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A Comparison of Palliative Radiotherapy Between 20 Gy in 5 Fractions and 30 Gy in 10 Fractions in Superior Vena Cava Syndrome Due to Carcinoma of Lung

*Masud MRI[1], Haque MN[2], Khan MR[3], Tuly BN[4], Husna MGZA[5], Alam S[6]

Abstract

A quasi-experimental study was conducted to compare palliative radiotherapy between 20 Gy in 5 fractions and 30 Gy in 10 fractions in superior vena cava syndrome due to carcinoma of lung. This study was done in National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, from September 2017 to August 2018. A total of 60 patients were enrolled in the study – 30 in each group. In Arm A, patients received 20 Gy in 5 fractions in 1 week, while in Arm B, patients received 30 Gy in 10 fractions in 2 weeks. Every patient was evaluated routinely to see the treatment outcome and toxicities. The mean age of Arm-A was 57.53±5.5 years and that of Arm-B was 57.40±5.4 years. After treatment, improvement of symptoms (e.g., edema, venous distension, dyspnea) of SVCS was observed. After 1 month of radiotherapy, complete resolution of venous distension occurred in majority of the patients (73.3% vs. 80%) and partial resolution occurred in rest of them (26.7% vs. 20%) in arms A and B respectively. Most of patients showed complete resolution of edema (83.3% vs. 86.7%), while few had partial resolution (16.7% vs. 13.3%) in arms A and B respectively. Symptoms of SVCS did not recur in any of the patients of both arms. Performance status also improved in all patients. Assessment of tumor response at the last follow-up showed partial response in 66.7% patients of Arm-A and 73.3% patients of Arm-B. Stable disease was observed in 33.3% patients of Arm-A and 26.7% patients of Arm-B. None of the patients showed disease progression. Toxicities included dysphagia (26.7% vs. 33.33%), fatigue (23.33% vs. 20%), nausea and vomiting (16.67% vs. 20%) and skin reaction (16.67% vs. 13.33%) in Arm-A and Arm-B respectively. All of those toxicities were grade-1 and easily controlled. There was no statistically significant difference between two treatment groups in terms of palliation of symptoms of SVCS, tumor response and toxicities. To summarize, although tumor response was not much satisfactory, both 20 Gy in 5 fractions and 30 Gy in 10 fractions are equally effective radiotherapy regimens in palliation of symptoms of SVCS due to lung cancer with tolerable toxicities. Hence, 20 Gy in 5 fractions can be a reasonable treatment choice in a resource-poor country like Bangladesh.

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1. *Dr. Md. Rakibul Islam Masud, Radiotherapist, Dept. of Radiotherapy, Mymensingh Medical College Hospital, Mymensingh.
2. Dr. Md. Nizamul Haque, Professor and Head, Dept. of Radiation Oncology, NICRH, Mohakhali, Dhaka.
3. Dr. Mojibur Rahman Khan, Assistant Professor and Head, Dept. of Radiotherapy, Mymensingh Medical College Hospital, Mymensingh.
4. Dr. Badrun Nahar Tuly, Medical Officer, Dept. of Oncology, Delta Hospital Limited, Mirpur, Dhaka.
5. Dr. Md. Golam Zel Asmaul Husna, Resident, Radiation Oncology, NICRH, Mohakhali, Dhaka.
6. Dr. Saiful Alam, Phase-B Resident, Radiation Oncology, NICRH, Mohakhali, Dhaka.

Address of Correspondence:
Email: dmch.k.65@gmail.com
Mobile: +8801754260797

Introduction

The superior vena cava carries blood from the head, arms, and upper torso to the heart; it carries approximately one third of the venous return to the heart. Superior vena cava syndrome (SVCS) refers to a constellation of symptoms and signs resulting from obstruction of the superior vena cava. The increased venous pressure in the upper body results in edema of the head, neck, and arms, often with cyanosis, plethora, and distended subcutaneous vessels. Nowadays, malignancy is the most common underlying process in patients with SVCS.[1] Approximately, 80% of all cases of SVCS are lung cancer.[2]

Radiotherapy is a treatment option for most patients with malignant SVCS.[3] The primary effect of palliative radiotherapy for SVCS is exerted by decreasing the extrinsic pressure on the SVC by the surrounding or invading malignant masses.[4] For intra-thoracic disease with an obstructive component in case of non-small cell carcinoma, 30 to 45 Gy in 2.5- to 3-Gy fractions over 2 to 3 weeks is generally recommended.[2] For patients with poor performance status or for whom daily radiotherapy over 2 to 3 weeks is logistically difficult, hypo-fractionated regimens (of 1 to 2 fractions) have been utilized with good palliative results.[2] Some guidelines emphasized either short- or long-course EBRT as the first-line radiation option in the palliative setting.[5] A retrospective study evaluated the efficacy of treating patients with SVCS with a regimen of three fractions of 8 Gy once a week to a total dose of 24 Gy compared to two fractions of 8 Gy within 1 week to a total dose of 16 Gy. Transient dysphagia was the main side effect in almost half of the patients in both programs. The 24-Gy regimen resulted in a complete resolution of symptoms in 56% of patients and a partial response in another 40%. However, no data clearly support a particular fractionation scheme.[6] Other studies used the radiation fractionations used were 6 Gy in a single fraction, 20 Gy in 5 fractions, 20 Gy in 10 fractions, and 30 Gy in 10 fractions for small cell lung cancer. The treatment intent is mainly palliative and rarely curative.[7,8]

Chemotherapy is also effective in case of small cell carcinoma. However, no significant difference in response rates to chemotherapy or radiation has been detected in most studies in case of small cell lung cancer.[9,10]

According to the guidelines of National Comprehensive Cancer Network (NCCN), palliative radiation regimen for SVCS in non-small cell lung cancer is 30-45 Gy in 2-3 weeks with 3 Gy per fraction.[11]

This quasi-experimental study was conducted to compare two treatment regimens with respect to symptom palliation, acute toxicity and find out more convenient modality of treatment in our perspective.

Methods

A quasi-experimental study was conducted in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, between September 2017 and August 2018. Total 60 Patients were selected from the radiation oncology outpatient department who met the selection criteria of the study. Sample was selected by purposive sampling technique. Among them, 30 patients were included in Arm A and they were treated by EBRT. Machine was Cobalt- 60 / 6 MV LINAC. Total dose of 20 Gy

was given in 5 fractions in 1 week. Another 30 patients were included in Arm B and they were treated by EBRT. Machine was Cobalt-60 / 6 MV LINAC. Total dose of 30 Gy was given in 10 fractions in 2 weeks.

Inclusion criteria:

a) Clinically diagnosed as superior vena cava syndrome with histopathology report proven carcinoma lung.
b) Karnofsky performance status >50
c) Age: (40-69) years
d) Minimum laboratory criteria required to include:
   i. Hemoglobin should be more than or equal to 10 gm/dl.
   ii. An absolute WBC count more than or equal to 4000 cells/ml.
   iii. A platelet count of more than or equal to 100,000 cells/ml.
   iv. Serum Bilirubin level of less than or equal to 1.5 times the upper limit of normal.
   v. AST and ALT level not more than three times the upper limit of normal.
   vi. Serum Creatinine level less than or equal to 1.5 times the upper limit of normal.

Exclusion criteria:

a) Patients who were previously treated with chest radiotherapy were excluded.
b) Eligible patient unwilling to participate in the study.

The follow up was conducted in three times:

- First follow-up: at the end of radiotherapy (Just after last fraction);
- Second follow-up: 4 weeks after completion of radiotherapy; and
- Final follow-up: 3 months after completion of radiotherapy.

In each follow up treatment response and toxicities were noted very carefully.

A semi structured questionnaire was used for data collection. Data were collected by taking detailed history, clinical examinations, investigations, imaging reports and supportive assessment tools. Subjects were briefed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. Informed consent was obtained accordingly. Patients were managed accordingly. After collection of all information, these data were checked, verified for consistency, and edited for finalized result. Data processing work consisted of registration schedules, editing, and computerization, preparation of dummy table, analyzing and matching of data. After editing and coding, the coded data were analyzed by using SPSS version 23.0. A P-value <0.05 was considered as statistically significant. Comparisons were done by using student's t-test and chi-square test. The study was approved by the ethical review committee of National institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh.

Results

Table I depicts the age distribution of the patients. Most of the patients in both groups was from >60 age group. Among the patients the lower class (monthly income less than 12,260 taka) was 58.33% comprising the major percentage of the patients. Rest of the participants (41.67%) were middle class (monthly income 12,260 taka to 31,640 taka). Differences between the groups were not statistically significant (P>0.05). Figure 1 shows that most common histopathological subtypes were

Squamous Cell carcinoma (40% vs. 43.33%), Adenocarcinoma (30% vs. 26.67%), Non-Small Cell Carcinoma, no special type (16.67% vs. 13.33%) and Small Cell carcinoma (13.33% vs. 16.67%) in Arm A and Arm B respectively. Table II shows that dyspnea, facial swelling and venous distension of neck were universal affecting all patients of both groups. Differences between the groups were not statistically significant (P>0.05).

Figure 2 shows the distribution of patients according to risk factors in Arm A, and Arm B, as smoking was most prevalent risk factor in both groups. After 1 month of the treatment complete resolution of edema was observed in 83.3% and partially in 16.7%; complete resolution of superficial venous distension was observed in 73.3%, while partial resolution was evident in 26.7% cases. However, there was no statistically significant difference between the groups (Table-III). The level of dyspnea was assessed before treatment, 1 month after treatment, and 3 months after treatment. There was significant improvement compared to the condition before treatment. However, there was no statistically significant difference between two arms (P>0.05) (Table-IV).

Table-V shows the distribution of patients based on Karnofsky Performance Score (KPS) as observed before treatment, 1 month after treatment, and 3 months after treatment. There was no statistically significant difference between two arms (P>0.05). Table-VI demonstrates tumor response 1 month after treatment and 3 months after treatment. However, there was no statistically significant difference between two arms (P>0.05). Table-VII shows treatment related toxicities of the patients of both arms. All of these toxicities were grade-1 and easily controlled. From the perspective of toxicity, there was no statistically significant difference between those two arms (P>0.05).

Table-I: Distribution of patients according to demographic characteristics (n=60)

Variables	Arm A (n = 30)	Arm B (n = 30)	P value
Age			
40-49	3 (10)	2(6.7)	
50-59	11 (36.7)	13(43.3)	0.819
>60	16(53.3)	15(50.0)	
Mean±SD	57.53±5.5	57.40±5.4	
Socioeconomic status			
Lower class	18 (60.0)	17(56.7)	0.793
Middle class	12 (40.0)	13 (43.3)	

Fig. 1: Distribution of patients according to histopathology (n=60)

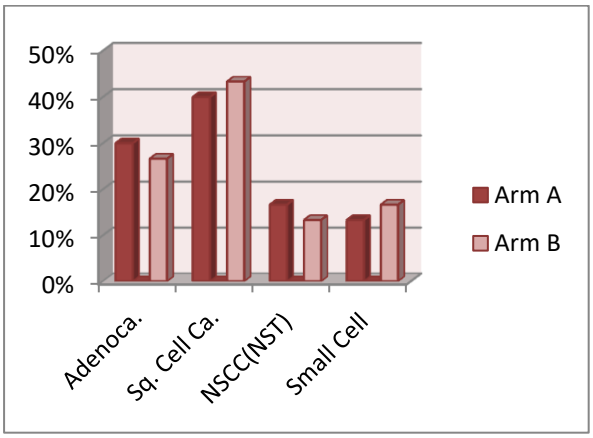

Table-II: Distribution of patients by clinical manifestations

Clinical symptoms	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
Dyspnea	30	100.0	30	100.0	-
Facial swelling	30	100.0	30	100.0	-
Venous distension of neck	30	100.0	30	100.0	-
Venous distension of chest wall	23	76.67	25	83.33	0.518
Arm Swelling	4	13.33	5	16.67	0.718
Cough	17	56.67	14	46.67	0.438
Hemoptysis	4	13.33	5	16.67	0.718
Chest pain	3	10.0	5	16.67	0.448

Fig. 2: Distribution of patients according to risk factors

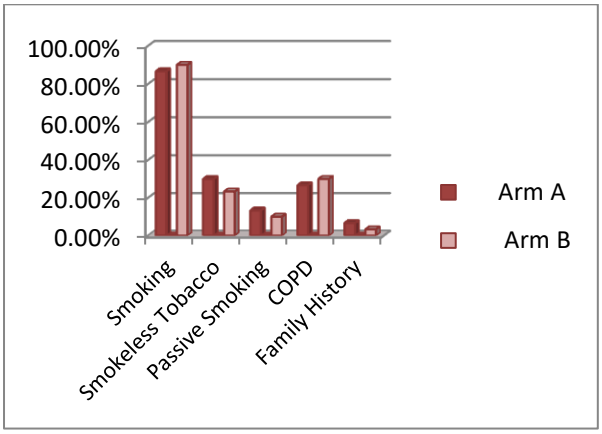

Table-III: Evaluation of resolution of edema and superficial venous distension (after 1 month of treatment) (n=60)

Variables	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
Resolution of edema					
Complete	25	83.3	26	86.7	0.718
Partial	5	16.7	4	13.3	
Resolution of superficial venous distension					
Complete	22	73.3	24	80.0	0.542
Partial	8	26.7	6	20.0	

Table-IV: Level of dyspnea (n=60)

Level of Dyspnea	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
Before treatment					
Grade 3	6	20.0	5	16.7	0.798
Grade 4	19	63.3	18	60.0	
Grade 5	5	16.7	7	23.3	
After 1 month of treatment					
Grade 1	4	13.3	6	20.0	0.733
Grade 2	23	76.7	22	73.3	
Grade 3	3	10.0	2	6.7	
After 3 months of treatment					
Grade 1	12	40.0	14	46.7	0.602
Grade 2	18	60.0	16	53.3	

Table-V: Karnofsky performance score (n=60)

Karnofsky performance score	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
Before treatment					
KPS 50	19	63.3	21	70.0	0.852
KPS 60	7	23.3	6	20.0	
KPS 70	4	13.3	3	10.0	
After 1 month					
KPS 60	7	23.3	5	16.7	0.795
KPS 70	8	26.7	8	26.7	
KPS 80	15	50.0	17	56.7	
After 3 months					
KPS 70	7	23.3	5	16.7	0.801
KPS 80	17	56.7	19	63.3	
KPS 90	6	20.0	6	20.0	

Table-VI: Assessment of tumor response (n=60)

Tumor response	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
After 1 month					
Partial Response	12	40.0	13	43.3	0.793
Stable Disease	18	60.0	17	56.7	
After 3 months					
Partial Response	20	66.7	22	73.3	0.573
Stable Disease	10	33.3	8	26.7	

Table-VII: Treatment related toxicity of patients (n=60)

Toxicity	Arm A (n = 30)		Arm B (n = 30)		P value
	N	%	N	%	
Dysphagia	8	26.67	10	33.33	0.573
Fatigue	7	23.33	6	20	0.754
Nausea & Vomiting	5	16.67	6	20	0.739
Skin Reaction	5	16.67	4	13.33	0.718

Discussion

Lee *et al.*[13] shows that the median age of the patients of lung cancer with SVCS was 60 years. In our study, the mean age was 57.53±5.5 years and 57.40±5.4 years in Arm-A & Arm-B respectively. These findings are in congruence with our study results. The present study showed that the histopathological subtypes were squamous cell carcinoma (40% vs. 43.33%), adenocarcinoma (30% vs. 26.67%), non-small cell carcinoma, no special type (16.67% vs. 13.33%) and small cell carcinoma (13.33% vs. 16.67%) in arm a and arm b respectively. These findings are in congruence with to the report of Wilson *et al.*[1]

Our study showed that dyspnoea, facial swelling and venous distension of neck were universal affecting all patients of both groups. Other findings were venous distension of chest wall (76.67% vs. 83.33%), cough (56.67% vs. 46.67%), arm swelling (13.33% vs. 16.67%), haemoptysis (13.33% vs. 16.67%) and chest pain (10% vs. 16.67%) in arm A and arm B respectively. These findings are in congruence with the report of Rimner *et al*.[4]

Our study also showed that majority of the patients (>90%) were exposed to tobacco in different ways e.g., smoking (86.67% vs. 90% in arms A & B respecctively), smokeless tobacco (30% vs. 23% in arms A & B respectively). Other risk factors include COPD (26.67% vs. 30% in arms A & B respectively), family history (6.67% vs. 3% in arms A & B respectively). The result more or less resembles with the findings from Rimner *et al.*[4]

Most of patients showed complete resolution of edema (83.3% vs. 86.7%), while few had partial resolution (16.7% vs. 13.3%) in arms A and B respectively 1 month after treatment. Complete resolution of superficial venous distension occurred in majority of the patients (73.3% vs. 80%) and partial resolution occurred in rest of them (26.7% vs. 20%) in arms A and B respectively 1 month after treatment. It shows significant improvement of symptoms like edema and superficial venous distension occurred in majority of the patients and there was no statistically significant difference between two arms. These results are in congruence to the study done by Lee *et al.*[12]

In this study, patients are treated with radiotherapy first. 20 Gy in 5 fractions was used for 61% of the patients and 30 Gy in 10 fractions was used for 39% of the patients. 68% patients had good relief from obstruction at the end of radiotherapy, but overall survival was poor. These findings are in congruence to the study of Egelmeers *et al.*[13] Before starting treatment, majority of the patients suffered from grade 4 dyspnea (63.3% vs. 60%) followed by grade 3 and grade 5 in Arm-A and Arm-B respectively (Table IV). The level of dyspnea was assessed 1 month after treatment. There was significant improvement compared to the condition before treatment. Most common was grade 2 dyspnea (76.7% vs. 73.3%). Level of dyspnea was again assessed 3 months after treatment. Majority suffered from grade 2 dyspnea (60% vs. 53.3%) in Arm-A and Arm-B respectively. A universal response to radiotherapy was observed and there was no statistically significant difference between two treatment arms.

Table V shows that, at the beginning of the treatment, most of the patients in both groups

had KPS score 50, 63.3% vs. 70.0% in Arm-A and Arm-B respectively. Rest of the patients had KPS score 60 (23.3% vs. 20%) and KPS score 70 (13.3% vs. 10%) in Arm-A and Arm-B respectively. There was no statistically significant difference as per KPS score in two arms. Performance status was assessed 1 month after treatment. Majority had KPS score 80 (50% vs. 56.7%) followed by KPS score 70 (26.7% vs. 26.7%) and KPS score 60 (23.3% vs. 16.7%). After 3-month treatment, majority had KPS score 80 (56.7% vs. 63.3%) followed by KPS score 70 (23.3% vs. 16.7%) and KPS score 90 (20% vs. 20%). Radiotherapy improved the performance status of the patients of both treatment groups. However, there was no statistically significant difference between two treatment arms.

During the assessment of tumor response after 1 month of treatment, most of the patients showed stable disease (60% vs. 56.7%) followed by partial response (40% vs. 43.3%). There was no statistically significant difference between two groups. Another important thing to notice is that none of the patients progressed clinically. Now if we look at results of tumor control 3 months after treatment, most of the patients showed partial response (66.7% vs. 73.3%) followed by stable disease (33.3% vs. 26.7%) in rest of the patients in Arm-A and Arm-B respectively (Table VI). Considering the palliative intent of tumor, we can say that these are impressive results. None of the patients showed progressive disease and most of the patients showed partial response.

Our results (Table VII) showed some of the treatment related toxicities which include dysphagia (26.7% vs. 33.33%), fatigue (23.33% vs. 20%), nausea and vomiting (16.67% vs. 20%) and skin reaction (16.67% vs. 13.33%) in Arm-A and Arm-B respectively. All of those toxicities were grade-1 and well-controlled. From the perspective of toxicity, there was no statistically significant difference between these two arms. Side effects of therapy were minimal. A retrospective study also showed that such side effects of treatment were minimal.[14] Dysphagia was the most common complaint (26%). Hence, in terms of toxicity profile, our study results perhaps closely resemble to the previous results.[14]

Conclusion

Our study showed that hypo-fractionated external beam irradiation can effectively palliate the symptoms of SVCS and improve performance status of all patients. However, in terms of tumor response, majority showed partial response, and none progressed clinically. Toxicity profile was acceptable. There was no statistically significant difference between two treatment arms e.g., 20 Gy in 5 fractions and 30 Gy in 10 fractions in terms of palliation of symptoms, improvement of performance status, tumor response and toxicity. Hence, 20 Gy in 5 fractions can be a reasonable treatment choice in a resource-poor country like Bangladesh.

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