

Admission criteria to the Danish Brain Cancer Program are moderately associated with magnetic resonance imaging findings

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ABSTRACT

INTRODUCTION: The objective of this study was to evaluate the Danish Brain Cancer Program by examining the criteria for admission to the program and the results of magnetic resonance imaging (MRI) of the brain in 359 patients referred to the program at the Odense University Hospital during one year. The admission criteria given by the Danish Health and Medicines Authority are as follows: 1. Prior computed tomography or MRI indicating tumour. 2. Progressive focal neurological deficits. 3. Epileptic seizure in adults. 4. Change in behaviour or cognition showing progression. 5. Headache with progression over 3-4 weeks.

MATERIAL AND METHODS: This was a retrospective analysis of the cerebral MRI of 359 patients. The patients were categorized by admission criteria and MRI outcome. The findings were grouped into four main outcomes: 1. Primary malignant intracerebral tumour. 2. Intracranial tumour (including meningioma and metastasis). 3. Acute pathology in total (including tumours and other acute pathologies). 4. Findings of no consequence.

RESULTS: We found 46 acute/subacute pathologies including 21 tumours of which eight were primary intracerebral malignant tumours and 313 scans did not have findings of any consequence. In the group with monosymptomatic headache, we found significantly fewer tumours ($p = 0.0066$, Fisher's exact test) and acute pathologies ($p = 0.0008$) than in the remaining groups. In the group with change in behaviour or cognition, we found significantly more primary intracerebral malignant tumours ($p = 0.0002$), tumours in all ($p = 0.0001$) and acute pathologies ($p = 0.0002$) than in the other groups.

CONCLUSION: Fewer tumours than expected were found. Significantly fewer pathologies were found in the group with monosymptomatic headache than in the remaining groups.

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The admission criteria to the Brain Cancer Program are divided into five categories [1] as presented in **Table 1**.

At Odense University Hospital (OUH), the program is set up so that the referring physician, usually the patient's general practitioner, calls the Neurology Department. The Neurology Department then provides the indication for inclusion into the Brain Cancer Program if relevant. A magnetic resonance imaging (MRI) is performed within 48 hours. The day after the scan, the patient is seen in the neurological outpatient clinic for follow-up/MRI results.

It was expected that approx. 10,000 patients nationwide would be included in the Brain Cancer Program, of which approx. 1,000 patients were expected annually to have either a malignant or a benign intracranial tumour [1, 2].

At the Department of Radiology, OUH, 359 patients were referred for MRI via the program from 1 February 2011 to 31 January 2012. At the department, we had the impression that relatively few of the patients had a primary brain tumour, but also that many patients had other relevant pathologies. We also had the impression that some of the reference categories yielded far fewer positive findings than others.

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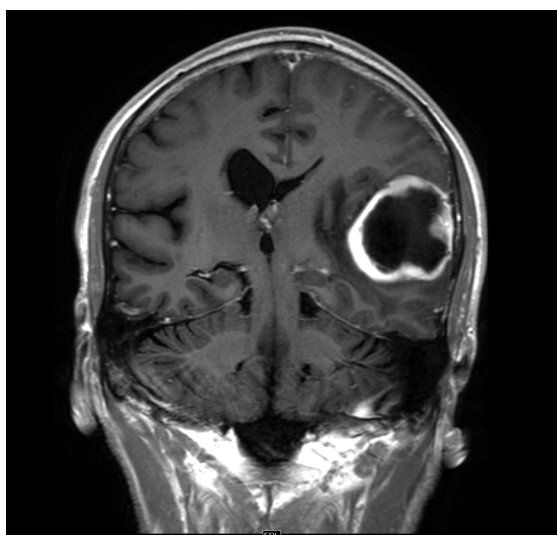


TABLE 1

Inclusion criteria of the Danish Brain Cancer Program.

1. Computed tomography or magnetic resonance imaging (performed on other indications) showing an intracranial process
2. New onset focal neurologic symptoms (e.g. hemiplegia, sensory disturbance, visual field defect or aphasia) progressing over days/weeks with no other plausible explanation, such as subdural haematoma or multiple sclerosis
3. New onset epileptic seizures in adults with no other plausible explanation, such as sleep deprivation or drug addiction
4. New onset of behavioural/personality change or cognitive deficits progressing over weeks/few months with no other plausible explanation such as known dementia, psychiatric disorder or drug addiction
5. New onset headache or significant change in prior headache pattern – progressive over 3-4 weeks, and where a thorough medical history and physical examination by a neurologist has not revealed other plausible explanations, such as prior trauma, sinusitis or drug addiction

The Danish Brain Cancer Program was established in 2009. The program refers to a well-defined set of events and procedures during the diagnostic work-up as well as the maximum duration of the diagnostic work-up in patients suspected of having a brain tumour.



Patient from Danish Brain Cancer Program with left-sided glioblastoma.

The purpose of this paper was to quantify the number of primary malignant brain tumours, the total number of intracranial tumours and other relevant pathology. Furthermore, we wanted to quantify the distribution of findings in relation to the five aforementioned reference criteria.

MATERIAL AND METHODS

We performed a retrospective analysis on data from the patients referred via the Danish Brain Cancer Program in the period from 1 February 2011 to 31 January 2012. A total of 364 patients were identified of whom 359 were included.

The five patients who were excluded had a previously known cancer and had been referred on suspicion of metastases. Included patients were characterized by age, sex, referral reason(s) and MRI findings. The referral reasons were divided into the five aforementioned criteria and a sixth category (named "other") in case none of the five criteria were present. Where the reference cause was unclear, we reviewed relevant medical records. In all cases, a reference cause was found, al-

though in several instances the case had to be assigned to the "other" category.

Data were then collected, and MRI findings were divided into four main categories:

1. "Primary malignant intracerebral tumour".
2. "All tumors": This category included the primary malignant intracerebral tumours as well as meningioma, pituitary tumours, extracranial tumours and metastases.
3. "All acute and subacute pathology": This category consisted of categories 1 and 2 as well as acute haemorrhages, acute infarction, acute multiple sclerosis (MS), subdural haematoma (SDH) and other acute and subacute findings. The pathologies in this group were chosen based on the consideration that they represent differential diagnoses to tumours and/or is an indication for the MRI outside the Brain Cancer Program.
4. "Findings of no consequence". This group consisted of findings that did not require treatment such as old infarctions, atrophy, sinusitis and normal findings.

In the cases where the MRI diagnosis was uncertain and in all cases with tumours, the relevant patient records were reviewed to achieve a definitive diagnosis. Subsequently, data were analyzed in relation to reference category, age and gender. For the statistical calculations, Fisher's exact test was used.

Trial registration: not relevant.

RESULTS

A total of 359 patients were included in this study. Of these, 21 had MRI-verified tumour, eight of which were primary malignant intracerebral tumours, five were meningiomas, three were pituitary tumours, four were metastases in patients without known primary cancer and one was an extracerebral tumour. In all, 25 patients had other acute or subacute pathology: three haemorrhages, 11 acute infarctions, one SDH, one acute MS, nine subacute MS (e.g. chronic SDH) and three others. Out of these 25 patients, three patients had two acute or subacute diagnoses. A total of 313 patients had no acute or subacute diagnoses.

The average age of the 359 patients was 47.5 years. The distribution in relation to radiological findings is shown in **Table 2**.

There were 153 men and 206 women. Two men and six women had a primary malignant intracerebral tumour. A total of nine men and 12 women had a tumour, while 25 men and 21 women had acute or subacute pathology.



TABLE 2

Age and findings.

	All (n = 359)	Primary malignant intracerebral tumour (n = 8)	All tumours (n = 21)	Acute og subacute pathology (n = 46)	Findings of no consequence (n = 313)
Men, n	153	2	9	25	128
Average age (SD), years	47.5 (45.5-49.5)	62.25 (50.5-74.0)	62.7 (54.5-70.9)	63.7 (58.9-68.6)	45.1 (43.1-47.2)
Median age, years	47	60	63.5	67	42

SD = standard deviation.

When grouped by referral reason, we found 11 patients referred after “other imaging”, 68 with “neurological deficits”, 100 with “epilepsy”, 48 with “Behavioral, Personality or Cognitive Deficits (BPCD)”, 145 with “headache” and 53 in the group “other”. A total of 48 patients each had two reference reasons and nine patients had three or more reference reasons each. Among the patients who were referred with only one indication, we found three of the “other imaging” group, 34 with “neurological deficits”, 91 with “epilepsy”, 16 with “BPCD” and 105 with “monosymptomatic headache”.

As shown in **Table 3**, we observed that out of the eight primary malignant intracerebral tumours, two were referred with “monosymptomatic epilepsy”, three with “monosymptomatic BPCD”, two had two indications and one had three or more indications. Six out of the eight had BPCD as one of their referral reasons.

The 46 cases with acute/subacute pathology, including the 21 with tumours, were widely distributed on the various referral reasons, as seen in Table 3. Ten tumours and 15 with acute/subacute pathology had BPCD as one of their referral reasons.

Statistically, two of the referral groups stand out: monosymptomatic headache and BPCD.

There were significantly fewer tumours in the group with monosymptomatic headache ($p = 0.0066$) than overall. There were also significantly fewer acute/subacute diagnoses ($p = 0.0008$). Regarding primary brain tumours in the group referred with headaches, there was no basis for statistical significance due to the low overall number of primary intracerebral tumours. We found significantly more “primary intracerebral tumours” ($p = 0.0002$), “all tumors” ($p = 0.0001$) and “acute/subacute pathology” ($p = 0.0002$) in the BPCD group than in the total group. The average age in the group was considerably higher than in the whole group: 57.9 years (53.3 to 62.4) versus 47.5 years (45.5 to 49.5).

DISCUSSION

In this paper, we examined a population of 359 patients referred for MRI via the Danish Brain Cancer Program to the Radiology Department, OUH. We found a total of 21 tumours, including eight primary malignant intracerebral tumours, five meningiomas, three pituitary tumours, four metastases in patients without known primary cancer and one extracranial tumour. Moreover, another 25 patients had intracranial pathology, where MRI may have been a relevant examination, although it did not necessarily have to be performed within 48 hours. In a report published by the Danish Health and Medicines Authority in 2009 regarding the Brain Cancer Program, it was expected that the program would reveal a brain tumour (including meningiomas and others) in approx. 10% of the referred patients [1, 2]. In the present study,



TABLE 3

Referral reason and findings. The values are n.

Indication	All referrals in the category	Primary malignant intracerebral tumour	All intracranial tumours	Acute/subacute pathology, incl. tumour
<i>Monosymptomatic</i>				
Prior CT/MRI	3	0	1	2
Neurological deficits	34	0	2	10
Epilepsy	91	2	5	10
BPCD	16	3	4	6
Headache	105	0	1	4
Other	53	0	1	3
2 indications	48	2	5	9
≥ 3 indications	9	1	2	2
Total	359	8	21	46

BPCD = Behavioral, Personality or Cognitive Deficits; CT = computed tomography; MRI = magnetic resonance imaging.

this figure is somewhat lower, namely 5.8%. The difference may, in part, be due to the fact that a total of 53 patients were referred even though they did not belong to one of the five reference groups identified in the Brain Cancer Program. However, in this sixth group (named the “other” group), we found one patient with an intracerebral tumour, which was not a significantly lower share than that observed for the whole group. Even if we excluded this group from the examination, we would still detect less than 7% “positive findings”.

The group referred with monosymptomatic headache had significantly fewer tumours, as well as significantly fewer acute and subacute pathologies. This group is relatively large (105 patients), and if we were to exclude this group as well as the sixth group, we would reach the expected percentage of approx. 10% tumours. A literature review shows that 25-77% of all patients with primary brain tumours and metastases have headache as one of their symptoms [3-5]. There are few reports of monosymptomatic headache as a symptom of brain tumour – one study found that approx. 8% of brain tumour patients [4] had monosymptomatic headache. These studies were all performed on material consisting of patients with previously known intracerebral tumours. Our study differs in that the patients had no known tumour at the time of inclusion. Large studies have shown that headache is very frequent, with a lifetime prevalence of up to 99%, and that approx. 4% of the population has chronic headache, defined as more than 15 headache days per month [6, 7]. Some of those who experience chronic headache would fulfill criterion 5 of the Brain Cancer Program, but to scan that many patients would be impossible. When, as in our study, there are so few positive findings in the group referred with monosymptomatic headache, we should consider

whether these patients should even be included in the Brain Cancer Program, especially when considering the high amount of resources this program demands.

Another group that stands out in our study is the group with BPCD. This group has significantly more primary malignant tumors, a higher total number of tumours and acute/subacute pathologies than other groups. However, the age composition of this group was higher than that observed in the other groups except the group referred after prior CT or MRI. Numerous studies have shown that brain tumours are more frequent in the elderly [3, 8]. Other studies have shown that 23-90% patients with an intracerebral tumour have at least one symptom belonging to our BPCD group [3, 9].

In our study, we found two patients with primary intracerebral tumor in the group with mono-symptomatic epilepsy. Studies have shown that 10-15% of epilepsy in adults is due to underlying tumour [10-12] and that monosymptomatic epilepsy in brain tumour patients is mostly found in the young [13].

We found that 57 of 359 patients fulfilled two or more of the reference criteria. Despite this, there were not significantly more pathological findings in these patients. This is probably due to the low number of patients in our study.

None of the three patients referred on the basis of prior MRI/CT with a suspected tumour but without fulfilling any of the other referral criteria had a primary malignant brain tumour.

Furthermore, we found 53 patients who did not meet the criteria of the program. This relatively high number may be due to ignorance of the exact wording of the Brain Cancer Program, especially regarding the "headache category", where many of the referred patients had only a few days' prior history of headache and not the three-week minimum stipulated in the guidelines. In several cases, we had the impression that the patient's fear of a tumour had been instrumental in motivating the physician towards referral.

At the OUH, the patient is not seen by a specialist in neurology before the scan, but is instead consulted via telephone by the neurologist. This procedure was chosen based on the consideration that a prior neurologic consultation is unlikely to reduce the number of scans considerably; it cannot, however, be ruled out that some patients might not have had the MRI performed if an examination had been done, but the examination in itself would probably not be more cost-effective than the scan.

Two recent studies published in the Danish Medical Journal [14, 15] found 139 tumours in 241 referred patients, whereas we found 21 tumours in 359 patients referred under the Brain Cancer Program. A total of 139

tumours in 241 patients is a surprisingly large number of positive findings considering the expectations from the Danish Board of Health; and the results of these two studies do not match our results. Their method differs from ours in that they included patients with tumours detected on prior scans (81 patients) and in that nearly all of these patients were included retrospectively, i.e. after the tumour diagnosis. They were divided into the four clinical referral categories based on a questionnaire and a neurological examination where the examiner knew the result of the scan a priori. At the Neurology Department of the OUH, patients diagnosed with brain tumour on a prior scan skip the first steps in the Brain Cancer Program and go straight to the Neurosurgery Department. Apart from 11 cases, all patients in our study were referred from their GP, whereas this was the case in only 49% in the two other studies. The 21 patients with tumours found in our study are thus the direct result of the Brain Cancer Program.

CONCLUSION

In relation to the publication from the Danish Health and Medicines Authority from 2009, we found fewer brain tumours than the expected approx. 10%. We found only eight primary malignant tumours (approx. 2%) and a total of 21 tumours including meningiomas, metastases and primary tumours (approx. 6%).

At the same time, our study showed that there were significantly fewer findings in the group referred on the indication of headache alone. We question whether this indication should remain part of the Brain Cancer Program.

Not surprisingly, we found that high age was significant in relation to findings of pathology of any kind, which may partly explain why there were significantly more tumours in the group with BPCD – which also had a more advanced age profile.

Additionally, 53 patients did not meet the referral criteria. This indicates a need to heighten awareness of the specifics of the referral criteria of the Danish Brain Cancer Program.

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