). In a linear model, an increase in 1 MRI per 100,000 capita per year results in a 0.004 (95% CI 0.002–0.006) increase in diagnosed intracranial tumors per 100,000 capita per year (p < 0.001). Subgroup analysis showed a correlation between MRI use and the annual age- and sex-adjusted incidence rates of extraaxial tumors (p = 0.04, Spearman’s rho = 0.28) but not intraaxial tumors (p = 0.394). Overall survival for unselected patients with intracranial tumors is longer with increasing number of cerebral MRI scans per capita in the county of residence at the time of the diagnosis (log rank, p = 0.029). However, after adjustment for year of diagnosis and catchment region of the Norwegian neurosurgical centers, the association between MRI scans per capita and overall survival was no longer statistically significant (p = 0.076).

Conclusions. Presumably due to the incidental discovery of benign extraaxial tumors, regional differences in the use of cerebral MRI in outpatients affect observed incidence rates of intracranial tumors.

Key Words • brain tumor • epidemiology • incidence • magnetic resonance imaging • neurosurgery • oncology
Methods

This is a national registry-based study of annual regional numbers of cerebral MRI scans per 100,000 capita and regional incidence rates of intracranial tumors in the Norwegian counties. The study was approved by the Regional Ethics Committee (Central Norway) and the Cancer Registry of Norway and followed the criteria from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.19

Study Period

The study period was 6 years, from January 2002 through December 2007. A relatively short period was chosen to reduce potential problems with temporal trends in reporting. Also, reliable data without any changes in classification or reporting were available from all data sources in this study period.

Number of Cerebral MRI Scans per Capita

The Norwegian Centre for Informatics in Health and Social Care (KITH) provided data on the number of cerebral MRI scans performed on an outpatient basis. Data were based on claims for reimbursements from private and public radiology services following radiological examinations. Data from the 19 Norwegian counties were analyzed separately except that data from the 2 northernmost counties were merged due to the low number of inhabitants in this region. Statistics Norway provided the population of the 19 counties in the various years of the study period. The annual number of cerebral MRI scans per 100,000 capita was calculated for each county.

The Norwegian Health Care System and the Incidence of Intracranial Tumors

Norway has a population of 5 million and a socialized health care system, with quite evenly distributed resources and uniform training and licensing for medical professionals. There are today only 4 neurosurgical centers offering brain tumor surgery, each serving one of 4 geographical health regions (Southeast, West, Middle, and North).

Reports to the Cancer Registry of Norway have been compulsory by law since 1952. All neoplasms and certain precancerous lesions are to be registered. Data are entered into the Cancer Registry of Norway from: 1) copies of all pathology and autopsy reports from all Norwegian laboratories, 2) clinical registration forms from treating doctors, and 3) information from Statistics Norway about cause of death noted on the death certificates of all persons registered in the Cancer Registry of Norway. The unique 11-digit personal identification numbers assigned to all Norwegian citizens ensure tracking of patients and limit the risk of duplicate registrations. Since 1998 the Cancer Registry of Norway has also acquired data files with outpatient and discharge diagnoses (ICD-10 C or D) on all patients treated for neoplastic disease in every Norwegian hospital and outpatient clinic. When C or D diagnoses are used for patients who are not registered in the cancer registry, the clinician will receive reminders. If patients undergo repeated surgery or if autopsy is performed, the database is updated through submission of additional histological reports. A study from 2001 to 2005 demonstrated 93.8% completeness of data on all cases of central nervous system tumors, including cases not verified histologically.2

Included Patients

From 2002 through 2007, primary central nervous system tumors were diagnosed in 6831 patients in Norway. We excluded 26 duplicate reports from patients with more than one histopathology, patients with tumors of the spinal meninges (133), medullary tumors (212), and cauda equina tumors (11), leaving 6449 patients with newly diagnosed primary intracranial tumors. Of these, 80 who were diagnosed incidentally at autopsy and 6 who were diagnosed by unknown means were excluded from the study. This left 6363 patients with primary intracranial tumors diagnosed in the study period. Based on the ICD-O-2 codes, tumors were grouped into major groups in coherence with the WHO classification of central nervous system tumors.11 We calculated the age- and sex-adjusted incidence of intracranial tumors per 100,000 capita diagnosed in the Norwegian counties per year.

Statistics

Statistical analyses were done with SPSS version 19.0.0. The statistical significance level was set at p ≤ 0.05. Q-Q plots were used to test for normal distribution of data. To examine correlations between regional incidence of intracranial tumors and regional incidence of undergoing cerebral MRI scans, we used Spearman’s rho. Linear correlation was also explored. Multivariable linear regression was used to adjust for possible temporal trends or regional differences in reporting to the national cancer registry. One-way ANOVA was used for comparisons between groups. Differences in survival were explored with the log-rank test.

Results

As shown in Fig. 1, the annual number of cerebral MRI scans increased substantially in the study period, with large regional differences. As shown in Fig. 2, there was also a steady annual increase in diagnosed intracranial tumors.

In the study period, there was an overall moderate positive correlation between the annual number of cerebral MRI scans per 100,000 capita and age- and sex-adjusted incidence rates of intracranial tumors in the various Norwegian counties (Spearman’s rho = 0.35, p < 0.001). As illustrated with categorical data in Fig. 3, the incidence of intracranial tumors increased with grouped incidence of cerebral MRI scans (p = 0.002). If assuming a linear relationship in a regression model, an increase in 1 MRI per 100,000 capita per year results in a 0.004 (95% CI 0.002–0.006) increase in diagnosed intracranial tumors per 100,000 capita per year (p < 0.001). The scatter plot in Fig. 4 illustrates the relationship.

Since a temporal relationship is possible if there were differences in reporting over time, and because there theoretically may be differences in reporting among the 4
MRI use and brain tumor incidence

In subgroups we observed a correlation between MRI use and the annual pooled incidence rates of extra-axial tumors (meningiomas, schwannomas, neurinomas, and adenomas) \( (p = 0.04, \text{Spearman's } \rho = 0.28) \), that remained significant after adjustment for year and health region (catchment region) \( (p = 0.014) \). However, no significant correlation was observed for intraaxial tumors \( (p = 0.394) \).

Of the 6363 patients diagnosed with intracranial tumors in the study period, 2329 (37%) were diagnosed based on radiological examinations only (that is, not histologically confirmed), 875 (38%) of these were radiologically diagnosed as meningiomas, 268 (11%) as nerve sheath tumors, 96 (4%) as pituitary adenomas, 159 (7%) as high-grade gliomas, 23 (1.0%) as low-grade gliomas, 216 (9%) as various other types, and 692 (30%) were classified as primary intracranial tumors of unknown origin. We observed a moderate and significant correlation between the number of MRI scans per 100,000 capita per year and the incidence rates of tumors diagnosed based on imaging alone \( (p = 0.001, \text{Spearman's } \rho = 0.32) \). However, there was no overall correlation between the annual number of cerebral MRI scans per 100,000 capita and the annual number of intracranial tumor operations per 100,000 capita \( (p = 0.178) \) adjusted for regional age and sex composition.

As shown in Fig. 5, overall survival for unselected patients with intracranial tumors was associated with the number of cerebral MRI scans per capita in the county of residence at the time of the diagnosis \( (\text{log-rank test}, p = 0.029) \). However, after adjusting for year of diagnosis and geographical health region (catchment region of the Nor-
Norwegian neurosurgical centers) in a Cox proportional hazards model, the association between cerebral MRI scans per 100,000 capita and overall survival was no longer statistically significant (hazard ratio 0.98, 95% CI 0.97–1.0, \( p = 0.076 \)).

**Discussion**

Magnetic resonance imaging technology has undoubtedly improved the ability to both diagnose and follow disease and treatment responses. The unprecedented safety and sensitivity may paradoxically be problematic since there are few arguments for limiting use. MRI use has therefore surged globally, and there is no reason to doubt that use will increase further. However, epidemiological consequences of widespread neuroimaging are not much studied. As demonstrated in the present population-based study, regional differences in MRI use affect observed incidence rates of intracranial tumors, and may even affect observed survival. Since we were able to study regional differences in MRI use in a homogeneous population served by socialized health care in a short time span and also adjust for possible temporal trends and possible regional differences in reporting, the relationship between cerebral MRI use and reported intracranial tumor incidence rates is presumably causal. If assuming a linear relationship, an increase in 1000 cerebral MRIs per 100,000 capita may increase observed incidence rates with around 4 intracranial tumors per 100,000. Uncontrolled increases in the use of MRI will not only boost incidence rates, but also place a burden on patients and the health care system. This should be of interest to the financiers and providers of health care.

In Norway, the first 3 MRI scanners were installed in 1986 at 2 hospitals 800 km apart. In an attempt to limit unwarranted use and costs, at first only licensed neurologists or neurosurgeons were allowed to order cerebral images. However, indications have broadened, and there has been a gradual increase in demands from clinicians and patients. As of January 2011, there were 108 human MRI scanners in Norway, 1 scanner per 46,000 inhabitants, and several types of licensed health professionals, including all physicians, physiotherapists, and chiropractors, order MRI studies with little or no limitations. MRI use has surged, and more than 50,000 cerebral MRI scans were carried out in Norwegian outpatients in 2010. Sev-
eral private radiology services, with reimbursement from the government, have been established. The increased availability and short waiting lists may also have contributed to more use. Further uncontrolled increases in use or improvements in imaging technology will increase detection rates in the future.

The most frequent incidental findings on cerebral MRI scans are brain infarcts, followed by cerebral aneurysms and primary tumors. Most incidental intracranial tumors are histologically benign, and surgery is usually not indicated without relevant symptoms or significant tumor growth. With few exceptions, it is not necessarily beneficial for patients to have an intracranial tumor diagnosed in a subclinical phase. Patients may suffer from emotional distress, need to be referred to specialists, and will often undergo surveillance imaging for years to come. However, due to increases in MRI use, incidence rates, case-mix, and treatment results will be affected. As seen, the number of cerebral MRI scans per capita may even affect observed survival, with increased survival in regions or periods with more neuroimaging. In Denmark, the observed incidence of vestibular schwannomas increased 6-fold over 3 decades, while the average tumor diameter decreased from 30 to 10 mm. A similar trend would probably be seen with respect to other extraxial tumors like meningiomas and pituitary tumors as well. Although we did not observe a significant correlation between cerebral MRI use and operation rates, the study period of 6 years is perhaps too short to expect a drift in indications for surgery. Also in the socialized health care system of Norway, treatment indications may be more uniform and stable than in other health care systems. With steady increases of incidental findings, clinical decisions may gradually drift toward more treatment of small indolent lesions, possibly with seemingly excellent results compared with the results of today or yesterday, but nevertheless with adverse events. This may put patients at unnecessary risks and give the false impression of a superior center, era, or treatment.

Awareness about the substantial impact of MRI use on a population-based level has considerable importance for epidemiological brain tumor research, especially in ecological studies comparing regions or countries, but also in clinical studies, since patient referral and patient selection will be affected. As demonstrated, the number of cerebral MRI scans per capita may even affect observed survival, with seemingly better survival in regions or periods with greater use of neuroimaging. This is perhaps no surprise since predominantly the observed incidence of benign tumors is increased due to a rise in MRI use. Also to be remembered, MRI use does not only differ between geographical regions and time periods as assessed in the present study, but presumably also varies with health complaints, among socioeconomic groups, genders, age groups, and not at least depends on MRI availability. Thus, differences in MRI use may act as a possible confounder in comparative studies concerning potential carcinogenic exposures, such as the use of mobile telephones, exposure to other electromagnetic fields, or air pollution. The main strength of the present population-based study is the quality and completeness of the registry-based data. The external validity is presumably high, and the findings may probably be relevant for other forms of incidental pathology as well. Norway has a very homogeneous population and the universal availability of free health care reduces possible confounders. Due to the national reimbursements for all radiology services, we have complete data on the frequency of cerebral MRI scans in our population, but we unfortunately have no information on who underwent MRI scans and why. Since detection rates depend on age, gender, and other risk factors that may affect the frequency of abnormal findings, theoretical regional differences in MRI indications may have affected the magnitude of the observed relationship between MRI use and incidence rates. Possible differences in image sequences in use, field of view, and the strength of the magnetic fields may also have affected results. The main limitation is the small population of Norway and the relatively low incidence of intracranial tumors, making the regional incidence rates vulnerable to bias or clustering due to chance. However, merging numbers from several years or several counties to obtain more robust incidence rates would not solve this problem since this would also even out the large regional and annual variations in MRI use. The resulting uncertainty of the point estimates of incidence rates limits the ability to study the statistical characteristics of the demonstrated relationship between MRI use and tumor incidence rates in more detail. Thus, it is so far unknown whether the relationship is linear or if observed incidence may reach a plateau with further increases in MRI use.

Conclusions

Largely due to the incidental discovery of benign extraxial tumors, regional differences in the use of cerebral MRI in outpatients affect observed incidence rates of intracranial tumors.

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Disclosure

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