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Original Article

A Prospective Study to Compare Intensity Modulated Radiation Therapy (IMRT) Planning by Flattening Filter (FF) versus Flattening Filter free(FFF) beam in Carcinoma Esophagus

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ABSTRACT

Background: Esophageal cancer was previously treated with 3-dimensional conformal radiation therapy (3D-CRT). In order to benefit from the clinical potential of preserving the lung and spinal cord, radiation therapy for esophageal cancer has switched from 3D-CRT to intensity-modulated-radiation-therapy (IMRT).

Aim: It is important to investigate whether esophageal cancer radiotherapy employing flattening filter-free compared to flattened beams has any advantages. The goal of this study is to extensively compare the dosimetric features, delivery effectiveness (response), and toxicity of a treatment regimen for esophageal cancer of Flattening Filter (FF) and Flattening Filter Free (FFF) photon beams using Intensity Modulated Radiation Therapy (IMRT) technology.

Material and Methods: The present study was conducted as a prospective observational study on 60 patients with esophageal cancer undergoing radiation in Department of Radiation oncology, Govt. Medical College of Central India and associated Hospital. All 60 participants were randomly assigned into either of the two treatment group (IMRT-FF and IMRT-FFF) and were compared for dose volume histogram, toxicities and response.

Results: Two groups were comparable with respect to baseline variables and tumor characteristics ($p>0.05$). Mean and maximum heart dose; minimum, maximum as well as mean dose of left lung; minimum and maximum dose of right lung and minimum and mean dose in spinal cord in IMRT-FF group were significantly higher in IMRT-FF group as compared to IMRT-FFF group ($p<0.05$). The response was significantly better in FFF group ($p<0.05$). We found no significant difference in toxicities to organ at risk between two treatment arm ($p>0.05$).

Conclusion: IMRT FF and IMRT FFF are standard photon beam used for management of patients with esophageal cancers. FFF photon beam in comparison to FF photon beam provides better OAR sparing by less scattered dose, improves quality of life and runs treatment process smoothly. The most beneficial character of FFF beam plan is clinically desirable and physically acceptable treatment plan at lower dose for target coverage and reduction of peripheral dose around target without compromising quality of beam.

Key Words: *Intensity Modulated Radiation therapy, Flattening filter, Flattening filter free, Esophageal cancer, Toxicities, Organs at risk*

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INTRODUCTION:

Esophageal cancer is classified as an aggressive and lethal disease that poses therapeutic obstacles to interdisciplinary oncology. According to the World Health Organization's GLOBOCAN 2020, esophageal cancer caused 6 million (3.1%) new cases and nearly 5 million (5.5%) deaths globally.[1] In accordance with the " National Cancer Registry Programme", in 2022, 1,400,000 new cancer cases were diagnosed in India.[2] It is estimated that 2,73,982 (19%) cases were caused by gastrointestinal cancers, while 52,000 (3.2%) cases were caused by esophageal cancers. The North-eastern region, where tobacco consumption is also significantly greater, had higher prevalence. Esophageal carcinoma is the third most prevalent gastrointestinal malignancy in India, impacting mainly men with the M:F ratio of 1.5:1.[2]

The two primary histological forms of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). SCC represents the most typical type of esophageal cancer in the world attributing to about 90% of esophageal carcinomas. Over the recent three decades, SCC prevalence rate has steadily decreased while AC has concurrently continued to increase in the western world and become most prevalent histological type in the western world right now.[3] The treatment depends on the location of the lesion and the cancer's stage at the time of diagnosis. Neoadjuvant chemoradiation (CRT) and resection for resectable disease, and radical concurrent CRT for unresectable disease are required for the treatment of locally advanced esophageal cancer.[4,5]

In comparison to 3D-CRT, IMRT has a better ability to paint a targeted dose, offers better dose consistency around the target, and provides improved conserving of surrounding normal, healthy tissue.[6] Additionally, IMRT has a higher likelihood of increasing low dosage to nearby healthy cells than 3D-CRT, and also has 3-5 times higher Monitor Unit (MU). Important features of IMRT include greater dosage conformity and a higher dose gradient beyond the target structure. A higher MU results in a bigger dose to the body as a whole and to the normal tissues, as well as a rise in the scattered dose from gantry head leaks. Therefore, it is better to reduce extra scatter from the gantry head and accelerate the transmission of the treatment regimen for IMRT. With advancements in radiotherapy treatment delivery and linear accelerator (LINAC) design, it is now feasible to remove the flattening filter (FF) from the gantry's head.[7]

To reduce the scatter contribution from the flattening filter (FF), which was initially intended to generate flattened dose profiles at a particular depth, it was thought sensible to remove the FF from the photon beam's path. The advancement of IMRT may lead to the elimination of the necessity for an FF in contemporary LINAC systems. Unfiltered photon beams have been extensively examined recently.[7-9] The forward peaked dosage profile is the defining feature of the flattening filter-free (FFF) beam.[10,11] With high energy beams (>15 MV), the FFF photon beam has a lower dose to the organ at risk (OAR), a higher dose rate than the flattened photon beam, and less neutron contamination. As a consequence, the therapeutic use of the FFF beam will lead to a quicker recovery period and a lower risk of radiation-induced secondary cancer.[12,13] The drop in mean energy and the rise in dose rate in the FFF beam are the two biggest changes from a physics perspective.[14] Therefore, it is important to investigate whether esophageal cancer radiotherapy employing flattening filter-free compared to flattened beams has any advantages. The goal of this study is to extensively compare the dosimetric features, delivery effectiveness (response), and toxicity of a treatment regimen for esophageal cancer of FF and FFF photon beams using IMRT technology. There is no clinical study has been done till now on this.

Material and Methods:

The present study was conducted as a prospective observational study on 60 patients with esophageal cancer undergoing radiation in Department of Radiation oncology, Govt Medical College of Central India and associated Hospital during the study period of 18 months i.e. from 1st December 2021 to 30th June 2022, a period of 18 months. All the histopathologically confirmed case of esophagus, taking IMRT by flattening filter and flattening filter free technique, belonging to 18 to 70 year of age with KPS Score of 70-80 were included in the study. Patient below the 18 years of age and not willing to participate in the study were excluded from the study. After obtaining ethical clearance from Institute’s ethical Committee, all the cases with esophageal cancer fulfilling inclusion and exclusion criteria were enrolled. Data regarding sociodemographic factors, clinical history, tumour, its stage, presence of metastasis, etc. was obtained and entered in proforma. Patients were then subjected to detailed examination, investigations, histopathological analysis, Chest X-ray and CECT/MRI Scan abdomen and pelvis if needed. All 60 participants were randomly assigned into either of the two treatment group following simple randomization i.e. IMRT-FF and IMRT-FFF.

The patients in two groups were compared for dose volume histogram, toxicities (cardiac- ECG, 2D-ECHO; esophagus & Lung-symptoms; Spinal cord-clinical examination). Patients were followed up at 0, 3, 6 months and response was evaluated according to RECIST criteria.[15]

Statistical analysis:

The findings were recorded on a predefined Proforma and was compiled using MsExcel. Data was analysed using IBM SPSS software version 20 (IBM SPSS, Illinois, Chicago) as mean standard deviation (SD) and percentage. Least significant difference for measuring intergroup variance of metric data was done by student's t-test, whereas non metric data was analyzed by Fisher’s exact test/chi square test. P value of less than 0.05 was considered as significant.

Results:

The present study was conducted on 60 patients with esophageal cancer who were categorized into two groups based upon treatment of modality used.

Mean age of patients with esophageal cancer of IMRT-FF group was 54.80±12.32 years whereas mean age of patients of IMRT-FFF group was 57.00±10.43 years. Two groups were comparable with respect to baseline variables (p>0.05) (Table1).

Table 1- Comparison of baseline variables between two groups

Baseline variables		IMRT-FF (n=30)		IMRT-FFF (n=30)		P value
		N	%	n	%	
Age (years)	<40	5	16.7	2	6.7	0.605
	41-50	3	10.0	5	16.7	

	51-60	14	46.7	14	46.7	
	>60	8	26.7	9	30.0	
Sex	Female	14	46.7	10	33.3	0.296
	Male	16	53.3	20	67.7	
Religion	Hindu	30	100.0	28	93.3	0.154
	Muslim	0	0.0	2	6.7	
Locality	Rural	10	33.3	12	40.0	0.59
	Urban	20	67.7	18	60.0	
Addiction	No	14	46.7	14	46.7	0.97
	Smoking	7	23.3	6	20.0	
	Tobacco	6	20.0	6	20.0	
	Alcohol	3	10.0	4	13.3	
KPS	70	18	60.0	19	63.3	0.79
	80	12	40.0	11	36.7	

KPS- Karnofsky Performing Scale
IMRT- Intensity Modulated Radiotherapy
FFF- flattening filter free
FF- flattening filter

We observed carcinoma of middle esophagus in majority i.e. 40.0% and 73.3% cases in IMRT-FF of IMRT- FFF groups respectively. Majority of patients belonged to stage IV in both the groups (60.0% in IMRT-FF and 50.0% in IMRT-FFF group). The majority of esophageal cancers were classified as moderately differentiated squamous cell carcinoma in both the groups (43.3% in FF and 56.7% in FFF). However, the observed difference in tumor characteristics between two groups was statistically insignificant (p>0.05) (Table 2).

Table 2- Comparison of tumor characteristics between two treatment groups

Tumor characteristics		IMRT-FF (n=30)		IMRT-FFF (n=30)		P value
		N	%	n	%	
Site	Lower	2	6.7	1	3.3	0.065
	Middle	12	40.0	21	73.3	
	Upper	16	53.3	8	26.7	
Stage	II	1	3.3	1	3.3	0.729
	III	11	36.7	14	46.7	
	IV	18	60.0	15	50.0	
HPR	IKSCC	1	3.3	0	0.0	0.56
	MDSCC	13	43.3	17	56.7	
	PDSCC	6	20.0	6	20.0	
	WDSCC	10	33.3	7	23.3	

IKSCC-Invasive Keratinising squamous cell carcinoma, MDSCC-Moderately Differentiated Squamous Cell Carcinoma, PDSCC- poorly differentiated squamous cell carcinoma, WDSCC- well differentiated squamous cell carcinoma

Mean heart dose as well as maximum heart dose was statistically significantly higher in IMRT-FF group as compared to IMRT-FFF group (p<0.05). Similarly, minimum, maximum as well as mean dose of left lung in IMRT-FF group were significantly higher in IMRT-FF group as compared to IMRT-FFF group. Minimum and maximum dose of right lung and minimum and mean dose in spinal cord in IMRT-FF group were significantly higher in IMRT-FF group as compared to IMRT-FFF group (p<0.05) (Table 3).

Table 3- Comparison of dosimetric analysis of heart, spinal cord, right lung, left lung and right lung between two groups

Dose (in Gy)	IMRT-FF (n=30)		IMRT-FFF (n=30)		P value
	Mean	SD	Mean	SD	
Heart Min	2.34	2.08	1.37	1.73	0.05
Heart max	43.56	15.07	31.85	18.48	**0.009**
Heart mean	19.72	9.00	13.70	8.25	**0.009**
Spinal Cord Min	0.97	1.18	0.41	0.46	**0.018**
Spinal Cord Max	33.83	13.39	27.43	13.93	0.07

Spinal Cord Mean	17.77	8.18	14.00	4.83	**0.03**
RL Min	2.46	2.28	1.24	1.01	**0.009**
RL Max	44.26	13.25	32.35	14.38	**0.001**
RL Mean	18.40	8.42	14.63	6.51	0.05
LL Min	1.44	1.0	0.61	0.46	**0.0003**
LL Max	47.30	11.55	38.36	14.71	**0.01**
LL Mean	20.21	8.50	15.82	7.05	**0.03**

RL- right lung, LL- left lug

In our study, 18 (60.0%) and 25 (83.3%) patients of IMRT-FF and IMRT-FFF group respectively had complete response and the response was significantly better in FFF group (p<0.05) (figure 1).

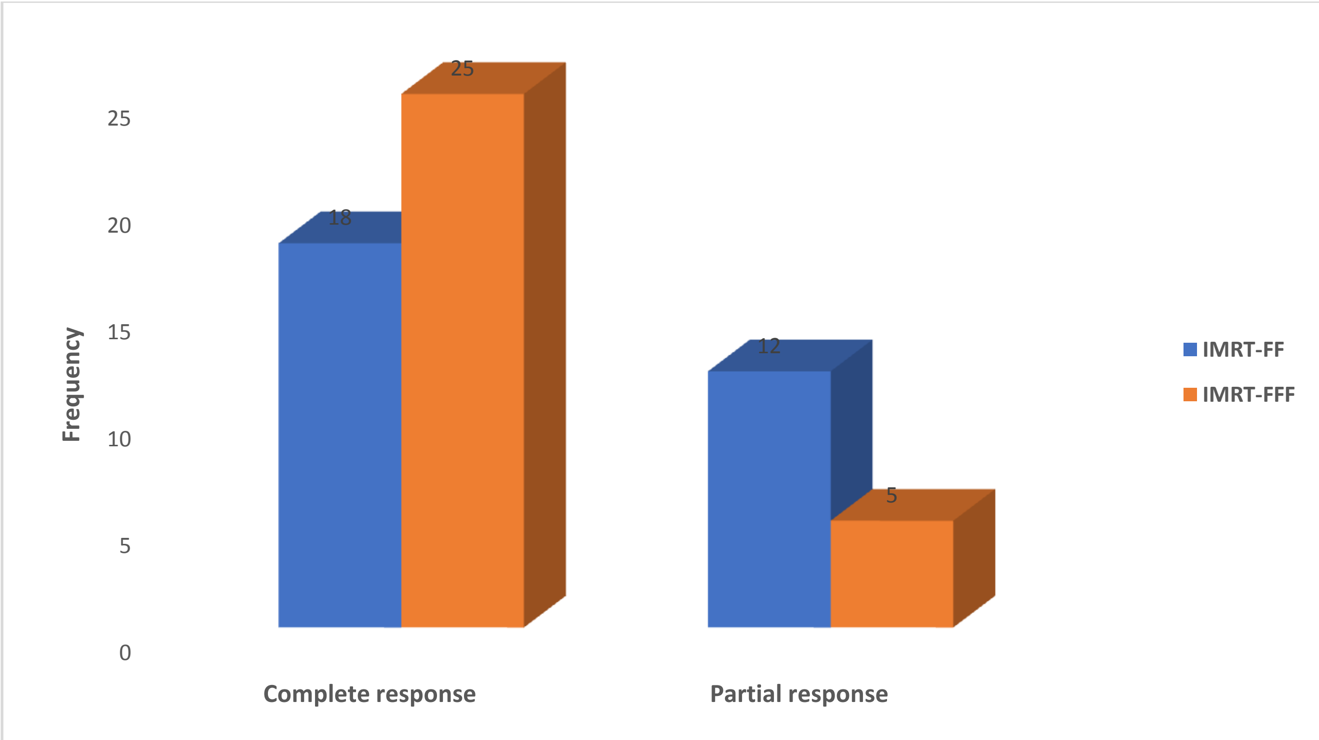

Figure 1: Comparison of response between the groups

With regard to toxicities, we found no significant difference in toxicities to organ at risk between two treatment arm (p>0.05) (Table 4).

Table 4- Comparison of toxicities between two groups at different time interval

Toxicities observed in organ at risk during observation period			IMRT-FF (n=30)		IMRT-FFF (n=30)		P value
			N	%	n	%	
Esophageal	0 month	WNL	30	60.0	30	83.3	1.0
		Dysphagia	0	0.0	0	0.0	
	3month	WNL	27	90.0	28	93.3	0.64
		Dysphagia	3	10.0	2	6.7	
	6 month	WNL	28	93.3	29	96.7	0.56
		Dysphagia	2	6.7	1	3.3	
Heart	0 month	WNL	30	60.0	30	83.3	1.0
		Other	0	0.0	0	0.0	
	3month	WNL	30	60.0	30	83.3	1.0
		Other	0	0.0	0	0.0	
	6 month	WNL	30	60.0	30	83.3	1.0
		Other	0	0.0	0	0.0	
Lungs	0 month	No	30	60.0	30	83.3	1.00

		Dry Cough	0	0.0	0	0.0	
	3month	No	28	93.3	29	96.7	0.5569
		Dry Cough	2	6.7	1	3.3	
	6 month	No	21	70	24	80	0.3751
		Dry Cough	9	30	6	20	
Spinal cord	0 month	NAD	30	60.0	30	83.3	1.00
		Weakness	0	0.0	0	0.0	
	3month	NAD	28	93.3	29	96.7	0.5569
		Weakness	2	6.7	1	3.3	
	6 month	NAD	29	96.7	29	96.7	1.00
		Weakness	1	3.3	1	3.3	

NAD-no abnormality detected, WNL- within normal limit

DISCUSSION:

Radiation treatment is the most often used therapy for esophageal cancer and is considered routine treatment. Nowadays, newer radiation methods such as three-dimensional conformal radiation treatment (3DCRT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and others are employed because they have less side effects than older approaches.[16] In external radiation therapy, the use of flattening filter free (FFF) radiation beams which are obtained by removing the flattening filter (FF) from standard linear accelerators is rapidly increasing, and the benefits of its clinical use are the issue of research. Advanced techniques in the treatment have increased the interest in operating linear accelerators in FFF mode. The differences of beams with non-uniform dose distribution created by removing FF were compared with the beams with uniform dose distribution used as a standard and examined. These differences were compared in the treatment plans of carcinoma esophagus patients who have different planning target volumes. Our study aimed to conduct dosimetric analysis, response and toxicities among patients treated with FF beam and FFF beam for esophageal cancer.

Organ related toxicities is a major concern during radiotherapy. Dosimetric analysis is important in determination of organ toxicities. In esophageal cancers, three organs are at higher risk of toxicities which included heart, lung and CNS. Kole *et al*[17] reported IMRT to be more effective in delivering target dose as well as reducing toxicity to adjacent organs as compared to other modality. Also IMRT is helpful in maintaining homogeneity.[17] Our study documented that mean dose were significantly higher in right & left lung and heart in IMRT-FF group as compared to IMRT-FFF group ($p<0.05$). The findings of present study were partially concordant with the findings of Saroj *et al*.[18] observed insignificant dose variation between FF and FFF photon beam IMRT plans. FF-based IMRT plan delivered a 15.51 % and 11.27% higher mean dose to both lungs and heart than the FFF plan, respectively. The integral dose for the heart and lungs was 11.21% and 15.51%, respectively, less in the IMRT plan with an FFF photon beam. A meta-analysis by Xu *et al*[19] concluded that IMRT is superior to other modality while assessing the survival of patients in cases of esophageal cancer whereas it was not associated with any benefit on radiation toxicity. In contrast to the FF photon beam, a filtered photon beam-oriented IMRT plan provides significant OAR sparing without losing the quality of the treatment plan. High monitor units (MUs), low Integral Dose (ID), and Beam on Time (BOT) are major highlights of the IMRT plan with FFF beam with lower dose.

In present study, significantly higher proportions of cases in FFF group had complete response (83.3%) as compared to 60% cases in FF group ($p<0.05$). Further, all the patients were follow-up till 6 months following radiotherapy and symptoms were assessed. The lung symptoms, i.e. dry cough increased following radiotherapy in both the groups as compared to baseline, the difference in lung involvement between two groups was statistically insignificant at each follow up ($p>0.05$). Similarly no statistically significant difference were observed for spinal cord and esophagus and decreases in symptoms throughout the follow up were observed. The findings of present study were supported by findings of Xu *et al*[19] and Tonison*et al*[20] in which no statistically significant difference was observed between 3DCRT and IMRT for radiation pneumonitis ($p>0.05$). None other study found in literature who reported symptomatic comparison.

CONCLUSION:

IMRT FF and IMRT FFF are standard photon beam used for management of patients with esophageal cancers. Based upon the findings of present study, it could be concluded that FFF photon beam in comparision to FF photon beam provides better OAR sparing by less scattered dose, improves quality of life and runs treatment process smoothly. The most beneficial character of FFF beam plan is clinically desirable and physically acceptable treatment plan at lower dose for target coverage and reduction of peripheral dose around target without compromising quality of beam. Additionally, higher MU for the FFF IMRT plan can be compensated by a high dose rate and reduction in overall treatment time has added a benefit in decreasing in room time for patients.

Conflict of Interest: None

REFERENCES

1. WHO. Source: Globocan (2020). Globocan 2020 2020; 419: 3–4. Available at: https://ascopost.com/news/december-2020/globocan- 2020-database-provides-latest-global-data-on-cancer-burden- cancer-deaths/#:~:text=Female breast cancer has now, with 685%2C000 deaths in 2020.
2. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS(2020); ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Glob Oncol;6:1063-1075. doi: 10.1200/GO.20.00122.
3. Vizcaino AP, Moreno V, Lambert R, Parkin DM(2002). Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. Int J Cancer. 2002 Jun 20;99(6):860-8. doi: 10.1002/ijc.10427. Erratum in: Int J Cancer;101(6):599.
4. Fawaz ZS, Kazandjian S, Tsui JM, Devic DS, Lecavalier-Barsoum M, Vuong T, et al(2018). What Is the Optimal Radiation Technique for Esophageal Cancer? A Dosimetric Comparison of Four Techniques. Cureus. 16;10(7):e2985. doi: 10.7759/cureus.2985.
5. Nieman DR, Peters JH(2013). Treatment strategies for esophageal cancer. Gastroenterology Clinics;42(1):187-97. doi: 10.1016/j.gtc.2012.11.007.
6. International Atomic Energy Agency. Transition from 2-D Radiotherapy to 3-D Conformal and Intensity Modulated Radiotherapy. IAEA TECDOC Series No. 1588. International Atomic Energy Agency; 2008.
7. Ong CL, Dahele M, Slotman BJ, Verbakel WF(2013). Dosimetric impact of the interplay effect during stereotactic lung radiation therapy delivery using flattening filter-free beams and volumetric modulated arc therapy. Int J Radiat Oncol Biol Phys; 86(4):743-8. doi: 10.1016/j.ijrobp.2013.03.038.
8. Georg D, Knöös T, McClean B(2011). Current status and future perspective of flattening filter free photon beams. Medical physics;38(3):1280-93. doi: 10.1118/1.3554643.
9. Reggiori G, Mancosu P, Castiglioni S, Alongi F, Pellegrini C, LobefaloF,et al(2012). Can volumetric modulated arc therapy with flattening filter free beams play a role in stereotactic body radiotherapy for liver lesions? A volume- based analysis. Medical physics; 39(2):1112-8. doi: 10.1118/1.3679858.
10. Hawkins MA, Bedford JL, Warrington AP, Tait DM(2012). Volumetric modulated arc therapy planning for distal oesophageal malignancies. Br J Radiol;85(1009):44-52. doi: 10.1259/bjr/25428720. Epub 2011 Mar 22.
11. Chapet O, Fraass BA, Ten Haken RK(2006). Multiple fields may offer better esophagus sparing without increased probability of lung toxicity in optimized IMRT of lung tumors. Int J Radiat Oncol Biol Phys;65(1):255-65. doi: 10.1016/j.ijrobp.2005.12.028.
12. Titt U, Vassiliev ON, Pönisch F, Dong L, Liu H, Mohan R(2006). A flattening filter free photon treatment concept evaluation with Monte Carlo. Med Phys;33(6):1595-602. doi: 10.1118/1.2198327.
13. Kry SF, Vassiliev ON, Mohan R(2010). Out-of-field photon dose following removal of the flattening filter from a medical accelerator. Phys Med Biol. 2010 Apr 21;55(8):2155-66. doi: 10.1088/0031-9155/55/8/003. Epub.
14. Vasishta A, Kelkar A, Joshi P, Hapse R(2019). The value of sonoelastography in the diagnosis of supraspinatus tendinopathy-a comparison study. Br J Radiol; 92(1095):20180951. doi: 10.1259/bjr.20180951. Epub 2019 Jan 28.
15. Padhani AR, Ollivier L(2001). The RECIST (Response Evaluation Criteria in Solid Tumors) criteria: implications for diagnostic radiologists. Br J Radiol;74(887):983-6. doi: 10.1259/bjr.74.887.740983.
16. Bai XH, Dang J, Chen ZQ, He Z, Li G(2020). Comparison between Intensity-Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy for Their Effectiveness in Esophageal Cancer Treatment: A Retrospective Single Institution Study. J Oncol; 2020:6582341. doi: 10.1155/2020/6582341.
17. Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA(2012). Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys;83(5):1580-6. doi: 10.1016/j.ijrobp.2011.10.053. Epub 2012 Jan 26.
18. Saroj DK, Yadav S, Paliwal N, Haldar S, Jagtap A, Kumar A(2022). Assessment of Treatment Plan Quality between Flattening Filter and Flattening Filter Free Photon Beam for Carcinoma of the Esophagus with IMRT Technique. Journal of Biomedical Physics and Engineering.
19. Xu D, Li G, Li H, Jia F(2017). Comparison of IMRT versus 3D-CRT in the treatment of esophagus cancer: A systematic review and meta-analysis. Medicine (Baltimore);96(31):e7685. doi: 10.1097/MD.0000000000007685.
20. Tonison JJ, Fischer SG, Viehrig M, Welz S, Boeke S, Zwirner K,et al(2019) Radiation Pneumonitis after Intensity-Modulated Radiotherapy for Esophageal Cancer: Institutional Data and a Systematic Review. Sci Rep; 9(1):2255. doi: 10.1038/s41598-018-38414-5.