Journal of Clinical Neuroscience 75 (2020) 112–116

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Proton beam therapy utilization in adults with primary brain tumors in the United States

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ARTICLE INFO

Article history:
Received 2 January 2020
Accepted 8 March 2020

Keywords:
Proton therapy
Utilization
Brain Tumors

ABSTRACT

The utilization of proton beam therapy (PBT) as the primary treatment of adults with primary brain tumors (APBT) was evaluated through query of the National Cancer Database (NCDB) between the years 2004 and 2015. International Classification of Diseases for Oncology code for each patient was stratified into six histology categories; high-grade gliomas, medulloblastomas, ependymomas, other gliomas, other malignant tumors, or other benign intracranial tumors. Demographics of the treatment population were also analyzed. A total of 1,296 patients received PBT during the 11-year interval for treatment of their primary brain tumor. High-grade glioma, medulloblastoma, ependymoma, other glioma, other malignant, and other benign intracranial histologies made up 39%, 20%, 13%, 12%, 13%, and 2% of the cohort, respectively. The number of patients treated per year increased from 34 to 300 in years 2004 to 2015. Histologies treated with PBT varied over the 11-year interval with high-grade gliomas comprising 75% and 45% at years 2004 and 2015, respectively. The majority of the patient population was 18–29 years of age (59%), Caucasian race (73%), had median reported income of over $63,000 (46%), were privately insured (68%), and were treated at an academic institution (70%). This study characterizes trends of malignant and benign APBT histologies treated with PBT. Our data from 2004 through 2015 illustrates a marked increase in the utilization of PBT in the treatment of APBT and shows variability in the tumor histology treated over this time.

1. Introduction

Improving the therapeutic ratio is one of the main goals of technology development in the field of radiation oncology. To this end, proton beam therapy (PBT) offers dosimetric advantages over photon radiation therapy due to steep dose fall off at depth characterized by the Bragg Peak. Decreased integral dose to normal brain and superiority in meeting surrounding tissue constraints has established the role of PBT in management of various central nervous system (CNS) tumors and in the setting of re-irradiation [1–6]. Studies have demonstrated the dosimetric advantages of PBT, allowing for reduction in radiation-induced toxicities such as neurocognitive decline and secondary malignancy [1,7]. A number of studies are evaluating tumor control, late toxicity, and quality of life in adults with primary brain tumors (APBT), however the data continues to mature [8,9]. These dosimetric and clinical advantages are being utilized at over 30 active proton centers in the United States located in 19 states and in the District of Columbia with more under construction [10,11].

Descriptive epidemiology of APBT is available; however less is known about the specific patient populations treated with PBT [12–14]. This study aims to further investigate the specific histologies of APBT treated with PBT using the National Cancer Database (NCDB).

2. Materials and methods

The NCDB is sponsored by the American College of Surgeons, Commission on Cancer, and the American Cancer Society and via hospital registry data collects approximately 70% of data from newly diagnosed cancer cases nationwide across over 1,500 accredited facilities [15]. The NCDB was queried for benign and malignant primary intracranial tumors treated with PBT between 2004 and 2015. International Classification of Diseases for

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https://doi.org/10.1016/j.jocn.2020.03.011
0967-5868/

Oncology codes were evaluated and subsequently stratified into six histology categories; high-grade gliomas, medulloblastomas, ependymomas, other gliomas, other malignant, or other benign intracranial tumors [16]. Patient characteristics and demographic variables were reported and compared.

3. Results

We identified 1,296 adult patients who received PBT from 2004 through 2015 as treatment of their primary brain tumor. High-grade glioma, medulloblastoma, ependymoma, other glioma, other malignant, and other benign intracranial histologies made up 39.4%, 20.2%, 13.4%, 12.2%, 12.8%, and 1.9% of the cohort, respectively. Reported World Health Organization Grade was I, II, III, IV, and unreported in 2.5%, 16.2%, 20.5%, 37.3%, and 23.5% of the population, respectively.

Patient characteristics and variables are summarized in Table 1. Males represented approximately 57.1% of the patient population. Younger patients were most likely to receive PBT, with 59.4% of patients between the ages of 18 and 29 years old and 77.5% less than 50 years of age. Charlson/Deyo comorbidity score was 0 in 89.1% of the patient population and 1 in 7.6% of the population. The majority of the APBT population was Caucasian race (73.4%), had median reported income of over $63,000 (45.7%), lived within 100 miles of the treatment center (82.2%), and received treatment at an academic institution (70%). Patients were most likely to have private insurance (67.9%) compared with Medicaid (15.9%) and Medicare (10.0%).

Table 1
Demographics and Patient Variables.

Patient Variable		Number of Patients (1,296 total)	Percentage of Patients
Age	18–29	770	59.4%
	30–49	235	18.1%
	50–69	233	18.0%
	>69	58	4.5%
Sex	Male	740	57.1%
	Female	556	42.9%
Race	White	951	73.4%
	Hispanic	167	12.9%
	Black	59	4.6%
	Asian/Pacific Islander	57	4.4%
	Unknown	56	4.3%
	American Indian	6	0.5%
Year of Diagnosis	2004	34	2.6%
	2005	40	3.1%
	2006	30	2.3%
	2007	39	3.0%
	2008	45	3.5%
	2009	59	4.6%
	2010	71	5.5%
	2011	104	8.0%
	2012	145	11.2%
	2013	196	15.1%
	2014	233	18.0%
	2015	300	23.1%
Charlson/Deyo Comorbidity Score	0	1,155	89.1%
	1	98	7.6%
	2	34	2.6%
	3	9	0.7%
Patient Income Quartile	$63,000 +	583	45.7%
	$48,000-$62,999	342	26.8%
	$38,000-$47,999	234	18.3%
	<$38,000	118	9.2%
Primary Payer	Private Insurance or Managed Care	880	67.9%
	Medicaid	206	15.9%
	Medicare	130	10.0%
	Insurance Status Unknown	30	2.3%
	Not Insured	26	2.0%
	Other Government	24	1.9%

The overall number of patients treated nationally with PBT increased substantially from 34 in 2004 to 300 in 2015, comprising 2.6% and 23.1% of the entire cohort, respectively (Fig. 1). APBT histologies treated over the 11-year interval varied as demonstrated in Figs. 2 and 3. High-grade gliomas comprised 75%, 28%, 45% of all tumors treated at years 2004, 2010, and 2015, respectively. The proportion of medulloblastoma treated doubled from 9% to 18%, as a percentage of the treated population from 2004 to 2015. Ependymoma comprised 4% and 12% of the treated population at years 2004 and 2015, respectively.

4. Discussion

From 2004 to 2015, the use of PBT for the treatment of intracranial malignancies has increased substantially. In particular, patients with medulloblastoma or ependymoma comprised a higher proportion of patients treated with PBT in 2015 compared to the 2004 cohort. Although the use of PBT increased for all disease sites treated, high-grade gliomas comprised a smaller percentage of patients treated in 2015 than in 2004, mirroring the trends seen for medulloblastoma and ependymoma. The substantial increase in use for medulloblastoma and ependymoma is likely secondary to multiple factors, including the well accepted use of PBT for these histologies in the pediatric population [1,2]. The data could be extrapolated to the adult population, likely contributing to the increase use in this population. Similarly, craniospinal irradiation is indicated in the ependymoma and medulloblastoma patient population and PBT offers superior dose distribution, reduction in normal organ dose, and potentially lower rates of secondary malignancy over photon based treatments [17].

These trends will be very interesting to monitor over time for a number of reasons. The number of indications and general acceptance of PBT is likely to increase, as there are a growing number of registries and prospective trials in APBT treatment incorporating particle therapy [18,19].

Additionally, the reimbursement models for radiation therapy as a whole are changing significantly beginning in January 2020 with the introduction of the alternative payment model (APM) for Medicare beneficiaries. The APM is anticipated to encompass 40% of the United States, and at this time there is no distinction for particle therapy in the reimbursement model [20]. Despite significant barriers in insurance coverage and prior authorization for PBT, our data demonstrates rapid growth in the use of PBT for management of APBT [21,22], suggesting the general acceptance of PBT among oncologists.

The Central Brain Tumor Registry of the United States (CBTRUS) reports primary intracranial neoplasms are non-malignant in 67.2% and malignant in 32.8% of cases. The most common malignant APBT cases are glioblastoma and other malignant gliomas, which represent 15.1% and 11.3% of all APBT cases, respectively [12]. Our study demonstrates that national trends in PBT use for APBT differ from the incidences of APBT reported by the CBTRUS, for example patients with glioblastoma made up 39.4% of the PBT patient population, as seen in Fig. 2. Our data suggest that adult patients with primary brain tumors treated with PBT have less comorbidities, higher income, are younger, and are more likely to have treatment at academic institutions. These findings are consistent with the demographic results reported by Ryckman et al., who analyzed photon and proton therapy trends in APBT through the NCDB between 2004 and 2014. In their analysis, only 0.6% of the APBT patient population was treated with PBT [13]. Our analysis

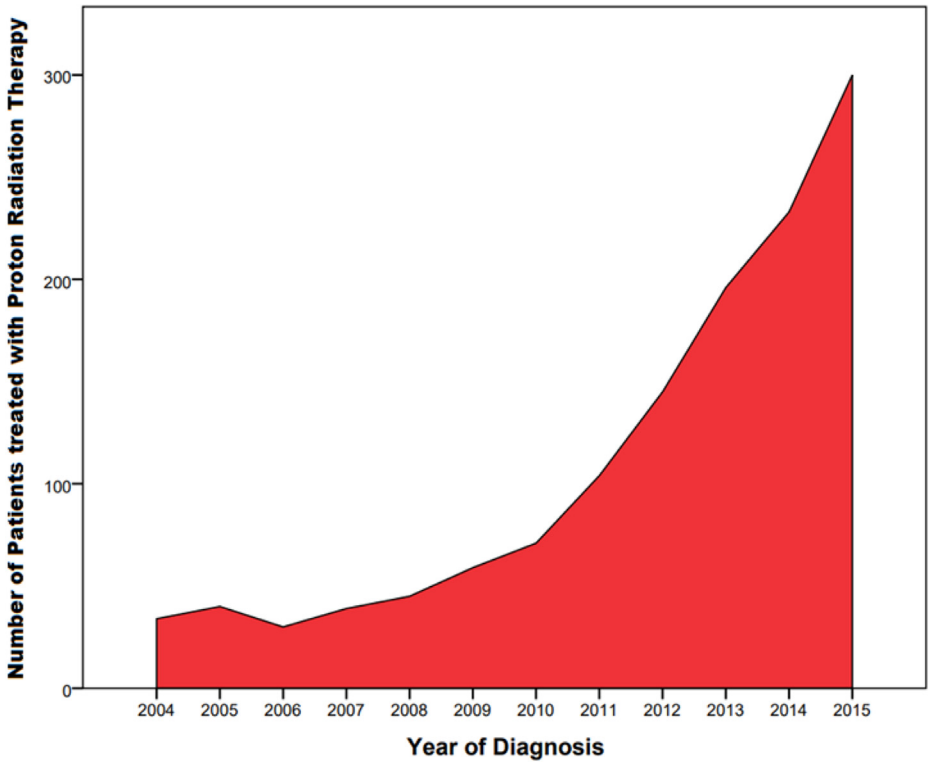

Fig. 1. Line graph demonstrating the total number of adult patients with primary brain tumors treated with proton beam therapy from 2004 to 2015.

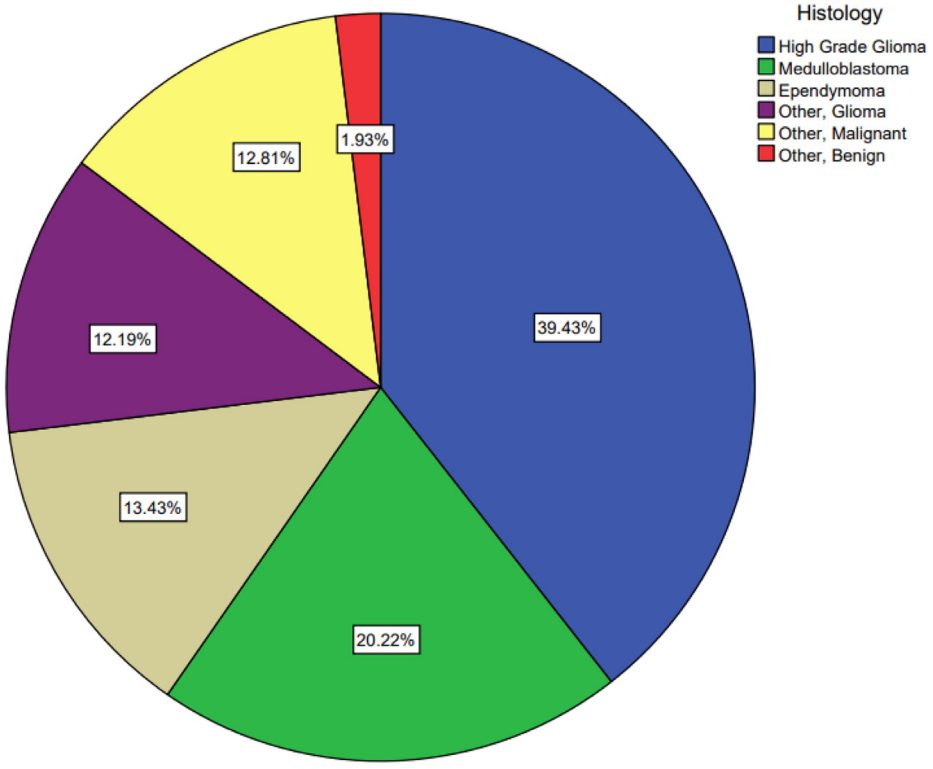

Fig. 2. Pie chart demonstrating the six histology categories treated as a percentage of the total adult primary brain tumor population from 2004 through 2015.

is distinguished by an additional year of accrued data in the NCDB and we report benign APBT histologies treated.

Tseng et al. evaluated both adult and pediatric CNS tumors treated with PBT from 2009 through 2017 under the umbrella of the Proton Collaborative Group (PCG) registry that consisted of 8 centers at time of publication. They identified 804 of 1,295 (62.1%) patients treated for CNS tumors were adults and the most common tumor classifications included astrocytic tumors, tumors of the

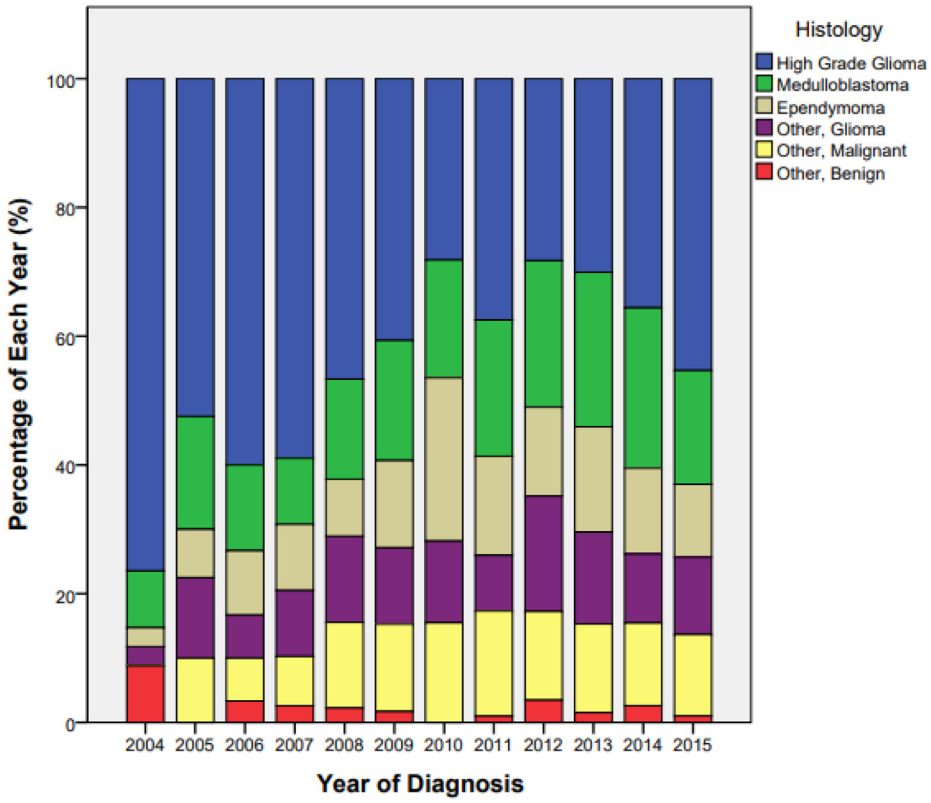

Fig. 3. Stacked bar graph demonstrating the six histology categories treated as a percentage of the total adult primary brain tumor population per year.

meninges, oligodendroglial tumors, and tumors of the sellar region [14]. Adding to these findings, our study highlights the changing trends overtime with reported annual trends as seen in Fig. 3.

Our study is limited due to the nature of a retrospective database review. As a national database, the NCDB is subject to biases based on errors or lack of reporting by the primary treating physician. Additionally, some important contributing factors go unreported or underreported and are unable to be analyzed. Strengths of using the NCDB are its ability to encompass a larger patient population and the ability to include more treatment related data. Our study details a larger cohort of adult patients than the Surveillance Epidemiology and End Results (SEER) data set from 2004 to 2013 and the previously mentioned PCG registry data set [14,23]. Additionally, the NCDB offers patient performance status and comorbidity information, as well as more treatment related information, including data on the specific radiation therapy modality used when compared to SEER.

In summary, our study characterizes the utilization of PBT in the management of malignant and benign APBT histologies treated over an eleven year span. Demonstrated in our review is the marked increase in the utilization of PBT in the treatment of APBT and variability in tumor histologies treated over this time.

5. Sources of support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.03.011.

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