RESEARCH ARTICLE

INDONESIAN JOURNAL OF CANCER

Profile of Primary Brain Tumor Patients Who Received Radiotherapy at Hasan Sadikin General Hospital Bandung in 2020–2021

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ARTICLE INFO

Received : 09 January 2023
Reviewed : 07 February 2023
Accepted : 18 November 2023

Keywords:
cancer, primary brain tumor, profile, radiotherapy

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ABSTRACT

Background: A brain tumor is a tumor that is most known for its dangerous progressivity. Brain tumor is classified into primary and metastatic types. One of the management for primary brain tumors is radiotherapy. This study aims to elucidate the medical profiles and Karnofsky Performance Status (KPS) of patients with primary brain tumors with radiotherapy in Hasan Sadikin General Hospital based on a hospital-based cancer registry (HCBR) in 2020–2021.

Methods: This study was conducted with a descriptive method. The sampling technique was total sampling using 22 medical records of primary brain tumor patients with radiotherapy from the year 2020–2021 which were registered in HCBR at the Radiotherapy Department, Hasan Sadikin General Hospital.

Results: Primary brain tumor patients with radiotherapy were mostly from the 25–34 years age group (27.3%), male gender (68.2%), with a regional origin of West Priangan (45.5%), the chief complaint was headache (45.5%), with topography presence of overlapping lesion in the brain (ICD-O code C71.8) (27.3%), histopathological type is predominantly astrocytic tumors (22.7%), majority of patients underwent subtotal resection (59.1%), adjuvant radiation therapy was mostly indicated (40.9%), with all patients using Linac external beam radiotherapy (EBRT) radiation device. Almost all patients can finish radiotherapy (95.5%). The waiting time for radiotherapy is mostly 5–6 weeks (31.8%).

Conclusions: Primary brain tumor infects more men than women, with a predominant age group of 25–34 years old. Histopathological findings are mostly of the astrocystic tumor type with most chief complain being headaches. The most common treatment is subtotal resection followed by radiotherapy using EBRT Linac with a positive one-year-postradiotherapy prognosis.

INTRODUCTION

A brain tumor is a tumor most known for its dangerous progressivity. Brain tumors are a serious health problem that can have a significant impact on a patient's quality of life. In Indonesia, brain tumors are a major concern, with the country having the highest prevalence of pediatric cancer cases in Southeast Asia, and brain tumors being the third-highest incidence. Radiotherapy is one of the treatments used to manage brain tumors, but it can have late treatment effects that can affect a patient's quality of life [1].

A recent study conducted in the Neurology Unit at Dr. Soetomo Hospital in Surabaya, Indonesia, evaluated the characteristics of patients with metastatic brain tumors. The study found that headache was the most common clinical symptom, reported by 78.2% of patients. Lung tumors were the most common

source of brain metastases (50%), followed by breast and nasopharynx cancers (13.6% each); 9% had unknown sources. The study also suggested that the frequency of metastatic brain tumors is gender and age-specific, and headaches with early-stage dementia are common among patients with metastatic brain tumors [2].

A brain tumor is the result of neurons or glial cells replicating at uncontrollable rate in the brain. Most brain tumor growth is localized; however, some can spread throughout the whole nervous system or even metastasize to other systems [3]. Brain tumor is classified into primary (70%) and secondary or metastatic type (30%). Approximately 24,000 primary brain tumors are diagnosed annually in the US. It is estimated that the prevalence rate reaches 8.2 in every 100,000 individuals. Despite being a less commonly found tumor (1.7% of all cancer types) compared to tumors of other organs such as lung, breast, or colon cancer, brain cancer can occur in various life stages from children, young adults, to the elderly [4,5]. However, its low incidence rate does not excuse the importance of recognizing this disease due to its high mortality rate in adults and children age group [6]. Except for trauma, neoplasm is the most common cause of death in children less than 19 years of age. A tumor of the central nervous system is a solid neoplasm that is most commonly found in pediatric patients, accounting for 20% of cancer-caused deaths [7]. Based on the Central Brain Tumor Registry of the United States 2022 (CBTRUS), brain tumors account to be 2% of overall cancer incidence and an average annual prevalence from 2015 to 2019 of 24.71 in every 100,000 individuals. Tumor of the central nervous system is the most common type of cancer in children. The incidence rate of primary brain tumors in children (0–14 years old) in the US reaches 5.96 in every 100,000 individuals [8].

Brain tumor management involves total resection if possible and doing an open biopsy, stereotactic biopsy, or partial resection. An anatomical pathology examination can then be done to determine the tumor's grading to decide further therapy approaches such as craniospinal radiation, radiotherapy, or radiation with adjuvant chemotherapy depending on the anatomical pathological results [9]. Radiotherapy is a clinical modality that utilizes pengion radiation to eradicate tumors [10]. Data regarding the characteristics of brain tumor patients with radiotherapy is still limited in Indonesia, especially in West Java. This is why this study presents the profile of primary brain tumor patients with radiation therapy. The novel data in this study can hopefully be beneficial in evaluating the proper treatment for primary brain tumors and become a basis for further promotive and preventive measures regarding primary brain tumors.

METHODS

This is a descriptive study with a retrospective method to identify various profiles of patients with primary brain tumors with radiotherapy in the Radiology Department of Hasan Sadikin General Hospital in the year 2020–2021 using a total sampling method from hospital-based cancer registry (HBCR) and undergoing radiotherapy from January 1st, 2020 to December 31st, 2021. The inclusion criteria for this study are primary brain tumor patients who received radiotherapy in Hasan Sadikin General Hospital Bandung in the year 2020–2021, while the criteria for the exclusion of this study are patients whose data are incomplete and who do not get the first dose of radiation therapy.

The main variables processed in this study included age, gender, residence, chief complaint, time of diagnosis, topography, histopathological type, grade, and incision type. We will also present data distribution of chief complaints by topography. Chief complaint is classified as headache, vision, balance, and neurological disturbance, while topography is classified based on the ICD-O code. Incision type is laid into unresectable, subtotal, total gross, and stereotactic surgery, while radiotherapy indication is divided into curative definitives, adjuvants, and palliatives. The secondary variable includes radiation therapy indication, radiation technique, radiation devices, therapy regiment, waiting time for radiation therapy in weeks, and post-radiation one-year survival probability.

The radiation techniques in this study were 2D, 3D-CRT, and IMRT, while the radiation devices used in this study were EBRT Linac and EBRT Cobalt-60. The Karnofsky Performance Status (KPS) is a scale that ranges from 0 to 100, with 100 being the highest level of functioning. The KPS is used to assess a patient's ability to perform activities of daily living, such as bathing, dressing, and eating, as well as their ability to perform more complex tasks, such as working and participating in recreational activities. Data was processed using Microsoft Excel 2013 and IBM SPSS V.25.

RESULTS

From 2020 to 2021, 2379 patients enlisted for radiation therapy in the Radiotherapy Department of Hasan Sadikin Hospital. Out of those, 55 were brain tumor patients with 44 patients (80%) having primary brain tumor and 11 patients (20%) with the metastatic type. Not all patients want to undergo radiotherapy. As many as 22 patients want to undergo radiotherapy (0.92% of the total patient enlisted). In contrast, the rest do not want, so not all patients to be included in further analysis. However, we still present the profile of all patients (whether undergoing radiotherapy or not). Study results are presented in **Table 1**.

Table 1. Profile of primary brain tumor patients with radiotherapy

Categories	n	%
Age (years old)		
0–14	5	22.7
15–24	3	13.6
25–34	6	27.3
35–44	3	13.6
45–54	3	13.6
55–64	1	4.5
≥65	1	4.5
Gender		
Male	15	68.2
Female	7	31.8
Residency		
Bogor Area	4	18.2
Purwakarta Area	3	13.6
Cirebon Area	3	13.6
West Priangan	10	45.5
East Priangan	1	4.5
Outside West Java	1	4.5
Chief complaint		
Headache	10	45.5
Vision disturbance	3	13.6
Balance disturbance	2	9.1
Neurologic disturbance	6	27.3
Others	1	4.5
Time of diagnosis		
Pre-operation	7	31.8
Post-operation	15	68.2
Topography (ICD-O)		
C70.0 Cerebral meninges	3	13.6
C71.0 Cerebrum	0	0.0
C71.1 Frontal lobe	1	4.5
C71.2 Temporal lobe	3	13.6
C71.3 Parietal lobe	0	0.0
C71.4 Occipital lobe	0	0.0
C71.5 Ventricle, NOS	0	0.0
C71.6 Cerebellum, NOS	2	9.1
C71.7 Brain stem	2	9.1
C71.8 Overlapping lesion of brain	6	27.3
C72.3 Optic nerve	2	9.1
C75.2 Craniopharyngeal duct	1	4.5
C75.3 Pineal gland	2	9.1
Histopathological type		
Astrocytic tumors	5	22.7
Oligodendrogliomas	3	13.6
Oligoastrocytomas	0	0.0
Ependymal tumors	1	4.5
Choroid plexus tumors	0	0.0
Other neuroepithelial tumors	0	0.0
Neuronal/glial tumors	0	0.0
Pineal tumors	1	4.5
Embryonal tumors	1	4.5
Cranial nerve tumors	0	0.0
Meningeal tumors	3	13,6
Tumors of the sellar region	1	4.5
Unapplicable	7	31.8
Grade		
1	2	9.1
2	4	18.2
3	2	9.1
4	3	13.6
Unknown	11	50.0
The extent of resection		
Unresectable	7	31.8
Subtotal	13	59.1
Gross total	1	4.5
Stereotactic surgery	1	4.5
Radiotherapy indication		
Curative-definitive	6	27.3
Adjuvant	15	68.2
Palliative	1	4.5
Radiation technique		
2D	4	18.2
3D-CRT	9	40.9
IMRT	9	40.9
Radiation device		
EBRT Linac	22	100.0
EBRT Cobalt-60	0	00
Radiotherapy completion		
Complete	21	95.5
Incomplete	1	4.5
Waiting time for radiotherapy (weeks)		
<1	3	13.6
1–2	3	13.6
3–4	4	18.2
5–6	7	31.8
>6	5	22.7
One year post radiation survival outcome		
Survive	14	63.6
Not survive	6	27.3
Unknown	2	9.1

ICD-O: International Classification of Diseases for Oncology, EBRT: External Beam Radiotherapy,
IMRT: Intensity Modulated Radiotherapy, 3D-CRT: Three-Dimensional Conformal Radiation Therapy

P-ISSN: 1978-3744 E-ISSN: 2355-6811

DISCUSSION

Based on patient age, most age groups had brain tumors at an age range of 25–34 years old (27.3%, n=6) with the youngest age recorded being 5 years old, the oldest at 69 years old, and with a mean age of 30 years old. This study is in accordance with a study from Tanzania which showed that brain tumor incidence peaks in the 15–39 years age range [1]. However, this finding differs from a previous study in Dr. Cipto Mangunkusumo Hospital, where most patients are a mean age of 43.8 years old, this is due to the study not including brain tumors in children as their population [12]. Furthermore, the second most common age group with brain tumors is 0-14 years of age. This finding is similar to the statistical report by the Central Brain Tumor Registry of the United States (CBTRUS) in 2015–2019 which states that brain tumor is a malignancy that is most found in the 0-14 year age group, replacing leukemia which was initially at the top of the list. The 2015–2019 CBTRUS also states that brain tumor incidence peaks above the 40 years age group [8].

However, the prevalence rate increase in developed countries is related to the advanced technology's role in rapid detection and accurate diagnosis of brain tumors, inversely proportional to developing countries where limitation is still commonly found, such as this study where the majority of patients did not undergo immunohistologic examination in the diagnosis process. Additionally, the majority of civilians have limited access to and awareness of early detection. This causes a high number of undiagnosed and unregistered cases, leading to the possibility of a biased decrease in the incidence and prevalence rate reported.

Patient demography in this study is divided into 6 territories which are Bogor area (Bogor, Depok, Sukabumi, and Cianjur), Purwakarta area (Subang, Purwakarta, Bekasi, and Karawang), Cirebon area (Cirebon, Indramayu, Majalengka, and Kuningan), West Priangan (Bandung, Garut, Cimahi, and Bandung Barat), East Priangan (Ciamis, Banjar, Tasikmalaya, Sumedang, and Pangandaran) and outside of West Java. This study found that most patients were from West Priangan (45.5%, n=10) and some from outside of West Java which was East Lampung (4.5%, n=1). This is attributable to most West Priangan society having easier access to Hasan Sadikin General Hospital which is a third-class healthcare facility and the highest referral hospital, especially in cancer treatment in West Java.

The incidence of brain tumors also varies based on gender. This study found a male-to-female ratio to be 2.1:1. Malignant brain tumors are more common in males compared to females while benign ones occur conversely [10,11]. This may be explained by the higher oncogenic and genetic mutation mechanism occurring in males, thus affecting the higher prevalence of malignant brain tumors. **Table 2** presents the distribution of tumor malignancies based on gender, with a total of subjects with histopathological examination (n=15). The most significant difference found in this study is benign meningioma is only found in females with a ratio of 2 from 3 samples (67%) showing histopathologies of benign meningioma. The aforementioned Tanzanian study also showed similar results. This may be related to reproductive and hormonal factor which causes females to be at higher risk compared to males [13]. Meningioma is known to express progesterone and estrogen receptors. Also, meningioma biopsy has been found to express luteinizing hormone-releasing hormone receptors, and it is also estimated that high testosterone levels are a protective factor against meningioma risk in males [14].

The most common histopathologic type found in this study is astrocystic tumor with subtypes that vary from glioblastoma, anaplastic astrocytoma, and diffuse astrocytoma. This result matches the report from CBTRUS which states that glioblastoma is a frequently found malignant brain tumor [8]. Another study reported meningioma to be another commonly occurring primary brain tumor. This varying phenomenon may be influenced by differences in ethnicity, geographical location, and living environment [15].

Most tumor topography showed overlapping lesions in brain lobes. This is due to the tumor's progressivity affecting its surrounding region. **Figure 1** presents that headache is the most commonly experienced chief complaint felt by patients with various lesion locations. Similar studies also placed headache as a main chief complaint in primary brain tumors [14,16]. A study by Vazquez-Barquero et al. [17] states that headache is an early symptom of intracranial tumors. Headaches can be caused by the increase in intracranial pressure [18]. Possible neoplasm-related headache mechanism may be due to venous traction that causes venous sinus displacement, traction of the middle meningeal artery and arteries of the brain base, direct pressure to cranial nerves with afferent pain fibers, or distension of intracranial and extracranial arteries [19]. Based on the International Classification of Headache Disorders (ICHD-3), headache can be attributed to brain tumors if it is correlated to neoplastic growth, signified by significantly worsening headache that progresses in parallel to worsening tumor condition, and/or significantly diminishing pain levels upon completion of tumor management [20].

Table 2. Tumor malignancy distribution based on gender

Tumor type	Male (n)	Female (n)
Malignant tumor	11	1
Benign tumor	0	3

P-ISSN: 1978-3744 E-ISSN: 2355-6811

Radiotherapy is a clinical modality that utilizes radioactive ionizing rays to eradicate tumors [10]. Primary brain tumor patients who enlisted for radiotherapy from 2020 to 2021 were recorded to be 44 individuals with only 22 patients who underwent radiation therapy (50%) and 21 samples who completed their therapy, except for 1 patient who did not complete radiotherapy due to death during therapy. Patients who enlisted but did not undergo radiotherapy can understand that it can be associated with poor initial conditions of the patients or economic limitations (because not all patients in this study have insurance). Healthcare facilities are also responsible for the number of patients who did not undergo radiotherapy. Some contributing factors may be due to quality or quantity limitations of the facilities involved. Based on data from Indonesian Radiation Oncology Society (IROS) in 2017, only 3 hospitals have radiotherapy facilities in West Java including Dr. Hasan Sadikin General Hospital, Santosa Bandung Hospital, and Al-Ihsan Hospital. This number is lacking considering the high incidence of cancer cases in West Java during the same year (66,204 cases) [21].

Radiotherapy can be used as a primary or adjuvant approach after operative measures in patients. The Tanzanian study also showed that patients with high-grade tumors and subtotal resection are usually referred to continuo adjuvant radiotherapy [11]. Another study in Finland also showed that before radiotherapy, patients mostly underwent partial resection [22]. This result matches findings in Hasan Sadiking Hospital's Radiotherapy Instalation where the majority of patients got subtotal resection (59.1%, n=13) and underwent radiotherapy with adjuvant indications (68.2%, n=15). Furthermore, some patients (31.8%, n=7) had unresectable tumors due to their vulnerable location such as being placed near the brainstem, causing further operative measures to be of low success rate. This condition forces radiotherapy to be a primary management measure or even a definitive curative measure.

During the time of this study, two types of radiation devices are utilized such as Cobalt-60 (60Co) and Linear Accelerator (Linac). The result of this study showed that all radiation therapy uses Linac. This is in line with the literature which states that in dosimetry, Linac has a higher radiation energy, modulated dose velocity, and a smaller penumbra focal point, thus minimizing the risk of damaging surrounding normal tissues [23]. Also, another benefit of Linac is its ability to administer higher doses, a more advanced technique involves its ability to be activated and deactivated according to the needs and desired controlled dose, and the less radioactive wastes it imposes on the environment.

Most patients in this study underwent 3D-Conformal Radiation Therapy (3D-CRT) (40.9%, n=9) and Intensity-modulated radiation therapy (IMRT) (40.9%, n=9) compared to the 2D technique (18.2%, n=4). Basic radiation therapy uses a 2D technique. Three-dimensional conformal radiation therapy (3D-CRT) is a more advanced modality that produces better outcomes compared to its 2D counterpart, while IMRT enables the administration of higher doses to the target volume while simultaneously reducing the risk of toxicity towards normal tissue in comparison to conformal 3D-CRT radiotherapy [24]. Radiotherapy involves an increase in the therapeutic

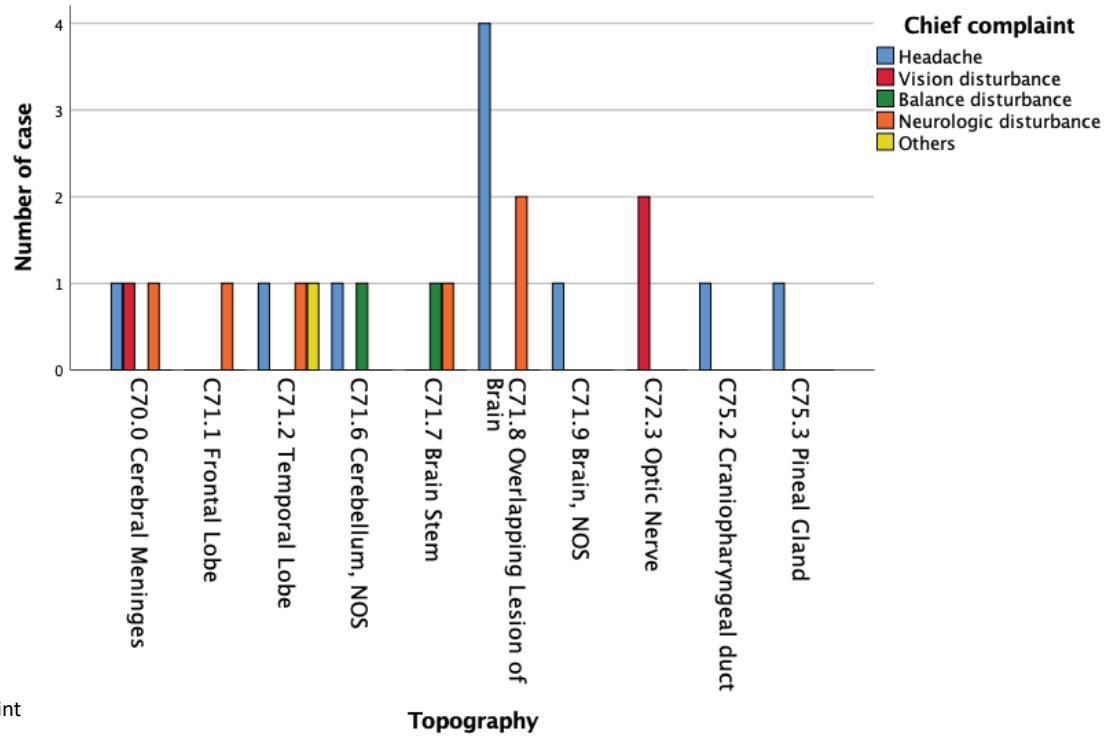

Figure 1. Distribution of chief complaint by topography

P-ISSN: 1978-3744 E-ISSN: 2355-6811

index (TI) to optimize the administered therapy. Various methods can be used to increase this index, one of which is the usage of physical modifiers of low-linear energy transfer (LET) radiations such as 3D-CRT and IMRT [10]. Administered radiation doses for patients differ based on the tumor's histopathological type. The total radiation dose is presented in **Table 3.**

The recommended dose for high-grade glioma patients is 60 Gy/30 fx [25]. The administered for high-grade glioma patients in this study still matches this recommendation (**Table 3**). A meta-analysis by Walker et al. [26] showed that increase in median survival rate increases in accordance with the administered dose, with a median survival of 13.5 weeks for administration of ≤45 Gy and administration of 60 Gy with a median survival of 42 weeks. Additionally administered doses for craniopharyngioma patients are also in accordance with the recommended those being External Beam Radiotherapy (EBRT) 54 Gy for subtotal resection patients [25]. A study by Stripp et al. [27] also showed that post-operative adjuvant radiation with sub-total resection has a better 10-year local control compared to patients with operative measures without radiotherapy. Furthermore, another study also showed that radiotherapy can increase prognosis in patients with high-risk low-grade glioma, which is defined as patients aged less than 40 years old with subtotal resection or more than 40 years of age with all types of resection [28]. This is in line with this study where the majority of patients were still alive within a year after radiotherapy was conducted (63.6%, n=14) and there were 11 patients with increased post-radiation KPS compared to pre-radiation KPS (68.7%) which can be seen in **Figure 2.** KPS is used to assess general physical in patients' quality of life.

Primary brain tumors are a rare type of cancer that can occur in both adults and children. These tumors are known collectively as primary brain tumors, and they can be malignant or benign. In adults, primary brain tumors are rare, with an estimated 23,380 new cases diagnosed in 2014, leading to 14,320 deaths. These accounted for 1.4% of all new cases of cancer and 2.4% of all cancer deaths. The five-year survival rate for primary brain tumors is 33.4%, although this rate varies widely among the specific types of tumors [29]. In general, primary malignant brain tumors result in a poor prognosis for the patient, with a relatively low 33.7% five-year relative survival [30]. Despite a lower survival rate and the possibility of tumor recurrence in patients with primary brain tumors, some studies suggest that long-term outcomes can be improved with acute rehabilitation [31].

Table 3. Total radiation dose for primary brain tumor

Histopathological type	Total radiation dose (Gy)
Glioblastoma	62–70
Anaplastic astrocytoma	60
Diffuse astrocytoma	60
Oligodendroglioma	60–64
Atypical meningioma	54
Transisional meningioma	60
Meningothelial meningioma	54
Medulloblastoma	54
Ependymoma	54
Craniopharyngioma	54
Pineoblastoma	54

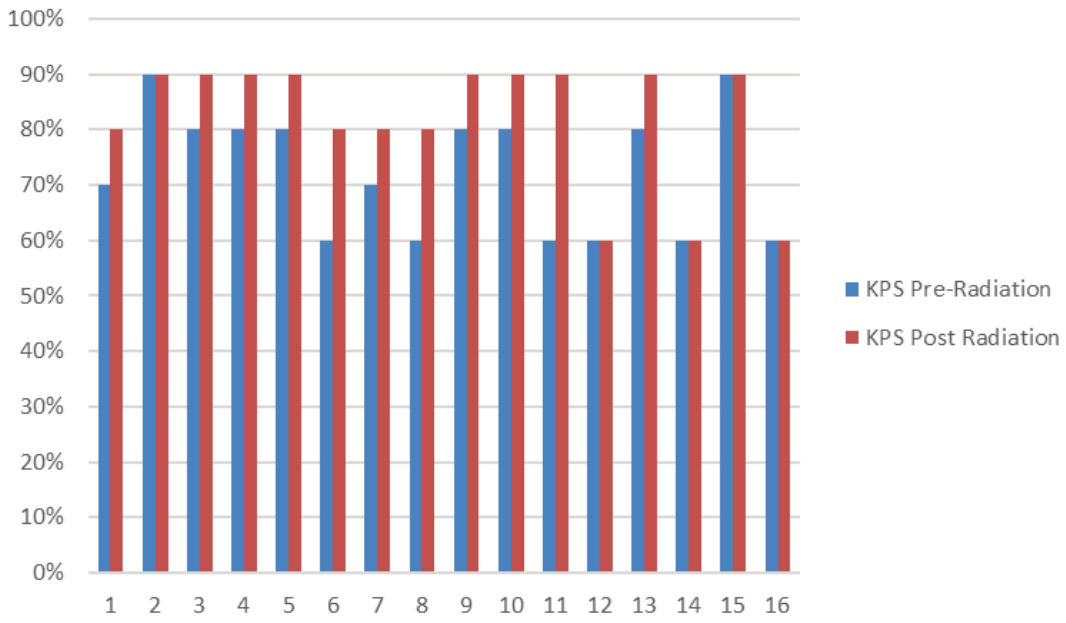

Figure 2. Karnofsky performance status of primary brain tumor patients with radiotherapy

P-ISSN: 1978-3744 E-ISSN: 2355-6811

The preferred treatment for primary brain tumors is the maximal safe surgical removal of the tumor followed by radiotherapy and chemotherapy. Although the extent of resection is a prognostic variable, the extent of safe tumor resection is dependent on tumor location, patient performance status, and, most importantly, patient age. Benefits of maximal resection include relief of mass effect, decreased tumor burden, improved diagnosis, and a trend toward prolonged survival. Radiation therapy is often used after surgery to kill any remaining cancer cells and to prevent the tumor from growing back. Chemotherapy may also be used to kill cancer cells that have spread beyond the tumor site. The specific treatment plan will depend on the type, size, and location of the tumor, as well as the patient's overall health and other factors [29].

Based on patients' waiting time from the time of admission to the first radiotherapy dose, it is found that the average time required is approximately 6 weeks with the longest time being 23 weeks. This suggests a relatively extended period for patients to be able to access radiotherapy, thus giving a significant amount of opportunity for cancer cells to proliferate and exacerbate patients' conditions. The time required for tumor cells to double themselves is called tumor doubling time (TD). A study from Japan showed that TD in meningioma is estimated to be at 54–8,579 days with a median of 1,082 days [32]. TD may differ depending on histopathological type, anatomical location of the tumor, and patient's age. The time between operative measures and radiotherapy also depends on the size of the resected areas.

In glioblastoma patients with subtotal resection, a delay in therapy of ≤ 4 weeks may increase mortality probability in patients. This also applies to patients with gross total resection with a delay in radiotherapy of over 8 weeks [33]. A retrospective study from Australia showed no significant difference in outcome from radiotherapy delay after dissection with an average time of 26 days. However, it was found that upon every additional day of radiotherapy delay from operative measures, a 2% mortality risk is increased [34]. However, an exception applies for patients with prognostic factors that are potentially beneficial such as complete resection and adjuvant chemotherapy such as the ones that applies in this study.

A lengthened waiting time for patients to undergo therapy may be attributed to facility limitations and a scarcity of healthcare workers which hinders an optimal output to compensate for the high number of patients. During the time of this study, only 11 radiation oncologists were readily available in West Java while brain tumor incidence was at a peak of 49,405,808 individuals, while the Indonesia Ministry of Health targets a ratio between specialist healthcare workers and civilians to reach 10.6:100,000 [30–32]. Primary brain tumor patients' waiting time to undergo radiotherapy in Hasan Sadikin General Hospital is found to be as long as 8 weeks, which is still relatively rapid in comparison to other hospitals in West Java [21].

Based on this study, it can be concluded that a majority of patients with primary brain tumor are from the 25–34 years old age group (27.3%, n=6), male gender (68.2%, n=15), West Priangan residents (45.5%, n=10), mostly had headaches as their chief complaint (45.5%, n=10), with a tumor diagnosis done post-operatively (68.2%, n=15), with topography presence of overlapping lesion in the brain (ICD-O code C71.8) (27.3%), astrocytic tumor histopathologic type (22.7%, n=5), most tumor grades are unknown (50,0%, n=11), a majority of patients underwent subtotal surgery (59.1%, n=13), indicated for adjuvant radiotherapy (68.2%, n=15), used 3D-CRT and IMRT as a radiotherapy method (40,9%, n=9 and 40,9%, n=9 respectively), and with all patients using EBRT Linac. Almost all patients completed radiotherapy (95.5%, n=21), waiting time for patients to receive their first dose of radiotherapy from the time of admission ranges from 5-6 weeks (31.8%, n=7), and most patients are still alive within a year after radiotherapy (63.6%, n=14).

CONCLUSIONS

Primary brain tumor prevalence is considered low compared to other malignancies, with a total number of patients with primary brain tumors undergoing radiotherapy at only 0.92% of all patients in the Radiotherapy Department in Hasan Sadikin Hospital during the year 2020-2021. Brain tumor affects all age groups from children to adults especially from the 25-34 years age group, with a male-predominant incidence rate compared to their female counterparts (2.1:1). Histopathological type, grade, tumor topography varies with the most common histopathological type being astrocytic tumors (22.7%). This study found that patients tend to have headaches as their chief complaint, and a predominant indication of adjuvant with subtotal resection medication and radiotherapy utilizing EBRT Linac. Waiting time for patients from the administration phase to their first radiation is about 5-6 weeks, and post-radiation conditions on patients revealed a good outcome with most patients surviving until the time when this research was conducted. Despite a lower survival rate and the possibility of tumor recurrence in patients with primary brain tumors, some studies suggest that long-term outcomes can be improved with acute rehabilitation.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics Approval

This study had been approved by the Research Ethics Committee of Universitas Padjadjaran number 772/UN6. KEP/EC/2022 and Dr. Hasan Sadikin General Hospital number LB.02.01/X.2.2.1/18476/2022.

Acknowledgment

The researchers would like to thank Prof. Ahmad Faried, MD, Ph.D (Sp.BS.(K)), Adi Sunardi, MD (Sp.Onk.Rad.(K)), medical record staff, the patients whose medical records were selected as subjects, and who helped in the process and gave contributions to this study.

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