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

Parisa Azimi, Sohrab Shahzadi, Mohammad Ali Bitaraf, Maziar Azar, Mazdak Alikhani, Alireza Zali, Sohrab Sadeghi, Ali Montazeri

Department of Neurosurgery, Shahid Beheshti University of Medical Sciences, 1Department of Neurosurgery, Tehran University of Medical Science, 2Neurosurgeon, Iran Gamma Knife Center, 3Mental Health Research Group, Health Metrics Research Centre, Iranian Institute for Health Sciences Research, ACECR, Tehran, Iran

ABSTRACT

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

Materials 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%).

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

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%), about 20% of brain tumors occur in children aged 15 years and younger and 79.9% of cases in adults. Single brain metastasis occurs in 16.3% of patients whereas multiple lesions account for 83.7% of patients. Thus to have an estimation this study was conducted to investigate on...
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. 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). However, Serizawa et al. showed that the BSBM and the modified RPA appeared to be better than the original RPA and GPA.

Additional measure
The GPA was developed by Sperduto et al. 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).

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)   |
| Cranipharyngioma                      | 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.

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 shed 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

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

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)| 12.4 (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) |

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)
brain metastases where there is evidence that most brain metastases initiate from lung cancer.[11] 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.[13] 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.

Acknowledgment

The authors would like to thank the staff of the Iranian Gamma Knife Centre, Tehran, Iran.

References

1. National Cancer Institute. Available from: http://www.cancer.gov/. [Last accessed on 2013 Feb 08].
2. Soffietti R, Rudá R, Trevisan E. Brain metastases: Current management and new developments. Curr Opin Oncol 2008;20:676-84.
3. Chang EL, Wefel JS, Maor MH, Hassenbusch SJ 3rd, Mahajan A, Lang FF, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery 2007;60:277-83.
4. Meyers CA, Smith JA, Bežjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with whole brain radiation and metoxafin gadolinium: Results of a randomized phase III trial. J Clin Oncol 2004;22:157-65.
5. Yavari P, Sadrolhefazi B, Mohagheghi MA, Madani H, Mosavizadeh A, Nahvijou A, et al. An epidemiological analysis of cancer data in an Iranian hospital during the last three decades. Asian Pac J Cancer Prev 2008;9:145-50.
6. Mehrazin M, Rahmat H, Yavari P. Epidemiology of primary intracranial tumors in Iran, 1978 2003. Asian Pac J Cancer Prev 2006;7:283-8.
7. Miabi Z. Metastatic brain tumors: A retrospective review in East Azarbyjan (Tabriz). Acta Med Iran 2011;49:115-7.
8. Sperduto PW, Berkley B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008;70:510-4.
9. Serizawa T, Higuchi Y, Nagano O, Hira T, Ono J, Saeki N, et al. Testing different brain metastasis grading systems in stereotactic radiosurgery: Radiation Therapy Oncology Group’s RPA, SIR, BSBM, GPA, and modified RPA. J Neurosurg 2012;117 Suppl:S1-7.
10. Johnson RH, Chien FL, Bleyer A. Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. JAMA 2013;309:800-5.
11. Frisk G, Svensson T, Bäcklund LM, Lidbrink E, Blomqvist P, Smedby KE. Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden. Br J Cancer 2012;106:1850-3.
12. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012;14:48-54.
13. Pestalozzi BC, Zahrnd D, Price KN, Holmberg SB, Lindtner J, Collins J, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast

Figure 3: Overall survival time (n = 220)
14. Stemmler HJ, Heinemann V. Central nervous system metastases in HER 2 overexpressing metastatic breast cancer: A treatment challenge. Oncologist 2008;13:739-50.

15. Villà S, Weber DC, Moretones C, Mañes A, Combescure C, Jové J, et al. Validation of the new Graded Prognostic Assessment scale for brain metastases: A multicenter prospective study. Radiat Oncol 2011;6:23.

16. Nieder C, Mehta MP. Prognostic indices for brain metastases—Usefulness and challenges. Radiat Oncol 2009;4:10.

17. Yomo S, Hayashi M. Upfront stereotactic radiosurgery in patients with brain metastases from small cell lung cancer: Retrospective analysis of 41 patients. Radiat Oncol 2014;9:152.