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Editorial

Screening for Brain Cancer: Why (Not)

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EDITORIAL

The incidence rate for primary nervous system tumors in adults (aged 20 years or older) is estimated to be 27.4 per 100,000 persons (data from 50 cancer registries, 2006 to 2010, in United States of America) [1]. Approximately one third are malignant, with the remainder being benign or borderline malignant. Despite continuous research, little is known regarding brain cancer risk factors (environmental and genetic).

In 2008, brain scanning with Magnetic Resonance Imaging (MRI) was offered to asymptomatic volunteers in the New York metropolitan area [2]. This mobile program was run by a non-profit organization, The Brain Tumour Foundation, and, as it was largely publicized, raised again the question: is it clinically and economically advantageous to scan asymptomatic individuals in search for brain/cranial disease (aneurysms, tumors or others)? Its defenders argue that a $200-$300 innocuous exam, presumably able to detect an early-stage tumor, would result in less costly and aggressive procedures and therapies, shorter hospital stays and prolonged overall survival. This would apparently ease the significant financial burden on treating a late-stage brain malignant tumor (up to $500.000 on treating a glioblastoma). In this program, 1700 brain scans led to the discovery of more than 50 abnormalities, including aneurysms, multiple sclerosis and neoplastic lesions.

In this era of emphasis on disease prevention and early diagnosis, cost-effective strategies improving treatment outcome on early-detected pathologies seem the correct path on rationalizing global health care. Clinical examination is not reliable, as neurological abnormalities mainly occur in late stages of neoplastic disease and are often subtle. Despite less expensive than other exams and broadly available, Computerized Tomography (CT) scan without contrast has a significant low sensitivity and a non-negligible radiation exposure burden. MRI, a more sensitive and fairly available imaging option, will predictably remain the best weapon on early detection. Full body check-ups (including brain MRI´s) are currently being publicized, as part of health insurance plans.

In general, cancer screening aims to detect cancer in its earliest stage possible, before symptoms appear and when the chances of responding to treatment are theoretically higher. Cervical cancer screening with Papanicolaou smears or fecal occult blood analysis for colorectal cancer are good examples

of successful programs, using simple screening tests and clearly reducing morbidity and mortality. One can distinguish between universal *population-based screening* and *selective screening,* targeting individuals with higher risk of developing neoplastic lesions, generally based on familiar history of cancer. In order to be considered efficacious, a cancer screening test must fulfil a major requirement: evidence must be available (preferably in controlled, randomized clinical trials) that an early detection and corresponding treatment will imply an improved outcome and/or reduced mortality. Some authors mention a life expectancy above 5 years and age under 70 years as a threshold for cancer screening.

As depicted by National Cancer Institute reports [3,4], many factors should be considered when weighing the real benefits of cancer screening programs. Regarding brain cancer, one can easily identify several issues that preclude an obvious benefit in systematic screening: its low incidence and prevalence; the cost of neuroradiological imaging and its false-positives (normal variations resembling subtle abnormalities), leading to anxiety and unnecessary costly invasive diagnostic procedures; the possibly harmful diagnostic and therapeutic procedures that may follow, namely brain biopsies and craniotomies. In addition, there is still no proof that early detection and treatment of malignant brain neoplasms will result in better overall survival. It is meaningful that malignant cerebral tumors, including glioblastoma and anaplastic astrocytoma, are still associated with very poor prognosis, with no suitable therapy significantly extending life expectancy (slightly over 1 and 2-3 years, respectively, with optimal treatment). Concerning estimation of average life-years saved, scanning for brain malignant tumors in an asymptomatic population easily seems an expensive inglorious effort [2].

Disease-specific mortality remains the most widely accepted endpoint in most clinical trials, assuming the cause of death can be accurately determined. Regarding brain tumors, given its short overall survival and overwhelming morbidity, its specific mortality is relatively easy to determine, despite significant co-morbidities, and misclassification on cause of death (connoted with an overestimation on effectiveness) is not a major concern. *Lead bias*, when screening detects disease earlier, not altering its course but artificially extending mean survival ratios, is not even a real issue in brain tumors. Regarding predictive value, according to Thaler et al. [5], in a group of 193 patients with malignant brain tumors, preceding MRIs were normal or inconclusive in 17 (8,8%) patients, a significant value only explained by the aggressive progression of this disease.

On the other hand, benign tumors, as the much more frequent, slow-growing and usually asymptomatic meningiomas, in many instances need no treatment at all. In a recent survey by Vernooij et al. [6], 31 benign tumors (including meningiomas, pituitary adenomas and vestibular schwannomas) were detected in 2000 high-resolution MRI´s performed on asymptomatic individuals. In the context of overdiagnosis, detecting lesions that lack pathological significance brings no clinical benefit and will lead to anxiety and unnecessary expenditure. An illustrative similar situation is the asymptomatic meningioma detected in a routine CT scan after traumatic brain injury.

An obvious difficulty in assessing the harm vs benefit for early detection of primary brain tumors comes with the relative impossibility of running long-term randomized controlled trials following two groups, with one group not receiving any treatment at all after early diagnosis. Case-control and cohort studies can provide indirect evidence, albeit the relevance of selection bias. Descriptive uncontrolled studies, based on the experience of physicians/hospitals or national registries may yield information regarding screening and the disease itself but can be imprecise and significantly biased.

A 2009 meta-analysis, by Morris et al. [7], regarding incidental findings in 19.559 asymptomatic individuals who underwent brain MRI in 16 different studies, unveiled an overall prevalence of 2,7%, including 135 neoplastic incidental findings (prevalence - 0.70%; number needed to scan - 143). Adding to this low prevalence, one cannot ignore the consequence of oversensitive MRI scans, displaying incidental foci without underlying pathology, requiring additional investigation and lowering its corresponding predictive value (see Katzman et al., 1999 – MRI images from 1000 asymptomatic individuals, 180 abnormal radiographic findings, 2 primary brain tumors, positive predictive value of only 0.011) [8]. Higher rates of false-positives are expected as neuroimaging advances and high-resolution MRI sequences are increasingly accessible, stressing the importance of proper follow-up, including consultation with neurologist or neurosurgeon. In some countries and/or health systems, concerns on unequal accessibility to MRI scans may also be relevant.

In conclusion, a rational analysis on clinical and epidemiological data indicates that screening for primary brain cancer is currently not recommended, based on its low prevalence, high costs and low effectiveness of intervention. In the future, more extensive longitudinal large-population based studies on risk factors will certainly improve knowledge on brain cancer´s epidemiological context and guide preventive and therapeutic strategies. Simultaneously, genetic studies will help clearly identify high-risk populations, namely with strong family history of cancer, as different mutations and polymorphisms are progressively being identified.

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