ORIGINAL ARTICLE

Brain metastases in cancer patients attending a Gamma Knife Center: A study from a single institute in Iran

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ABSTRACT

Background: This study was aimed to explore data on brain metastases in cancer patients attending the Iranian Gamma Knife Center.

Meterials and Methods: This was a retrospective study. In all 5216 case records of patients who referred to the Iranian Gamma Knife Center for treatment of brain tumors during year 2003-2011 were reviewed. Data were explored to identify patients who developed brain metastases due to cancer and assessed the information as applied to cancer patients including survival analysis.

Results: Two hundred and twenty patients were identified as having brain metastases due to cancer. The mean age of patients was 54.0 (standard deviation [SD] =12.7) years. Patients were followed for an average of 7 months after treatment with gamma-knife. The median survival time for different the Graded Prognostic Assessment (GPA) was: GPA: 0-1, 4.0 ± 0.4 months; GPA: 1.5-2.5, 6.0 ± 0.7 months; GPA: 3, 9.0 ± 0.9 months; and GPA: 3.5-4.0, 12.0 ± 1.8 months and the overall median survival was 7.0 (SD = 0.6) months.

Conclusion: The findings suggest that many cancer patients in Iran might develop brain metastasis. Although, this is not a very high incidence compared with the existing statistics from other countries, there is an urgent need to explore the issue further.

Key words: Brain metastases, epidemiology, Iran, gamma-knife

Introduction

Metastatic brain tumors are the most common intracranial neoplasm in adults. It is estimated that over 25% of all cancer patients will be diagnosed with metastatic brain. Most brain metastases initiate from lung cancer (50%), breast cancer (15-20%), unknown primary cancer (10-15%), melanoma (10%), and colon cancer (5%).[1]

The observation of increasing incidence is most likely related to the aging population, improved systemic treatment for the primary disease, and improved imaging techniques.[2] As a result, brain metastases are an increasing source of morbidity and mortality as well as cognitive impairment at the time of cancer diagnosis.[3,4]

Although cancer registry in Iran is enforcing since 1989, there are no exact statistics about brain metastases in Iran. Informal data indicate that the incidence of brain metastases in Iran is increasing. It has been shown that the second most frequent cancer sites among patients are brain and central nervous system (CNS) (13.6%),[5] about 20% of brain tumors occur in children 15 years and younger and 79.9% of cases in adults.[6] Single brain metastasis occurs in 16.3% of patients whereas multiple lesions account for 83.7% of patients.[7] Thus to have an estimation this study was conducted to investigate on

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brain metastasis in cancer patients receiving Gamma-knife in Tehran, Iran.

Materials and Methods

Patients and data collection

A retrospective study was conducted to review all case records at the Iranian Gamma Knife Center during a 9-year period from 2003 to 2011 in Tehran, Iran. The year 2003 was chosen because the center was opened on year 2003. To analyze the data, demographical and clinical information were extracted from case records. For patients with brain metastasis this included recording of gender, age, type of disease, tumor size, mass location and the Graded Prognostic Assessment (GPA) staging.[8] The GPA was selected because it is as prognostic as the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) and more accurate than the other indices such as the score index for radiosurgery and the basic score for brain metastases (BSBM).[8] However, Serizawa *et al*. showed that the BSBM and the modified RPA appeared to be better than the original RPA and GPA.[9]

Additional measure

The GPA was developed by Sperduto *et al*.[8] to further guide clinical decision making for brain metastases. It considerers 4 factors: Patient age, Kanofsky performance status, presence of extracranial metastases, and the number of intracranial lesions. Each of the above-mentioned variables is assigned a score of 0, 0.5, or 1. The final score is the sum of all scores ranging from 0 to 4, with higher scores indicating having a better prognosis in terms of median survival.

Treatment planning and radiosurgery

Treatment planning and radiation dosimetry for brain metastases were performed. After application of stereotactic frame under local infiltration of anesthetics, imaging was performed with the goal of conformal and selective coverage of the tumor images. Images were transferred to planning workstation and treatment planning was done using GammaPlan version 5.34. GKS was performed using the Leksell Gamma Knife model C system (Elekta Instruments, Stockholm, Sweden). Posttreatment magnetic resonance imaging (MRI) scans of patients with brain metastases treated with Gamma-knife were used to determine local control and disease progression. Local control failure was defined as an increase in target lesion diameter of at least 20% when compared to the smallest documented total valium on MRIs.

Statistical analysis

The Kaplan–Meier analysis was performed to estimate the overall survival time and the survival duration for the patients' subgroups. Neurological death was defined as death attributable to CNS metastases including tumor recurrence and/or carcinomatous meningitis. All statistical analyses were performed using the PASW Statistics 18 Version 18 (SPSS Inc., 2009, Chicago, IL, USA).

Ethics

The Ethics Committee of Iranian Gamma Knife Center approved the study protocol.

Results

In all 5216 case record were reviewed. The characteristics of the brain disorders treated at the Iranian Gamma Knife Center are shown in Table 1. Of these, 220 cases of brain metastases were identified. The characteristics of the brain metastatic patients and their scores on the GPA are shown in Table 2. The mean age of patients was 54.0 (standard deviation [SD] =12.7) years ranging from 19 to 82. Patients were followed for average 7.1 (SD = 1.3)

Table 1: Brain disorders treated at the Iranian Gamma-Knife Center during 2003-2011 (*n*=5216)

Disorder treated	Number (%)
Vascular disorders	
Arteriovenous malformation	450 (8.6)
Aneurysm	-
Cavernous malformation	100 (1.9)
Other vascular disorders	19 (0.36)
Benign tumors	
Vestibular schwannoma	722 (13.8)
Trigeminal schwannoma	5 (0.09)
Other schwannomas	10 (0.19)
Meningioma	1670 (32.0)
Pituitary adenoma	794 (15.22)
Pineal region tumor	95 (1.8)
Craniopharyngioma	67 (1.3)
Hemangioblastoma	27 (0.5)
Hemangiopericytoma	6 (0.11)
Chordoma	57 (1.1)
Glomus tumor	84 (1.6)
Other benign tumors	89 (1.7)
Malignant tumors	
Glial tumors (grades I-II)	39 (0.75)
Glial tumors (grades III-IV)	437 (8.4)
Metastatic tumor	220 (4.2)
Chondrosarcoma	5 (0.09)
Nasopharyngeal carcinoma	-
Other malignant tumors	81 (1.6)
Functional targets	
Trigeminal neuralgia	210 (4.0)
Parkinson's disease	1 (0.02)
Pain	-
Epilepsy	23 (0.44)
Obsessive-compulsive disorder	-
Other functional targets	3 (0.02)
Ocular disorders	
Uveal melanoma	-
Glaucoma	-
Other ocular disorders	-
Orbital tumor	2 (0.04)
Total	5216 (100)

months after treatment with Gamma-knife (ranging from 1 to 25 months). Of these 220 cases, 107 patients had prior treatment including surgery alone, whole brain radiotherapy (WBRT) alone, and WBRT plus surgery while the remaining 113 patients had not received any treatment before Gamma-knife surgery. The distribution of the GPA score for patients is also shown in Figure 1. The distribution of GPA for those who received prior treatment was as follows: 27 (25.2%), GPA: 0-1; 61 (57.0%), GPA: 1.5-2.5; 11 (10.3), GPA: 3; and 8 (7.5%), GPA: 3.5-4.0.

Table 2: The characteristics of patients with brain metastasis (*n*=220)

Characteristics	Number (%)
Age (years)	
Mean (SD)	54.0 (12.7)
Range	19-82
Gender	
Male	78 (35.5)
Female	142 (64.5)
Primary tumor	
Breast	83 (37.8)
Lung	30 (13.7)
Colorectal	20 (9.0)
Kidney	19 (8.7)
Melanoma	9 (4.0)
Other*	37 (16.8)
Unknown	22 (10.0)
Total target volume (ml)	
Mean (SD)	11.4 (10.5)
Range	0.5-66
Number of lesions	
1	97 (43.9)
2	75 (34.1)
3	20 (9.2)
>3	28 (12.8)
Dosage at the tumor margin (Gy)	
Mean (SD)	18.7 (2.5)
Range	12-24
Isodose level	
Mean (SD)	47.8 (11.1)
Range	32-97
GPA score	
0-1	49 (22.3)
1.5-2.5	114 (51.8)
3	35 (15.9)
3.5-4	22 (10.0)
Treatment before Gamma-knife	
Surgery alone	12 (5.4)
WBRT alone	56 (25.5)
Surgery+WBRT	39 (17.7)
Without prior treatment	113 (51.4)

SD: Standard deviation, GPA: Graded Prognostic Assessment, WBRT: Whole brain radiotherapy. *Other tumors included 5 sarcoma, 4 thyroid, 4 uterine, 4 ovarian, 4 prostat, 3 stomach, 1 esophageal, 1 hepatoma, 2 testicular, 2 bladder, 1 pancreas, 1 maxillary sinus, 1 salivary gland , 1 cervical carcinoma, 1 penis carcinoma, 1 gallbladder and 1 oral carcinoma

The local tumor control rate was 96.1% at last follow-up time. The results obtained from survival analysis indicated that the median survival time for the different GPA score were significantly differed: GPA: 0-1, 4 ± 0.4 months; GPA: 1.5-2.5, 6 ± 0.7 months; GPA: 3, 9 ± 0.9 months; and GPA: 3.5-4.0, 12 ± 1.8 months. The overall survival time was 7 ± 0.6 months. The survival curves are shown in Figures 2 and 3. The neurological and nonneurological death were occurred in 36 (19.4%) and 147 (80.6%) of patients, respectively. About 17% of patients were still alive at last follow-up.

Discussion

This was a retrospective study analyzing the data from a Gamma Knife Center in order to shad a light on the epidemiology of brain tumors in Iran. The findings showed that breast cancer was the most common solid tumors that metastasized to the CNS, followed by the lung cancer. This is, however, different from what we already know about

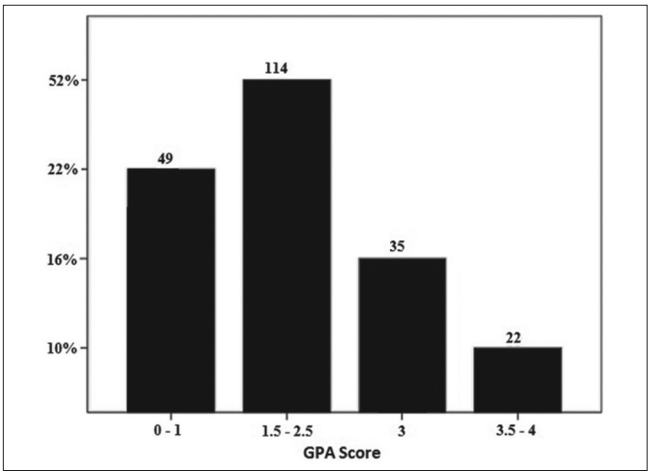

Figure 1: The distribution of the Graded Prognostic Assessment score (*n* = 220)

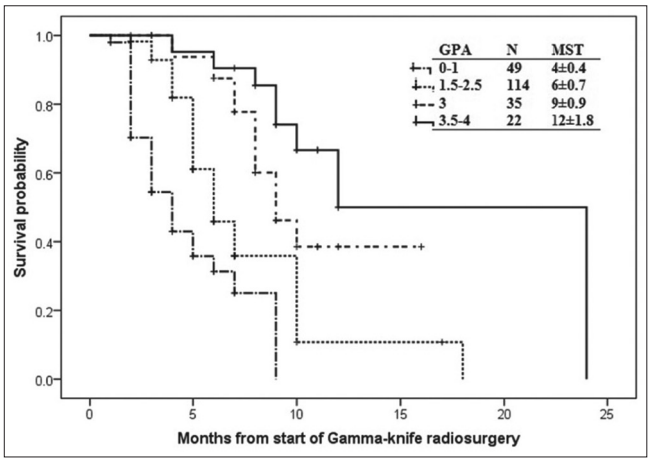

Figure 2: The survival curve according to the Graded Prognostic Assessment score of patients (*N* = number of patients; MST = median survival time)

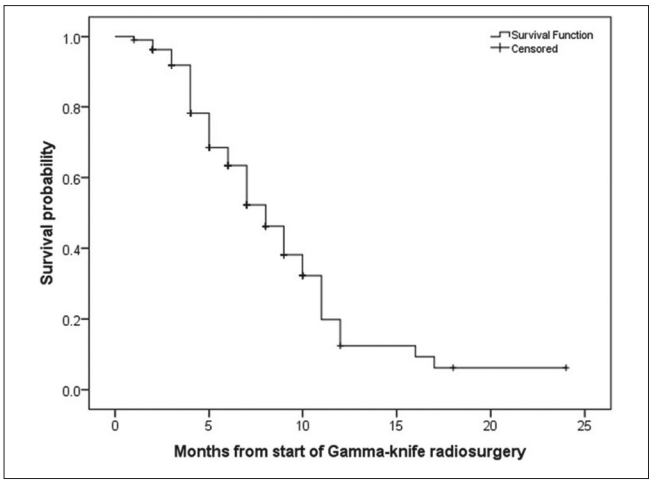

Figure 3: Overall survival time (n = 220)

brain metastases where there is evidence that most brain metastases initiate from lung cancer.[1] One explanation for such observation might be due to the fact that there were fewer men (35.5%) than women (64.5%) in the present study. In addition, there is evidence that breast cancer with distant involvement is increasing. For instance a recent study reported a small, but statistically significant increase in the incidence of breast cancer with distant involvement in the United States between 1976 and 2009 for women aged 25-39 years, without a corresponding increase in older women.[10] Recently, similar findings were reported from elsewhere.[11-14]

Villà *et al*.[15] showed that the mean overall survival times for the GPA groups were: Group 0-1, 3.3 months; Group 1.5-2.5, 5.6 months; Group 3, 7.8 months and Group 3.5-4, 8.2 months, while Nieder *et al*.[16] indicated 2.0, 3.6, 5.1, and 11.3 months, respectively. These studies showed statistically significant differences in overall survival among patients who differed in GPA classification, which is in line with our findings. Our experience also suggests that reducing the neurological death rate by adequately controlling brain metastasis might contribute to prolonging overall survival.[17] In addition, although Gamma-knife surgery provided durable local tumor control, repeated treatment may be needed in some patients to achieve a better local control and distant brain metastasis.

Despite increasing interest in the use of Gamma-knife surgery, a strategy that attempts to omit the use of whole brain radiotherapy (WBRT), surgery or WBRD plus surgery in the management of brain metastasis must be adapted with great caution. The argument that the pathology of brain metastasis cannot be ignored due to disseminated nature of its malignancy, remains challenging.

The findings from this study showed that a high proportion of brain metastatic patients had advance stage of disease at their presentation and at the time of diagnosis. One may argue that this could be a reflection of the lack of a comprehensive cancer control program in Iran. Perhaps the implementation of an effective plan for fighting against cancer might help to reduce this high prevalence brain metastasis.

This was a descriptive study with limited objectives. Future studies are needed to provide more information on the topic in order to be able to reduce risk factors and help patients and their families to have a better end of life conditions.

Conclusion

The findings suggest that many cancer patients in Iran might develop brain metastasis. Although this is not a very high incidence compared to the existing statistics from other countries, there is an urgent need to explore the issue further.

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