

Epidemiological Study of Metastatic Brain Tumors in Miyazaki Prefecture: A Regional 10-year Survey in Southern Japan

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Abstract

Advances in cancer treatment have improved the survival of patients with cancer, with a concomitant increase in the proportion of patients with metastatic brain tumors (MBTs). In this study, we used cancer registries established in Japan after 2016 and available patient data by organ in order to conduct an accurate epidemiological study. To the best of our knowledge, this is the first study to report on the detailed epidemiological data on MBT at the prefectural level in Japan using the Miyazaki Brain Tumor Database and Miyazaki Cancer Registry. This study included 425 new cases of MBTs diagnosed in Miyazaki Prefecture from 2007 to 2016. As per our findings, the most frequent primary tumor in Miyazaki Prefecture was found to be in the lung (49.4%), followed by colon/rectum/anus (9.4%) and breast (8.5%). Among patients with MBTs, 59.1% were males, a number closely similar to that of Japan, as shown in the Japanese Brain Tumor Registry (55.5%). The median age at diagnosis was 68 and 63 years in Miyazaki Prefecture and Japan, respectively. Although more patients were symptomatic in Miyazaki Prefecture than in Japan (88.5% vs. 15.5%), fewer patients opted for surgery (33.6% vs. 61.9%), probably because of their advanced age at diagnosis. As per the findings of this study, the annual incidence rate of new MBTs (i.e., ratio of the number of new cancer registrations to that of new MBT patients in Miyazaki Prefecture) was at 0.41%. The number of tumor sites in MBTs was independent of the total number of cancers per organ. Considering the expansion of cancer registries worldwide, including those on brain tumors, further epidemiological analysis of MBTs is deemed warranted.

Keywords: metastatic brain tumor, epidemiology, incidence

Introduction

Recent advances in cancer treatment were able to improve the survival rates of patients with cancer, with a concomitant increase in the proportion of patients with metastatic brain tumors (MBTs).¹ Epidemiological research in Japan has demonstrated that MBTs account for <20% of all intracranial brain tumors.² Nonetheless, this finding is limited to patients with MBT who visited a neurosurgeon over the disease course and thus does not represent the

exact number of patients with MBT. Previous autopsy data have revealed a slightly higher incidence of intracranial metastases, which ranged from 16% to 26%.³ Notably, symptomatic brain metastases have been reported in 8%-10% of patients with cancer outside Japan.^{4,5} Additionally, the number of patients with MBTs in Japan has been estimated to be considerably higher than that of patients with primary central nervous system tumors.⁶

We have recently reported the population-based epidemiological data of primary brain tumors in Miyazaki Pre-

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fecture.⁷⁾ Therefore, we conducted a 10-year survey between 2007 and 2016. In this registry, 2,360 brain tumors were newly diagnosed, of which 425 cases (18.2%) were MBTs. Using this registry, we aimed to identify the clinical characteristics of MBTs in Miyazaki Prefecture that have not been previously evaluated. Moreover, we aim to determine whether the number of significant MBT sites depends on the total number of cancers in each organ. To date, the exact number of patients with cancer in each organ is yet to be determined in Japan, and no reports have shown the precise ratio of brain metastases in each organ. Here, we could use the Japan's population-based cancer registry to determine the precise number of cancers in each organ since 2016. Utilizing this database to estimate cancer incidence rates could help us resolve this clinical question. This is the first study to report epidemiological data on MBTs in Miyazaki Prefecture based on the Miyazaki Brain Tumor Database and Miyazaki Cancer Registry.

Materials and Methods

Study population

Miyazaki Prefecture is located southwest of the Japanese archipelago and southeast of Kyushu, which is the third largest island in Japan. With an area of approximately 7,735 km², Miyazaki is the 14th largest prefecture in Japan. The estimated population of Miyazaki Prefecture is 1,052,337 (as of September 1, 2022). Following the decennial census, annual population movement into Miyazaki Prefecture from 2007 to 2016 was deemed negligible (−0.97% to +0.28%). Conversely, Japan's fixed population is estimated to be 124,750,000 (as of April 1, 2022).

There are 16 neurosurgical hospitals and clinics in Miyazaki Prefecture affiliated with the Neurosurgery Department of Miyazaki University Hospital. These hospitals and clinics have specialized staff and modern medical equipment for performing diagnostic computed tomography (CT) and magnetic resonance imaging (MRI) and are also well-equipped to cater to patients with brain tumors. Finally, this study was approved by the Institutional Review Board of Miyazaki University Hospital (approval number 360).

Summary of registered patients

Characteristics of all new patients diagnosed at these 16 facilities between 2007 and 2016 were recorded as follows: age, sex, district of residence, date of diagnosis, and pathological diagnosis. All information was carefully confirmed in order to avoid repeat registrations. The district of residence was defined as the district where the patient had resided within the Miyazaki Prefecture for at least 1 year before diagnosis. Meanwhile, the onset referred to the first day of hospitalization for inpatients and brain tumor diagnosis, as revealed via CT or MRI. Of these enrolled pa-

tients, those with MBTs classified according to the World Health Organization (WHO) in 2021 were included in this study.⁸⁾

Incidence rate

The number of patients with cancer in Miyazaki Prefecture was obtained from the Miyazaki Prefecture Regional Cancer Registry Report (2013-2016), which was prepared based on the notification of the National Cancer Registry Project. Meanwhile, the number of patients with MBTs in Japan was obtained from the Brain Tumor Registry of Japan (2005-2008).²⁾ Based on these data, we were able to summarize the total number of patients with MBTs in Miyazaki Prefecture, along with information such as sex, age, presence of symptoms, presence of tumor removal, and primary site. We then compared the number of patients having each cancer in Miyazaki Prefecture with those having MBTs in Japan. From 2013 to 2016, the ratio was calculated as the number of new cancer cases reported by the Miyazaki Regional Cancer Registry to that of new MBT cases reported by the Miyazaki Brain Tumor Database. This ratio was defined as the annual incidence rate of new MBTs for each cancer.

Results

Frequency of MBTs and distribution of primary sites

From 2007 to 2016, 2,340 brain tumors were newly diagnosed and registered in Miyazaki Prefecture, of which 425 cases (18.2%) were MBTs, with an average annual incidence of 42.5 cases. The Miyazaki Cancer Registry, which started in 2013, was able to record 34,569 cancer cases, with a mean annual incidence of 8642.3 cases in Miyazaki Prefecture from 2013 to 2016.

Table 1 and Fig. 1 show the distribution of primary MBT sites and incidence of MBT in Miyazaki Prefecture and Japan, respectively. The most frequent primary tumor in Miyazaki Prefecture was the lung (49.4%), followed by colon/rectum/anus (9.4%), breast (8.5%), stomach (3.5%), skin (melanoma) (3.1%), esophagus (2.6%), and ovary/uterus (2.6%). Meanwhile, in Japan, the most common primary tumor was the lung (46.1%), followed by breast (14.5%), colon/rectum/anus (9.0%), ovary/uterus (4.3%), kidney (4.2%), stomach (3.5%), and esophagus (2.6%).

Sex, median age, symptoms, and surgery for MBTs

In Table 2, patient information as regards sex, median age, symptoms, and surgery were summarized among the 425 cases in Miyazaki Prefecture and 3200 cases in Japan, as per the Brain Tumor Registry of Japan (2005-2008). In Miyazaki Prefecture, 251 (59.1%) males and 174 (40.9%) females were determined to have MBTs. This sex ratio in Miyazaki Prefecture was similar to that in Japan as a whole, where 1775 (55.5%) males and 1425 (44.5%) females were found to have MBTs. In contrast, different trends were ob-

Table 1 Distribution and proportion of metastatic brain tumors in each cancer (a comparison between Miyazaki Prefecture and Japan)

Primary site	Number of cases (%)			
	Miyazaki (2007-2016)		Japan (2005-2008)	
	Male	Female	Total	Total
Lung	138 (55.2)	72 (41.1)	210 (49.4)	1476 (46.1)
Breast	0 (0)	36 (20.6)	36 (8.5)	463 (14.5)
Colon/Rectum/Anus	23 (9.2)	17 (9.7)	40 (9.4)	289 (9.0)
Kidney	5 (2)	5 (2.9)	10 (2.4)	135 (4.2)
Stomach	13 (5.2)	2 (1.1)	15 (3.5)	104 (3.3)
Head and neck	1 (0.4)	0 (0)	1 (0.2)	53 (1.7)
Esophagus	11 (4.4)	0 (0)	11 (2.6)	83 (2.6)
Liver	8 (3.2)	2 (1.1)	10 (2.4)	59 (1.8)
Thyroid	2 (0.8)	4 (2.3)	6 (1.4)	47 (1.5)
Ovary/Uterus	-	11 (6.3)	11 (2.6)	137 (4.3)
Skin (Melanoma)	8 (3.2)	5 (2.9)	13 (3.1)	27 (0.8)
Bladder	4 (1.6)	1 (0.6)	5 (1.2)	19 (0.6)
Lymphatic gland	4 (1.6)	3 (1.7)	7 (1.6)	28 (0.9)
Hematopoietic	0 (0)	0 (0)	0 (0)	18 (0.6)
Testis	1 (0.4)	-	1 (0.2)	25 (0.8)
Pancreas	2 (0.8)	2 (1.1)	4 (0.9)	7 (0.2)
Gall bladder	1 (0.4)	1 (0.6)	2 (0.5)	13 (0.4)
Unknown primary	17 (6.8)	11 (6.3)	28 (6.6)	114 (3.6)
Others	12 (4.8)	3 (1.7)	15 (3.5)	103 (3.2)
Total	250 (100)	175 (100)	425 (100)	3200 (100)

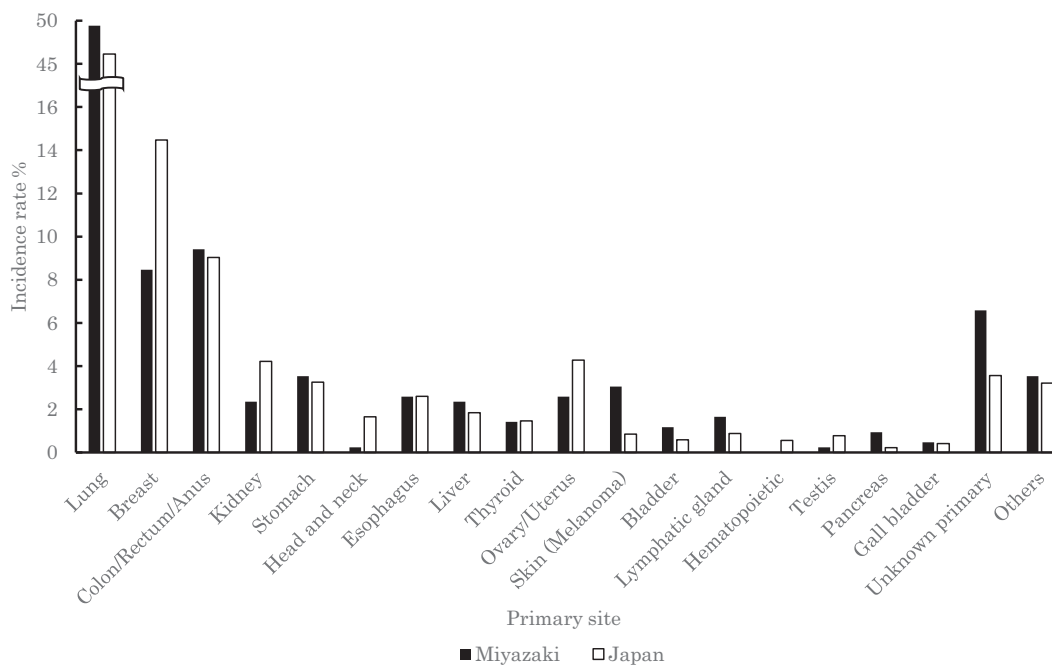
**Fig. 1** The proportion of metastatic brain tumors for each cancer in Miyazaki Prefecture/Japan.

Table 2 Sex-specific rates, median age, symptoms of metastatic brain tumor, and removal of metastatic brain tumor (comparison between Miyazaki Prefecture and Japan)

		Miyazaki (2007-2016)	Japan (2005-2008)
Sex	Number of cases (%)	Male	251 (59.1)
		Female	174 (40.9)
Age	Median	68	63
Symptom	Yes	376 (88.5)	496 (15.5)
	No	46 (10.8)	2704 (84.5)
	Unknown	3 (0.7)	0 (0)
Operation	Yes	143 (33.6)	1981 (61.9)
	No	276 (64.9)	1219 (38.1)
	Unknown	6 (1.4)	0 (0)

served between patient data (median age, symptoms, and surgery) in Miyazaki Prefecture and those in Japan. The median age of patients with MBTs in Miyazaki Prefecture was 68 years, whereas that in Japan was 63 years; this implies that patients in Miyazaki Prefecture were more likely to be older. With regard to symptoms, although 88.5% of patients in Miyazaki Prefecture had symptoms at the time of MBT diagnosis, only 15.5% of patients in Japan exhibited symptoms. With regard to surgery, only 33.6% of patients in Miyazaki Prefecture underwent surgery at the time of MBT diagnosis; meanwhile, in Japan, this number corresponds to 61.9% of patients.

Annual incidence rate of new MBTs for each cancer in Miyazaki Prefecture

The average annual incidence rate of new MBTs in Miyazaki Prefecture has been summarized in Table 3. Excluding ovary/uterus and testis, which are related to sex, the highest incidence of MBTs irrespective of sex was in the lung (1.56%), followed by esophagus (0.69%), skin (melanoma) (0.60%), and kidney (0.47%). Among males, testis (2.56%) showed the highest incidence, followed by the lung (1.5%), skin (melanoma) (0.96%), esophagus (0.8%), and kidney (0.67%). Conversely, women had the highest incidence of MBTs in the lung (1.67%), followed by breast (0.34%), thyroid (0.24%), skin (melanoma) (0.24%), and colon/rectum/anus (0.22%). The average annual incidence rate of new MBTs was at 0.41%. The annual incidence rate of new MBTs according to year in Miyazaki Prefecture is indicated in Table 4. As per our findings, we observed no consistent trend in the annual incidence rate of new MBTs for each cancer.

Discussion

Epidemiology of MBTs in Miyazaki Prefecture

This is the first study that examined MBTs diagnosed and registered at a neurosurgical facility in Miyazaki Pre-

fecture. No reports of similar epidemiological studies on MBTs have been published at the prefectural level in Japan.

In this study, 18.2% of newly diagnosed and registered brain tumors in Miyazaki Prefecture from 2007 to 2016 were found to be MBTs. However, a similar investigation in Iceland performed between 1954 and 1963 reported that the incidence of MBTs was at <20%.⁹⁾

Lung was determined to be the most frequent primary MBT site in Miyazaki Prefecture (49.4%). The subsequent trend was similar to that of primary MBT sites in Japan (Table 1, Fig. 1). Based on the Metropolitan Detroit Cancer Surveillance System and the Dutch series, previous studies have reported the approximate incidence of different cancers as follows: lung cancer, 16%-20%; renal cancer, 7%-10%; melanoma, 7%; breast cancer, 5%; and colorectal cancer, 1%-2%.^{4,5)} The incidence of breast cancer was lower in Miyazaki as compared to that in Japan as a whole. A subtype of breast cancer, that is, triple-negative breast cancer (both hormone receptor and HER2-negative), has been presumed to induce brain metastasis even when the tumor is not systemically advanced,¹⁰⁾ which may have contributed to the difference in terms of incidence rates. Another variable affecting the lower incidence rate was the lack of occurrence of MBTs due to breast cancer among men in Miyazaki Prefecture.

Regarding sex differences in Miyazaki Prefecture, 59.1% of men and 40.9% of women were found to have MBTs, and these numbers were not significantly different from those in Japan. However, men had more MBTs than women, as has been previously reported. This is apparently because of the higher incidence of lung cancer in men.^{11,12)}

Most MBTs in Miyazaki Prefecture were symptomatic (88.5%), and a higher proportion of MBTs tended to be nonsurgical (64.9%) (Table 2). This may be attributed to the higher incidence of MBTs in older individuals in Miyazaki Prefecture (Table 2), which may have substantially lowered the tumor removal rate. However, this result may

Table 3 Average annual incidence rate of metastatic brain tumors for each cancer in Miyazaki Prefecture

Primary site	Average annual incidence rate of new MBTs (%)		
	Male	Female	Total
Lung	1.50	1.67	1.56
Breast	0.00	0.34	0.34
Colon/Rectum/Anus	0.27	0.22	0.25
Kidney	0.67	0.00	0.47
Stomach	0.11	0.14	0.12
Head and neck	0.13	0.00	0.10
Esophagus	0.80	0.00	0.69
Liver	0.07	0.15	0.10
Thyroid	0.45	0.24	0.28
Ovary/Uterus	-	0.13	0.13
Skin (Melanoma)	0.96	0.24	0.60
Bladder	0.20	0.00	0.14
Lymphatic gland	0.57	0.21	0.40
Hematopoietic	0.00	0.00	0.00
Testis	2.56	-	2.56
Pancreas	0.00	0.13	0.07
Gall bladder	0.18	0.18	0.18
Unknown primary	1.76	3.64	2.69
Others	0.06	0.16	0.08
Total	0.43	0.39	0.41

Table 4 The annual incidence rate of metastatic brain tumors for each cancer in Miyazaki Prefecture per year

Primary site	Annual incidence rate of new MBTs by year (%)			
	2013	2014	2015	2016
Lung	1.28	1.54	1.71	1.68
Breast	0.31	0.14	0.41	0.44
Colon/Rectum/Anus	0.23	0.32	0.39	0.07
Kidney	0.95	0	0.53	0.40
Stomach	0.18	0.18	0.10	0
Head and neck	0	0.40	0	0
Esophagus	0	1.60	1.40	0
Liver	0.18	0	0.22	0
Thyroid	0.41	0.51	0.56	0
Ovary/Uterus	0	0.0	0.58	0
Skin (Melanoma)	0	0.53	1.10	0.83
Bladder	0	0.60	0	0
Lymphatic gland	0	0	0	1.46
Hematopoietic	0	0	0	0
Testis	14.29	0	0	0
Pancreas	0	0	0.29	0
Gall bladder	0.31	0	0	0.35
Unknown primary	3.39	0	0	7.87
Others	0	0	0.12	0.17
Total	0.33	0.37	0.50	0.46

also be influenced by differences in the duration of studies.

Annual incidence rate of MBTs for each cancer in Miyazaki Prefecture

In this study, the average annual incidence rate of new MBTs (i.e., the ratio of the number of new cancer registrations to that of new patients with MBT in Miyazaki Prefecture) was found to be at 0.41%. Excluding ovary/uterus and testis, which are related to sex, the highest incidence of MBT was determined to be in the lung (1.56%), whereas the incidence of MBT was <1% in all other cases. There is no accurate statistical data published as regards the incidence of MBTs based on cancer registries, and it has been generally accepted that at least 8%-10% of patients with cancer will develop MBTs.⁵⁾ Interestingly, previous studies have shown that approximately 70% of newly diagnosed patients with cancer develop MBTs within 1 year of diagnosis,⁵⁾ which is contradictory to the findings of this current study.

Finally, we have discussed whether the number of MBT sites depends on the total number of cancers in each organ. In Miyazaki Prefecture, the incidence of cancers in each organ were colon/rectum/anus (15.3%), lung (13.2%), stomach (12.3%), breast (8.6%), and liver (5.9%); these findings were inconsistent with the newly calculated incidence

rates of MBTs. These results revealed a slight relationship between the total number of cancers in each organ and the number of primary MBT sites.

Currently, databases of clinical cases are being compiled in various fields, as new epidemiological studies on MBTs are deemed desirable. Although this current study is significant, it has some limitations. First, although the number of newly enrolled and diagnosed patients with MBT and all newly enrolled patients with cancer in the same year was known, the number of all living patients with cancer in that year was undetermined. Thus, the actual incidence rate of new MBTs remains unknown. Second, the number of new patients with MBT depends on the number of patients who visited neurosurgery hospitals and clinics in Miyazaki Prefecture. Thus, patients who underwent surgery or received radiotherapy such as Gamma Knife outside of Miyazaki Prefecture and never visited a neurosurgery hospital in Miyazaki Prefecture were not included in this database; therefore, the data may be underestimated. Third, as there have been no similar studies, we could not compare the incidence rate with previous studies.

Conclusion

This is the first study to report on the epidemiological data on MBTs in Miyazaki Prefecture based on 425 new MBT cases reported in the Miyazaki Brain Tumor Database and Miyazaki Cancer Registry. As per our findings, lungs were determined to be the most common primary MBT site in Miyazaki Prefecture (49.4%), which is similar to the trend observed in Japan. Moreover, most MBTs in Miyazaki Prefecture were determined in older individuals and those who have not undergone surgery regardless of being symptomatic. Furthermore, in this study, the average annual incidence rate of new MBTs in Miyazaki Prefecture was found to be at 0.41%, which indicates a lower incidence rate than that in previous reports. With the expansion of cancer registries worldwide, such as brain tumors, further epidemiological analysis of MBTs is deemed warranted.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest. Authors who are members of Japan Neurosurgical Society (JNS) filed self-reported Conflict of Interest Disclosure Statement Forms online via the JNS member website.

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