Trends and Outcomes in the Treatment of Gliomas
Based on Data during 2001–2004 from the Brain Tumor Registry of Japan

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Abstract

The committee of Brain Tumor Registry of Japan (BTRJ) was founded in 1973 and conducts surveys and analyses of incidence, therapeutic methods, and treatment outcomes of primary and metastatic brain tumors with the cooperation of the Japan Neurosurgical Society members. Newly diagnosed 3,000–4,000 primary brain tumors and 600–1,000 brain metastases patients were enrolled in each year. This report describes the trends and treatment outcomes of gliomas from BTRJ volume 13, including 13,431 patients with primary brain tumors who newly started treatment from 2001 to 2004. Data from 382 diffuse astrocytomas (DAs), 121 oligodendrogliomas (OLs), 90 oligoastrocytomas (OAs), 513 anaplastic astrocytomas (AAs), 126 anaplastic oligodendrogliomas (AOs), 106 anaplastic oligoastrocytomas (AOAs), and 1,489 glioblastomas (GBMs) were analyzed for overall survival (OS) and progression free survival (PFS) depending on age, symptoms, Karnofsky performance status, location of the tumor, extent of resection (EOR), initial radiotherapy and chemotherapy. The 5-year PFS rates of the patients with DA, OL + OA, AA, AO + AOA, and GBM were 57.0%, 74.6%, 28.7%, 54.0%, and 9.2%, and the 5-year OS rates were 75.0%, 90.0%, 41.1%, 68.2%, and 10.1%, respectively. Higher EOR ≥ 75% in DA and OL + OA and that ≥ 50% in AA, AO + AOA, and GBM significantly prolonged OS. Complications and cause of death were also reported. BTRJ has been edited for all the patients, researchers, and especially for clinicians at bedside to give useful information about brain tumors and to contribute to the advances in brain tumor treatment. This report revealed various clinical problematic issues pertaining to the diagnosis and treatment of gliomas.

Key words: brain tumor registry, glioma, glioblastoma, astrocytoma, oligodendroglioma

History of Brain Tumor Registry of Japan

The committee of Brain Tumor Registry of Japan (BTRJ) was founded by Professors Keiji Sano and Kintomo Takakura in 1973. The previous chairman of BTRJ were Prof. Sano Keiji, Takakura Kintomo, and Nomura Kazuhiro and the current chairman is Shibui S. To contribute to advances in brain tumor treatment, the BTRJ has been used to investigate the current status of brain tumor incidence, therapeutic methods, and treatment outcomes. From the beginning, data have been registered as a result of collaboration among approximately 300 institutions; the first volume of information, which described data from 1969 to 1974, was issued in 1977 by the BTRJ. For patients with major brain tumors that were first treated in 1969, namely diffuse astrocytomas (DAs), glioblastomas (GBMs), meningiomas, pituitary adenomas, and neurinomas, the 5-year survival rates were 27.3%, 1.7%, 40.8%, 43.2%, and 31.1%, respectively, showing rates < 50% even for benign brain tumors. The BTRJ is issued every few years; thus far, a total of 13 volumes have been published. In 1992, the BTRJ started to publish its data in the journal Neurologia medico-chirurgica. In 2004, the committee of BTRJ was placed under control of the Scientific Advisory Committee of the Japan Neurosurgical Society (JNS) and has continued conducting surveys and analyses with the cooperation of the JNS members. Among the approximately 1,000 institutions that employ JNS
members, 200–300 institutions participated and
3,000–4,000 primary brain tumors and 600–1,000
brain metastases patients who newly started treatment
were enrolled in each year. Regarding data
delivered between 1973 and 2000, paper-based
questionnaires were distributed to the JNS-certified
facilities. The following data were collected and
analyzed at the BTRJ office in the Department of
Neurosurgery, National Cancer Center: patients’
information such as place and date of birth; name
and site of the brain tumor; therapeutic method;
and treatment outcome. Data obtained in and after
2001 were registered online using the University
Hospital Medical Information Network (UMIN)/
Internet Data and Information Center for Medical
Research system (INDICE) at the University of Tokyo,
and volume 13 was issued in 2014.7 In volume
13, patients who had been under treatment for 5
years and more were included, and the pathological
diagnosis, patient backgrounds, clinical diagnosis,
treatment content, and therapeutic outcomes were
registered online starting in 2009 on the basis of
existing linkable anonymized data. All data were
analyzed using Microsoft Excel VBA (Microsoft
Corporation, Redmond, Washington, USA), SAS
version 9.3, and JMP version 8 (SAS Institute Inc.,
Cary, North Carolina, USA) at the Department of
Mathematics, Tokyo University of Science, Shin-
juku, Tokyo. Survival time was calculated using
the Kaplan-Meier method. Based on the 2007 World
Health Organization Classification of Tumours of
the Central Nervous System,8 all primary and meta-
static brain tumor patients’ ages, genders, median
overall survival (OS), and median progression free
survival (PFS) were listed, and the median OS/PFS
of the 25 most frequent types of brain tumors were
listed according to the initial symptoms, treatment
modality, and age. This survey and research was
performed based on ethical guidelines for epidemi-
ology research 2008 and approved by the internal
board by the National Cancer Center.

Estimate of the Number of Gliomas
in Japan

Although the exact number of patients with primary
brain tumors in Japan remains unclear, it is estimated
to be approximately 20,000 per year. In a survey conducted from 1989 to 2008 in Kumamoto
Prefecture (Japan), reports on brain tumors from 5,448
patients were gathered and showed that the inci-
dence of brain tumors was 14.1 people per 100,000
population.9 According to a survey on brain tumors
in the United States (US)10 conducted from 2005
to 2009 and in the Republic of Korea in 2010,11
the incidences of primary brain tumors in the US
and Republic of Korea were 20.59 and 20.06 per
year per 100,000. Due to the increasing number of
elderly people and the fact that asymptomatic brain
tumors can be diagnosed on the basis of computed
tomography/magnetic resonance imaging findings,
the incidence of primary brain tumors has been
gradually increasing. The incidence of meningiomas
per 100,000 population was 7.49, that of gliomas
was 6.60, that of pituitary adenomas was 2.94,
that of neurinomas was 1.70, and that of primary
central nervous system lymphomas was 0.46.10
The incidence of brain tumors in Kumamoto when
classified by histological type was the same as that
found in the US. A simple calculation based on
data from Kumamoto prefecture9 and the US,10 as
well as on the Japanese population of 127 million
in 2013, would show the following equation: 127
million people × 14.1 – 20.59/100,000 people =
18,000–25,000 people. Thus, the number of patients
with primary brain tumors in Japan is estimated to
be approximately 20,000 per year. The registration
of all cancer cases is scheduled to begin in Japan as
well in 2016 and the exact number of brain tumor
patients will be shown.

In BTRJ volume 13 (2001–2004),7 13,431 cases
of primary brain tumors were registered, most from
university hospitals in Japan, and gliomas were the
most frequently encountered. Assuming that there
are 20,000 patients with primary brain tumors in
Japan, the annual number of occurrences of major
types of gliomas is estimated to account for 287
patients with pilocytic astrocytoma (PA), 569 patients
with DA, and 314 patients with oligodendroglial
tumors, which include oligodendrogliomas (OLs)
and oligoastrocytomas (OAs), 764 anaplastic astro-
cytomas (AAs), 314 anaplastic oligodendrogial tumors,
which include anaplastic oligodendroglioma (AO)
and anaplastic oligoastrocytoma (AOA), 2,217 GBMs,
107 ependymomas, and 82 anaplastic ependymomas.

This report mainly describes grades II–IV of the
DA, OL, OA, AA, AO, AOA, and GBM on the basis of
Related page numbers in BTRJ volume 13 are shown
in brackets [ ].

The Etiology of Gliomas

All types of gliomas, except for PA, more frequently
occur in men than in women [17–20, 34], consistent
with the data from the US and Republic of Korea.10,11
The mean onset age was 14.8 years for PA, 35.7
years for DA, 40.6 years for OL + OA, 51.9 years for
AA, 48.5 years for AO + AOA, and 62.2 years for
GBM, showing an older onset age for higher-grade

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gliomas. The incidence rates of DA, OL + OA, AA, AO + AOA, and GBM in subjects aged < 20 years were 15%, 5%, 7%, 2%, and 3%, respectively, whereas those in subjects aged ≥ 70 years were 5%, 3%, 14%, 5%, and 25%, respectively, showing that oligodendroglial tumors are less common in children and elderly subjects. Fifty-six per cent of GBM cases occurred in elderly patients aged ≥ 60 years. The incidence of GBM increased with age, with the following incidence rates per 100,000 subjects: < 20 years, 0.14; 45–54 years, 3.66; 55–64 years, 8.16; and 65–74 years, 13.21.10)

The main symptoms of gliomas were headache, seizure, and focal symptoms such as hemiparesis. Seizures at onset were more frequent in oligodendroglial tumors, and the incidence rates of DA, OL + OA, AA, AO + AOA, and GBM were 38%, 60%, 28%, 31%, and 13%, respectively [37]. The incidence rates of seizures occurring during the entire treatment course for DA, OL + OA, AA, AO + AOA, and GBM were reported to be 45%, 64%, 41%, 46%, and 30%, respectively [46]. Anticonvulsants were used for more than half of glioma cases [53]. These data are compatible with 70–90% of grade II glioma cases [2] and 29–49% of GBM cases [13] with seizures at onset. The incidence rates of any focal symptoms at onset of DA, OL + OA, AA, AO + AOA, and GBM were 25%, 16%, 44%, 34%, and 59%, respectively [37]. GBMs and oligodendroglial tumors were reported to show intratumoral bleeding at onset [44] and its incidence was < 2% (AO + AOA: 2.2%, GBM: 1.1%).

Asymptomatic gliomas are rare, with incidence rates of only 8% in DA, 10% in OL + OA, 3% in AA, 5% in AO + AOA, and 3% in GBM. The incidence of asymptomatic grade II glioma was reported to range from 3.0% to 9.6% [15,16] but such glioma is rarely diagnosed in GBM patients.

The prevalence rates of patients with Karnofsky performance status (KPS) scores ≥ 90 were 65%, 80%, 39%, 57%, and 25% in DA, OL + OA, AA, AO + AOA, and GBM. The prevalence rates of patients with a KPS ≤ 70 were 13%, 9%, 34%, 19%, and 49%, respectively [44]. Among the GBM patients, only a quarter had very mild symptoms and half had severe symptoms at onset.

Among 2,827 glioma cases, 2.7% were accompanied with other systemic cancers, mostly before they were diagnosed [46]. The incidence of accompanying systemic cancer or other central nervous system tumors was 3.4% in glioma patients and 0.6% in GBM patients.

The incidence rates of radiological findings of single and multiple lesions at onset of DA, OL + OA, AA, AO + AOA, and GBM were 95%, 99%, 92%, 96%, and 89%, and 5%, 1%, 7%, 4%, and 9%, respectively [39]. The incidence of leptomeningeal metastases (LMMs) at onset was reported to be < 1% in AA or GBM. GBM was reported to have multiple lesions at onset, with an incidence of 0.5–20% [17].

Gliomas commonly occur in the cerebrum, especially in the frontal lobe at an incidence rate of 41% in DA, 38% in AA, and 31% in GBM [40]. In particular, oligodendroglial tumors are more common in the frontal lobe, with incidence rates of 68% and 61% in OL + OA and AO + AOA. The incidence rates of infratentorial lesions in DA, OL + OA, AA, AO + AOA, and GBM were 15.2%, 0.5%, 14.0%, and 8.8%, respectively, demonstrating that oligodendroglial tumors in infratentorial lesions are less common.

Regarding hereditary tumors, 37 patients had brain tumors associated with neurofibromatosis type I [47]. The incidence rates of glioma per the total number of cases of each histological type were as follows: PB, 6 patients (3.1%); DA, 5 patients (1.8%); AA, 3 patients (1.2%); and GBM, 7 patients (0.7%).

Prognosis of Glioma Patients

I. Overall survival

Table 1 shows the patients’ median OS and PFS [55] according to glioma type. The median OSs of the DA, AA, and GBM patients were not reached (NR), 38.0 months, and 15.0 months, respectively, and the median PFSs were 84.1, 19.0, and 8.1 months, respectively. Among the DA cases, the gemistocytic astrocytoma subtype had a shorter median OS and a PFS ≤ 76.1 and 36.0 months, respectively. One of the reason is that gemistocytic astrocytomas presented at a significantly older age than other variants and the median age of diffuse (n = 269), fibrillary (n = 71), protoplasmic (n = 29), and gemistocytic astrocytoma (n = 13) were 38.2, 33.3, 34.0, and 46.2 years. Similar age distribution was reported by Surveillance, Epidemiology, and End Results Program (SEER) database and median age of fibrillary and gemistocytic variants were 37.7 years and 46.8 years, respectively [18]. The Kaplan-Meier survival curves of OS and PFS between OL and OA, or between AO and AOA were similar, and the 5-year OS rates of OL, OA, AO, and AOA were 90.6%, 89.3%, 67.8, and 68.7%, respectively. The 5-year PFS rates of DA, OL + OA, AA, AO + AOA, and GBM were 57.0%, 74.6%, 28.7%, 54.0%, and 9.2%, and the 5-year OS rates were 75.0%, 90.0%, 41.1%, 68.2, and 10.1%, respectively. Table 1 also shows the 5-year OS from the nationwide cancer registries of the US (1995–2009) [10] and Republic of Korea (1999–2004) [19].
Table 1  Overall survival and progression free survival (months)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Registered number</th>
<th>Rate</th>
<th>Estimated number</th>
<th>PFS med</th>
<th>5-y PFS (%)</th>
<th>OS med</th>
<th>5-y OS (%)</th>
<th>USA</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>193</td>
<td>1.4%</td>
<td>287</td>
<td>NR</td>
<td>73.8</td>
<td>NR</td>
<td>92.1</td>
<td>94.1</td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>60</td>
<td>0.4%</td>
<td>89</td>
<td>NR</td>
<td>78.9</td>
<td>NR</td>
<td>98.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>382</td>
<td>2.8%</td>
<td>569</td>
<td>84.1</td>
<td>57.0</td>
<td>NR</td>
<td>75.0</td>
<td>47.1</td>
<td>51.6</td>
</tr>
<tr>
<td>Gemistocytic astrocytoma</td>
<td>29</td>
<td>0.2%</td>
<td>43</td>
<td>36.0</td>
<td>31.6</td>
<td>76.1</td>
<td>70.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioblastoma</td>
<td>211</td>
<td>1.6%</td>
<td>314</td>
<td>NR</td>
<td>74.6</td>
<td>NR</td>
<td>90.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>121</td>
<td>0.9%</td>
<td>180</td>
<td>109.1</td>
<td>76.5</td>
<td>NR</td>
<td>90.6</td>
<td>79.1</td>
<td>73.5</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>90</td>
<td>0.7%</td>
<td>134</td>
<td>NR</td>
<td>72.2</td>
<td>NR</td>
<td>89.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>513</td>
<td>3.8%</td>
<td>764</td>
<td>19.0</td>
<td>28.7</td>
<td>38.0</td>
<td>41.1</td>
<td>25.9</td>
<td>25.2</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>232</td>
<td>1.7%</td>
<td>345</td>
<td>71.0</td>
<td>54.0</td>
<td>NR</td>
<td>68.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>126</td>
<td>0.9%</td>
<td>188</td>
<td>52.0</td>
<td>49.9</td>
<td>102.1</td>
<td>67.8</td>
<td>49.4</td>
<td>50.4</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>106</td>
<td>0.8%</td>
<td>158</td>
<td>80.1</td>
<td>58.6</td>
<td>NR</td>
<td>68.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>1,489</td>
<td>11.1%</td>
<td>2,217</td>
<td>8.1</td>
<td>9.2</td>
<td>15.0</td>
<td>10.1</td>
<td>4.7</td>
<td>8.9</td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td>47</td>
<td>0.3%</td>
<td>70</td>
<td>12.0</td>
<td>25.9</td>
<td>17.0</td>
<td>21.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>72</td>
<td>0.5%</td>
<td>107</td>
<td>117.0</td>
<td>73.1</td>
<td>NR</td>
<td>88.5</td>
<td>82.5</td>
<td>81.5</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>55</td>
<td>0.4%</td>
<td>82</td>
<td>22</td>
<td>35.1</td>
<td>NR</td>
<td>58.1</td>
<td>53.2</td>
<td></td>
</tr>
<tr>
<td>Central neurocytoma</td>
<td>65</td>
<td>0.5%</td>
<td>97</td>
<td>NR</td>
<td>79.0</td>
<td>NR</td>
<td>98.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BTRJ is a hospital-based registry that compares population-based data from the US and Republic of Korea. The 5-year OS rates were much higher in Japan than in those countries. Figure 1 shows the 5-year OS from 1969 to 2004 reported in each BTRJ.1–7,20) Most of the patients with gliomas had improved prognoses; however, the prognoses of the patients with GBM were still poor. This was reported in the era before temozolomide (TMZ; Merck; Kenilworth, New Jersey, USA). The median OS of patients with GBM in the US and Republic of Korea was reported to be improved after the introduction of TMZ or bevacizumab.19,21) Prognosis of patients with GBM is expected to be shown in next volume of BTRJ.

Table 2 shows the median OS in each glioma subtype group according to the KPS score at onset. With the exception of the patients in the AO + AOA group, those with a KPS score ≥ 90 showed a significantly prolonged OS compared with those with a KPS ≤ 80 (log rank, p < 0.001). For the patients with DA, OL + OA, AA, AO + AOA, and GBM, and a KPS score ≥ 90 with virtually no neurological symptoms, the 5-year OS rates were 85.4%, 92.4%, 55.0%, 68.2%, and 19.9%, respectively. As the pattern of recurrence was previously reported, most patients with DA, OL + OA, AA, AO + AOA, and GBM developed local recurrence at incidence rates of 89%, 94%, 89%, 87%, and 88% [57]. Approximately 80% of GBM were reported to recur within 2 cm of the initial tumor bed.22,23)

**II. Extent of resection (EOR)**

The EOR in this report was based mainly on
Table 2  Overall survival and 5-year OS depending on a Karnofsky performance status score at onset

<table>
<thead>
<tr>
<th>KPS</th>
<th>DA (n = 351)</th>
<th>OL + OA (n = 205)</th>
<th>AA (n = 487)</th>
<th>AO + AOA (n = 227)</th>
<th>GBM (n = 1,381)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–60</td>
<td>36</td>
<td>19.0</td>
<td>30.3%</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>70</td>
<td>14</td>
<td>86.1</td>
<td>63.6%</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>80</td>
<td>51</td>
<td>NR</td>
<td>51.7%</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>NR</td>
<td>77.3%</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>90–100</td>
<td>250</td>
<td>NR</td>
<td>85.4%</td>
<td>169</td>
<td>NR</td>
</tr>
</tbody>
</table>


the surgeon’s description in the patient’s clinical record. Gross total resection (GTR), which means complete resection, was performed in 15%, 36%, 12%, 31%, and 18% of the DA, OL + OA, AA, AO + AOA, and GBM cases, respectively. An EOR ≥ 95% and GTR were achieved in 29%, 56%, 25%, 47%, and 34% of those cases, respectively. One of the reasons that oligodendroglial tumors have a higher EOR than astrocytic tumors is that those tumors locate mainly in frontal lobe. Smith et al. reported that 35% of 216 grade II glioma cases had GTR, of which 47% had an EOR ≥ 90%.24) Sanai et al. also reported that 63% of 500 GBM cases had an EOR ≥ 95%. 25) Increasing EORs of gliomas should be needed from these data.

With an EOR of 1–50% (including biopsy), 50–75%, 75–95%, 95–99%, or GTR, the 5-year OS rates were respectively 63.8%, 54.5%, 80.8%, 97.5%, and 95.7% in DA; 50.0%, 47.3%, 67.4%, 88.1%, and 86.9% in OL and OA; and 26.4%, 54.0%, 49.8%, 48.1%, and 62.1% in AA; 33.4%, 45.9%, 41.1%, 68.1%, and 68.1% in AO + AOA; and 5.8%, 6.7%, 3.7%, 12.6%, and 15.1% in GBM. In the GBM cases with an EOR of 1–50% (including biopsy), 50–75%, 75–95%, 95–99%, or GTR, the median OSs were 12.0 months, 15.0 months, 14.0 months, 18.0 months, and 19.0 months, respectively.

No difference in OS was found between the DA or OL + OA cases with an EOR of 1–50% and those with an EOR of 50–75%. Meanwhile, the OS was significantly prolonged in the cases with an EOR ≥ 75% compared with those with an EOR of 1–75% (log rank, p = 0.04 in DA and p = 0.0006 in OL + OA). For grade III/IV glioma cases, the OS was significantly prolonged in those with an EOR ≥ 50% compared with those with an EOR of 1–50% (log rank p = 0.02 in AA, p = 0.01 in AO + AOA, and p = 0.005 in GBM).

In the volumetric analysis of EOR, OS was significantly improved with EOR ≥ 80% for grade II gliomas24) and EOR ≥ 78% for GBMs.25)

III. Initial therapy

More than 95% of the patients with gliomas underwent biopsy or tumor resection [49]. Initial radiotherapy (RT) [62] was performed in 56%, 52%, 89%, 79%, and 87% of the patients with DA, OL + OA, AA, AO + AOA, and GBM, respectively [50]. Re-RT was performed in 10–15% of the patients in each subtype group [51]. Chemotherapy was performed in 78%, 82%, and 69% of the patients in the AA, AO + AOA, and GBM groups, respectively [48]. TMZ was approved in 2006 in Japan and therefore, the most frequently used chemotherapeutic agents are nimustine chloride (ACNU), platinum-containing drugs, vincristine, and interferon. More than 80% of the patients who underwent chemotherapy received an ACNU-based regimen [52]. Because ACNU induces bone marrow suppression especially in elderly patients, ACNU is not generally used for patients aged ≥ 70 years. Steroids were used in 27%, 27%, 45%, 37%, and 53% of the patients in the DA, OL + OA, AA, AO + AOA, and GBM groups, respectively.

For the OS of patients in the DA group, depending on initial treatment, the 5-year OS of the subjects who underwent surgery alone (operation [OP]), OP + RT, and OP + chemoradiotherapy (CRT) were 85.6% (n = 142), 68.8% (n = 91), and 66.9% (n = 111), respectively, indicating that the OS of the patients who received early RT with or without chemotherapy was significantly worse than the OS of the patients who underwent observation alone after OP (log rank p = 0.002) (Fig. 2A). The median ages of the patients in the OP-only and OP + RT groups were 33.8 years and 38.9 years, respectively; the proportions of patients aged ≥ 40 years were 36% and 48%, respectively; and the proportions

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of those with an EOR ≥ 75% were 61% and 36%, respectively. This shows that the OP-alone group included younger patients and patients with a greater extent of resection. A multivariate analysis of 258 patients aged ≥ 20 years who had supratentorial DA was conducted according to age, KPS score, resection extent, and whether they underwent early RT. The hazard ratio (HR), 95% confidence interval (CI), and p values were as follows; in the subjects aged ≥ 40 years, HR: 1.88 (95% CI, 1.09–3.32; p = 0.02); in the patients with a KPS score ≤ 80, HR: 2.89 (95% CI, 1.60–5.10; p = 0.0006); and in the patients with an EOR ≤ 75%, HR: 2.77 (95% CI, 1.54–5.18; p = 0.0006). This means that although age ≥ 40 years, KPS score, and resection extent were significant prognostic factors, undergoing early RT had a HR

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of 0.93 (95% CI, 0.51–1.66; p = 0.81).

Similarly, in the OL + OA group, the 5-year OS rates of the subjects who underwent OP alone, OP + chemotherapy, OP + RT, and OP + CRT were 96.6% (n = 60), 96.7% (n = 40), 77.3% (n = 43), and 86.2% (n = 116), respectively, indicating that the OS of the patients who underwent early RT was significantly worse than the OS of the patients who underwent observation alone or chemotherapy after OP (log rank p = 0.007) (Fig. 2B). A multivariate analysis of 193 patients aged ≥ 20 years who had supratentorial OL + OA revealed the following HR, 95% CI, and p values: in the subjects aged ≥ 40 years, 2.88, 1.19–8.04, and p = 0.02; in the patients with a KPS ≤ 80, 1.73, 0.68–4.04, and p = 0.24; and in patients with an EOr ≤ 75%, 5.39, 2.36–12.6, p < 0.0001. While age and EOR were significant prognostic factors, undergoing early RT was associated with worse prognosis in the OL + OA group, with an HR of 2.86 (95% CI, 1.19–7.97; p = 0.02). Only 14% of the 193 patients died, indicating a low event rate, which might have influenced the results.

OS was reported to not significantly differ between early RT and non-early RT for patients with grade II gliomas. Patients with grade II glioma survived longer. However, in order to obtain conclusive findings regarding the effect of early RT, studies with longer follow-up periods are necessary.

In the AA group, the median OSs of the subjects who underwent OP alone, OP + RT, and OP + CRT were 14.0 months (n = 42), 28.0 months (n = 67), and 41.0 months (n = 381), respectively, indicating that the OS of the patients with OP + CRT was significantly longer than the OS of the patients with OP + RT (log rank p = 0.04) (Fig. 2C).

In the AO + AOA group, the OSs of the subjects who underwent OP alone, OP + RT, and OP + CRT were 64.1 months (n = 21), 77.1 months (n = 18), and NR (n = 163), respectively (Fig. 2D). The number of patients who underwent OP alone or OP + RT was small, without any significant difference between the groups.

In the GBM group, the OSs of the subjects who underwent OP alone, OP + RT, and OP + CRT were 6.1 months (n = 144), 12.0 months (n = 272), and 17.0 months (n = 991), respectively, demonstrating that OP + CRT, mainly with ACNU, significantly improved OS (log rank p < 0.0001). The frequency rates of OP alone, OP + RT, and OP + CRT in the patients aged 20–69 years were 7.5%, 11.7%, and 76.6%, respectively, and the median OSs of the patients were 6.1 months (n = 80), 14.0 months (n = 125), and 17.0 months (n = 815), respectively. OP + CRT significantly improved OS compared with OP + RT (log rank p = 0.007) (Fig. 2E). ACNU-based regimens were used in 80.4% of the patients, and platinum-based regimens were used in 14.4% of the patients. The median OSs of the patients aged ≥ 70 years who underwent OP alone, OP + RT, and OP + CRT were 6.0 months (n = 63), 11.0 months (n = 138), and 13.0 months (n = 140), respectively. OP + RT significantly improved OS compared with OP alone (log rank p < 0.001), but no significant difference was observed between OP + RT and OP + CRT (log rank p = 0.06) (Fig. 2F).

For the patients aged 20–69 years who had supratentorial GBM with a KPS ≥ 70 (n = 510), the median OS and PFS were 18.0 months and 8.1 months, respectively. These data are similar to those reported in previous clinical studies. The median OS and PFS of the patients who underwent RT + ACNU were 19.0 months and 6.2 months, respectively, in the phase II study of the Japan Clinical Oncology Group (JCOG) 0305.27) and those of the patients who underwent RT + TMZ were 14.6 months and 6.9 months, respectively, in the phase III study of RT alone versus RT + TMZ.28) The median OS of the patients diagnosed with GBM between 2007 and 2009 in the US was reported to be about only 7–9 months, but that of the patients who underwent RT + TMZ was 14 months.21) Sixty-seven and 18% of patients with GBM underwent OP + CRT and OP + RT, respectively, which shows that most of the patients in Japan received aggressive therapies. However, 72.8% of the patients underwent OP + RT, but only 47% of the patients underwent OP + RT + TMZ in the US in 2008. Chang et al. also reported that only 54% of patients with grade III/IV gliomas underwent CRT between 1997 and 2000.22) Considering that most of the patients in Japan received aggressive therapies, including RT + CRT, the OS of Japanese patients might be superior to that of the US patients.

IV. Adult and juvenile gliomas

According to the patients’ ages, the 5-year OS rates of the subjects aged < 20 years, 20–39 years, 40–59 years, and ≥ 60 years were respectively 60.0%, 83.2%, 79.6%, and 38.2% in DA, and 18.0%, 65.0%, 53.0%, and 24.0% in AA, indicating that the subjects aged < 20 years and those aged ≥ 60 years who had both DA and AA had poorer prognoses than those aged 20–59 years (log rank p < 0.05 in DA and p < 0.0001 in AA) [65]. For GBM, the median OSs of the subjects aged < 20 years, 20–59 years, and ≥ 60 years were 17.0, 18.0, and 13.0 months, respectively, and their 5-year OS rates were 7.8%, 16.4%, and 4.0%, respectively. No significant difference was observed between the juvenile patients and the adult patients aged < 60 years in patients with GBM.
The patients aged < 20 years rarely (n = 11) had OL + OA, and all the patients survived for > 5 years. The 5-year OS rates of the subjects aged 20–39 years, 40–59 years, and ≥ 60 years were respectively 97.3%, 88.1%, and 55.4% in OL + OA, and 74.0%, 66.9%, and 60.9% in AO + AOA. Patients aged ≥ 40 years who had OA + OL (log rank p < 0.001) and those aged ≥ 50 years who had AO + AOA (log rank p < 0.03) had significantly poorer prognoses.

V. Supratentorial and infratentorial lesions
The incidence rates of infratentorial DA, AA, and GBM were 14%, 13%, and 4%, respectively [66]. Infratentorial oligodendroglial tumor is rare. Infratentorial OL + OA cases have not been reported in this report, and the incidence of infratentorial AO + AOA was only 2%.

The patients with infratentorial DA and AA had significantly poorer prognoses, and the 5-year OS rates of the patients with supratentorial and infratentorial lesions were 79.5% and 46.2% in DA, and 42.4% and 31.4% in AA, respectively.

Supratentorial and infratentorial GBM had no significant differences, and their median OS rates were 15.0 months and 14.0 months, respectively. For the GBM patients aged 20–69 years, with a KPS ≥ 70, no significant difference in median OS was observed between the frontal lobe (18.0 months, n = 207), temporal lobe (16.1 months, n = 199), parietal lobe (20.1 months, n = 87), and occipital lobe (18.1 months, n = 37). However, the median OS of the patients with cerebellar GBM was 27 months (n = 22), indicating a better prognosis as previously.

VI. Brainstem gliomas
The reported number of patients with brainstem gliomas was 186 [75], of whom 66% (n = 123) had histological diagnoses (AA: 20.4%, DA: 19.9%, GBM: 10.2%, and PA: 8.6%). The median OS rates of the patients aged < 20 years and 20–59 years were 18.1 months (n = 16) and NR (n = 20) in DA (log rank p = 0.007), 15.0 months (n = 14) and 31.0 months (n = 17) in AA (log rank p = 0.11), 14.0 months (n = 7) and 9.0 months (n = 9) in GBM (log rank p = 0.2), and 9.0 months (n = 38) and 92.1 months (n = 17) in histologically unknown gliomas (log rank p = 0.007). Patients aged < 20 years who had both DA and unknown gliomas had poorer prognosis. Adult patients with brainstem gliomas had better prognoses than children, consistent with our report.

VII. Complications
The incidence of complications that occur during the treatment course for each glioma type was reported to be 11%, 11%, 20%, 19% and 21% in DA, OL + OA, AA, AO + AOA, and GBM, respectively [70]. Major complications include pneumonia, with incidence rates of 3–10%. The respective incidence of intracranial hemorrhage and cerebral infarction is < 3%. Deep venous thrombosis and pulmonary embolism are life-threatening complications that are often observed in approximately 10% of higher-grade gliomas, and their incidence in BTRJ is < 3% (GBM: 2.3%).

VIII. Causes of death
Most of the patients died of neurological causes including LMM, accounting for 84%, 72%, 86%, 75%, and 83% of DA, OL + OA, AA, AO + AOA, and GBM cases. Meanwhile, the mortality rates by LMM were 3%, 3%, 6%, 4%, and 4%, respectively [67]. Pneumonia-related mortality rates with neurological deterioration were 39%, 52%, 49%, 50%, and 48%, respectively.

Treatment-related death is not so rare, accounting for 3–6% of deaths. Among the patients with DA, OL + OA, AA, AO + AOA, and GBM who were treated in a single hospital without transferring to another hospital were 71%, 77%, 59%, 68%, and 50%, respectively [69]. The number of patients who were transferred to hospices and other institutions for palliative care was small, their proportions being 10%, 4%, 17%, 11%, and 26%, respectively. For place of death, the proportions of those who died in hospitals with a neurosurgical unit were 71%, 76%, 78%, 64%, and 70%, respectively; those who died in hospices, and nursing care institutions without a neurosurgical unit were 71%, 77%, 59%, 68%, and 50%, respectively [69]. The number of patients who were transferred to hospices and other institutions for palliative care was small, their proportions being 10%, 4%, 17%, 11%, and 26%, respectively. For place of death, the proportions of those who died in hospitals with a neurosurgical unit were 71%, 76%, 78%, 64%, and 70%, respectively; those who died in hospices, and nursing care institutions without a neurosurgical unit were 71%, 77%, 59%, 68%, and 50%, respectively [69]. The number of patients who were transferred to hospices and other institutions for palliative care was small, their proportions being 10%, 4%, 17%, 11%, and 26%, respectively. For place of death, the proportions of those who died in hospitals with a neurosurgical unit were 71%, 76%, 78%, 64%, and 70%, respectively; those who died in hospices, and nursing care institutions without a neurosurgical unit were 71%, 77%, 59%, 68%, and 50%, respectively [69]. The number of patients who were transferred to hospices and other institutions for palliative care was small, their proportions being 10%, 4%, 17%, 11%, and 26%, respectively. For place of death, the proportions of those who died in hospitals with a neurosurgical unit were 71%, 76%, 78%, 64%, and 70%, respectively; those who died in hospices, and nursing care institutions without a neurosurgical unit were 71%, 77%, 59%, 68%, and 50%, respectively [69]. The number of patients who were transferred to hospices and other institutions for palliative care was small, their proportions being 10%, 4%, 17%, 11%, and 26%, respectively. For place of death, the proportions of those who died in hospitals with a neurosurgical unit were 71%, 76%, 78%, 64%, and 70%, respectively; those who died in hospices, and nursing care institutions without a neurosurgical unit were 71%, 77%, 59%, 68%, and 50%, respectively [69].
was based on cumulative retrospective data in Japan, so the data analysis had various limitations and its interpretation requires caution. However, analysis of the data registered by a number of neurosurgeons has revealed various problematic issues pertaining to the diagnosis and treatment of brain tumors.

From this report, the causes of poor prognosis of GBM include: most patients are elderly; most patients have a poor KPS score; the asymptomatic onset of GBM is rare and cannot be diagnosed during a systematic health screening; cases of GTR of the tumor are rare; complications such as pneumonia are common; and medical treatments, especially available drugs, are limited.

Based on this report, we hope that various research and clinical trials will be carried out, evidence pertaining to the treatment of brain tumors will be established, and the therapeutic outcomes of all patients with malignant brain tumors will improve.

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**Conflicts of Interest Disclosure**

The authors declare no conflict of interest (COI). All authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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