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Toxicity Profile of Intensity Modulated Radiotherapy Vs. 3D-Conformal Radiotherapy in Head and neck cancer: A Retrospective study

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ORIGINAL ARTICLE

Toxicity Profile of Intensity Modulated Radiotherapy Versus 3D-Conformal Radiotherapy in Head and Neck Cancer: A Retrospective Study

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Abstract

Background: **Most head and neck patients have historically been treated with photon-based radiation techniques, such as intensity modulated radiation therapy (IMRT), there is a growing awareness of the potential clinical benefits of proton therapy over IMRT in the definitive, postoperative and reirradiation settings given the unique physical properties of protons.**

Aim of the work: **To assess toxicity profile of IMRT in comparison to 3D conformal radiotherapy (3DCRT) and to assess predictors for progression free survival and overall survival rates.**

Patients and methods: **This retrospective cohort study included 131 head and neck cancer patients who were recruited from El Hussein University Hospital over 10 years then they were divided into 2 groups according to the type of radiotherapy.**

Results: **Both groups were comparable regarding age, sex, and associated medical disorders except for ischemic heart disease and smoking. Sites of primary tumors were comparable except tongue and nasopharynx. Most of 3DCRT group received TPF as induction chemotherapy and most of IMRT group received concurrent chemotherapy. Dose of irradiation was higher significantly among IMRT group. Grades of early and late toxicity were higher among 3DCRT group. There was no statistically significant difference between both groups regarding response to treatment. Mortality cases were higher significantly among 3DCRT group. Cox regression analysis was performed to assess predictors for progression free survival and overall survival in each group.**

Conclusion: **IMRT provide good choice as radiotherapy technique for head and neck cancers with adequate efficacy similar to other techniques and better toxicity profile.**

Keywords: Adverse events, Head and neck cancer, Radiotherapy, Toxicity

1. Introduction

Around 70% of head and neck cancers require radiotherapy as definitive or postoperative radiation concurrently with chemotherapy or targeted agents.[1]

Advancement in imaging techniques, improved identification of target volume, 3D image reconstruction, computer optimized algorithms have led to evolution of radiation delivery from 2D Radiotherapy to three dimensional conformal radiotherapy (3DCRT) with geometric modulation of beam shape that conform as closely as possible to the target volume in terms of adequate dose to the tumor and minimal possible dose to normal tissue.[2]

Further progress in conformal radiotherapy led to logical evolution of Intensity Modulated Radiation Therapy (IMRT) where simultaneous geometric and intensity modulation of radiation beams allows delivery of non-uniform fluence from any given position of the treatment beam to optimize the composite dose distribution.[3]

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The primary aim of this retrospective study was to asses and analyzes the toxicity Profile of IMRT Vs. 3DCRT in Head and neck cancer among Egyptian patients.

2. Patients and methods

2.1. Design

Retrospective cohort study.

2.2. Participants

One hundred and thirty one patients with head or neck cancers were eligible to be enrolled in the study and were recruited from El Hussein University Hospital during the duration between January 2011 and December 2020.

2.3. Inclusion criteria

All patients who fulfilled the following criteria were enrolled in the study: patient with histopathology confirming head and neck cancers; Patient younger than 70 years old; Performance status 0–3 WHO; Confirmed nonmetastatic disease; Received treatment, induction chemotherapy or radical concurrent chemo-radiotherapy at clinical oncology department of El Hussein University hospital.

2.4. Exclusion criteria

All patients who had one of the following criteria were excluded from the study: patient who has double malignancy; pathology other than head and neck cancer; performance status 4 WHO; End stage heart, liver, or renal disease.

2.5. Grouping

Patients were divided according to the type of radiotherapy into two groups:

3DCRT group: included 56 patients who received 3DCRT.

IMRT group: included 75 patients who received IMRT.

2.6. Methods

Patient's data were retrivied from the archive and the following data were collected: patient related data: age, sex, family history, and performance status; disease related data: date of first diagnosis, extent of disease, histopathology, grade, and TNM stage, Treatment related data: (radiotherapy and chemotherapy), response and related toxicities; Radiotherapy treatment technique, Treatment related toxicity with a special attention to radiotherapy toxicity; response to treatment according to RECIST criteria; progression free survival from date of starting treatment till progression, recurrence or death; overall survival from date of diagnosis till date of last follow up or death.

2.7. Statistical analysis

All data were tabulated in SPSS sheet version 21. Chi square test was used to compare data of categorical type. Student t-test was used to compare normally distributed data. Cox regression analysis was used to assess predictors of survival. The results were considered significant at level less than 0.05.

3. Results

There was no statistically significant difference between both groups regarding demographics and associated medical disorders while there was a statistically significant difference between both groups regarding presence of IHD found higher in IMRT group ($P = 0.03$) and regarding presence of smoking found higher in 3DCRT group ($P = 0.019$) (Table 1).

Table 1. Demographics of both groups.

Demographics and co-morbidities	3DCRT group no. = 56	IMRT group no. = 75	*P* value
Age at presentation (years)			
Mean ± SD	54.21 ± 8.90	54.32 ± 12.08	0.956
Range	32–68	19–76	
Sex			
Female	17 (30.4%)	20 (26.7%)	0.643
Male	39 (69.6%)	55 (73.3%)	
Performance status (WHO)			
I	55 (98.2%)	75 (100.0%)	0.245
II	1 (1.8%)	0 (0.0%)	
Diabetic			
No	45 (80.4%)	53 (70.7%)	0.206
Yes	11 (19.6%)	22 (29.3%)	
Hypertensive			
No	49 (87.5%)	59 (78.7%)	0.189
Yes	7 (12.5%)	16 (21.3%)	
IHD			
No	56 (100.0%)	69 (92.0%)	0.030
Yes	0 (0.0%)	6 (8.0%)	
Yes	0 (0.0%)	0 (0.0%)	
Yes	0 (0.0%)	1 (1.3%)	
Family history			
No	43 (76.8%)	67 (89.3%)	0.053
Yes	13 (23.2%)	8 (10.7%)	
Smoking			
No	11 (19.6%)	29 (38.7%)	0.019
Yes	45 (80.4%)	46 (61.3%)	

Table 2. Comparison between both groups regarding TNM staging, pathology grading and pathological lesion.

TNM staging	3DCRT group no. = 56	IMRT group no. = 75	*P* value
T stage			
2	11 (19.6%)	10 (13.3%)	0.508
3	18 (32.1%)	30 (40.0%)	
4	27 (48.2%)	35 (46.7%)	
N stage			
0	14 (25.0%)	22 (29.3%)	0.001
1	14 (25.0%)	31 (41.3%)	
2	26 (46.4%)	12 (16.0%)	
3	2 (3.6%)	10 (13.3%)	
M stage			
0	56 (100.0%)	0 (0.0%)	NA

There were no statistically significant differences between both groups regarding T and M staging while there was statistically significant difference between both groups regarding *N* staging as most of IMRT group had N0 or N1 while most of 3DCRT group had N2 lesions ($P = 0.001$) (Table 2).

There was statistically significant difference between both groups regarding mucositis and xerostomia as higher grades were reported more frequently among 3DCRT group ($P < 0.001$) in both of them. There was statistically significant difference between both groups regarding grade of skin toxicity as higher grades were reported in IMRT group ($P = 0.001$). Frequency of higher grades of dysphagia, neuropathy and weight loss were reported among 3DCRT group than IMRT group with statistically significant differences ($P = 0.03.0.049$, 0.04 resp.). Both groups were comparable regarding grades of vomiting, CNS, ear and eye acute toxicity (Table 3).

There were statistically significant differences between both groups regarding grades of late toxicity on different organs (Table 4).

Cox regression analysis of 3DCRT group revealed that age, T stage, N stage and type of chemotherapy did not affect significantly PFS among 3DCRT group. Sex is a significant predictor for PFS as male patients had longer PFS than females with statistically significant difference among 3DCRT group ($P = 0.001$). Cox regression analysis of 3DCRT group revealed that age at presentation affected OS significantly ($P < 0.001$). Sex is significant predictor for OS as males had better survival than females ($P = 0.006$). T staging and N staging affected significantly OS ($P = 0.029$, 0.004 resp.). Smoking did not affect OS (Table 5).

There was no statistically significant effect of age at presentation on PFS rates among IMRT group. Sex affected significantly PFS as males had better

Table 3. Acute toxicity.

3D-CRT concurrent Chemoradiation acute toxicity grades	3DCRT group no. = 56	IMRT group no. = 75	*P* value
Mucositis			
1	6 (11.3%)	10 (13.7%)	0.000
2	19 (35.8%)	62 (84.9%)	
3	28 (52.8%)	1 (1.4%)	
Xerostomia			
0	1 (1.9%)	7 (9.6%)	0.000
1	14 (26.4%)	46 (63.0%)	
2	35 (66.0%)	19 (26.0%)	
3	3 (5.7%)	1 (1.4%)	
Skin			
0	1 (1.9%)	0 (0.0%)	0.001
1	26 (49.1%)	14 (19.2%)	
2	25 (47.2%)	59 (80.8%)	
3	1 (1.9%)	0 (0.0%)	
Dysphagia			
0	1 (1.9%)	0 (0.0%)	0.030
1	5 (9.4%)	10 (13.7%)	
2	37 (69.8%)	60 (82.2%)	
3	10 (18.9%)	3 (4.1%)	
Neuropathy			
0	19 (35.8%)	26 (35.6%)	0.049
1	24 (45.3%)	43 (58.9%)	
2	10 (18.9%)	4 (5.5%)	
Vomiting			
0	23 (43.4%)	31 (42.5%)	0.991
1	19 (35.8%)	27 (37.0%)	
2	11 (20.8%)	15 (20.5%)	
Weight loss			
0	10 (18.9%)	21 (28.8%)	0.040
1	30 (56.6%)	39 (53.4%)	
2	8 (15.1%)	13 (17.8%)	
3	5 (9.4%)	0 (0.0%)	
Ear			
0	29 (54.7%)	45 (62.5%)	0.254
1	19 (35.8%)	25 (34.7%)	
2	5 (9.4%)	2 (2.8%)	
Eye			
0	41 (77.4%)	48 (66.7%)	0.443
1	8 (15.1%)	18 (25.0%)	
2	4 (7.5%)	5 (6.9%)	
3	0 (0.0%)	1 (1.4%)	

PFS rates than females among IMRT patients ($P = 0.001$). T stage is considered statistically significant predictor for PFS ($P = 0.001$) while N sage did not affect significantly PFS. Pathology grade and type of concurrent chemotherapy did not affect PFS. Cox regression analysis of IMRT group revealed that age at time of presentation, N stage and pathological grade did not affect overall survival significantly. Sex affected significantly overall survival as males had better OS than females ($P < 0.001$). T stage affected OS significantly ($P = 0.005$). Smoking is considered significant

Table 4. Late toxicity.

3DCRT concurrent chemoradiation late toxicity grades	3DCRT group no. = 56	IMRT group no. = 75	*P* value
Fatigue			
0	3 (5.4%)	3 (4.0%)	0.001
1	11 (19.6%)	37 (49.3%)	
2	11 (19.6%)	17 (22.7%)	
Not	31 (55.4%)	18 (24.0%)	
Mucous membrane			
0	4 (7.1%)	8 (10.7%)	0.002
1	13 (23.2%)	39 (52.0%)	
2	7 (12.5%)	10 (13.3%)	
3	1 (1.8%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Salivary glands			
0	5 (8.9%)	27 (36.0%)	0.000
1	8 (14.3%)	23 (30.7%)	
2	9 (16.1%)	7 (9.3%)	
3	3 (5.4%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Skin			
0	4 (7.1%)	7 (9.3%)	0.000
1	8 (14.3%)	40 (53.3%)	
2	10 (17.9%)	9 (12.0%)	
3	3 (5.4%)	1 (1.3%)	
Not	31 (55.4%)	18 (24.0%)	
Subctanous tissue			
0	4 (7.1%)	15 (20.0%)	0.000
1	9 (16.1%)	34 (45.3%)	
2	8 (14.3%)	7 (9.3%)	
3	4 (7.1%)	1 (1.3%)	
Not	31 (55.4%)	18 (24.0%)	
Ototoxixty			
0	13 (23.2%)	30 (40.0%)	0.001
1	9 (16.1%)	25 (33.3%)	
2	1 (1.8%)	2 (2.7%)	
3	2 (3.6%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Eye			
0	17 (30.4%)	47 (62.7%)	0.002
1	7 (12.5%)	9 (12.0%)	
2	0 (0.0%)	1 (1.3%)	
3	1 (1.8%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Spinal cord			
0	16 (28.6%)	42 (56.0%)	0.001
1	9 (16.1%)	15 (20.0%)	
Not	31 (55.4%)	18 (24.0%)	
Brain			
0	20 (35.7%)	54 (72.0%)	0.000
1	2 (3.6%)	3 (4.0%)	
2	3 (5.4%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Larynx			
0	9 (16.1%)	25 (33.3%)	0.000
1	3 (5.4%)	15 (20.0%)	
2	8 (14.3%)	17 (22.7%)	
3	5 (8.9%)	0 (0.0%)	
Not	31 (55.4%)	18 (24.0%)	
Joint			
0	21 (37.5%)	41 (54.7%)	0.003
1	2 (3.6%)	13 (17.3%)	
2	1 (1.8%)	2 (2.7%)	
3	1 (1.8%)	1 (1.3%)	
Not	31 (55.4%)	18 (24.0%)	

(*continued on next page*)

predictor for OS ($P = 0.03$). Type of concurrent chemotherapy affected OS as Cisplatin patients had better OS ($P = 0.003$) (Table 6).

4. Discussion

In the current study, there was no statistically significant difference between 3DCRT and IMRT groups regarding age, sex. This came in hand with a study by Moretto et al., who reported no difference between both groups regarding demographics.[4] Chen et al., also reported comparable age and sex between both groups.[5] Same results were obtained in other studies.[6–9]

In the current study, both groups were comparable regarding associated comorbidities except for IHD. Yao et al., in his study reported similar findings.[9]

In our study, there was no difference between both groups regarding TNM staging, while N stage differed significantly between both groups as most of IMRT group had N0 or N1, while most of 3DCRT group had N2 lesions.

Regarding acute toxicities, there was significant difference between both groups, mucositis, skin toxicity, xerostomia and dysphagia (grade 1 and 2 more frequent with IMRT and grade 3 more frequent with 3DCRT). In concordance with the current study, Krishna et al., reported reduced severity of mucositis among IMRT group while there was no significant differences were present regarding dysphagia, skin toxicity and xerostomia.[10] Dahele et al., also reported high grades of xerostomia appeared more frequently with 3DCRT.[7]

As regard late toxicities, grade 1 affection of different organs especially mucus membranes, salivary gland, skin and ear was more frequent among IMRT group, while grade 2 and more affection was more frequent with 3DCRT. Similarly, Krishna et al., reported higher grade of salivary gland and mucus membrane affection among 3DCRT after 3 months of treatment.[10] Xerostomia had higher incidence among 3DCRT group in a study by Rathod et al.,[6] Fatigue and appetite loss were more frequent among IMRT group with high grade as a late complication. This came in

Table 5. Cox regression analysis to evaluate predictors of PFS and overall survival among 3DCRT group.

	Total no.	No. of event	PFS (months)		95% CI		Log rank test		
			Mean	SE	Lower	Upper	X^2	*P* value	Sig.
Predictors of progression free survival									
Age at presentation (years)									
≤55 yrs	30	8	84.389	9.177	66.402	102.376	0.574	0.449	NS
>55 yrs	24	7	67.459	10.736	46.417	88.500			
Sex									
Female	15	8	42.019	15.496	11.647	72.392	10.623	0.001	HS
Male	39	7	93.220	7.377	78.761	107.679			
T stage									
T 2	11	2	94.364	13.199	68.493	120.234	3.166	0.205	NS
T 3	18	3	84.171	9.364	65.818	102.524			
T 4	25	10	62.314	11.839	39.109	85.519			
N stage									
N 0	13	4	70.938	13.795	43.901	97.976	7.169	0.067	NS
N 1	14	6	64.962	14.712	36.125	93.798			
N 2	25	4	95.262	9.025	77.573	112.950			
N 3	2	1	2.000	0.707	0.614	3.386			
Predictors of overall survival									
Age at presentation (years)									
≤55 yrs	29	10	80.483	8.900	63.039	97.926	16.160	0.000	HS
>55 yrs	23	19	34.204	8.024	18.477	49.931			
Sex									
Female	16	12	30.667	10.950	9.204	52.129	7.532	0.006	HS
Male	36	17	73.241	7.833	57.888	88.594			
T stage									
T 2	11	3	85.273	14.639	56.580	113.965	7.047	0.029	S
T 3	18	9	66.211	10.114	46.388	86.035			
T 4	23	17	40.670	9.258	22.524	58.816			
N stage									
N 0	13	8	55.567	12.269	31.519	79.615	13.181	0.004	HS
N 1	14	10	50.357	11.422	27.970	72.744			
N 2	23	9	72.984	11.078	51.271	94.698			
N 3	2	2	4.000	1.000	2.040	5.960			
Smoking									
No	10	8	30.600	11.974	7.130	54.070	3.362	0.067	NS
Yes	42	21	67.770	7.666	52.745	82.795			

Table 6. Cox regression analysis to evaluate predictors of PFS and overall survival among IMRT group.

	Total no.	No. of event	PFS (months)		95% CI		Log rank test		
			Mean	SE	Lower	Upper	X^2	*P* value	Sig.
Predictors for progression free survival									
Age at presentation (years)									
≤55 years	32	9	47.129	3.587	40.098	54.160	0.044	0.834	NS
>55 years	40	9	47.157	3.463	40.369	53.946			
Sex									
Female	20	9	30.450	5.765	19.150	41.750	11.408	0.001	HS
Male	52	9	51.742	2.460	46.920	56.564			
T stage									
T 2	9	4	57.556	2.305	53.038	62.073	14.662	0.001	HS
T 3	30	3	51.554	3.253	45.178	57.931			
T 4	33	11	37.67	4.318	29.206	46.133			
N stage									
N 0	22	3	52.727	3.368	46.126	59.329	2.842	0.417	NS
N 1	30	7	47.844	4.021	39.963	55.726			
N 2	12	5	38.850	5.795	27.492	50.208			
N 3	8	3	36.688	3.886	29.070	44.305			

(*continued on next page*)

Table 6. (continued)

	Total no.	No. of event	PFS (months)		95% CI		Log rank test		
			Mean	SE	Lower	Upper	X^2	*P* value	Sig.
Pathology grade									
Grade 2	52	11	48.903	2.974	43.074	54.732	0.020	0.887	NS
Grade 3	4	1	32.667	1.089	30.533	34.800			
Type of concurrent chemotherapy received									
AUC 2	23	6	42.217	4.175	34.035	50.400	0.125	0.724	NS
Cisplatin	49	12	47.736	2.973	41.908	53.563			
Predictors for overall survival									
Age at presentation (years)									
≤55 yrs	32	3	60.205	3.032	54.263	66.148	3.301	0.069	NS
>55 yrs	40	14	51.614	2.059	47.58	55.649			
Sex									
Female	20	10	46.853	2.749	41.466	52.241	13.396	<0.001	HS
Male	52	7	58.704	2.158	54.475	62.933			
T stage									
T 2	9	2	61.000	0.000	61.000	61.000	10.527	0.005	HS
T 3	30	6	56.805	2.807	51.303	62.306			
T 4	33	9	48.325	1.820	44.757	51.892			
N stage									
T 0	22	4	55.825	1.507	52.872	58.778	1.319	0.517	NS
T 1	30	7	54.369	2.291	49.878	58.859			
T 2	12	6	49.771	4.364	41.218	58.325			
T 3	8	0	–	–	–	–			
Pathology grade									
Grade 2	52	16	53.327	2.082	49.246	57.409	0.061	0.805	NS
Grade 3	4	1	52.500	3.182	46.263	58.737			
Smoking									
No	29	12	58.499	2.914	52.788	64.209	4.705	0.030	S
Yes	43	5	51.685	1.786	48.184	55.186			
Type of concurrent chemotherapy received									
AUC 2	23	13	50.181	2.067	46.13	54.233	8.931	0.003	HS
Cisplatin	49	4	59.913	2.695	54.63	65.195			

agreement with Rathod et al., who reported comparable incidence of fatigue early but fatigue was more pronounced with IMRT later on but he did not find differences regarding anorexia at any time.[6]

This result is against what was reported by Morreto et al., as he claimed that grade 2 or more late toxicities was comparable between both groups.[4] Lee et al., and Plazi et al., also did not reported significant differences between both techniques in incidence of acute toxicities.[11,12]

4.1. Conclusion

IMRT had the advantage of providing high dose of irradiation to the tumor with minimal distribution to the normal surrounding organs. IMRT had protective effect against xerostomia, dysphagia, mucositis and skin toxicity. IMRT was not associated with better disease course but was associated with lower mortality rates and better survival. Se, T stage, smoking, type of chemotherapy affected significantly PFS and OS.

Conflict of interest

Authors declare that there is no conflict of interest, no financial issues to be declare.

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