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ORIGINAL ARTICLE

Helical IMRT Experience in Adult Medulloblastoma Radiotherapy

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OBJECTIVE

This study aimed to report the characteristics and treatment results of radiotherapy applied with the helical IMRT technique in the adult medulloblastoma patient group.

METHODS

In this study, adult medulloblastoma patients who received radiotherapy with the Helical Tomotherapy technique in the Ankara City Hospital Radiation Oncology Clinic between March 2019 and October 2022 were analyzed retrospectively. Primary endpoints are reporting of patients' survival and toxicity results.

RESULTS

The analysis was performed on 15 patients. The median follow-up time of the study was 9.4 (1.2–34.7). The median OS is 11.8 (3.9–37.26). The median PFS was 8.5 (1.28–34.73) months. A correlation close to the limit of significance was found between the risk group and PFS (p=0.051). Changes were recorded in the blood values of the patients before the treatment and before the boost treatment. It was determined that the white blood cell (p=0.001) and lymphocyte counts (p=0,001) decreased significantly before the boost treatment. The relationship of these values with lymphocyte count before boost treatment could not be shown statistically.

CONCLUSION

Radiotherapy with HT technique of adult MBL cases, which we rarely encounter in the clinic, has reversible and acceptable acute toxicity rates.

Keywords: Adult; helical IMRT; medulloblastoma; radiotherapy.

INTRODUCTION

Medulloblastoma is a CNS tumor that is among the tumors of embryological origin and is often located in the posterior fossa. It is a CNS tumor classified as a grade 4 tumor in the WHO CNS tumor classification due to survival rates and poor pathological features such as a high proliferation index.[1,2] It is mostly known as a childhood tumor and is the second most common tumor in this age group.[3] In adulthood, the incidence of this disease decreases considerably; it constitutes less than 1% of CNS tumors in this age group.[4]

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Medulloblastoma treatment requires a multimodal treatment regimen, including surgery, radiotherapy, and systemic agents, which is the standard today.[5] Because they are rarely observed in the adult age group, studies on treatment were mostly conducted in the pediatric patient group, and the data obtained from these studies were applied to the adult age group. Although there are no studies with high evidence value for treatment in the adult age group, the guidelines published by many groups provide guidance for treating these patients.[5–8]

Cerebro-spinal fluid (CSF) circulation is important in the spread of medulloblastomas. The malignant cells in the CSF circulation must be eradicated to control the disease. Therefore, radiotherapy applications in standard treatment are planned as additional boost treatment to the posterior fossa after craniospinal irradiation (CSI). CSI requires experience and caution, and it can be performed with many different techniques; the fact that the target volume is large, has an irregular structure, and is close to many critical structures in this large area makes this irradiation difficult. Especially when we consider the adult patient group, it is expected that while the size disadvantage of this area increases compared to the childhood patient group, the severity of the expected late side effects will decrease.

Craniospinal irradiation has evolved from determining the area of the patient with two-dimensional treatment to tomography-based IMRT techniques or specialized radiotherapy applications such as proton therapy.[9] The biggest problem of 3D-based planning and standard IMRT applied in many centers is still planning with more than one isocenter due to the size of the area and the difficulty of set-up. The isocenters number can be up to 3 areas for adult medulloblastoma patients. Hot areas in the gap junction region may impose extra care and attention on all treatment practitioners.[10]

Tomotherapy treatment means cross-sectional treatment derived from the word tomography.[11] The main idea is to place a linear accelerator on a CT-like ring gantry, modulating the treatment beam with a multi-leaf collimator system (MLC) to irradiate the patient as the patient moves along the long axis into the gantry. The system is also capable of cross-sectional imaging with MVCT for treatment area verification. Technical differences provide that large areas can be irradiated with a single plan, and area control can be achieved more easily than multi-isocentric plans.[12] On the other hand, cross-sectional irradiation (usually a 5 cm jaw opening) also causes some uncertainties and treatment concerns. Firstly, the increase in total treatment time and the continuation of CSF circulation makes difficult the estimation of the radiobiological effect on tumor control. Again, besides the better dose conformity provided by this technique, the side effect profile that will create the high volume low dose area is unclear.

This study aimed to report the characteristics and treatment results of radiotherapy applied with the helical IMRT technique in the adult medulloblastoma patient group.

MATERIALS AND METHODS

In this study, adult medulloblastoma patients who received radiotherapy with the Helical Tomotherapy technique in the Ankara City Hospital Radiation Oncology Clinic between March 2019 and October 2022 were analyzed retrospectively. We used Packer staging criteria to determine the risk classification of patients. The data from the planning system of the patients and their clinical characteristics from the hospital information system were recorded.

Simulation

Patients were immobilized at 5 points with a thermoplastic head-neck mask. CT images were obtained in the supine position in all patients, and the image section thickness was chosen as 2.5 cm. While the CT imaging area was determined to include the entire cranium cranially, the proximal 1/3 of the femur caudally was included in the imaging area. All patients were informed about the length of the treatment period and the importance of simulating in a comfortable treatment position.

Contouring

Target areas were determined according to the 2-phase treatment. In the first phase of treatment, all CSF circulation areas were targeted as CTV_CSI. At the end of the CTV drawing, the points specified in the SIOPE guideline were checked to ensure target accuracy and prevent possible misses due to IMRT.[13] The PTV_CSI margin is generally given differently in the cranial and spinal sections. The PTV margin was chosen as 5 mm (range 3–5 mm) in the cranial part and 7 mm (5–10 mm) in the spinal part. The boost area definition differs between clinicians. Posterior fossa boost or tumor bed boost was chosen for the boost target.

Planning

In the Planning tab, firstly, target structures (PTV brain, PTV spinal) and critical organs (OAR) determination

are defined. After the target and critical organ separation, the structures were ranked according to their anatomical proximity and importance to adjust the dose modulation. In our clinical routine, the field width (FW) is determined as 5 cm, the pitch factor is 0.430, and the modulation factor is 2.00, among the in-device parameters for craniospinal area irradiations. For boost plans, after choosing a 2.5 cm jaw width, a modulation factor of 2.5, and a pitch factor of 0.287, plans were created with 6 MV energy, which is the only energy value of the device. Optimization was made so that 100% of the PTV total volume would cover 95% of the prescribed dose, and the maximum dose limitation was defined as not exceeding 110% of the prescribed dose.

Primary Endpoint
Reporting of patients' survival and toxicity results.

Secondary Endpoint
Reporting the technical features of the treatment.

Statistical Analysis
Data exported SPSS. 26 (IBM Corp, Armonk, NY, USA). Nonparametric tests were used. Categorical demographic characteristics of the patients were calculated with Chi-square and Fisher's exact tests. Spearman's rank correlation test was used for univariate correlation analysis. Kaplan-Meier was used in univariate survey analyses and compared with the log-rank test. The statistically significant limit was accepted as 0.05 and below.

The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from Ankara City Hospital Ethics Committee with the number E1-22-2759 (29.06.2022).

RESULTS

Seventeen patients aged 18 years and older admitted with the diagnosis of medulloblastoma in the Radiation Oncology Clinic of Ankara City Hospital between March 2019 and October 2022 were analyzed retrospectively. Two of the 17 patients were excluded. One patient left the treatment at the seventh fraction, and the other one did not accept the treatment. Therefore, the analysis was performed on 15 patients. The median follow-up time of the study was 9.4 (range 1.2–34.7). The median age at presentation for RT was 29 (range 20–45). Six (40%) of the patients were female, and 9 (60%) were male. When evaluated in terms of risk group, 10 (66.7%) patients were standard risk; 5 (33.3%) were high risk. Spinal seeding was detected in 1 (6.7%) patient at diagnosis. The median time from surgery to RT was 36 days (range 28–54). All chemotherapy regimes were applied concurrent with radiotherapy. Daily oral temozolomide (75 mg/m²/day) was used for 1 patient; intravenous weekly vincristine (1.5 mg/m²/week) was used for 4; intravenous cisplatin (80 mg/m²/week) one day in a week + etoposide (120 mg/m²/week) three days in a week were used in 8 patients. Median RT duration is 42 days (range 36–65). The median CSI dose is 36 Gy (30.6–36). The median total RT dose is 54 Gy (54–55.8). The boost volume was posterior fossa in 10 patients (66.7%) and tumor bed in 5 patients (33.3%). Median treatment time was 607.4 sec (range 422.9–702.4). Median 99.4% (97.3–99.9) by volume receiving 95% of the target dose, and median 92.2% (85.8–97.5%) by volume receiving 100% of the target dose. Characteristics are summarized in Table 1. The mean and median values for planning parameters are summarized in Table 2.

Survival Analysis
All patients were alive at a median follow-up of 9.4 months (1.2–34.7). The median OS is 11.8 (range 3.9–37.26). No significant correlation was found between age (p=0.343); gender (p=0.51); risk group (p=0.234); simultaneous chemotherapy (p=0.517); molecular profile (p=0.173); total treatment time (p=0.302); the time between RT-surgery (p=0.315) and overall survival. During the follow-up period, 2 (13.3%) patients relapsed; the median PFS was 8.5 (range 1.28–34.73) months. There is no significant relationship between PFS and total RT time (p=0.784), gender (p=0.389); age (p=0.960); seeding (p=0.782); boost volume (p=0.527); molecular profile (p=0.265); simultaneous CT (p=0.782); and surgery-RT duration time (p=0.693). A correlation close to the limit of significance was found between the risk group and PFS (p=0.051).

Change in Hematological Parameters During Radiotherapy
Changes were recorded in the blood values of the patients before the treatment and before the boost treatment. It was determined that the white blood cell (p=0.001) and lymphocyte counts (p=0.001) decreased significantly before the boost treatment. Before switching to boost volume therapy, two patients (13.3%) had grade 3 leukopenia, three patients (20%) had grade 3 lymphopenia, and 10 patients (66.7%) had grade 4 lymphopenia. At the end of the treatment, grade 3 leukopenia was observed in 1 patient (6.7%), and grade 4 lymphopenia was observed in 1 patient (6.7%). The

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Table 1 Patient and treatment characteristics

Patient no	Gender	Age	Risk group	Seeding	Total treatment day	Concurrent Chemotherapy	CSI/total dose (gy)	Molecular profile	Residue
Patient 1	M	20	STD	No	42	Cisplatin+Etoposide	34,2 / 54	UNDEFINE	No
Patient 2	M	36	HIGH	No	40	Cisplatin+Etoposide	36 / 54	UNDEFINE	Yes
Patient 3	M	31	STD	No	42	Cisplatin+Etoposide	30,6 / 54	UNDEFINE	No
Patient 4	F	42	STD	No	45	Cisplatin+Etoposide	30,6 / 54	UNDEFINE	No
Patient 5	M	21	HIGH	No	41	Vincristine	36 / 54	UNDEFINE	Yes
Patient 6	M	29	STD	No	51	Cisplatin+Etoposide	36 / 54	SHH	No
Patient 7	F	22	STD	No	46	Cisplatin+Etoposide	36 / 54	SHH	No
Patient 8	F	22	HIGH	No	65	No	36 / 54	SHH	-
Patient 9	F	45	HIGH	Yes	46	Vincristine	36 / 54	SHH	No
Patient 10	F	23	HIGH	No	44	Vincristine	36 / 54	SHH	Yes
Patient 11	M	45	STD	No	41	Cisplatin+Etoposide	36 / 54	UNDEFINE	No
Patient 12	F	28	STD	No	40	Temozolomide	36 / 54	UNDEFINE	No
Patient 13	M	23	STD	No	36	Vincristine	36 / 54	UNDEFINE	Yes
Patient14	M	31	STD	No	56	Cisplatin+Etoposide	36 / 54	SHH	No
Patient 15	M	34	STD	No	42	No	36 / 55,8	SHH	No

CSI: Craniospinal irridation; Gy: Gray; F: Female; M: Male; HIGH: High risk; STD: Standart risk; SHH: Sonic hedgehog activate

existence of a relationship between body integral dose and the development of lymphopenia was also tested. For this purpose, body V20, V25, and V30 values were recorded. In the analysis, the relationship of these values with lymphocyte count before boost treatment could not be shown statistically (Table 3).

No relationship was found between the development of lymphopenia and age (p=0.932), gender (p=0.765), and the presence of simultaneous chemotherapy (p=0.565). There is no relationship between pre-treatment blood values and applied dose.

DISCUSSION

In this study, we reported our adult medulloblastoma radiotherapy experience with tomotherapy to obtain two data: 1. Treatment results of adult medulloblastoma patients, a rare patient group, and 2. Experience using tomotherapy in this disease group. In our cohort of 15 patients, at a median 9.4-month follow-up, the median survival was calculated as 11.8 months, and the median PFS was 8.5 months. No patients were dead at analysis. Only the disease risk group showed a close relationship to the significance limit among the variables examined on survival parameters.

Medulloblastoma has an incidence of 0.6–1 case per million in adult patients.[4] Radiotherapy data most commonly come from pediatric trials, so craniospinal radiotherapy is essential for adult patients too.[6,14] Standard treatment includes maximal safe resection, craniospinal radiation (CSI), and chemotherapy (CT).[6,7,15] The difference in treating adult and pediatric medulloblastoma cases is generally observed in the chemotherapy schemes. The low tolerance to the systemic agents selected in childhood in the adult group caused this difference.[8] Although standard care is still based on clinical classification, molecular classification began to be translated into clinics.[16,17]

Although our short follow-up series could not provide generalizable data in terms of overall survival, it was thought that acute toxicity data would contribute to the literature on helical tomotherapy experience and integral dose effects. Grade 3 nausea, vomiting, dermatitis, and esophagitis were not reported in any patients. The hematological toxicity records were evaluated, and it was observed that the patients experienced severe hematological toxicities at the end of the CSI phases. On the other hand, the non-standard use of chemotherapy and the different selection of systemic agents make it difficult to comment on the factors affecting the development of hematological toxicity.

One of the largest series evaluating treatment outcomes of adult MBL cases is the study by Ma et al.[18] using the SEER database. This study reported treatment results of 857 patients diagnosed between 1973 and 2015, and overall survival was reported as five years. One of the interesting results of the study is that the survival of the patients who received chemotherapy

Table 2 Planning parameters

CSI dose	Total dose	Heart mean dose	Spleen mean dose	Lung V5	Lung V20	Pitch factor	Treatment time	Total MU	Coverage V95%	Coverage V100%
Med 36Gy (30.6–36)	Med 54Gy (54–55.8)	Med 812cGy (473–1238)	Med 523cGy (334–891)	Med 802.5cGy (100–1721)	Med 99cGy (26.8–224)	Med 0.43 (0.29–0.49)	Med 607.4 (422.9–702.4)	Med 206.764 (139.993–247.261)	Med 99.4 (97.3–99.9)	Med 92.2 (85.8–97.5)

CSI: Craniospinal irradiation; MU: Monitor unit; Med: Median; Gy: Gray

Table 3 Relationship between lymphocyte counts and integral dose parameters

Dose parameter	p	R score
Body V20	p=0.091	R: -0.444
Body V25	p=0.096	R: -0.445
Body V30	p=0.061	R: -0.494

was found to be lower than those who did not (54 m vs. 67 m / HR 1.4515, 95% CI 1.26–1.671, p<0.001). On the other hand, the effect of radiotherapy on survival was also shown in adult patients (66 months vs. 25 m HR 0.581, 95% CI 0.48–0.70, p<0.001).

In a recent systematic review, the treatment results of adolescent and young adult MBL cases were evaluated with 18 studies, and 5-year survival was reported between 40% and 89%.[19] The difficulty created by the differences in the practices in reaching the general opinion was also emphasized in this study. Reducing the heterogeneity in studies with clinical studies and standardizing treatment parameters related to treatment timing, chemotherapy selection, and radiotherapy dose characteristics will provide more accurate data on survival outcomes.

The second issue we focus on is the clinical experience regarding the application of the helical tomotherapy technique in this patient group. Craniospinal irradiation is a radiotherapy application that is technically challenging and requires experience due to its field size and proximity to many critical organs. This issue can become more challenging in adult patients considering the area size. The irradiation technique is chosen in different ways, such as two-dimensional, three-dimensional, and current IMRT techniques, depending on the knowledge and experience of the clinic.

We think that the fact that our hospital is a tertiary center effectively reaches a high number of patient data in a short time compared to the literature. In our center, treatment with a helical tomotherapy device is generally planned for patients undergoing CSI. Especially in the adult age group, the increase in the number of isocentres and caused uncertainty has been effective in this trend.

Studies on the use of helical tomotherapy in CSI in the literature started with dosimetric studies (Table 4), and then clinical data were contributed. The result generally obtained in dosimetric studies is HT superiority in target volume wraps, and on the other hand, integral dose increases as expected. Another issue to consider when evaluating these studies is that not all CTs used in planning belong to the adult patient group.

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Table 4 Dosimetric studies on using HT for CSI

Study	Patient number	Comparaising techniques	Results
Zong-Wen et al. 2017[20]	5	HT VMAT 3D-CRT	- In the HT technique, high-dose areas were found to be lower, while low-dose areas were found to be higher. - Conformity is lower in the 3D-CRT technique.
Sun et al. 2019[10]	12	HT IMRT VMAT	- HT offers superior outcomes regarding PTV conformity, PTV homogeneity and critical OAR sparing compared with IMRT/VMAT.
Hegazy et al. 2022[21]	5	3D-CRT HT	- Minimum dose values for PTV are more optimal for HT plans. - Lower maximum and mean doses for OAR with the HT technique - Longer treatment time with HT

Studies reporting clinical data were studied in heterogeneous patient groups. HT: Helical tomotherapy; CSI: Craniospinal irridation; VMAT: Volumetric modulated arc therapy; 3D-CRT: 3 dimensional conformal radiotherpy

Gupta et al.[22] reported the results of feasibility studies on using HT in CSI in 2016. Clinical results of 20 patients with a median age of 15 were reported with a median follow-up of 5 years. Four (20%) patients needed growth factor or platelet support during craniospinal irradiation. Significant late neurotoxicity was reported in only one (5%) patient. No symptomatic radiation pneumonia or second new malignancy was reported in any of the patients.

Schiopu et al.,[23] on the other hand, reported a series of 45 diseases with different diagnoses in 2017. Similarly, while there were acute hematological toxicities of Gr3 and above, late toxicity of Gr3 and above was not reported.

A current valuable study on this subject was reported by Turcas et al.[12] in 2023. In this study, 55 publications evaluating HT in CSI were examined. Nine of these studies are data of adult patients undergoing CSI for different diagnoses, and hematological toxicities have been reported to a large extent. Other noted toxicities are xerostomia, alopecia, and nausea and vomiting. The researchers reported that there are studies indicating better target wrapping with HT, and similar results were obtained with other techniques in terms of toxicity.

The retrospective nature of our study, the short follow-up period, and especially the difference in chemotherapy schemes are its weaknesses. On the other hand, it is thought to contribute to the literature regarding adult medulloblastoma cases and report the results of the HT experience, which has not yet become widespread in the use of CSI.

CONCLUSION

Radiotherapy with HT technique of adult MBL cases, which we rarely encounter in the clinic, has reversible and acceptable acute toxicity rates. More patient data are needed on the contribution of this technique to survival in this patient group that has not yet reached a standard treatment scheme.

Ethics Committee Approval: The study was approved by the Ankara City Hospital Ethics Committee (no: E1-22-2759, date: 29/06/2022).

Authorship contributions: Concept – G.A.İ.; Design – G.A.İ., A.K.A., B.T.; Supervision – G.A.İ., İ.P.A.; Materials – G.A.İ., İ.P.A., Z.G.; Data collection and/or processing – A.K.A., B.T.; Data analysis and/or interpretation – İ.P.A., A.K.A., B.T.; Literature search – G.A.İ., İ.P.A.; Writing – G.A.İ., İ.P.A., Z.G., Y.T., A.K.A., B.T.; Critical review – Y.T., İ.P.A.

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