J Neurooncol
DOI 10.1007/s11060-010-0482-4

CLINICAL STUDY – PATIENT STUDY

Intracranial tumors in Kuwait: a 15-year survey

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Received: 7 July 2010 / Accepted: 22 November 2010

Abstract The dearth of literature on intracranial tumors (ICT) in Kuwait has necessitated this study whose objective is epidemiological. It is based on the records of the Department of Pathology, Al-Sabah Hospital, Kuwait, where virtually all brain biopsies in Kuwait were examined. Between 1995 and 2009, 439 males (53.41%) and 383 females (46.59%) had primary intracranial tumors (PICT). Most (69%) were younger than 50 years, with 16% children and adolescents and 4% elderly (≥70 years); meningioma (28%), pituitary adenoma (19%), glioblastoma (15%), astrocytoma (13%), and medulloblastoma (5%) were the most common. In childhood and adolescence, astrocytoma (35.34%) and medulloblastoma (22.56%) predominated. The mean age-adjusted incidence rate/100,000 was: PICT: 3.02; astrocytic tumors: 0.93; meningioma: 0.96; pituitary adenoma: 0.44; and medulloblastoma: 0.13. All showed a declining trend which was only statistically significant for medulloblastoma ($P = 0.007$). A modest correlation between the percentage of elderly in the general population and incidence rates was found ($r = 0.411$). Tumors with significant male preponderance were high-grade astrocytic tumors, silent pituitary adenoma (SA), and nerve sheath tumor. Meningioma had a female to male ratio of 2.24. The peak frequency for functional pituitary adenoma and females was in the age range of 20–29 years, while for SA and males it was 40–49 years. About 5% of ICT were metastatic, with cancers of breast (26%), lung (17%) and gastrointestinal (11%) origin as the most common. In conclusion, the epidemiology of PICT in Kuwait is characterized by low incidence rates and a distinct age distribution.

Keywords Intracranial tumors · Astrocytic tumors · Meningioma · Pituitary adenoma

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Introduction

Intracranial tumors represent a heterogeneous group of primary and metastatic tumors linked by their location. They have different histological features and biological behavior, probable etiological factors, and variable clinical presentation. Despite these differences, tumor location may, at times, be the major unfavorable factor limiting complete surgical resection and promoting local recurrence or mortality. Since many of these tumors are often associated with high morbidity and mortality, they create considerable problems for families and health care delivery systems.

The incidence rate and relative frequencies of intracranial tumors show significant world-wide and inter-ethnic variations [1]. Although to some extent this may be a reflection of the state of diagnostic facilities, availability of relevant manpower and hospital practice and reporting systems [2], the effect of local environmental factors must not be ignored. Critical reviews of earlier reported trend analyses of intracranial tumors have aroused controversy. Central to the controversy is whether reported rising trends were factual or a manifestation of better diagnostic techniques [1, 3]. However, some recent reports suggest that the incidence rate has stabilized or even slightly declined during the last decade [4]. Despite these conflicting reports, trend analysis of

Published online: 07 December 2010

these tumors in any given locality is considered invaluable because a significant change in trend may trigger off a search for local environmental causative agents.

A recent report from the Kuwait Cancer Registry shows a general increase in cancer incidence rate between 1974 and 2006 [5]. However, the incidence rate of brain tumors in the report does not adequately expose the magnitude of the problem posed by intracranial tumors. This is due to the fact that only malignant tumors are reported to the Cancer Registry.

The objective of this study is to establish a record of the descriptive epidemiology of intracranial tumors with histological diagnosis seen in Kuwait between 1995 and 2009. Although this is a hospital-based rather than population-based study, the results are expected to give a good reflection of intracranial tumors in Kuwait. This expectation is borne out of the fact that virtually all intracranial tumor biopsies in Kuwait during the study period were examined in the Department of Pathology, Al-Sabah Hospital, Kuwait.

Materials and methods

All new cases of intracranial tumors diagnosed between 1995 and 2009 were identified from the records of the Department of Pathology, Al-Sabah Hospital, Kuwait. The sections were reviewed in order to reconfirm the diagnosis. Immunohistochemistry (IHC) was done or repeated if necessary. The World Health Organization (WHO) classification of tumors of the central nervous system (2007) was applied in this study. For the purpose of analysis, astrocytic tumors were classified as low grade (WHO grades I and II) and high grade (WHO grades III and IV). This clinical classification, which takes cognizance of biological behavior and prognosis, would be expected to yield large sample size for statistical analysis. Pituitary adenomas were classified according to their functional status and IHC. Patient characteristics were extracted and analyzed. Age standardized incidence rates (ASIR) of primary tumors were based on Segi's world standard population [6]. Average incidence rates for 3-year overlapping periods were calculated. Graphs of these averages, also known as 3-year moving averages, were used for trend analysis. Ordinary least square (OLS) regression of log transformation of the moving averages was used to determine the significance of linear trend lines. Similarly, Chi square (χ^2) test was applied for statistical significance of differences where the total number of cases was at least 20.

Results

Between 1995 and 2009, a total of 868 patients—463 males and 405 females—had histologically confirmed intracranial tumors in Kuwait. One woman had synchronous primary and metastatic tumors. Consequently, 869 tumors were available for analysis. These comprised 822 (94.59%) primary (PICT) and 47 (5.41%) metastatic (MICT) tumors. Available data were insufficient for analysis of patient nationality.

Primary tumors

The mean age standardized incidence rate (ASIR) of PICT during the study period was 3.02/100,000 with a standard deviation (SD) of 0.54/100,000. There were 439 (53.41%) males and 383 (46.59%) females with PICT. The ages of all but 1 (0.12%) patient were recorded. These varied from 24 days to 83 years. The age distribution curve displayed 2 peaks. The first peak was minor and occurred in the first decade of life. A second and more prominent peak was observed in the range of 40–49 years. Most (69.22%) patients were below the age of 50. About 16.18% were children and adolescents (<20 years old). Only 3.89% of the patients were elderly ($\geq$70 years old). The proportion of the elderly in the general population varied from 0.69 to 0.95% with a mean of 0.81%. The ASIR for this age group varied from 0 to 0.76/100,000 with a mean of 0.4/100,000. The coefficient of correlation (r) between the percentage of the elderly in the population and incidence rates, using 3-year moving averages was 0.411 ($P = 0.085$) with a coefficient of determination (r^2) of 0.169. There was dissociation between the curves of the 3-year moving averages of the percentage of the population and incidence rates of this age group (Fig. 1).

The most common primary tumors were meningioma (27.62%), pituitary adenoma (18.49%), glioblastoma (14.96%), astrocytoma (12.65%), medulloblastoma (5.11%), oligodendroglioma (3.41%) and nerve sheath tumor (3.29%). Together, they formed about 85.53% of all PICTs. In childhood and adolescence, astrocytoma (35.34%) and medulloblastoma (22.56%) were the most common.

The graph of 3-year moving averages of each of PICT and its four most common types (Fig. 2) had a negative trend line which was significant for only medulloblastoma ($t = -3.303$; $P = 0.007$). Despite this, a rising trend was observed after the 2003–2005 period in the graph of astrocytic tumors.

Astrocytic tumors

Astrocytic tumors had a mean ASIR of 0.95/100000 with an SD of 0.28/100000. There were 137 males and 90 females, aged between 2 and 83 years, with astrocytic tumors. The sex preference was statistically significant ($\chi^2 = 9.731$; $P = 0.0018$). Eighty (35.24%) tumors were low grade while 132 (65.76%) were high grade.

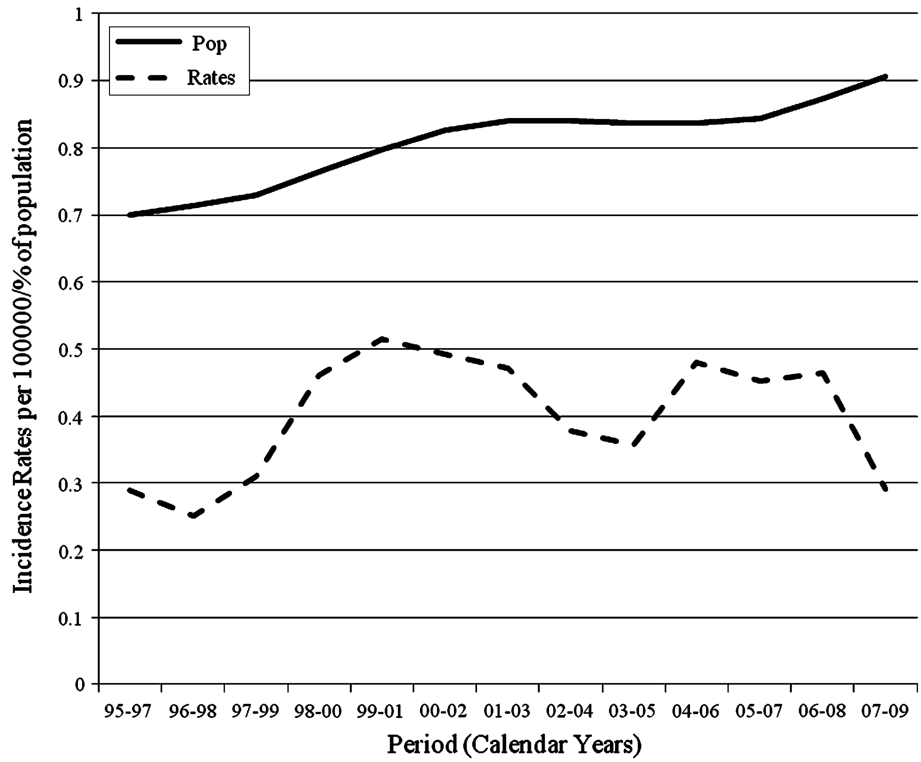

Fig. 1 Three-year moving averages of percentage of population aged ≥70 years and incidence rates/100,000

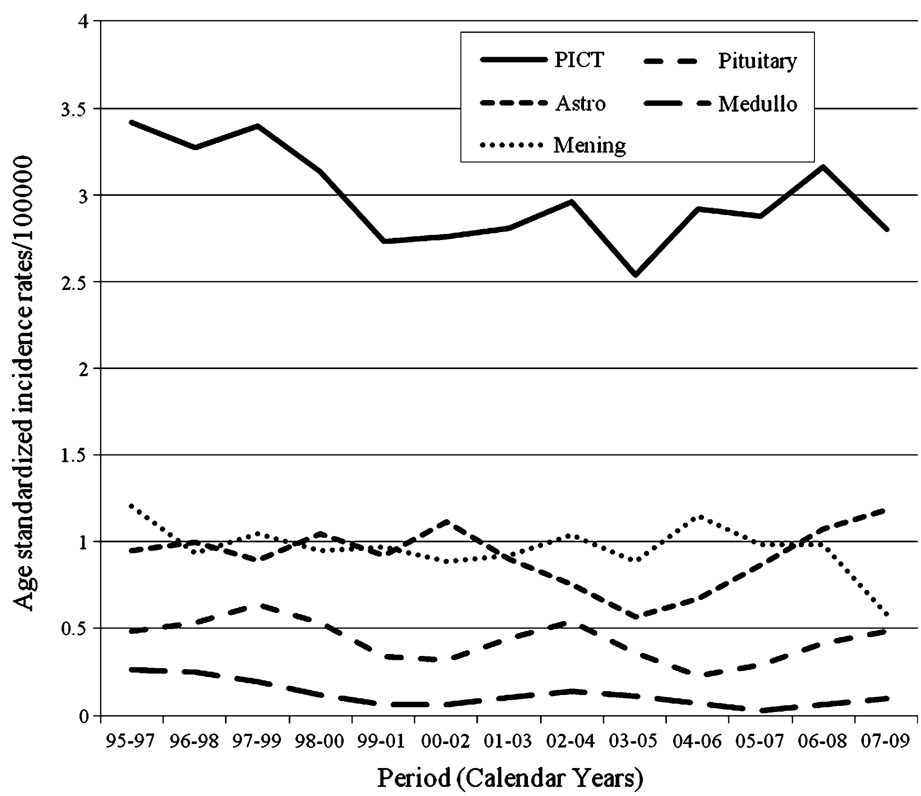

Fig. 2 Three-year moving averages for primary intracranial tumors (*PICT*), astrocytic tumors (*Astro*), meningioma (*Mening*), pituitary adenoma (*Pituitary*) and medulloblastoma (*Medullo*)

Low-grade astrocytic tumors affected 40 males and 40 females. Their peak frequency was in the first decade of life. Most (91.25%) occurred before the age of 40 and predominantly (55%) in childhood and adolescence. Pilocytic astrocytoma was the most common (66.25%) low-grade astrocytic tumor and occurred in 26 males and 27 females. About 71.70% of patients with pilocytic astrocytoma were children and adolescents.

High-grade astrocytic tumors were observed in 97 males and 50 females. About 82% of these had glioblastoma. The male predominance in this group was statistically highly significant ($\chi^2 = 15.027$; $P = 0.0001$). The peak frequency was in the range of 40–49 years. Most patients (73%) were older than 40 and about 10% were children and adolescents.

Oligodendroglial tumors

There were 17 males and 11 females with oligodendroglioma. The age range varied from 8 to 65 years with a median of 39 years. About 54% of the patients were between 30 and 50 years old, while only 4% were children.

Ependymal tumors

Ependymoma was diagnosed in 14 males and 5 females with an age range of 2–70 years and a median age of 22 years. Most patients (68.42%) were below the age of 30 years. The peak frequency was in the first decade of life, when 47.37% of the tumor occurred. In this age group, 75% of the tumors were infratentorial. On the other hand, all tumors (100%) in patients aged 10 years and above were supratentorial.

Tumors of the meninges

These included meningioma (227), vasoformative tumors (7), hemangiopericytoma (2), solitary fibrous tumor (2) and lipoma (1).

Meningioma had a mean ASIR of 0.96/100,000 with SD of 0.35/100,000. It was diagnosed in 157 females and 70 males. The female preponderance was highly significant statistically ($\chi^2 = 33.344$; $P < 0.0001$). The age of 1 (0.44%) patient was not available. The ages of the rest varied from 5 to 76 years with a peak frequency (32%) in the range of 40–49 years. Low frequency (5%) was observed in both the elderly and before the age of 30, respectively.

Tumors of the sellar region

These comprised pituitary adenoma (152) and craniopharyngioma (17).

Pituitary adenoma (PA) had a mean ASIR of 0.44/100,000 with an SD of 0.2/100,000. Patients with PA comprised 90 males and 62 females aged between 16 and 72 years. The male predominance was statistically significant ($\chi^2 = 5.158$; $P = 0.0231$). The tumor was functional (FA) in 32 men and 33 women, but silent (SA) in 58 men and 29 women. The sex difference was significant only for the silent tumors ($\chi^2 = 9.667$; $P = 0.0019$) and was most glaring after the age of 40. While 66% of FA were seen before the age of 40, 64% of SA occurred at the age of 40 and above. Sex and functionality, as independent factors, differed in age distribution. The peak frequency for males and SA was in the range of 40–49 years. On the other hand, FA had its peak frequency in females aged 20–29 years and in males between 30 and 39 years old (Fig. 3).

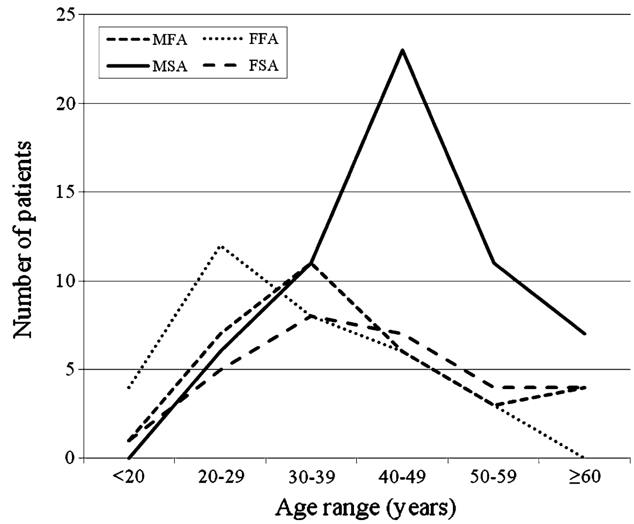

Fig. 3 Distribution of pituitary adenoma according to age, sex and functionality. *MFA* Males with functional adenoma, *MSA* males with silent adenoma, *FFA* females with functional adenoma, *FSA* females with silent adenoma

Embryonal tumors

These comprised medulloblastoma (42), supratentorial primitive neuroectodermal tumor (6) and atypical teratoid-rhabdoid tumor (1).

Medulloblastoma had a mean ASIR of 0.13/100,000 with an SD of 0.09/100,000. It occurred in 23 males and 19 females aged between 24 days and 53 years. The age distribution was bimodal. A major peak (55%) occurred in the first decade and a minor (14%) in the range of 30–39 years. About 5% of the patients were aged 40 and above.

Tumors of cranial nerves

Nerve sheath tumor was diagnosed in 19 males and 8 females whose ages varied from 21 to 66 years. The median age was 43 years. The sex difference was statistically significant ($\chi^2 = 4.481$; $P = 0.0343$). Most (74%) patients were aged 30 years and above.

Miscellaneous tumors

Other tumors comprised hemangioblastoma (14), non-Hodgkin's lymphoma (13), ganglio-glioma (10), neurocytoma (7), choroid plexus tumors (6), oligoastrocytoma (5), chordoma (4), germ cell tumor (3) and pineocytoma (2).

Metastatic tumors (MICT)

There were 24 males and 23 females with MICT. The ages of 2 patients (4.26%) were not available. Most (82.98%) MICT occurred after the age of 30 with a peak frequency (33%) in the range of 50–59 years. Their frequency was 7% in childhood, 2% in adolescence and 13% in patients aged 60 years and above.

Metastatic breast (26%), lung (17%) and gastrointestinal tract (11%) cancers were the most common MICT. Information on the site of the primary tumor was not available in 6 (12.77%) cases (Fig. 4). Fifty-two percent of metastatic tumors in females were of breast origin, while 29.17% of metastatic tumors in men were of lung origin. Most (87.5%) intracranial metastatic lung tumors occurred in men.

Discussion

Despite the flaws inherent in retrospective studies and the absence of a Brain Tumor Registry, the study has given an insight into the magnitude of intracranial tumors in Kuwait. The overwhelming majority of intracranial tumors were primary. There is a wide variation in the relative frequencies of primary and metastatic intracranial tumors reported in the literature [7]. This may be a reflection of data source, data collection practices and the availability of advanced diagnostic facilities in the various centers. Studies based on autopsy and/or radiological data tend to yield a higher frequency of metastatic tumors [8]. In contrast, the converse holds true for studies, like this one, based on surgical pathology records. Metastatic tumors are usually underrepresented in the latter because many are not biopsied. In addition, the inclusion of large numbers of benign tumors is contributory to the extremely low relative frequency of metastatic tumors observed in this study.

Unlike in economically developed countries [9–11], the epidemiology of PICT in Kuwait is characterized by a low incidence rate, the predominance of patients younger than 50 years, a remarkably high frequency in childhood and adolescence, and an extremely low frequency in the elderly.

The low incidence rate is consistent with other reports from economically developing countries [12, 13]. On the other hand, the age distribution pattern may be peculiar to the Middle East. Data from Iran indicate that about 28% and 3% of PICT occur before the age of 20 years and in the elderly, respectively. Mehrazin et al. have attributed this unusual age distribution, in part, to population structure. According to their report, children and adolescents formed about 50% of the Iranian population in 2002 [14]. While population structure may arguably be an important contributory factor in Iran, it probably has an insignificant role in the epidemiology of PICT in Kuwait for two reasons. Firstly, the percentage of children and adolescents in the Kuwaiti (26.9%) and US (24%) populations in 2009 [15, 16] is more or less similar. Secondly, a significant

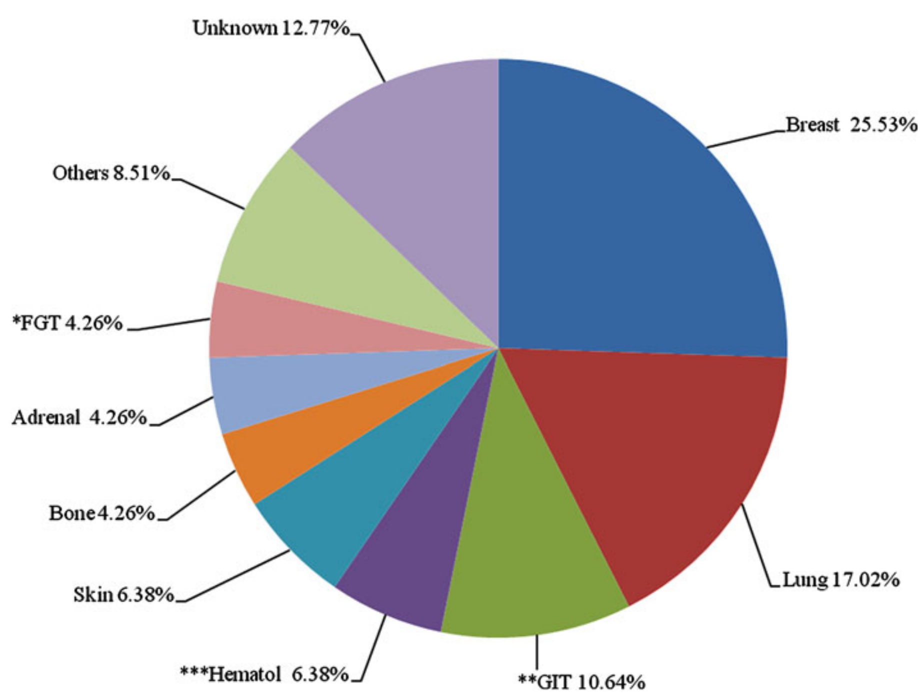

Fig. 4 Relative frequency of various metastatic intracranial tumors in Kuwait ($n = 47$). **FGT* Female genital tract; ***GIT* gastro-intestinal tract, ****Hematol* hematological malignancies

correlation could not be established between the percentage of the elderly in the general population and incidence rates either statistically or by the graphs of their 3-year moving averages. More importantly, only about 17% of the changes in incidence rates could be attributed to changes in the population of the elderly. The observation of Nasseri and Mills [17] that patients of Middle East origin with brain tumors in California were significantly younger than non-hispanic, non-Middle Eastern white people lends further support to this contention. Therefore, more studies are necessary to determine the major factors affecting the age distribution of PICT in Kuwait. In this regard, the role of low index of suspicion in symptomatic elderly patients in Kuwait deserves special attention. McKinney [1] is of the view that symptoms of intracranial tumors in the elderly are often attributed to other causes and are consequently under-investigated. This view has been buttressed by Legler et al. [18] who have attributed the dramatic increase in the relative frequency of PICT in the elderly in their study to a more aggressive diagnostic approach.

Meningioma, pituitary adenoma, glioblastoma, astrocytoma and medulloblastoma were the most common primary intracranial tumors in this series. On the other hand, germ cell tumors were uncommon. In this respect, the distribution of specific histological types of PICT in Kuwait is similar to that of Western countries but markedly differs from that of Far Eastern countries where germ cell tumors constitute up to 2.8% of PICT [19].

Trend analysis of PICT and its most common components displayed a negative trend line which was statistically significant only for medulloblastoma. These findings suggest that with the exception of medulloblastoma the incidence rates of these tumors had probably stabilized during the study period. However, the rising trend observed in the incidence rate of astrocytic tumors after the 2003–2005 period calls for caution. Future studies will determine the significance of this change.

A statistically significant male preference was observed for astrocytic tumors, pituitary adenoma and nerve sheath tumor. The sex difference was apparently dependent on tumor grade for astrocytic tumors and on functionality for pituitary adenoma. Thus, while no sex significantly predominated in the low-grade astrocytic tumors, a strong male predilection was observed for high-grade tumors. The relatively high frequency of pilocytic astrocytoma in the group of low-grade astrocytic tumors was the major contributory factor to this dichotomy. Pilocytic astrocytoma in this series showed an insignificant female predominance. This is at variance with other studies which have established male predilection of variable statistical significance for this tumor [20, 21].

Similarly, significant male preponderance, which was most pronounced after the age of 40, was observed for silent pituitary adenoma (SPA) but not for functional pituitary adenoma (FPA). Furthermore, FPA and SPA differed in age distribution. In contrast to FPA where most patients were less than 40-years-old, SPA occurred predominantly after the age of forty. The peak frequency of FPA was in the 20- to 39-year age group as opposed to the 40- to 49-year group for SPA. These differences may in part be manifestations of the differences in the underlying mechanism of clinical presentation.

Breast and lung cancers were the most common metastatic intracranial tumors (MICT) in this study. The predominance of metastatic breast cancer in women is a reflection of the distribution of the primary cancers in the female population. Conversely, the predominance of metastatic lung cancer in men is at variance with the distribution of primary cancers in Kuwait. In the male population, colorectal cancer is the leading primary cancer while lung cancer is the fourth most common solid malignant tumor [5]. The dramatic drop in the frequency of MICT after the 50- to 59-year age range remains unexplained.

Conclusion

The results suggest that PICT has an age distribution pattern in Kuwait which is strikingly different from that in economically developed countries but similar to that in Iran, another Middle Eastern country. Since population structure is probably non-contributory, there is a strong need to determine the role of genetic and environmental factors in the epidemiology of PICT in Kuwait.

As healthcare delivery expands in Kuwait, more private hospitals will be expected to offer full-scale neurosurgical services. Consequently, it is necessary to expand the current reporting system of the Kuwait Cancer Registry to include all tumors of the central nervous system irrespective of their perceived biological behavior. This will facilitate population-based studies and enhance surveillance and planning.

Conflict of interest There was neither sponsorship nor funds from any source for this work. All authors do not have any conflict of interest.

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