Original Article

Biological Evaluation of Grid versus 3D Conformal Radiotherapy in Bulky Head and Neck Cancer

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Abstract

Grid radiotherapy is one of the treatment techniques applied to treat patients with advanced bulky tumors. **Purpose:** This study aims to estimate the difference in biological and dosimetric parameters of the grid radiotherapy technique for the treatment of bulky head and neck (H and N) tumors and compare it with conventional conformal radiotherapy. **Subjects and Methods:** Three-dimensional conformal and grid radiotherapy were designed by the Monaco treatment planning system (TPS). Eight bulky tumors of (H and N) cases were selected, using a single fraction 15–20 Gy. Dose-volume histogram of the tumors and organs at risk (OARs) used to calculate the equivalent uniform dose (EUD) (Gy) by Matlab program. Furthermore, dosimetric parameters of the tumors from the TPS were compared for two techniques (grid radiotherapy and the conventional conformal radiotherapy). **Results:** Grid attained a lower EUD (Gy) in tumors and OARs as compared to conformal therapy, as Grid principle protects about half of the tumor area from the radiation leads to less coverage of the tumor. Also, where OARs in closed with tumors and the shielding by multi-leaf (1 cm) were more effective than other techniques, lead to a decrease of radiobiological values according to its definition by Niemierko. Radiobiological results showed significant differences between the two methods, and dosimetric data obtained by the TPS for tumours for two plans were $P < 0.05$. **Conclusions:** The grid plan achieves lower values of EUDs than the conformal technique for OARs. Hence, it achieves more sparing and fewer complications for these organs.

Keywords: Conformal, dose volume histogram, equivalent uniform dose, grid, matlab

Received on: 23-11-2021 **Review completed on: 21-02-2022** **Accepted on: 22-02-2022** **Published on: 05-08-2022**

Introduction

Grid radiotherapy (RT) is one of the treatment techniques applied to treat patients with advanced bulky tumors. It is employed as an effective curative and palliative hypo-fractionation technique. Grid plan radiotherapy is achieved through the utilization of many small beams in the field with a high dose single fraction radiation. Specific areas of the target tissue are directly irradiated, whereas the surrounding areas are protected from direct high dose radiation.[1] Many researchers suggested that bystander effect, which refers to effects seen in cells that are indirectly radiated, abscopal effect, vascular damages, and immunomodulation reactions occur by radiobiological mechanisms in Grid RT.[2-4]The most application of grid RT, a single large radiation dose can be delivered to the tumor(concept of grid RT), followed by a short course of conventional RT to achieve rapid tumor symptom relief.[5]

This study aims to estimate the difference in biological and dosimetric parameters in Grid plan and 3D conformal techniques for head and neck (H and N) cases in radiotherapy plans and evaluate the differences of these two techniques. The current search is the first practical study in this subject.

Subjects and Methods

Computed tomography simulator

Computed tomography (CT) simulator of type Somatom AS, (Siemens Healthineers, Germany), provided with 24

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Quick Response Code:	**Website:** www.jmp.org.in
	DOI: 10.4103/jmp.jmp_141_21

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How to cite this article: Alanizy NA, Attalla EM, Abdelaal AM, Yassen MN, Shafaa MW. Biological evaluation of grid versus 3D conformal radiotherapy in bulky head and neck cancer. J Med Phys 2022;47:136-40.

multi-slices per rotation was used to scan the cases in this study.

Monaco SIM workstation

Three-dimensional RT treatment planning system (TPS) of type (Monaco, Elekta, Sweden) was used in this study.

Equivalent Uniform Dose (Gy)

Niemierko first defined the equivalent uniform dose (EUD) (Gy) as the absorbed dose, that is, if given uniformly, would tend to the same cell death as the actual heterogeneous absorbed dose. EUD (G) can be used for both tumors and normal tissues. It can be computed directly from calculating dose points or from the corresponding dose-volume histograms (DVHs) *such as:*

$$\text{EUD (Gy)} = (\sum V_i D_i^{\,a})^{1/a} \qquad 1$$

where Di is the dose delivered to a sub-volume, and is a unitless model parameter that is specific to the normal structure or tumor of interest.[6,7]

Matlab program

This programme is Math works, Inc., Natick, MA of version (MATLAB R2018a), this development software has served as a useful tool for processing the pencil beam data sets. MATLAB is a numeric computation and visualization soft-ware system. This programme can estimate different biological models as TCP, NTCP and EUD, where EUD model file is written in command order with C++ language and imported in to Matlab programme to get TCP and NTCP values.

It is commonly used by students, engineers, and researchers across a wide range of subjects. Also, it can be created with complex and simple codes.

System Requirements

Windows 10 (64-bit), 7SP1 (64-bit), Windows server 2016 (64-bit), 2012 R2 (64-bit), and 2012 (64-bit). Any Intel or AMD x86-64 processor with logical cores and AVX2 instruction set support four. A full installation of all Math Works products may take up to 23 GB of disk space and Ram4 GB (At least 8 GB recommended). Dose volume histogram (DVH) for each case in both plans exported to Matlab program to calculate EUD(Gy) for tumor and organs at risk (OARs) [Figure 1].

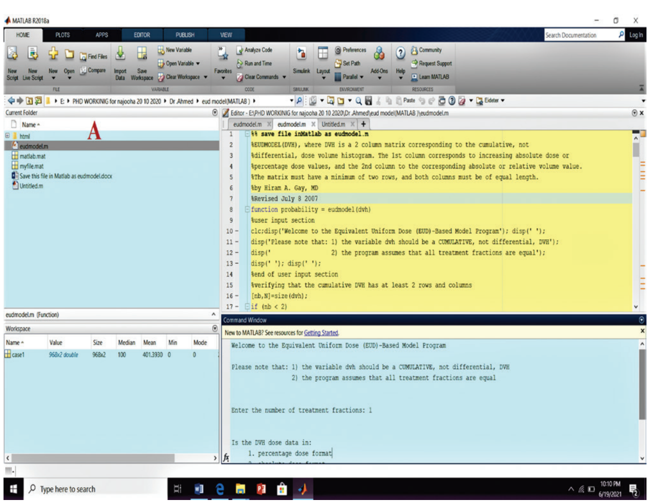

Figure 1: Screenshots for Matlab program used in this study to calculate the equivalent uniform dose (Gy) from volume dose histogram

Data collection

Eight cases (generally, bulky tumor cases are rare) were selected with H and N bulky tumors >6 cm, taken from TPS. They were scanned on a Siemens CT simulator, followed by export of CT images to the Monaco SIM workstation. Subsequently, bulk mass and OARs, which were close to the tumor, were delineated. When the delineation was completed, the CT images were sent to the Monaco workstation to design the treatment plans (as scenarios) of the Grid. Each radiation field is divided into several sub-fields with an area of 1 cm^2, while the distance between two sub-fields is 2 cm and 3D-conformal therapy plan for each case was performed by TPS [Figure 2].

Table 1: The comparison between equivalent uniform dose (Gy) for organs at risk of H and N tumors in conformal and grid radiotherapy using Matlab program from dose volume histogram by treatment planning system

OARs	EUD (Gy), mean±SD		*P*
	Conformal RT	Grid RT	
Brainstem	12.8±15.2	3.39±3.2	0.048
Right optic nerve	15.73±16.1	2.98±4.25	0.049
Left optic nerve	6.85±4.82	1.97±2.91	0.012
Right eye	7.39±4.6	1.96±2.27	0.045
Left eye	12.49±9.26	1.86±2.21	0.04
Right parotid	7.16±5.19	1.24±1.42	0.034
Left parotid	5.95±5.72	1.01±1.7	0.09
Optic chiasm	3.14±2.5	1.39±1	0.04
Right cochlea	7.24±7.18	2.02±2.72	0.042
Left cochlea	4.58±5.9	1.64±2.26	0.14
Right lung	1±0.18	0.05±0.369	0.001
Left lung	5.34±5.44	0.61±1.12	0.001
Spinal cord	6.89±4.4	3.35±2.81	0.02
Heart	1.66±1.78	0.91±1.26	0.08
P	4.48E-05		

EUD (Gy): Equivalent uniform dose (Gy), RT: Radiotherapy treatment, SD: Standard division, OARs: Organs at risks

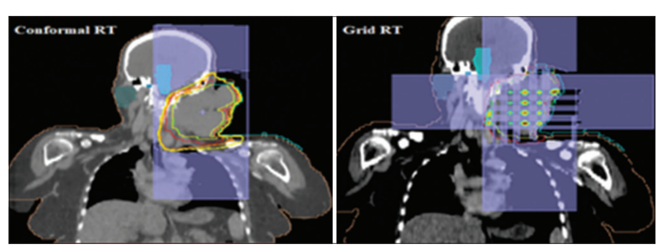

Figure 2: Screenshots for conformal and GRID (by Multi-leafs collimators) plans show the difference between techniques MLCS: Multi-leafs collimator

Statistical data analysis

The data were analyzed statistically, and the statistically significance difference was set at a threshold of $P < 0.05$. The Microsoft Excel 2016 was employed, mean and standard deviation (SD) were calculated and t-test tool was utilized in the calculation of P value. Chaikh *et al*., 2014 illustrated that the use of statistical tests in radiotherapy and they reported " In radiotherapy it is rare to use a large number of patients in order to validate the novel irradiation technique at the level of a common department. For practical reasons, it would be welcome to use only few patients for realizing the statistical analysis, and then to generalize the results to a large population".[8]

Results

EUD (Gy) of OARs in Grid and 3D conformal radiotherapy by Matlab program.

Grid RT and 3D conformal plans of the H and N cases were compared using the biological model EUD (Gy) for OARs and the evaluation of EUD (Gy) for OARs in both techniques is shown in Table 1. The mean ± SD of EUD (Gy) for OARs in 3D conformal plans results in significantly differences in brainstem, right (rt) and left (lt) optic nerve, rt. and lt. eyes, rt. parotid, optic chiasm, rt. cochlea, rt. and lt. lungs and spinal cord in conformal therapy versus with Grid RT were $P < 0.05$. While, the differences of EUD (Gy) for other OARs presented nonsignificant $P > 0.05$ in the lt. parotid, lt. cochlea, and heart in conformal therapy versus in Grid technique.

Furthermore, Table 1 shows the P values for each OARs and a strong significant difference between conformal and Grid therapy models concerning EUD (Gy) for all values for OARs, $P = 4.48\text{E-}05$.

Table 2 explains the results of the EUD (Gy) values for the H and N cases which were calculated by the Matlab program. There were clear differences between EUD (Gy) values in case 1 and case 5, respectively, when conformal therapy technique (64.6 and 41.95 Gy) was replaced by Grid technique (1.839 and 16.55 Gy) is shown in Figure 3.

The results also revealed a decrease in the moderate EUD (Gy) values in cases 2, 3, 4, 7 and 8 were (14.78, 14.55, 14.83, 14.44,

Table 2: The comparison between the equivalent uniform dose (Gy) for H and N different tumor cases in Three dimensions-conformal and grid radiotherapy treatment techniques calculated by Matlab program

Number of cases	Site of tumor	EUD (Gy)	
		Conformal RT	Grid RT
1	Paranasal sinus	64.6	1.839
2	Larynx	14.78	10.18
3	Oral cavity	14.55	9.38
4	Right ethmoid and maxillary	14.83	9.46
5	Oral cavity	41.95	16.55
6	Paranasal sinus	18.89	17.51
7	larynx	14.44	9.63
8	Left parotid	15.33	9.65
P	0.046		

EUD (Gy): Equivalent uniform dose (Gy), RT: Radiotherapy treatment

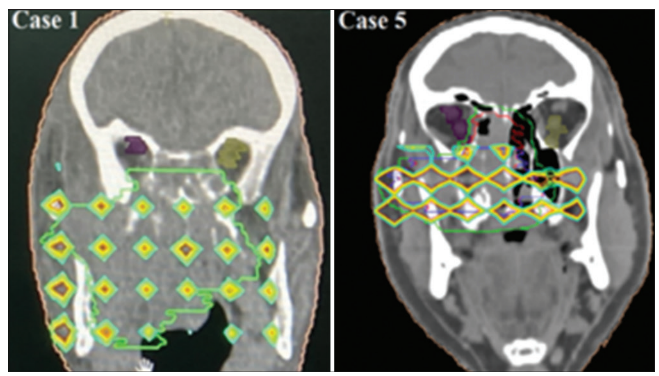

Figure 3: Screen shots for cases (1 and 5) views for Grid techniques, these cases had many critical structures were in the district of the tumor, which lead to great different in EUD (Gy) when compare between conformal and Grid plans Case 1 (Paranasal sinus) and case 5 (oral cavity), EUD (Gy): Equivalent uniform dose (Gy)

Table 3: The comparison between D2 (Gy), D50 (Gy), D95 (Gy), and D98 (Gy) in different H and N cases in conformal and grid radiotherapy treatment calculated by treatment planning system

Case	Site of tumors	D2 (Gy)		D50 (Gy)		D95 (Gy)		D98 (Gy)	
		3D-CRT	Grid RT	3D-CRT	Grid RT	3D-CRT	Grid RT	3D-CRT	Grid RT
1	Paranasal sinus	16.97	16.33	15.38	9.26	14.6	5.1	14.82	4.16
2	Larynx	15.68	14.25	14.75	8.83	13.83	4.78	13.83	4.21
3	Oral cavity	15.45	13.41	14.68	7.94	13.81	4.63	13.36	3.72
4	Right ethmoid and maxillary	15.31	13.59	15	8.27	14	4.5	13.55	3.91
5	Oral cavity	16.35	16.03	15.48	9.15	14.57	6.36	13.8	7.43
6	Paranasal sinus	15.90	13.95	14.99	10.98	14.36	4.96	14.16	5.14
7	Larynx	15.19	13.79	14.96	8.74	14.7	5.03	12.99	4.45
8	Left parotid	15.96	13.83	15.1	7.37	14.44	4.44	13.36	2.27
P		0.0002		3.41E-07		1.79E-10		1.84E-07	

3D-CRT, Dose near maximum (D2) Gy, mean dose (D50) Gy, Dose received by 95% volume (D95) Gy, and Dose near minimum (D98) Gy for the tumors. 3D-CRT: Three dimensions conformal radiotherapy, RT: Radiotherapy treatment

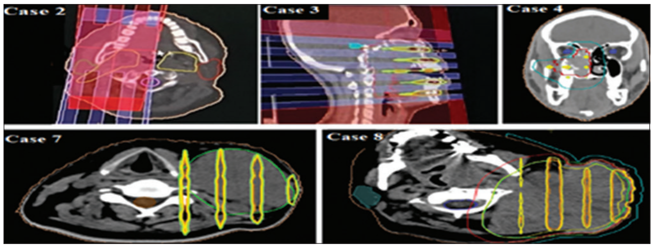

Figure 4: Screen shots for different cases (2,3,4,7, and 8) views for Grid techniques in H and N bulky tumors, the difference of EUD (Gy) values depend up on the site of the tumor and how OARs near to tumor, Case 2 (Larynx), case 3 (oral cavity), case 4 (Rt. Ethmoid and maxillary), case 7 (larynx) and case 8 (Lt. parotid)

and 15.33 Gy, respectively) after switching from conformal to Grid therapy were (10.18, 9.38, 9.46, 9.63, and 9.65 Gy, respectively), as shown in Figure 4. However, there was only a slight difference in EUD (Gy) values in case 6 (17.89 Gy) in 3D-conformal to (18.51 Gy) in Grid plans, as shown in Figure 5. From the estimation of total results shown in Table 2, the results show a significant difference between conformal and Grid therapy models concerning EUD (Gy) values for OARs, $P = 0.046$.

Table 3 presents a summary of dosimetric parameters in the H and N cases as a result of the utilization of the conformal and Grid techniques. These parameters included the dose near maximum (D2) Gy, mean dose (D50) Gy, Dose received by 95% volume (D95) Gy, and Dose near minimum (D98) Gy for the tumors. It is clear that nearly similar values of D2 were obtained for conformal and Grid techniques. On the contrary, D50 values exhibited a sharp drop after replacement of conformal therapy by Grid plans, especially in cases 2, 3, 4, 7, and 8 (14.75, 14.68, 15, 14.96, and 15.1 Gy) versus (8.83, 7.94, 8.27, 8.74, and 7.37 Gy, respectively). The results in Table 3 confer a representation for the quality of dose coverage in the previous plans, where the conformal style achieved a good dose coverage for the tumor (high values of D95 and D98). On the other hand, there was a weak dose coverage (small values of the D95 and D98) using the grid technique. The statistical analysis showed a significant difference between grid and conformal RT techniques concerning D2, D50, D95, and D98 ($P < 0.001$).

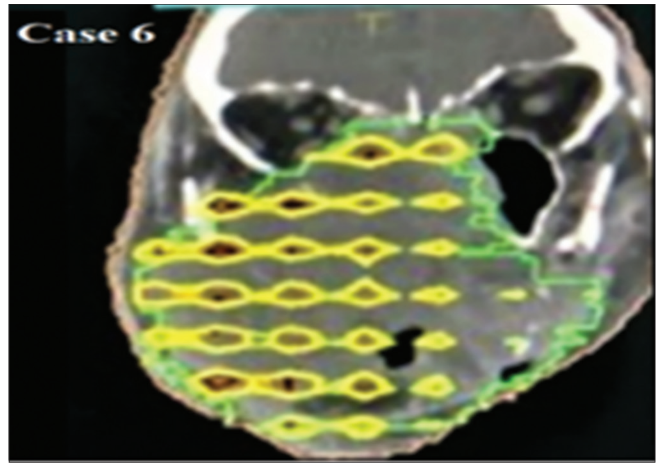

Figure 5: Screen shots for case 6 (Paranasal sinus) in axial view for Grid

Discussion

Local control of bulky tumors with standard irradiation therapy could be a challenging topic, since treatment may involve a large volume of normal tissues receiving high doses of radiation.[9] Grid therapy is a procedure that was established to treat patients with advanced bulky tumors. However, patients with massive or bulky tumors that produce complex symptoms pose a challenging problem for the oncologists.[10] In the present study, we provided the biological model (EUD) (Gy) for tumor and OARs. Grid achieved lower EUD (Gy) for OARs in comparison to conformal therapy in many cases in this study, these might be due to the fact that OARs are close to the target, and the shielding of many sub volumes by multileaf collimators in the Grid plan is more significant than in conformal plan. EUD (Gy) for OARs in cases 1 and 5 have high differences between the two plans conformal and grid. In these cases, many critical structures were in the vicinity of the tumor. As a consequence, there were relatively large portions of low-dose volumes of the target. By definition, the EUD (Gy) is the sum of all sub-volumes receiving the dose in the tumor. Hence, any partial volumes receiving a radiation dose close or near zero would lead to a very low tumor EUD (Gy).[11] Furthermore, the results showed a significant difference between the conformal and grid therapy models with respect to EUD (Gy) for tumor ($P < 0.05$), where Grid achieved lower EUD (Gy) for tumor in comparison to conformal therapy. The variation in tumor coverage between conformal and Grid techniques in cases (2, 3, 4, 7, and 8) can be explained through the notion that the Grid mechanism protects many parts of a radiation field (about half area of the tumor), especially for large target volumes that lead to decrease in tumor coverage.[12] However, Grid radiotherapy can influence the different processes to kill tumor cells, when compared with conventional radiotherapy.[10] The radiobiology processes of grid radiotherapy lead to killing tumor cells by bystander effect, Radiation-induced bystander effects are biological processes that occur after cell irradiation and influence nearby cells cause death non irradiated. In addition, the abscopal effects, vascular damage, and immunomodulation reactions, all these factors kill nearly all tumor cells.[3,4] In addition, a dosimetric comparison was made between conformal and grid techniques in different H and N cases. These comparisons included the dosimetric parameters of (D2) Gy, (D50) Gy, (D95) Gy, and (D98) Gy for the tumor.

Although the higher tumor dose coverage in conformal therapy compared to Grid radiotherapy, Grid radiotherapy improved the results in this technique. In the grid, the activity to kill cells will increase by inducing reoxygenation of tumor cells. The reoxygenation process leads to enhancing tumor radiosensitivity for RT. Generally, oxygen is transported to the tumor area through the blood vessel, which increases the partial pressure of oxygen in the tumor tissue, thereby causing reoxygenation of hypoxic cells).[13] Furthermore, the results show a significant reduction in OARs doses using the Grid RT in comparison to the conformal technique ($P < 0.05$). From all the results presented above, the Grid technique shows more advantages in the treatment of bulky tumor when compared to the conformal plans. Several investigators reported that this technique has the advantage of higher potential to repair normal tissues. Furthermore, researchers reported the significant tumor responses without serious toxicities.[14] A high dose used in grid radiotherapy has been beneficial in addition to increasing the biological radiation dose delivered to the tumors, immunologic effects and radiation-induced bystander effects that may be occurred. In addition, low EUDs (Gy) for OARs lead to increased radiation tolerance and reduced toxicity. In fact, the toxicity of radiation treatment means the side effect of radiotherapy to organs.[15,16]

Conclusions

To sum up the results, it is clear that the grid process achieves lower EUD (Gy) values with most OARs than the conformal technique. Hence, it achieves more sparing and fewer complications for these organs. Conformal and Grid plans have similar maximum dose values (D2 values). On the other hand, the conformal technique achieves higher EUD (Gy) values for tumors than the Grid technique, as it confers better coverage.

Further studies will be needed, including the biological models of tumor control probability and normal tissue complication probability for Grid radiotherapy. Furthermore, dosimetric studies for the Grid plan before using it in any radiotherapy center will be needed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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