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ORIGINAL ARTICLE

Differences in Parotid Dosimetry in Whole Brain Irradiation Plans Covering Cervical Vertebrae One Versus Two

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ABSTRACT

Background: Whole-brain radiation therapy (WBRT) is one of the most frequently employed therapies in radiation oncology. When managing cases that have several brain metastases, WBRT is commonly used in the palliative care context. WBRT is often provided utilizing opposing lateral fields with 6 MV photons and gantry-rotation or multi-leaf collimators (MLCs) designed to spare the lenses bilaterally. The present work aims to evaluate dose received by parotid glands (PG) in WBRT in plans covering cervical vertebrae one versus two.

Methods: This prospective-clinical trial was conducted on Clinical Oncology and Nuclear Medicine Department, in Zagazig University Hospitals from (September 2022 to May 2023) where the eligible patients received WBRT.

Results: There was high significant correlation between C1 plan and C2 plan concerning PTV mean dose, but there was non-significant correlation regarding PTV V95, V90 and V105. Statistical analysis of results showed, there was significant correlation between plan C1 and plan C2 regarding total PG that received more than 25Gy ,and one of the gland that received more than 20 Gy. There was non-significant correlation between plan C1 and plan C2 regarding the PG volume, but there was high significant correlation regarding the PG mean dose, V20 and V25.

Conclusions: The dose given to the PGs is much increased when the inferior border of a typical whole-brain field is extended to include the C2 vertebral body. This is expected to lead to a higher xerostomia incidence.

Keywords: Whole brain radiotherapy (WBRT), xerostomia, parotid dose.

INTRODUCTION

Whole brain radiation therapy (WBRT) is essential for management of cases with both detectable brain metastases (BMs) and the prevention of microscopic lesions [1].

Radiotherapy has historically been used extensively in BMs management. Palliative WBRT in managing cases with numerous BMs has previously been revealed to enhance neurological symptoms and median overall survival from around 1 to 2 months to 3 to 6 months [2].

Cases with a good prognosis and minimal brain illness are increasingly treated with stereotactic radiosurgery as technology advances. Nevertheless, WBRT continues to play a crucial role in cases with a high number of BMs or worse outcomes [3,4].

WBRT dose ranging between 2000 and 4000 cGy. No standard dosage fractionation for WBRT, but cases are now frequently managed with 3750 cGy in 15 fractions [5].

WBRT has well-known side effects including as tiredness, baldness, and neurocognitive abnormalities. To present, no reports of dry mouth or xerostomia have been made. To our knowledge, no research have described xerostomia after WBRT, there are many papers discussed this point [6].

The poor prognosis related to BMs previously had little significance in assessing WBRT side effects on the long-term, as it wasn't anticipated that cases would survive for a long time to had these late impacts. Nevertheless, reducing its toxic effects and promoting quality of life (QOL) are crucial [7].

Because of the poor prognosis for metastatic tumors, side effects from this treatment are frequently overlooked. Several prognostic approaches have categorized cases with BMs, with overall survival range of 3-12 months [8].

Attempts have been undertaken to investigate the neurocognitive implications of WBRT, in addition to potential strategies to minimize these toxicities. We know very little about the WBRT impacts on parotid gland (PG) dosage and xerostomia [9].

Cases undergoing routine WBRT without PGs prospective delineation led to clinically severe acute xerostomia in around 35% of instances [10].

Most research has concentrated on WBRT neurocognitive deleterious impact, however xerostomia has never been reported [11].

Several studies conducted over many years on head and neck RT have demonstrated the need to reduce radiation exposure to the PGs to improve QOL and reduce dry mouth. Despite having large dosages, the PGs are not generally avoided or demarcated during WBRT [12].

The present work aims to evaluate the dose received by PGs in WBRT in plans covering first cervical vertebra versus second cervical vertebra, and to make a dosimetric analysis.

METHODS

This prospective-clinical trial was conducted on Clinical Oncology and Nuclear Medicine Department, in Zagazig University Hospitals from (Septemper 2022 to May 2023) where the eligible patients received WBRT. Verbal and written informed consent was obtained from all participants after an explanation of the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB).

Cases with the following criteria were included; cases undergoing WBRT at a dosage of 30-63 Gy in 10–20 fractions (2–3 Gy per fraction) for any diagnosis. Histopathologically-proven malignancy.

Normal hematological, renal and liver functions.

Cases with the following characteristics were excluded, cases with prior exposure to PG radiation or impaired mental status.

All study population had the following diagnostic work up thorough medical history, clinical and radiological (MRI brain) examination, and laboratory investigation.

Treatment Plan:

Radiotherapy protocol:

Cases received three-dimensional external-beam radiotherapy (RT) using a linear accelerator with an energy of 6 MeV or Co-60. Prior to therapy, all patients had CT simulation. CT scans were acquired at 2mm intervals from the skull's vertex to the top of the thoracic spine. The entire brain, left and right PGs were contoured.

Immobilization:

The position of the patient remained identical for localization on a CT scanner or simulator and during subsequent treatment. All the patients were treated in supine position, using a thermoplastic head mask for simulation and treatment.

Planning:

The CT simulation pictures were used to create two options for treatment for every individual. Six MV photons were used in an opposed lateral arrangement to give therapy in each plan. The first plan extended the inferior field border to encompass all of C1, while the second plan established to encompass all of C2.

The WBRT strategies were alternatively standard; isocenters were positioned within the posterior orbit to generate a quasi-half beam approach and restrict divergence to the contralateral lens, and MLCs were utilized for establishing a 1 cm field edge margin on the bony landmarks demarcating the inferior border of the cranial contents. The mean dose to PGs was compared between the two planes in light of the changes in the WBRT, and statistical significance was established. The plans were also assessed to see if the frequently recognized dosimetric planning limitations (limiting both parotids to <25 Gy and at least one to a mean dose of <20 Gy) would be violated by extending the lower field border to cover C2.

RT dose prescription:

Any dose from 30Gy to 36Gy. Dose-volume statistics was obtained using Treatment Planning System (Precise PLAN Release 2.12–151204 silicon graphic workstation). Mean dose to PGs was compared between the two planes.

STATISTICAL ANALYSIS:

All data were gathered, tabulated, and statistically assessed employing Microsoft Office Excel 2010 and SPSS 22.0 for Windows. Continuous data were expressed as mean ± SD and median (range), whereas categorical variables were expressed as a percentage. The Shapiro-Wilk test was used to ensure that continuous variables were normal. The Wilcoxon signed ranks test was utilized to compare two dependent groups with non-normally distributed data. The McNemar test was applied to compare matched categorical data. All tests were two-sided. A p-value of <0.05 was considered statistically significant.

RESULTS

Eighteen cases (36 PGs) were included in our study, who received whole cranial irradiation. The cases data were illustrated in table (1), median age was 52 (ranges from 25 to 72 years), the male to female ratio was 1:1. 22.2% of patients were proved to have breast cancer, 22.2% with NSCLC, 11.1% with SCLC, and 44.4% with other tumers like ranal cell carcinoma.,all patients (100%) were presented with symptoms like headache,

33.3% had dizziness,16.7% had sizures and 1% had symptoms like vomiting, decreased alterness, visual disturbance and gait ataxia. The ECOG scale of these patients were 1 and 2 (Table 1).

Table (2) outlines the characteristics of brain foci. All patients (100%) needed dexamethasone administration. Most of patients (17) were treated with total dose of 30Gy (3Gy/f) as palliation, and (one) of the patients were treated with 36Gy (2Gy/f) as radical in medulloblastoma.

The dose volume histogram (DVH) parameters of the planning target volume (PTV) according to table (3) demonstrated that the average dose to plan C1 was 2980.83 cGy and to plan C2 was 2983.55 cGy. There was high significant correlation between C1 plan and C2 plan regarding PTV mean dose.

There was high significant correlation regarding the PG mean dose, V20 and V25. There was significant correlation between plan C1 and plan C2 regarding total PG that received more than 25Gy, and one of the gland that received more than 20 Gy (Table 4).

Skin toxicity G1 occurred in 5.6% of cases the recived whole cranial irradiation, alopecia G1 occurred in 61.1% of cases and CNS toxicity G1 (50%), G2 (16.7%) and G3 (5.6% of cases) (Table 5).

Table (1): Basic characteristics among the studied patients (N=18).

Basic characteristics		All studied patients (N=18)	
		Mean±SD (range)	
Age (years)		50.50±14.38 (25-72)	
		No.	%
Sex	Male	9	50%
	Female	9	50%
Primary	Breast	4	22.2%
	NSCLC	4	22.2%
	SCLC	2	11.1%
	Others	8	44.4%
ECOG PS	ECOG 1	9	50%
	ECOG 2	9	50%
Clinical picture	Headache	18	100%
	Seizures	3	16.7%
	Vomiting	1	5.6%
	Gait ataxia	1	5.6%
	Decreased alertness	1	5.6%
	Dizziness	6	33.3%
	Visual disturbances	1	5.6%
	Papilledema	0	0%
	Nuchal rigidity	0	0%

Table (2): Basic characteristics and management of brain foci.

Basic characteristics		All studied patients (N=18)	
		Mean ± SD (Range)	
Max. diameter of large focus (cm)		3.64±1.47 (2 – 6.90)	
		No.	%
Number of brain foci	One lesion	9	50%
	Two lesion	3	16.7%
	≥three lesions	6	33.3%
Perifocal edema	Absent	9	50%
	Mild	5	27.8%
	Moderate	4	22.2%
Intralesional Hemorrhage	Absent	17	94.4%
	Present	1	5.6%
Management			
Dexamethasone	No	0	0%
	Yes	18	100%
Mannitol	No	18	100%
	Yes	0	0%
Radiotherapy dose	30Gy – 3Gy/f	17	94.4%
	36Gy – 2Gy/f	1	5.6%

Table (3): Comparison between C1 plan and C2 plan regarding dose volume histogram (DVH) parameters of planning target volume (PTV) among the studied patients (N=18).

	C1 plan (N=18)	C2 plan (N=18)	Test[a]	P
	Mean±SD (Range)	Mean±SD (Range)		
DVH parameters of PTV				
PTV Dmean (cGy)	2980.83±54.44 (2926-3089)	2983.55±54.65 (2928-3092)	-3.742	<0.001
PTV V95 (%)	94.88±4.11 (90-99)	95.44±3.71 (90-99)	-1.414	0.157
PTV V90 (%)	98.55±0.85 (97-100)	98.61±0.77 (97-100)	-1.000	0.317
PTV V105 (%)	10.88±2.24 (8-15)	10.94±2.8 (8-15)	-1.000	0.317
a: Wilcoxon signed ranks test.				

Table (4): Comparison between C1 plan and C2 plan regarding dose volume histogram (DVH) parameters of parotid glands among the studied patients (N=18).

	C1 plan (N=18)	C2 plan (N=18)	Test[a]	P
	Mean±SD (Range)	Mean±SD (Range)		
DVH parameters of PTV				
Parotid volume (cc)	31.81±1.76 (28.5-35)	31.81±1.76 (28.5-35)	0.000[a]	1.000
Parotid Dmean (cGy)	839.66±364.35 (234-1498)	1160.16±521.53 (241-2296)	-5.232[a]	<0.001
Parotid V20 (%)	10.91±7.10 (0-23)	12.69±7.47 (0-24)	-4.727[a]	<0.001
Parotid V25 (%)	6.38±5.07 (0-14)	8.58±6.07 (0-22)	-4.882[a]	<0.001
	No. (%)	No. (%)		
Total parotid dose<25Gy				
No	0 (0%)	8 (22.2%)	6.125[b]	0.013
Yes	36 (36%)	28 (77.8%)		
One gland<20Gy				
No	0 (0%)	6 (16.7%)	4.167[b]	0.041
Yes	36 (36%)	30 (83.3%)		
a: Wilcoxon signed ranks test. b: McNemar's test				

Table (5): Radiotherapy toxicity among the studied patients (N=18).

Radiotherapy toxicity	All studied patients (N=18)	
	No.	%
Skin toxicity		
G0	17	94.4%
G1	1	5.6%
Alopecia		
G0	7	38.9%
G1	11	61.1%
CNS toxicity		
G0	5	27.8%
G1	9	50%
G2	3	16.7%
G3	1	5.6%

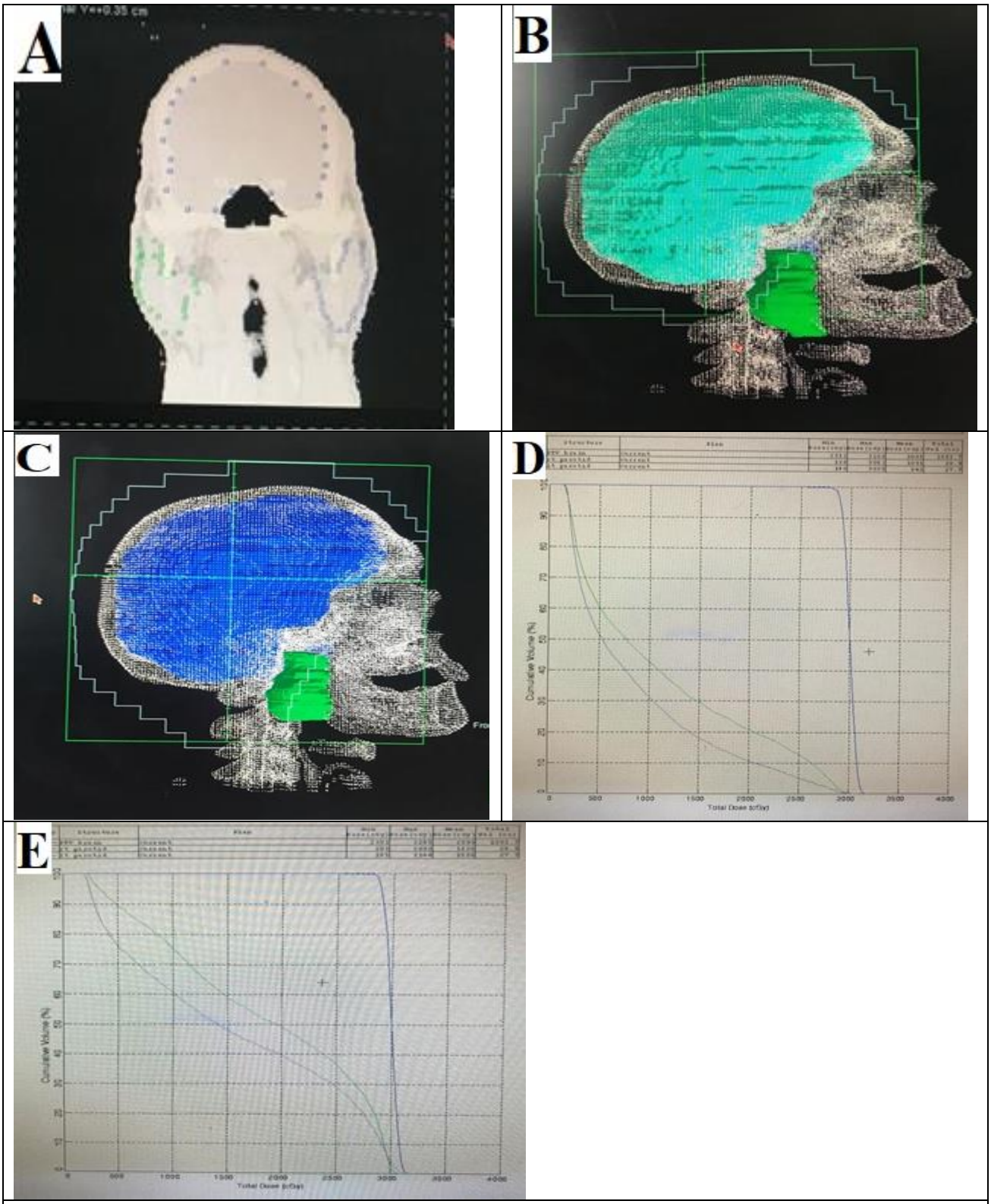

Figure 1: Case (1) a case of met lung cancer to brain, male patient, 63y old, received 30Gy (3Gy/f). (A) Delineation of case 1, PTV brain (blue color), LT parotid (Purple color), and RT parotid (green color). (B)Lateral beam eye view of case 1 (plan 1 to C1). (C) lateral beam eye view of case 1 (plan 2 to C2). (D) DVH parameters of (plan 1 to C1) in case 1. (E) DVH parameters of (plan 2 to C2) in case 1.

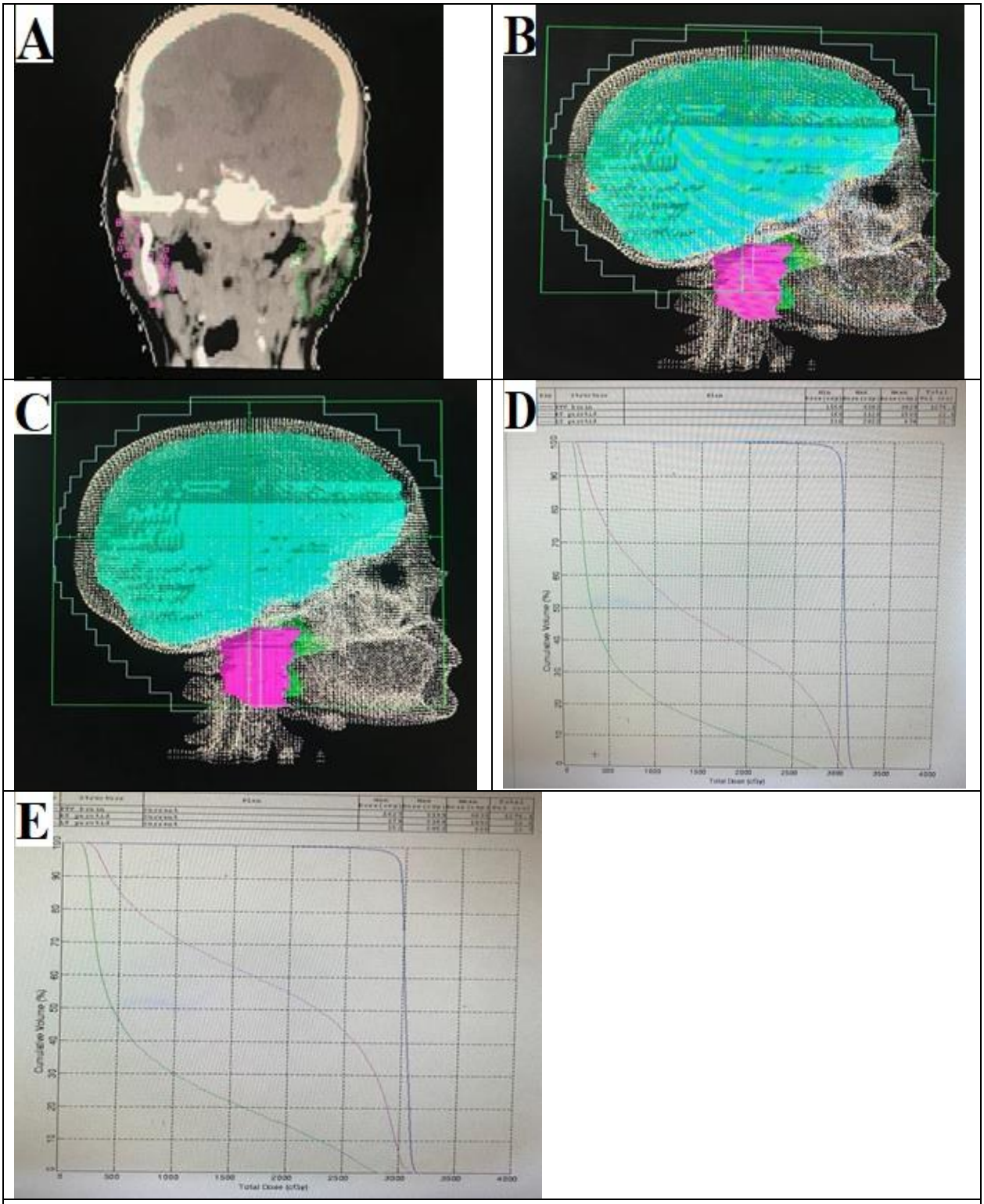

Figure2: Case (2) a case of met breast cancer,female patient, 62y old, received 30Gy(3Gy/f). (A) Delineation of case 2, PTV brain (blue color), LT parotid (Purple color), and RT parotid (green color). (B) Lateral beam eye view of case 2 (plan 1 to C1). (C) Lateral beam eye view of case 2 (plan 2 to C2). (D) DVH parameters of (plan 1 to C1) in case 2. (E) DVH parameters of (plan 2 to C2) in case 2.

DISCUSSION

WBRT is a potential option for cases with identified BMs as well as for microscopic lesion prevention. WBRT employment has declined slightly recently because of the developments in radiation technology, enabling the more targeted delivery of radiation, and growing worries over the

WBRT-related late toxicity [1].

Additionally, the PGs are not usually identified as organs at risk (OARs) for planning treatment strategy. The WBRT treatment design consists of two opposing lateral beams, with the inferior field border terminating at the inferior border of the cervical spine C1, C2. It is uncertain how the variation in the inferior beam edge will affect the PG dosage [13].

In this study we aim to compare the dose delivered to the PGs in plans covering first cervical vertebrae versus second cervical vertebrae, and to show a dosimetric improvement of the plan extended to the second vertebrae.

This clinical trial study was conducted in Clinical Oncology and Nuclear Medicine Department (Linac unit) in Zagazig University Hospitals. This study was conducted on (18) patients who receive WBRT.

In the current study, we found that median age was 52 (ranges from 25 to 72 years), 50% of cases were males. There were 22, 2% of patients were proved to have breast cancer, 22.2% with NSCLC, 11.1% with SCLC, and 44.4% with other tumors like renal cell carcinoma. All patients (100%) were presented with symptoms like headache, 33.3% had dizziness, 16.7% had seizures and 1% had symptoms like vomiting, decreased alertness, visual disturbance and gait ataxia. The ECOG scale of these patients were 1 and 2.

In agreement with our results, Park et al. [14] who The objective was to assess the feasibility and efficacy of non-coplanar WBRT (NC-WBRT) for parotid-sparing. They found that of fifteen cases previously subjected to WBRT, the median age was 59 years with range 47-84. Regarding sex of patients, there were 9 males and 6 females. Regarding to Primary sites of tumor, 46.6% of had lung cancer, and 26.6% had breast cancer and there was one patient in each of who had cancer with tonsil, stomach, colon and ovary.

Also, Cho et al. [15] they reported that of 53 patients underwent WBRT. Thirty-two cases were male, with median age of 60 years (28-80). The primary tumors were lung cancers (64.1%), breast cancer (15.1%), gastrointestinal tumors (15.1%), brain tumors (3.7%), and bladder cancer (1.88).

As well, Wang et al. [16] who aimed to test the hypothesis that WBRT correlated with clinically severe xerostomia, which is related to PG dosage. In addition, to test this idea, they conducted prospective observational research on individuals undergoing routine WBRT. They reported that the median age was 61 (23-88) years and out of 73 cases 59% were females, with. Regarding diagnosis, there was breast cancer in 12 (16%), lung cancer in 49 (67%), melanoma in 5 (7%) and other in 7 (10%). However, they reported that as regard ECOG PS, was 0 in 21 (29%), 1 in 33 (45%), 2 in 15 (21%) and 3 in 4 (5%).

Moreover, Wong et al. [17] who aimed to investigate prospectively QOL and symptoms (self-rated) in BMs cases following WBRT. They discovered that of the cases with BMs who were subjected to WBRT, 58% were female. The median age of the cases was 64 years (35-88). The most prevalent primary malignancies were lung (59%) and breast (26%). Extracranial metastases were most commonly found in bone (16%), lung (8%), and lymph nodes (6%). The most commonly reported symptoms before WBRT were weakness, headaches, unbalance, and weariness. Seizures, difficulty speaking, and vomiting were the least common symptoms reported by cases.

In our study, regarding outlines the characteristics of brain foci, 9 cases had one lesion, 3 cases had 2 lesions and 6 cases had more than three lesion. The median of maximum diameter of large focus was 2cm (ranging from 2 to 9.9 cm). 27.8% of cases had pri-focal edema and 5.6% had intralesional hemorrhage.

In line with our results, Steinmann et al. [18] who aimed to assess which QoL approachs enhance or lower after palliative RT. They found that regarding intracranial tumor status, there was >3 metastases in 83 (56%), 1-3 metastases in 65 (44%), largest metastasis >2 cm in 53 (35%) and minor percentage of cases with unknown number (3%) or diameter (12%) of metastases.

Also, Wong et al. [17] they reported that 24% of cases with BMs who were subjected to WBRT showed a single BM, and 76% had multiple BMs. 76% of the cases had at least one extracranial metastasis location.

In our study, as regard the course of treatment of the patients, most of patients (94.4%) were treated with total dose of 30Gy (3Gy/f) and 5.6% of the patients were treated with 36Gy (2Gy/f).

In consistent with our results, Wu et al., [8] who aimed to investigate the PG dose in relation to the inferior WBRT field extent compared to C1 or C2. They discovered that out of the 45 patients examined, 26 received WBRT to C2 and 19 had WBRT to C1 and. In fifteen fractions, 24 cases received 3750 cGy, while 21 cases got 3000 cGy in ten fractions. $P < 0.936$ indicates that there were no changes in the cases who got WBRT to C1 or C2, and who received 3000 cGy or 3750 cGy.

Also, Wang et al. [16] they reported that the majority of cases received RT with inferior field borders placed at the bottom of C1 (82%) and C2 (18). 30 Gy in 10 fractions was the most often utilized fractionation.

As well, in Wong et al. [17] the most prevalent radiation dose were 3,000 cGy in 10 fractions (7 cases) and 2,000 cGy in 5 fractions (114 cases).

In our results, according to the DVH parameters of the planning target volume (PTV), the average mean dose to plan C1 was 2980.83 cGy and to plan C2 was 2983.55cGy. In plan C1 and plan C2, the V95, V90 and V105 were ranging (from 90 to 99), (from 97 to 100), (from 8 to 15) respectively. There was high significant correlation between C1 plan and C2 plan regarding PTV mean dose, but there was no significant correlation regarding PTV V95, V90 and V105.

In line with our results, Bhide et al. [19] they found that as regard planning target volume (PTV) for conformal RT (CRT), the average dose range to the PTV1 was 23.1 ± 4.7 Gy and to the PTV2 was 23.6 ± 3.3 Gy.

In our findings, according to DVH parameters of PGs among the studied patients, the DVH parameters of the PGs in C1 plan and C2 plan, the average mean dose to PG in C1 plan is 839.66cGy and in C2 plan is 1160.16cGy. The total PGs received more than 25Gy in 22.2% of cases in plan C2. One of the PG received more than 20 Gy in 16.7% of cases in plan C2. There was no significant correlation between plan C1 and plan C2 regarding the PG volume, but there was high significant correlation regarding the PG mean dose, V20 and V25. Our results revealed that there was significant association between plan C1 and plan C2 regarding total PG that received more than 25Gy, and one of the gland that received more than 20 Gy.

In supporting our results, Orton et al. [12] who aimed to compare the dosages given to PGs in C1 and C2 programs.. They showed

that for 25 Gy, 30 Gy, and 37.5 Gy plans, the mean dose to both PGs was considerably higher in WBRT plans covering C2 than in plans confined to covering C1. The study reports dosimetric differences between C1 plans and C2 plans. For example, the mean parotid dosage for the 25 Gy plan was 15.3 Gy vs. 11.9 Gy ($p<0.01$); for the 30 Gy plan, it was 18.3 Gy vs. 14.3 Gy ($p<0.01$); and for the 37.5 Gy plan, it was 23.4 Gy vs. 18.5 Gy ($p<0.01$).

As well, Wu et al. [8] they found that when WBRT was given to C1 instead of C2, the total mean doses to the left and right parotids (19.53 Gy vs. 26.35 Gy, $p < 0.001$), 19.67 Gy vs. 25.07 Gy, $p = 0.003$), and 19.63 Gy vs. 25.71 Gy, $p < 0.001$) were all lower when given C1 instead of C2. A mean dose restriction was also considered, and the V20 to the combined parotids was analyzed. V20 to the total PGs was less in patients receiving C1 treatment than it was in those receiving C2 treatment (17.50 cc vs. 26.82 cc, $p = 0.002$).

Also in line with our results, Trignani et al. [20] who evaluated PGs inclusion in the WBRT fields and determined the received dose by comparing executive 2D and 3D approaches for WBRT. According to their findings, a dose-volume histogram analysis revealed that two out of seven cases (28%) received an excessive dosage of parotids, with a mean dose exceeding 20 Gy.

In the present study, regarding RT toxicity among the studied patients, skin toxicity G1 occurred in 5.6% of cases the received whole cranial irradiation ,alopecia G1 occurred in 61.1% of cases and CNS toxicity G1 (50%), G2(16.7%) and G3(5.6% of cases).

In accordance with our results, McTyre et al. [21] they found that numerous toxicities, such as neurocognitive impairments like, somnolence, exhaustion and memory loss, vomiting, nausea, dermatitis, and alopecia are linked to WBRT treatment.

As well, Wong et al. [17] and Steinmann et al. [18] they revealed that the adverse effects of WBRT included neurocognitive alterations, alopecia, and fatigue.

CONCLUSION

The dose given to the PGs is much increased when the inferior border of a typical WB field is extended to include the C2 vertebral body. This is expected to lead to a higher xerostomia incidence.

Conflict of interest: none

Financial disclosure: none

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