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ORIGINAL ARTICLE - BRAIN TUMORS

The role of computed tomography in the screening of patients presenting with symptoms of an intracranial tumour

Sharri Junadi Mortensen[1,2] · Shima Naebi Bjerrum[1] · Stine Frost Hedegaard[1,2] · Anna Tietze[3] · Hanne Gottrup[2] · Gorm von Oettingen[1]

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Abstract

Background To improve the quality of care for brain cancer patients, the Danish Ministry of Health has set standards for the diagnosis and treatment. When a patient is suspected of having a malignant tumour involving the brain, it is required that a magnetic resonance imaging of the cerebrum (MRI-C) be obtained within seven calendar days of referral from a primary care provider. This standard has the potential to consume MR imaging time that might otherwise be used for evaluation or treatment monitoring of other patients. This study primarily aims to assess the sensitivity of computed tomography of the brain (CT-C) for the detection of intracranial tumour as the initial diagnostic imaging.

Methods This is a single-center retrospective study of patients referred to the IBCP with brain cancer suspicion. The average follow-up was 37 months. All included patients underwent a CT-C scan and subsequently a MRI-C if deemed necessary. The study population was divided into two groups based on the findings: tumour versus non-tumour. Sensitivity and specificity of the CT-C was calculated.

Results Eight hundred seventeen patients were included. Median age was 55 years and 50% were male. CT-C had a sensitivity of 98.5% and a specificity of 98.4%. The overall mortality rate was 7% in the non-tumour group and 58% in the tumour group over the course of the study period. The tumour group was on average older compared to the non-tumour group (65 years [55–75 years] vs 52 years [38–65 years]) $p < .001$). The only symptom associated with brain tumour was the presence of a focal deficit ($p = .002$).

Conclusion This study shows that CT-C scans are highly sensitive and specific and can be used as the primary screening tool for patients referred with a suspicion for brain cancer.

Keywords Brain tumour · Diagnostic imaging · CT-C · MRI-C

Abbreviations

CT-C	Computed tomography of the brain
EPJ	Electronic patient journal
IBCP	Initial brain cancer pathway
ICP	The Danish integrated cancer pathway
MRI-C	Magnetic resonance imaging of the cerebrum

Introduction

Brain cancer is known to have a devastating prognosis. The worldwide incidence rate of primary malignant brain and other CNS tumours was estimated to 3.4 per 100,000 in 2012 [9]. The latest statistics from the Danish Cancer Registry indicate an increasing number of people in Denmark being diagnosed with brain tumours. In 2015, there were 1807 patients diagnosed with primary brain tumours [19]. However, the most common intracranial tumours are metastatic brain tumours with an incidence of 3500 patients per year in Denmark, which correlates to 20–30% of patients with systemic cancers

✉ Sharri Junadi Mortensen

[1] Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

[2] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

[3] Institute of Neuroradiology, Charité Universitätsmedizin, Berlin, Germany

[12]. Due to the unacceptable waiting times until diagnosis and poor survival rate for cancer patients in Denmark compared to other Nordic countries, a political initiative for improvement was taken. The improvement implied integrated cancer pathways as organizational and clinical standards for the diagnostics and treatment for all cancer types including brain cancer. Denmark implemented an initial pathway in brain cancer diagnostics, called integrated brain cancer pathway (IBCP) in 2009. The overall goal of IBCP is to prevent potential delay in diagnostics in case of cancer diagnosis and to improve patient outcome by prompt treatment initiation, as many brain tumours tend to progress rapidly [21].

The content of the IBCP is defined by the Danish Health Authority and the referral to this pathway is initiated by the primary care physician based on five predefined criteria. The IBCP currently includes a magnetic resonance imaging of the cerebrum (MRI-C) within 7 days of referral as the primary imaging screening tool, which is considered the gold standard [21]. However, most often, a computed tomography scan of the cerebrum (CT-C) is obtained prior to the MRI-C; still, it is not obtained routinely and is not included in the guidelines.

The neuroradiology of brain tumours can roughly be categorized as the following: initial tumour diagnosis, preoperative planning, intraoperative guidance, and post-operative control imaging. This study is focused on the imaging modality for the initial tumour diagnosis. The gold standard technique for diagnosing a brain tumour is a MRI-C [7, 23], as it provides good soft tissue contrast [16], has a high spatial resolution, and a large range of tissue characteristics that may be measured [1]. The sensitivity and specificity of CT in comparison with MRI varies with specific disease process, but, in general, is understood to provide less information than MRI in the setting of tumour [4]. However, access to MRI-C can be limited due to long waiting lists and an overall restricted availability. In contrast, CT-C is less costly and faster to obtain.

We therefore hypothesize that CT-C can safely be used as the initial imaging modality in screening patients who present with symptoms that may indicate a brain tumour. When an abnormality is identified on a non-contrast CT or in the setting of persistent clinical symptoms and suspicion, it can be followed by a MRI-C.

Objectives

The goal of our study was (i) to assess how sensitive and specific CT-C is as a primary screening imaging modalities in the initial diagnostic part of the IBCP compared to MRI-C which is currently the gold standard and (ii) to evaluate the current referral criteria in regards to their statistical association with brain cancer.

Methods

Study design and setting

This is a single-center retrospective study of patients referred to the IBCP at the Department of Neurology with the referral diagnosis for brain cancer suspicion. Patients were included by their referral diagnosis code during the period of 1st of December 2011 until 31st of January 2014. After obtaining approval from the Danish Health Authority and Data Protection Agency, patient data was gathered via their personal social security number from electronic patient journal (EPJ) and the imaging database. No patient consent is required in Denmark after obtaining approval from the above-mentioned authorities. The minimum follow-up period was 2 years, and the maximum up to 4 years. We used a centralized data access to ensure that all brain cancer patients could be re-assessed within the region, even if they might have been referred to other hospitals or clinics within the region.

The data collection was performed by two medical research assistants. The data was checked by a neurosurgical fellow/neurosurgeon during the collection period in order to guarantee validity.

Integrated brain cancer pathway

IBCP is initiated by probable cancer suspicion by the primary care physician/ in the initial clinical evaluation based on the following five criteria: [21]

1) Newly onset headache or substantial changes in former headache without any other likely cause.
2) Newly onset focal neurological deficits, with rapid progression without any other likely cause
3) Newly onset epileptic seizure in adults without any other likely cause
4) Newly onset cognitive impairment without any other likely cause
5) Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, performed for another reason than suspected brain cancer, showing an intracranial space-occupying lesion suggestive of brain cancer

Criteria 1–4 constitute the clinical inclusion criteria which is of relevance in this study.

Participants and variables

Patients were characterized by age, sex, referral diagnosis, and symptoms at the time of referral. Our altered IBCP protocol included a primary CT-C after a complete neurological examination by a neurologist. Patients with a primary MRI-C without a previous CT-C were excluded.

The study population was then divided into two groups based on the MRI-C imaging results: (i) tumour (including all primary as well as metastatic brain tumours) versus (ii) non-tumour (such as prior stroke, non-surgical meningioma, migraine, and other conditions). Lesions suggestive of meningioma were categorized as a tumour despite their benign nature if they were space-occupying lesions and thereby requiring surgery due to their size, peri-focal oedema, and/or location [2]. For the purposes of this study, we classified the rest of the meningioma as non-tumour, as they were incidental findings and the findings had no consequences for further treatment.

A total number of 901 patients were suspected of brain tumour and referred to the IBCP during the study period, meeting the initial inclusion criteria.

Fifty-three patients were excluded, as MRI-C without prior CT-C had been performed. Additionally, 31 patients were excluded due to following reasons: Patients referred to another department because of non-neurological findings and diagnosis (referral mistake), no records available, travelled back to home country after vacation, cerebral haemorrhage, spinal tumours, or dismissal after the clinical neurological examination without CT-C or MRI-C examination.

Bias

Due to the Danish National Health registry, the selection bias is considered very low in this study since all patients referred with the suspicion of brain cancer were included if they have obtained a CT-C in the process.

Statistical methods

Descriptive statistics were used to summarize the study population. Data for continuous variables are presented as medians with quartiles. Categorical data are presented as counts with frequencies. Depending on the distribution of the data, *t* tests or Wilcoxon signed-rank tests were used to compare continuous data between the groups. Categorical data were compared using Fisher's exact tests. All two-sided hypothesis tests were considered statistically significant with a level of $p < 0.05$. MRI-C was used as a gold standard for calculation of sensitivity and specificity of CT-C. SAS software was used for the statistics (SAS Institute Inc., Cary, NC, USA).

Results

Participants

Eight hundred seventeen patients were included in the study. None of the patients were lost to follow-up, due to the Danish National Health Care Registration System using Social Security Number. The average follow-up period in the study was 37 months (24–50 months).

Descriptive and outcome data

Patient's demographics and presenting symptoms are summarized in Table 1. They had a median age of 55 years (15–100 years), 50% were male. Six hundred seventy-five patients (82%) were referred from their general practitioner and 142 patients (18%) were referred from other hospital departments in the region. Three hundred seventy patients (45%) were referred to undergo an additional MRI-C due to either concerning result found on the CT-C or from persistent clinical suspicion.

The tumour group consisted of 135 patients (16.5%). This study found a significantly higher age in the tumour group compared to the non-tumour group, 65 years (55–75 years) versus 52 years (38–65 years), ($p < .001$).

The overall mortality was 147 patients (15%), with 7% in the non-tumour group, and 58% in the tumour group with the tumour or sequel thereof as the underlying cause of death over the course of the study period. The cause of death was not ascertained in two cases in the non-tumour group, as the patients were found dead and an autopsy was not performed. These two patients were considered as died from other causes than brain cancer, which was also the case for the rest of the patients in the non-tumour group (Table 2).

Main results

Clinical symptoms

Patients were further categorized by their symptoms at the time of referral that would initiate the IBCP prior to the neurological examination at the Department of Neurology.

Table 1 Selected baseline characteristics

Characteristics	Patients ($n = 817$)
Demographics	
Female	409 (50%)
Age (years)	55 [15–100]
Referred from	
General practice	675 (83%)
Another department	142 (17%)
Symptoms	
Focal deficits/paraesthesia	316 (39%)
Headache	392 (48%)
Cognitive	113 (14%)
Seizure	145 (18%)
Found by scans	38 (5%)

Table 2 Baseline characteristics in tumour versus non-tumour group

Characteristics	Tumour ($n = 135$)	Non-tumour ($n = 682$)	P value
Demographics			
Female	64 (47.4%)	345 (50.6%)	0.5110
Age (years)	65 [55–75]	52 [38–65]	< 0.0001
Referral symptoms			
Focal deficits	58 (43.0%)	198 (29.0%)	0.0022
Paraesthesia	4 (3.0%)	62 (9.1%)	0.0147
Headache	51 (37.8%)	341 (50.0%)	0.0108
Cognitive deficits	22 (16.3%)	91 (13.3%)	0.4124
Seizure	15 (11.1%)	130 (19.1%)	0.0265
Verified by scans	29 (21.5%)	9 (1.3%)	< 0.0001
Additional imaging			
MRI	128 (94.8%)	242 (35.5%)	< 0.0001
Mortality	98 (58.3%)	49 (6.9%)	< 0.0001

Headache was the most common symptom involving 392 patients (48%). Two hundred fifty-nine patients (31%) presented with focal neurological deficits and 66 patients (8%) with paraesthesia. Cognitive symptoms (such as altered memory and thinking skills) were present in 113 (14%) of the patients. One hundred forty-five patients (18%) had a new-onset epileptic seizure without any other likely cause.

A focal deficit was found in 58 (43%) of the tumour patients, whereas 198 (29%) of the non-tumour patients presented with focal deficits as an initial symptom. This was the only symptom found to be associated with the presence of a brain tumour ($p = .002$) (Table 2).

The symptoms "headache", "paraesthesia", and "seizure" were found to have a statistically significant association with non-tumour-related causes ($p = .011$, $p = .015$, $p = .027$) (Table 2).

Sensitivity and specificity

CT-C detected 133/135 brain tumour cases, resulting in a sensitivity of 98.5% ($CI_{95\%}$ 96.5–100%). The two cases that were not detected had a non-specific space-occupying lesions on the CT-C, where a MRI-C was performed because of equivocal CT-C findings and subsequently confirmed the presence of a brain tumour (Table 3).

Table 3 Sensitivity and specificity of CT-C

MRI CT	Non-tumour	Tumour	Total
Non-tumour	671 (99.7%)	2 (0.3%)	673
Tumour	11 (7.6%)	133 (92.4%)	144
Total	682	135	817

Out of 682 non-tumour patients, CT-C correctly excluded in 671 patients, giving CT-C a specificity of 98.4% ($CI_{95\%}$ 97.4–99.3%). The CT-C of 11 patients was suggestive of cancer, but the diagnosis was later rejected by MRI-C (Table 3).

Seventeen patients from the non-tumour group were re-referred during the follow-up period with continuous suspicion of brain tumour. All of them were cleared with a new CT-C scan and/or MRI-C.

Discussion

The quality and success of any pathway program for diagnosing brain cancer is highly dependent on well-defined inclusion criteria, its efficiency with regard to straightforward referral procedures, the acceptance by the referring general practitioner, as well as the possible improved patient outcome [13]. The integrated cancer pathway (ICP) is a government-run system that attempts to streamline many different cancer diagnostics and treatment plans. The aim is to standardize, improve, and create a timely diagnostics and treatment for cancer patients according to national evidence-based clinical guidelines [21].

MRI is currently used as the gold standard for the evaluation of patients with brain tumours, providing highly accurate information on primary diagnostics, treatment monitoring, and potential tumour progression [15]. Relatively, non-specific findings on CT-C are appreciated more clearly on MRI-C, allowing a more precise diagnosis [8]. This study has shown that CT-C, however, can be used as primary screening tool prior to obtaining an MRI, allowing for a faster and less expensive diagnostic tool to support or reject the suspicion of a brain tumour. Brain tumours were detected with a high sensitivity of 98.5% ($CI_{95\%}$ 96.5–100%). There were two patients with MRI-verified brain tumours, where the primary CT-C report did not detect the tumour but merely the presence

of an intracranial, non-specific lesion. Nevertheless, the findings on the CT-C warranted an additional MRI, where a tumour was diagnosed. Thus, none of the patients were misdiagnosed on primary CT-C scans.

Despite the more detailed imaging properties of MRIs, studies have shown that CT-C can play a role in demonstrating calcification, bleedings, and is the only imaging tool when MRI is contraindicated [24]. It has been shown that CT scans can be valuable in the assessment of meningioma, distinction of tumour from oedema, and if the anatomic relation to osseous structures has to be evaluated, for example in tumours that are in close proximity to the scull base; however, beam hardening artefacts, especially in the posterior fossa, can impede correct diagnoses [3, 11]. There is also the high radiation exposure with CT-C to consider in comparison to MRI-C that does not emit the damaging ionizing radiation [17]. Nevertheless, CT-C continues to be the first choice in cases requiring immediate treatment, such as subdural hematomas [14].

MRI is more time consuming and less cost-effective. The MRI capacity at Danish Hospitals is increasing, but remains relatively limited in most radiology departments. Therefore, a number of patients still undergo a primary CT-C, followed by MRI-C if further diagnostics are required or if a tumour is present. MRI-C remains the modality of choice if anatomical details have to be evaluated and different tumour components have to be defined. This information is essential for the surgical approach and potential radio-chemotherapy. Moreover, advanced MRI methods allow detailed tumour diagnostics in particular gliomas that can be important for the choice of treatment [6, 22]. The Danish Health Authority reported a significant increase in MRI examinations as a part of cancer pathways during the past years, which requires considerable health care resources. [20] For these to be used appropriately, the imaging of each cancer pathway needs to be evaluated, and the recommended imaging tool should be based on evidence-based studies.

Our study further showed that recent onset of focal neurological deficits is the only referral symptom showing statistically significant association with brain cancer ($p < .001$). Furthermore, the results showed significantly higher age in the tumour group compared to the non-tumour group, 65 versus 52 years old ($p < .001$). The remaining symptoms, such as headache, paraesthesia, and seizure, are shown to have a statistically significant association with non-tumour-related causes. This suggests that the IBCP inclusion criteria might be too comprehensive and non-specific. Narrowing referral criteria may therefore help save health care resources and possibly avoid unnecessary patient concerns. Larger studies are, however, warranted in order to further investigate the IBCP referral criteria.

Another finding of our study was that 84% of the IBCP-enrolled patients did in fact not have a brain cancer. By using CT-C, these patients would be excluded faster from the IBCP. MRI-C, which may not be available ubiquitously, has the potential to prolong diagnostics and thereby causing unnecessary concerns for the patients and possible delays in initiation of appropriate treatment.

The average follow-up period in the study was 37 months (24–50). None of the patients, who were re-referred to the IBCP during the follow-up period, had been misdiagnosed after having a CT-C at their primary presentation, as none were found to have a missed brain cancer diagnosis in the follow-up duration.

Limitations

One limitation of our study may lie in the fact that we did not classify tumour types and grades in the patients included, and therefore cannot estimate an exact progression rate for the primary and secondary brain tumours that are of interest in this paper. However, we do not think that this have altered our results in regard to the main subjective of the paper, which is whether a CT-C can be used as the primary screening tool for patients presenting with symptoms of an intracranial tumour.

Another limitation might be the length of the follow-up. However, the most common brain cancers are known to be highly progressive with a short survival rate if left untreated. Glioblastoma is the most common and most aggressive brain tumour. Regardless of any treatment procedures, they are always fatal with a median life expectancy of 9–12 months from detection. Similarly, the prognosis for patients with metastatic brain tumour is generally poor; median survival is 1 month for patients who are not receiving treatment [5, 10, 18].

And finally, the study design is retrospective and, therefore, is prone to selection bias or recall bias. However, since this is a sample from the National Danish registry, we believe that these biases may have been minimized.

Conclusion

This study shows that CT-C scans are highly sensitive and specific and can safely be used as the primary screening tool for patients suspected of having a brain tumour. Using a CT-C primarily is both of economic significance and might reduce psychological distress for patients and their families by reducing possible waiting time. However, an additional MRI-C is warranted if CT-C is equivocal, if there remains a strong clinical suspicion in spite of a negative CT-C, and if a space occupying lesion has been demonstrated and has to be elucidated in more detail.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent For this type of study, formal consent is not required.

Disclosure None of the people involved have any personal or institutional financial interest in drugs, materials, or devices described in this submission. Nothing to disclose.

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