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Research Article

Treatment planning based dosimetric impact of Radiotherapy on Anxiety-Related Cognitive Impairment in Head, Neck and Brain Tumour Patients

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ABSTRACT

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Radiotherapy is a common method for treating cancer, but it can have unintended side effects such as cognitive impairment (anxiety). This study aims to investigate the dosimetry impact on cognitive impairment including anxiety caused by radiotherapy for head, neck, and brain tumors based on treatment planning systems. This analytical cross-sectional study was conducted in 2024 at the Isfahan Radiotherapy Center (Seyed al-Shohada Hospital). It involved 30 patients with head, neck, and brain tumors who underwent radiotherapy using treatment planning systems (Prowess Panther). The treatment planning system (TPS), Prowess Panther, accurately calculated the radiation doses to brain structures associated with cognitive functions like memory, which helped assess the link between radiation exposure and anxiety. The doses received by brain structures related to memory (amygdala) were calculated using the treatment planning systems (Prowess Panther) and compared with the incidence of cognitive impairment (anxiety). Data analysis was performed using SPSS-24 software and analyzed. Results indicated a significant correlation between the doses received by memory-related brain structures and the incidence of anxiety. Specifically, 23.3% of patients experienced mild or higher anxiety levels (score of 14 or more), with an average anxiety score of 8.63 (±3.56). The patient treatment outcomes showed that most of them well responded to radiotherapy. However, those receiving higher doses of memory-related brain structures experienced increased anxiety, which may affect long-term recovery. These patients had higher average, maximum, and minimum doses compared to those who did not experience anxiety after treatment. These findings suggest that precise dosimetry of memory-related brain structures in radiotherapy planning may help mitigate the risk of developing memory-related neurocognitive disorders, thereby improving patient outcomes.

KEYWORDS

Radiation therapy, Neurological memory disorder (anxiety), Treatment planning system.

I. INTRODUCTION

Cancer, a leading cause of death globally, accounted for approximately 10 million deaths in 2020 alone [1]., characterized by the rapid and uncontrolled growth of abnormal cells that can metastasize to other organs. [2,3]. This uncontrolled proliferation can result from

minor disruptions in the regulatory signals governing normal cell growth, leading to significant health impacts, particularly in developing countries where cancer-related mortality is steadily increasing [4,5].

Radiotherapy is one of the primary treatment methods for cancer, and it is estimated that more than half of cancer patients will undergo radiotherapy during their treatment. In this method, high-energy rays such as X-rays, gamma rays, or electrons with controlled energy are used to destroy or shrink cancer cells. Radiotherapy can be used alone to treat certain types of cancer. It can also be used in conjunction with other treatment methods such as surgery or chemotherapy [6].

A brain tumor refers to an abnormal growth of cells within the brain or spinal canal. The growth of these tumors can lead to increased pressure inside the skull and spinal canal. The origin of the tumor can be from brain tissue itself or it can spread to the brain from elsewhere (metastasis). Generally, a brain tumor is an abnormal mass (neoplasm) inside the skull or spinal canal. Brain tumors are categorized into two types: benign (non-cancerous) and malignant (cancerous) [7,8].

Today, the choice of radiotherapy technique for brain tumors is usually between three-dimensional conformal radiotherapy (3-D CRT), intensity-modulated radiation therapy (IMRT) with fixed beam angles, or volumetric modulated arc therapy (VMAT). The selection of the appropriate method depends on various factors, such as the type and location of the tumor, the overall health of the patient, and the availability of equipment and treatment facilities [9].

Radiotherapy, a common cancer treatment, can have a range of side effects that vary depending on the treated area, radiation dose, and the patient's overall health [10]. When treating head and neck cancers, the brain often receives incidental doses of radiation, potentially causing neurocognitive changes and affecting the patient's quality of life [22,23].

Radiotherapy, a common method for cancer treatment, can damage not only cancerous cells but also healthy brain and nervous system cells. This damage can lead to various neurological disorders, including memory problems. One of the most common cognitive disorders associated with radiotherapy is memory impairment. It is estimated that 20 to 50 percent of patients undergoing radiotherapy for head and neck cancers or brain tumors experience varying degrees of memory impairment. Symptoms of memory impairment in radiotherapy patients may include [11]:

• **Difficulty Learning and Retaining New Information:** Patients may have trouble learning new things such as names, dates, or directions.

• **Difficulty Remembering Old Information:** Patients may struggle to recall information they previously knew, such as past events or personal details.

• **Difficulty with Concentration and Attention:** Patients may find it challenging to focus on a task or conversation for extended periods.

• **Difficulty Finding Words:** Patients may have trouble finding the right words to express their thoughts [12].

There is no definitive treatment for memory impairment in patients undergoing radiotherapy, but various methods can help manage this issue, including [13]:

• **Cognitive Strategies:** Patients can use various strategies such as making lists, using calendars, and setting reminders to assist with their memory.

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• **Cognitive Strategies:** Patients can use various strategies such as making lists, using calendars, and setting reminders to assist with their memory.

• **Cognitive Exercises:** Some studies have shown that cognitive exercises can help improve memory in patients undergoing radiotherapy.

• **Medications:** Certain medications, such as cholinesterase inhibitors, may help alleviate symptoms of memory impairment in some patients.

Anxiety is a natural and common reaction to stress or danger. It is an uncomfortable and nervous feeling or state associated with various physical and psychological symptoms [14].

Symptoms of anxiety include [15]:

• **Physical Symptoms:** Palpitations, sweating, trembling, rapid breathing, muscle pain, dry mouth, nausea, headache, dizziness, fatigue.

• **Psychological Symptoms:** Feelings of nervousness or agitation, difficulty concentrating, irritability, restlessness, trouble sleeping, feelings of fear or panic, negative thoughts.

This study aims to investigate the dosimetric impact of radiotherapy on cognitive impairment, specifically focusing on anxiety levels in patients with head, neck, and brain tumors. The study aims to derive the dosimetric data from the patient's plan created within the TPS. By assessing doses received by memory-related brain structures, especially the amygdala, the correlation between radiation exposure and the incidence of anxiety in this patient population was examined.

II. MATERIAL AND METHODS

In this study, data related to radiotherapy doses and clinical characteristics of patients undergoing radiotherapy for brain, head-and-neck tumors were collected over a two-month follow-up period. This information included the contouring of organs associated with neurological anxiety-related complications. The Prowess Panther is employed as a treatment planning system (TPS). In this study, 30 patients who followed inclusion and exclusion criteria and provided written consent were examined.

Using Equation 1 and the data from prior studies, an initial sample size of 25 was calculated to study neurological side effects from radiotherapy. Accounting for a 30% non-cooperation rate, the final sample size was adjusted to 30, with participants selected from the Isfahan radiotherapy center (Seyed al-shahada Hospital)

$$n = \frac{Z_{1-\alpha}^2 . p(1-p)}{d^2} \quad (1)$$

$$Z_{1-\alpha}^2 = (1.96)^2$$
$$p = 0.04$$
$$\alpha = 0.05$$
$$d = 0.10$$

Selection Criteria:

1. Adults (aged 18 and above) with a diagnosis of brain or head-and-neck tumors undergoing radiotherapy.

2. Patients who provided written informed consent to participate in the study.

3. Patients able to complete follow-up evaluations during the 2-month study period.

Exclusion Criteria:

1. Patients with pre-existing neurological disorders (such as epilepsy, dementia, or significant cognitive impairments) that could confound the study results.

2. Patients with metastatic brain tumors or tumors outside the scope of the study (i.e., non-head-and-neck regions).

3. Patients who experienced significant complications during treatment, such as severe infections or other conditions that required immediate medical intervention.

4. Patients unable or unwilling to complete the Beck Anxiety Inventory or follow-up assessments.

The aim of this study was to assess grade 1 toxicity related to cognitive neurological disorders (according to CTCAEv4.03), meaning that the patient should be able to maintain independence in performing daily activities. Patient follow-up was conducted in two stages: 1) before the start of radiotherapy and 2) 2 months after the completion of radiotherapy. At each stage, patients were asked to complete a questionnaire to collect clinical information.

In this study, information was collected in three stages:

A. *Treatment Planning and Contouring:*

During the treatment planning stage for patients with brain tumors, a three-dimensional conformal radiation therapy (3D-CRT) technique was utilized. Each patient's treatment plan included the careful contouring of organs at risk, with a specific focus on the amygdala due to its association with cognitive functions.

To reduce the risk of cognitive impairment associated with radiation exposure, the maximum dose to the amygdala was restricted to 20 Gy. Additionally, the mean dose was maintained below 12 Gy. This is recommended to minimize neurological side effects while effectively targeting the tumor [25,26].

B. *Data Extraction:*

Patient records were reviewed, and the necessary clinical and dosimetry information, including the prescribed dose for the mentioned organs, was extracted.

C. *Patient Follow-up:*

Patients were followed up for two months after the completion of radiotherapy to assess the occurrence of anxiety-related neurological side effects.

All patients were followed up for 2 months to assess potential neurological side effects of radiotherapy, including anxiety.

Anxiety is a natural bodily response to challenges and dangerous situations. This response is associated with symptoms such as palpitations, muscle tension, and mental worries. While anxiety can be beneficial at normal levels, it can sometimes escalate into uncontrollable and excessive fear and worries, causing disruptions in an individual's daily life.

The Beck Anxiety Inventory (BAI) is a tool designed to measure the level of anxiety in individuals. This questionnaire consists of 21 questions that are designed to be easily answered by people of all ages, including both adolescents and adults. As previously mentioned, individuals answer these questions based on their perceptions of their characteristics and traits. The questions cover a broad range of topics, including the following:

- Feeling hot
- Trembling legs
- Palpitations
- Fear of impending disaster
- Numbness and tingling
- Nervousness
- Panic
- Shaking hands
- Dizziness and confusion
- Feeling unsteady
- Fear of losing control
- Difficulty breathing
- Feeling weak
- Muscle tension
- Fear of death and oblivion
- Fainting and weakness
- Startling easily
- Indigestion
- Blushing and flushing
- Sweating

Each question is answered based on the severity of the symptoms experienced, and responses are scored from 0 to 3, with the total score ranging from 0 to 63. This inventory helps in evaluating the intensity of anxiety symptoms and can aid in understanding the impact of anxiety on daily functioning [16].

0 to 13: Mild or no symptoms of anxiety and depression

14 to 19: Mild anxiety and depression

20 to 28: Moderate anxiety and depression

29 to 63: Severe anxiety and depression

In this study, mild or higher anxiety and depression (a score of 14 or more) were considered as the endpoint. The questionnaires used in this study are included.

Besides, data were described using statistical measures such as mean, standard deviation, frequency, and percentage frequency. To compare two groups for significant differences, the Chi-square (χ^2) test with an alpha level of 0.05 was used. All statistical analyses were conducted using SPSS version 24, with a significance level of 5%.

For the analysis of the Beck questionnaire, descriptive statistics including mean, standard deviation, frequency, and percentage frequency were employed. To assess the normality of the distribution of errors in quantitative variables, the Kolmogorov-Smirnov test was used. For inferential statistics, the Mann-Whitney U test and the Kruskal-Wallis test were applied. All analyses were performed in SPSS version 24, with a significance level of 5%.

III. RESULT

In this study, the 30 patients with cancers of the head, neck, and brain tumors, who were treated at the Isfahan Radiotherapy Center (Seyed al-shahada Hospital) between 2023 and 2024, were examined. The average age of the patients was 44.6 years, with 70.0% of them being female. 66.7% of the patients received chemotherapy concurrently with radiotherapy, and 23.3% had a history of surgery. The oldest participant in this study was a 71-year-old woman, and the youngest was a 20-year-old woman. Eleven patients (36.7%) had a family history of cancer. The patients' body mass index (BMI) ranged from 18.5 to 24.9. (Table 1)

TABLE 1: THE CLINICAL CHARACTERISTICS OF PATIENTS

Frequency (Percentage)	Levels of Variable	Variable
7(23.3)	20-35	age
13(43.3)	36-50	
9(30.0)	51-70	
1(3.3)	>71	
21(70)	women	sex
9(30)	Men	
7(23.3)	Yes	Surgical History
23(76.7)	No	
11(36.7)	Yes	Underlying Disease
19(63.3)	No	
11(36.7)	Yes	Family History of Cancer
19(63.3)	No	
0(0.0)	>18.5	Body Mass Index (BMI)
15(50.0)	<18.5	
14(46.6)	24.9	
1(3.3)	>25	
0(0%)	>29.9	
0(0%)	<30	
0(0%)	39.9	
20(66.7)	Yes	Chemotherapy
10(33.3)	No	

Two months after the end of treatment, patients were examined for potential side effects. The findings of this examination are presented in Table 2 and illustrated in Fig. 1. As shown in Table 2 and Fig. 1, the average levels of anxiety were categorized as follows:

TABLE 2: MEAN ANXIETY SCORES BASED ON QUESTIONNAIRE DIMENSIONS

Dimension	Mean (Standard Deviation)	Frequently(percent)
Mild or No Depression (0 to 13)	2.13(0.75)	(76.6) 23
Mild Anxiety and Depression (14 to 19)	0	0 (0)
Moderate Anxiety and Depression (20 to 28)	22.75 (1.15)	4 (13.4)
Severe Anxiety and Depression (29 to 63)	39.66 (2.22)	3 (10.0)
Total Anxiety	8.63 (3.56)	7 (23.3)

As indicated, the overall anxiety levels among the patients revealed that 23.3% experienced anxiety (score of 14 or more), while the average anxiety score was 8.63 (±3.56).

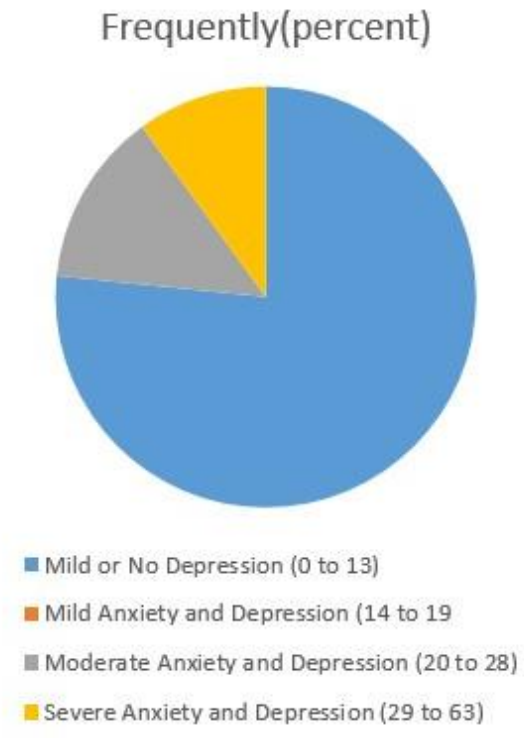

Fig. **1**: Mean Anxiety Scores Based on Questionnaire Dimensions

The frequency of responses from cancer patients undergoing radiotherapy to various items on the Beck Anxiety Inventory is presented in Table 3 and illustrated in Fig. 2. The items with the highest percentage of "Not at All" responses included "Dizziness and Lightheadedness," "Variable (Unstable) Mood," "Feeling of Suffocation," "Hand Tremors," and "Difficulty Breathing," each receiving 80.0% of responses.

TABLE 3: FREQUENCY OF RESPONSES TO VARIOUS ITEMS ON THE BECK ANXIETY INVENTORY

Item	Not at All (%)	Slightly (Didn't bother me much) (%)	Moderately (Very unpleasant but I tolerated it) (%)	Severely (I couldn't tolerate it) (%)
1. Numbness and tingling	60.0	23.3	13.3	3.3
2. Feeling of warmth	56.7	26.7	13.3	3.3
3. Trembling in legs	63.3	23.3	13.3	0.0
4. Inability to relax	70.0	16.7	13.3	0.0
5. Fear of a bad event	70.0	20.0	13.3	0.0
6. Dizziness and lightheadedness	80.0	13.3	10.0	0.0
7. Palpitations and breathlessness	76.7	10.0	10.0	3.3
8. Variable (unstable) mood	80.0	10.0	10.0	0.0
9. Panic	76.7	10.0	13.3	0.0
10. Nervousness	76.7	13.3	10.0	0.0
11. Feeling of suffocation	80.0	13.3	6.7	0.0
12. Hand tremors	80.0	10.0	10.0	0.0
13. Body tremors	76.7	16.7	6.7	0.0
14. Fear of losing control	76.7	16.7	6.7	0.0
15. Difficulty breathing	80.0	10.0	10.0	0.0
16. Fear of dying	76.7	16.7	6.7	0.0
17. Fearful (state of fear)	70.0	20.0	6.7	3.3
18. Indigestion and stomach discomfort	70.0	23.3	6.7	0.0
19. Fainting	63.3	23.3	6.7	6.7
20. Blushing	53.3	33.3	10.0	3.3
21. Sweating (not due to heat)	56.7	26.7	13.3	3.3

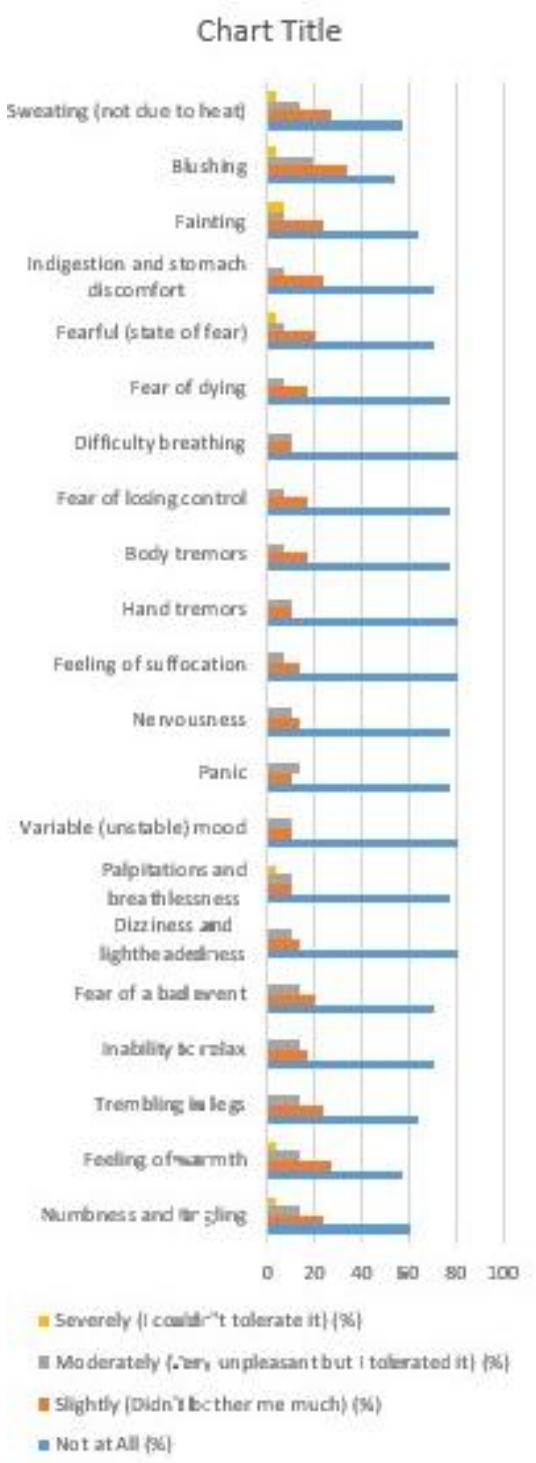

Fig. **2**: Frequency of Responses to Various Items on the Beck Anxiety Inventory.

A comparison of dosimetric data revealed that patients with anxiety complications received higher average, maximum, and minimum doses to the amygdala compared to those without complications. The average dose to the amygdala in patients with anxiety was 16.5 Gy (±3.2 Gy), while patients without anxiety had an average dose of 10.2 Gy (±2.8 Gy). The maximum dose recorded for the amygdala in the anxiety group was 24.0 Gy, while in the non-anxiety group, it was 15.0 Gy. These results indicate a significant correlation between radiation doses received by the amygdala and the incidence of anxiety in patients undergoing radiotherapy.

IV. DISCUSSION

Radiotherapy, as one of the three effective treatment methods for cancer, plays a key role in treating more than half of the patients. The main goal of radiotherapy is to inflict maximum damage to the tumor while causing the least damage to the surrounding healthy tissues. Therefore, in treatment planning, the priority is to apply the maximum dose to the tumor while considering dose limitations for the surrounding organs at risk (OAR). However, during radiotherapy, it is inevitable that doses also reach non-target tissues and organs also receive some level of radiation exposure, which can lead to side effects, both acute and long-term.

In patients undergoing treatment, while a considerable amount of research exists on the dosimetric aspects of radiotherapy and its immediate effects, there is limited literature exploring the psychological consequences, such as anxiety and depression. Furthermore, the role of these side effects on patients' quality of life is an area of growing concern. The present study contributes to this body of research by investigating the relationship between radiotherapy doses and the onset of anxiety in patients with head, neck, and brain tumors.

Studies conducted on dosimetry, anxiety, and depression in patients undergoing radiotherapy are very limited and mostly focus on the impact of these side effects on patients' quality of life. McDowell and colleagues conducted a study in 2018, the results of which were similar to the findings of the present study regarding the incidence of these side effects. In this study, most patients were treated with a dose of 2 Gy

per fraction. Consequently, 25 percent of the patients exhibited symptoms of depression and 37 percent showed symptoms of anxiety, which had a significant impact on their quality of life [19]. These results are similar to the findings in our study, where 23.3% of patients experienced mild or higher levels of anxiety.

Jaspers and colleagues conducted a study in 2019 to investigate the impact of radiotherapy on the memory of patients with low-grade glioma. In this study, 29 patients were treated with DR-AVLT, and their memory was assessed before treatment and 18 months after treatment using the Auditory-Verbal Learning Test (AVLT). The results showed that 14 out of 29 patients (48%) experienced learning impairments after radiotherapy [20]. While cognitive impairments were not directly assessed in our study, the link between radiotherapy and cognitive dysfunction may also contribute to the psychological symptoms of anxiety.

Mr. Ma and colleagues, in a 2017 study titled "Prospective Evaluation of the Effects of Hippocampal Radiation Dose-Volume and Memory Deficits After Cranial Radiotherapy," examined the relationship between hippocampal radiation dose and memory loss in patients undergoing cranial radiotherapy. In this study, the HVLT/R test was used to assess patients' memory. The results indicated a direct relationship between the hippocampal radiation dose and memory decline across a wide range of doses. Specifically, receiving a 22 Gy dose to 50% of the hippocampus led to a 20% reduction in patients' memory [21]. Our findings also suggest a dose-dependent relationship between radiotherapy and psychological distress, specifically anxiety.

In the present study, as shown in the table from the previous section, the side effect of anxiety was examined 60 days after treatment. According to the results from the previous chapter, mild or higher levels of anxiety and depression (a score of 14 or more) were considered the final side effects. Overall, 7 patients experienced anxiety as a side effect. Additionally, the minimum, average, and maximum doses in patients with this side effect were significantly higher than in patients without the side effect.

V. CONCLUSION

In this study, the possibility of dosimetric comparison between patients with and without neuropsychological anxiety disorders undergoing treatment for head, neck, and brain tumors was investigated. The results showed that dosimetric factors were higher in patients with anxiety disorders compared to those without. However, to determine the impact of the dose per session on damage to the amygdala and other sensitive organs, more experimental studies and long-term patient follow-ups are needed to assess the effects and their relationship with dosimetric factors.

Additionally, the average anxiety scores in cancer patients undergoing radiotherapy showed significant differences across variables such as gender, family history of cancer, and chemotherapy.

OTHER RECOMMENDATIONS

This study commenced after receiving ethical approval from the research committee of Khorasgan Islamic Azad University. This study was conducted with the permission and support of Isfahan Islamic Azad University, Iran.

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