

A brain cancer pathway in clinical practice

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ABSTRACT

INTRODUCTION: Danish healthcare seeks to improve cancer survival through improved diagnostics, rapid treatment and increased focus on cancer prevention and early help-seeking. In neuro-oncology, this has resulted in the Integrated Brain Cancer Pathway (IBCP). The paper explores how the pathway works in the initial phase in a clinical setting with emphasis on pathway criteria.

MATERIAL AND METHODS: All patients admitted during the first two-year period to a regional neurology department in Denmark and fulfilling the IBCP inclusion criteria were included. Data regarding onset symptoms, diagnosis and time for diagnostic work-up were obtained and supplemented by a retrospective review of patient records. Sensitivities, specificities and positive predictive values of the inclusion criteria were calculated with magnetic resonance imaging scan of the cerebrum as index of validity.

RESULTS: The strength of the pathway inclusion criteria was determined largely by the number of criteria fulfilled and by the type of predominant symptoms. The criteria identify the majority of patients with symptomatic brain malignancy and were also highly predictive of general structural brain lesions.

CONCLUSION: The introduction of the pathway is a major step forward in the efforts to optimize brain cancer patients' illness trajectory.

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TRIAL REGISTRATION: not relevant.

In the 1990s when the Danish National Board of Health compared epidemiological data on prevalence, survival and mortality rates in cancer patients with data from the other Nordic countries, it became evident that Danish cancer patients in general had poorer survival rates than those of the neighbouring countries [1]. Ultimately, these findings sparked a massive effort by Danish healthcare to improve cancer survival through improved diagnostics, rapid treatment and an increased focus on cancer prevention and early help-seeking [1-3].

In 2007, the Danish government and the Danish Regions agreed to the goal that pathway programmes should be instituted for all cancer types before the end of 2008. A cancer pathway programme is defined as “a

patient pathway in which the individual steps are planned as pre-booked, well-defined events as far as concerns time and content” [1].

The Danish Integrated Cancer Pathway (IBCP) integrates the organizational, clinical and monitoring aspects of 34 types of cancer disease and aims at standardized, optimized and faster diagnostics and treatment for cancer patients according to national evidence-based clinical guidelines [4, 5].

The aim of this study is to measure how the IBCP works in the initial phase in a clinical setting. In this paper emphasis is on the evaluation of the clinical inclusion criteria.

DANISH NATIONAL INTEGRATED BRAIN CANCER PATHWAY

With the implementation of the IBCP, which is the result of the joint effort of the Danish Board of Health and the Danish Neuro-Oncology Group (DNOG), a stronger focus has been given to brain tumour patients. The annual incidence of primary central nervous system tumours (benign and malignant) in Denmark (population 5.5 million) is about 20/100,000 [4, 6]. This number is slightly higher than similar numbers in the other Nordic countries and the rest of the world [7, 8].

Until the introduction of the IBCP, referral for suspected brain cancer and subsequent neurological examination and diagnostic work-up was mostly elective with the exemption of cases with acutely ill patients admitted via emergency care.

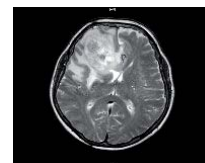
With the full implementation of the IBCP, brain cancer has undergone a change of status and is now considered to require urgent specialist physician contact. The core of the IBCP is: fast referral from primary care, fast neurological work-up followed by fast visitation to neurosurgical primary evaluation and/or treatment and primary or secondary oncology treatment.

The pathway programme requires close and efficient intra- and interhospital cooperation between departments specialized in neurology, neurosurgery, oncology and radiology as well as with the primary care sector. A general practitioner may enrol a patient into the IBCP by referring the case to emergency diagnostic work-up in the regional neurological department. For a patient to be eligible for diagnostic evaluation in the IBCP, a minimum of one of five inclusion criteria must be met (Table 1). The referring physician is required to in-

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Integrated brain cancer pathway patient with glioblastoma.



TABLE 1

Inclusion criteria of the Integrated Brain Cancer Pathway (IBCP). Criteria 2-5 constitute the clinical inclusion criteria.

1. Computed tomography or magnetic resonance imaging scan of the cerebrum, performed for another reason than suspected brain cancer has shown an intra-cranial space-occupying lesion suggestive of brain cancer
2. Recent debut of (a) focal neurological symptom(s) progressing over days/weeks without any other likely cause, e.g. subdural haematoma or MS
3. Recent debut of an epileptic seizure in adults without any other likely cause, e.g. substance abuse or sleep deprivation
4. Recent changes in personality or behavior and cognitive deterioration progressing over weeks without any other likely cause, e.g. primary dementia, psychiatric illness or substance abuse
5. Recent debut of headache or marked changes in former headache pattern, progressing over weeks where thorough medical history and examination by a neurologist has not revealed another likely cause

form the patient of the strong clinical suspicion of brain malignancy [4].

Neuro-oncology is a resource-demanding and complex area of medicine and there is a special need for co-ordination of treatment and care among the involved specialist departments. When a patient receives the diagnosis of malignant brain tumour, this will in most cases mark the beginning of a lifelong course of treatment and care anchored in a neurology department. This is due to the frequently very progressive nature of the disease and common co-symptoms of cognitive deterioration and focal deficits, symptoms that are best managed by neurology specialists. The regional neurology departments are therefore in an optimal position to provide an anchor function throughout the illness trajectory, which also provides excellent opportunities to register data from the individual cases. "Ledelse af cancerforløb" (*Management of cancer pathways*) (Danish Health Institute, 2008) [9] compiles recommendations for the further course of the National Integrated Cancer Pathways as a whole based on interviews with key personnel within the health administrations. From this report, it is evident that there is a need for further registration of clinical and management data on cancer pathway patients and their illness trajectories.

MATERIAL AND METHODS

Serving as a neurology specialty function for a patient catchment area of approximately 350,000 individuals, our department implemented the IBCP in April 2009. At our facility, there are specialist departments in neurology and radiology, whereas neurosurgery and oncology consults and treatment require transfer to other hospitals in the region.

To continuously monitor and empirically optimize

the brain cancer illness trajectory in the department, a local clinical database has been established where all patients admitted in to the local IBCP are registered. This prospective database is expected to be used as a tool for continuous evaluation of diagnostics and treatment quality in accordance with National Board of Health guidelines.

Data were obtained from a structured form filled out for each patient during admission by the involved healthcare personnel. Data regarding referral, symptoms, diagnosis and time for diagnostic work-up were obtained. This was supplemented by a retrospective review of patient records and radiology reports. The study was approved by the Danish Data Protection Agency.

Statistics

Data deriving from a two-year period were extracted from the local clinical SPSS based database. Sensitivities and specificities of the clinical inclusion criteria were calculated using magnetic resonance imaging (MRI) scans of the cerebrum as index of validity. Sensitivity refers to the ability of the IBCP clinical inclusion criteria to detect all cases of brain tumours and structural brain lesions. Specificity refers to the ability of the IBCP clinical inclusion criteria to discriminate patients with brain tumours/*structural brain lesions* from patients without these diagnoses. The term structural brain lesion refers to all tumours, cysts, vascular malformations, ischaemic, demyelinating and haemorrhagic lesions. The positive predictive values (PPV) were estimated by calculating the proportion of patients with the radiological diagnoses of either primary brain tumour or structural lesions among patients who entered the IBCP on the clinical inclusion criteria alone. The clinical inclusion criteria are criteria 2-5 in Table 1.

Trial registration: not relevant.

RESULTS

A total of 241 patients were enrolled in the IBCP at our facility during the first two-year period after its implementation, (female:male ratio 1:1.1, mean age 57.8 years (19-92)).

Findings on conventional MRI with gadolinium contrast were: solitary neoplasm (incl. meningioma) (n = 122), multiple neoplasms (n = 19), ischaemic stroke (n = 16), other structural lesions (n = 24), no structural lesions (n = 60). Thus, 59% of the enrolled patients had primary or secondary tumours, and overall about 75% had a structural brain lesion.

Onset symptoms and inclusion criteria

Eighty-one (33.6%) of the 241 patients were included in the IBCP on criterion 1 (Table 1), with a computer tomog-

raphy (CT) or MRI scan already showing a suspected tumour; and 94% of these patients were ultimately diagnosed with either primary or secondary brain malignancy. The most common indications for diagnostic imaging in this group were suspected stroke, seizures, suspected dementia and unclear symptoms. When investigating their history upon admission, nearly all of these patients did, in fact, meet at least one of the clinical inclusion criteria and did as such qualify directly for diagnostic evaluation in the IBCP.

70% (n = 166) presented with a focal neurological deficit at the first neurology consult, either mono-symptomatic or in combination with other symptoms. Of the presenting focal signs, paresis (29%), paraesthesia (24%), motor control deficiency (25%), visual disturbance (24%) and speech disturbance (21%) were found to be nearly equally common. The most common isolated symptom was one or more focal deficits (17%, n = 40), and the pure combination of a focal deficit and headache was the most common symptom cluster leading to inclusion in the IBCP (21%, n = 50) (Figure 1A).

Similar observations were made regarding the patients who had malignant intracranial lesions, but the symptom cluster of focal deficit and cognitive change (17%, n = 23) was found to be just as frequent as focal deficit in combination with headache (16%, n = 22) (Figure 1B).

The most common accessory onset symptom not listed among the clinical inclusion criteria was vertigo/dizziness which was reported by 10% of the patients (n = 25).

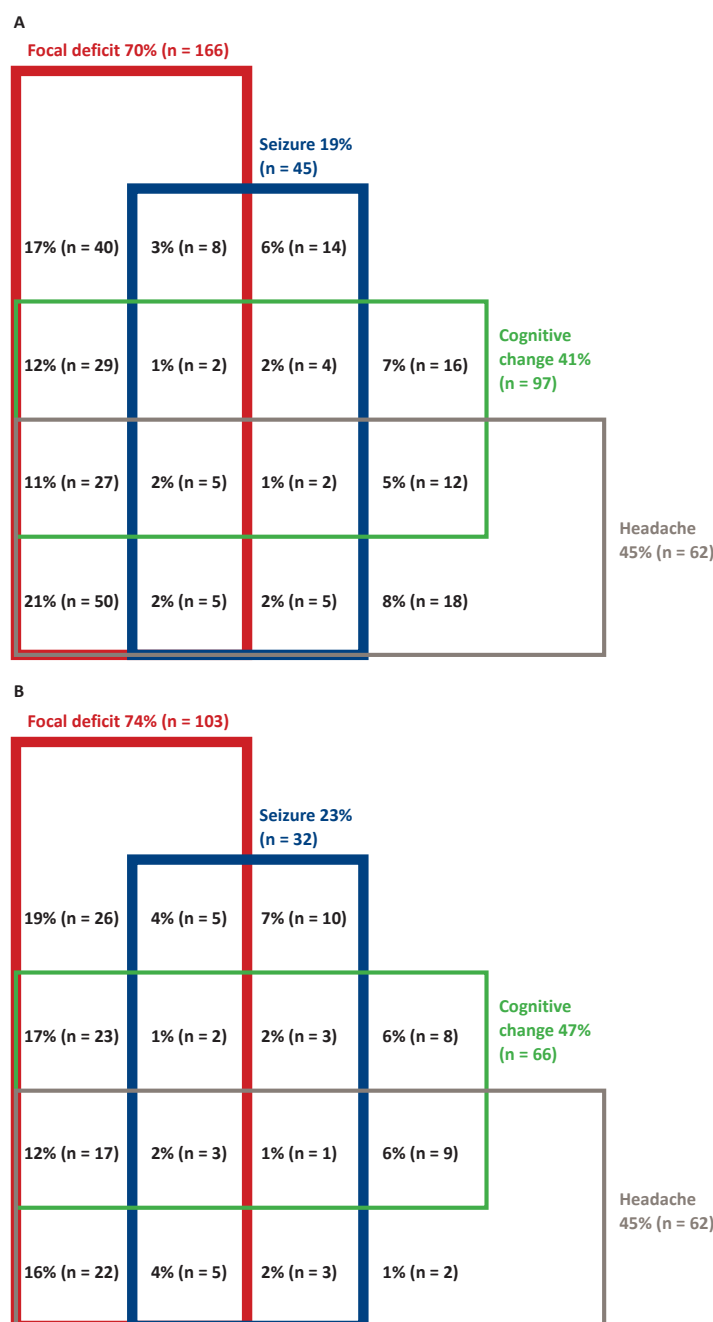
The sensitivity of the inclusion criteria for general intracranial structural lesions was found to be substantially higher for certain symptoms as was the specificity for intracranial primary tumours. The specificity of the clinical inclusion criteria for tumour-specific and general structural lesions was found to increase with the number of inclusion criteria fulfilled, and certain symptom clusters had a substantially higher sensitivity and specificity than others (Table 2). The combination of focal deficit and cognitive change seems to produce a very high and balanced specificity and positive predictive validity both for brain tumours and structural brain lesions in general. If headache is also present in the symptom cluster, specificity increases further.

The PPV of the overall clinical inclusion criteria in regards to primary brain tumour was 51% (122/241), for malignant structural brain lesions 59% (primary and secondary brain tumours both) and for undifferentiated structural brain lesions 75%. As isolated symptoms, especially focal deficits and headache, seem to be highly predictive of brain tumour (61%), while the symptom combination of focal deficits with change in behaviour and cognition has the highest predictivity for brain tumour (71%) (Table 2).

A clear pattern emerged from an comparison of the number of clinical inclusion criteria fulfilled with later MRI findings: There was a positive relationship between the number of clinical inclusion criteria fulfilled and MRI findings of neoplasms (Figure 2). The strength of the cri-

FIGURE 1

Venn diagram showing the distribution of patients with different combinations of onset symptoms among all patients in the Integrated Brain Cancer Pathway, n = 237^a (A) and among patients with brain tumour, n = 139^b (B).



a) Four patients included on criterion 1 met none of the clinical inclusion criteria.

b) Two patients with tumour met none of the clinical inclusion criteria.



TABLE 2

Sensitivity, specificity and positive predictive value of the individual clinical inclusion criteria and certain symptom clusters in regards to brain tumours and structural brain lesions in general.

	Se _{tumour}	Se _{struct.}	Sp _{tumour}	Sp _{struct.}	PPV _{tumour} %	PPV _{struct.} %
Focal deficit	0.71	0.69	0.36	0.37	61	77
Change in behaviour or cognition	0.47	0.49	0.58	0.66	37	40
Headache	0.44	0.45	0.35	0.28	61	82
Seizures	0.23	0.19	0.61	0.50	50	65
Focal deficit and headache	0.33	0.34	0.60	0.57	54	70
Focal deficit and cognitive change	0.32	0.28	0.80	0.80	71	81
Focal deficit, headache and cognitive change	0.16	0.14	0.88	0.85	63	72

PPV = positive predictive value

Se = sensitivity

Sp = specificity

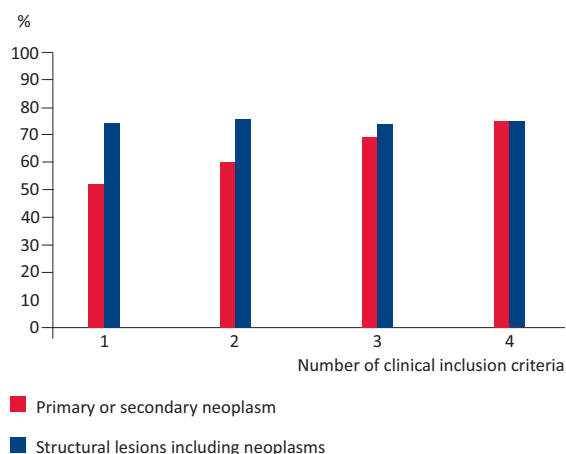
teria is determined largely by the number of criteria fulfilled, but also by which symptoms are predominant.

DISCUSSION

Cancer pathways have been established in several EU countries and are continuously being improved. A brain cancer pathway was attempted introduced in the UK in the early 00's. The referral guidelines for this model, which include more strict criteria than the Danish version, have previously been questioned [10, 11]. Today, far from all patients with suspected brain tumours in the UK are diagnosed within the context of the UK pathway [12]. It is a crucial quality of any pathway programme that it is accessible, well-known by general practitioners and that the criteria for inclusion are as exhaustive as possible without compromising sound health economic practice.

FIGURE 2

Diagram showing magnetic resonance imaging findings in relation to number of clinical inclusion criteria fulfilled at the time of admission.



The Danish IBCP inclusion criteria are more broadly defined than those of the UK brain cancer pathway programme which, in theory, would lead to a high sensitivity, but a lower specificity for the specific disease entity of primary malignant brain tumours. We find that the current Danish pathway criteria as a whole had a high PPV for structural brain lesions in general. The individual clinical inclusion criteria were found to have varying degrees of sensitivity and specificity: The recent onset of a progressing focal neurological deficit showed a high sensitivity for brain tumours as well as general structural lesions. The symptom cluster of progressing focal deficit in combination with progressing cognitive/behavioural change had a high specificity. This was even more apparent if the symptom cluster was supplemented with recent onset of a progressing new headache type.

Although this material is too limited to allow definitive conclusions about the exhaustiveness of the clinical criteria, it seems that the criteria catch the majority of symptomatic brain tumours.

CONCLUSION

The Danish IBCP is a major step forward in the unified effort by implicated primary care physicians and specialist departments and the Danish Board of Health to optimize the illness trajectory for brain cancer patients. We find that the clinical inclusion criteria catch nearly all patients that get diagnosed with brain malignancy, but also that the criteria are highly sensitive when it comes to structural brain lesions in general; and in both cases, the number of patients with those diagnoses increases with the number of inclusion criteria fulfilled. Certain symptoms were found to be more likely to represent an underlying malignant illness than others. The combination of focal deficits and cognitive change in particular enjoyed both a high specificity and predictive validity.

Finally, it must be stressed that no set of clinical guidelines can stand alone without the specialized clinical neurological examination and history-taking and that the clinical inclusion criteria of the IBCP cannot replace these in any way.

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