Original Article

CLINICAL OUTCOME OF HIGH DOSE RADIOTHERAPY WITH OR WITHOUT CONCURRENT CHEMOTHERAPY IN ESOPHAGEAL CANCER (EC): A STUDY FROM NORTH – EAST INDIA

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Abstract

OBJECTIVE: The objective of this study is to evaluate the clinical outcomes of high dose radiotherapy 63 Gray (Gy) with or without concurrent chemotherapy in Esophageal Cancer (EC) patients of North-East, India.

MATERIAL AND METHODS: All reported EC patients belonging to different states of North-East and treated with radical intent with high dose radiotherapy with or without concurrent chemotherapy during the period 2017-2018 (2 years) at State Cancer Institute (SCI),Gauhati Medical College (GMC), Assam, India were included in the study. This study was retrospective in nature and two years retrospective data were analyzed for clinical outcome. Statistical analysis of data was done using Statistical Packages for Social Sciences (SPSS) and Disease Free Survival (DFS) was calculated using Kaplan-Meier method.

RESULTS: Total 105 patients were treated during the period. All patients received a total dose of 63 Gy radiation. Out of 105 patients, 76 patients (72.4%) received concurrent chemotherapy and 29 patients (27.6%) not received chemotherapy only due to co-morbidities. Here, at first follow up, 89 (84.8%) patients showed complete response, 10 (9.5%) showed partial response and 6 (5.7%) showed progressive disease. Treatment related toxicities were assessed. None of the patient developed > Grade 2 toxicity.
Further, Median Disease Free Survival (DFS) was 13 months with estimated mean was 16.98 months. Also, Standard Error (SE) =1.683, Confidence Interval (CI) =13.682-20.279.

CONCLUSION: The high dose radiation (63 Gy) with concurrent chemotherapy as weekly regimen of Cisplatin or Paclitaxel plus Carboplatin is an effective definitive treatment of Stage I – IVA EC with acceptable toxicity. Median DFS is minimal in EC irrespective of the treatment. The rate of survival is decreasing rapidly before the median DFS and the rate of survival is constant after the Median DFS.

KEY WORDS: Esophageal cancer (EC); high doses; radiotherapy; concurrent chemotherapy; median disease free survival; Kaplan-Meier Plot.

1. INTRODUCTION

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world [1]. Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 [2].

EC is one of the most lethal malignancies. EC ranks seventh in terms of incidence (604,000 new cases) and sixth in mortality overall (544,000 deaths), the latter signifying that esophageal cancer is responsible for one in every 18 cancer deaths in 2020. According to a report published by National Cancer Registry Programme (NCRP), the incidence of esophagus cancer in North-East Indian States was much higher than any other parts of the world for the both males and females occurrence of is rising in North-East Indian States over the years [3].The prognosis for EC is poor, with a 5-year survival rate of 19% and only 0.9% for advanced EC [4].

EC is conditionally subdivided into Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EAC). ESCC and EAC are two distinct subtypes considering geographical and demographic prevalence, etiology, as well as histo-pathological, epidemiologic and molecular aspects [5].EAC arises from the metaplastic Barrett's Esophagus (BE) in the context of chronic inflammation secondary to exposure to acid and bile. The main risk factors for developing ESCC are cigarette smoking and alcohol consumption. ESCC is the most prevalent type worldwide, responsible for over 80% of EC cases [6] and particularly predominant in Asia and Africa, while EAC occurs more often in Western countries [7].

Patients with EC may have unspecific symptoms like tiredness, nausea, vomiting, weight loss etc., at an early stage, which makes it difficult to diagnose [8]. The late diagnosis of carcinoma in a thin walled tube without serosa, liable to undergo fatal perforation and having a tendency to spread widely up and down through the length of the esophagus in patients who are usually old and ill presents a difficult clinical situation for treatment. But, tumors presenting with loco-regional disease are potentially curable, although the cure rate is modest. Although the survival rate has been slowly improving likely because of multi-modality strategies and improved supportive care, the survival rate remains modest at 20% at 5 years.

The overall poor prognosis of advanced EC has motivated multiple strategies in an effort to improve outcomes, including preoperative chemo-radiotherapy, preoperative and preoperative chemotherapy, definitive chemo-radiotherapy, and postoperative chemo-radiotherapy. Definitive chemo-radiotherapy and combined modality with surgery are both curative options used widely in clinical practice [9-12].

Definitive chemo-radiotherapy is the preferred treatment for those with unresectable disease or a contraindication to surgery or who express a strong preference against surgery [9-12].A 2003 Cochrane review found that the combined chemo-radiotherapy led to an absolute increase in mortality difference of 7% at 2 years compared with radiation alone. Radiation Therapy Oncology Group (RTOG) 85-01 compared a higher dose of radiotherapy (64Gy in 32 fractions over 6.5 weeks) alone with a lower dose (50Gy in 25 fractions over 5 weeks) combined with chemotherapy on week 1 and 5 (infusion fluorouracil, 1000 mg/m2 on day 1 to 4, with Cisplatin, 75 mg/m2 on day 1). The chemo-radiotherapy group also received 2 further cycles of Cisplatin and fluorouracil on weeks 8 and 11. Long term follow-up showed that 5-year survival was 26% for the chemo-radiotherapy and 0% for the radiotherapy arm of the patients. A follow-up trial (INT 0123) showed that a higher dose of radiotherapy (64.8Gy) with chemotherapy was not superior in terms of survival or disease control than a lower dose (50.4Gy) with chemotherapy, but was more toxic [13]. Therefore, the standard radiation dose for patients treated with concurrent 5-FU and Cisplatin chemotherapy is 50.4Gy. Cisplatin and fluorouracil represent the mainstay choice of chemotherapy, although other choices have been studied. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020 also recommend a dose of 50-50.4Gy (1.8-2Gy/day) as definitive radiotherapy [14].

However, the standard dose of radiotherapy remains controversial. Although 50.4 Gy has been accepted as standard dose in western countries, Based on the theory of radiation biology, 50.4 Gy is just adequate to control microscopic cancer cell, but inadequate to control a gross tumor lesion [15].A radiation dose of more than 60 Gy or even nearly 100 Gy is required to control and cure a gross solid tumor [15]. According to statistics, only a few patients with EC received a radiation dose of 50.4 Gy would achieve complete response and obtain a long term survival [16]. A pooled analysis from Song et al, showed that a higher radiation dose could improve clinical outcomes without significantly increasing radiation related toxicities which was contradictory to RTOG 94-05 [17].

He et al [18] used modern radiation delivery techniques to determine whether high radiation dose could confer benefits in terms of Local Control (LC) or Overall Survival (OS). He concluded that local tumor control might be improved by higher dose of greater than 50.4 Gy, when delivered with modern techniques and concurrent chemotherapy, at the consequence of increased toxicity without impact on overall survival.

However, Zhang et al [19] reported that radiation dose >51Gy improved Loco-Regional Control (LRC), DFS and survival in patients treated with 5- fluorouracil (5-FU) based chemotherapy. Yang-Gun Suh et al [20] also reported that high dose radiotherapy of 60Gy or higher with concurrent chemotherapy improves LRC and Progression Free Survival(PFS) and may also improve the survival of stages II-III EC patients. Kim et al [21] too reported that a higher radiation dose (> 60 Gy) is associated with increased LRC, PFS, and OS in patients with stage II-III EC treated with definitive Conformal Radiation Therapy (CRT).

A retrospective study found that higher than standard radiotherapy dose may lead to better survival for Non-Operated Localized Esophageal Squamous Cell Carcinoma (NOL-ESCC) patients undergoing Concurrent Chemo-Radiotherapy(CCRT) [22]Wolf et al [23] also concluded that the use of radiation doses over 54 Gy and the addition of chemotherapy ($p = 0.002$) were associated with improved OS. Furthermore, in multivariate analysis, high dose radiotherapy was a significant prognostic factor for improved LRC, PFS and OS.

Nevertheless, no consensus has been reached globally on the appropriate radiation dose of definitive CCRT for EC. Although 50.4 Gy is the standard dose as per evidence, many trials now support the use of high dose radiotherapy (>60 Gy) which may have better outcomes but needs to be validated in large groups with adequate support and evaluation.
In this study, we investigated the clinical outcomes of high dose radiotherapy with or without concurrent chemotherapy in EC patients of North-East India. The rationale behind choosing this topic is that although many studies have been conducted to show that high dose of radiotherapy leads to better OS rate and PFS but no consensus has been reached globally on the appropriate radiation dose of definitive CCRT for EC.

2. MATERIAL AND METHODS

2.1 PATIENTS

A Retrospective study was conducted in State Cancer Institute (SCI), Gauhati Medical College (GMC) with approval from Institutional scientific and ethical committee. Data collection was done from the hospital record. All histologically proven EC cases treated with definitive chemo-radiotherapy during the period 2017 – 2018 (two years) were included in the study. Inclusion- Exclusion criteria were applied (Table 1).

TABLE 1: INCLUSION – EXCLUSION CRITERIA

INCLUSION CRITERIA	EXCLUSION CRITERIA
Histologically proven cases of EC treated with definitive radiotherapy (63 Gy) with or without concurrent chemotherapy.	Patients who failed to complete the treatment. Patients who received <63 Gy radiotherapy. Patients who received neo-adjuvant chemotherapy. Prior History of double primary (h/o) cancer irradiation or chemotherapy History of double primary (h/o) cancer.

2.2 RADIOTHERAPY

Radiotherapy was delivered with linear accelerator using 6 Megavoltage (MV) photons. A total of 63Gy was delivered with conventional fractionation schedule (5 days/week, 1.8 Gy/fraction daily). Cone down technique was used in all patients. In phase I, two field technique using Anterior-Posterior (AP)/Posterior-Anterior (PA) portals were used to include the primary tumor with a cranio-caudal margin of at least 5 cm and circumferential margin of 1.5 cm to the tumor. A dose of 39.6 Gy (22 fractions) were used in phase I before cone down. In phase II, three field technique[Three-Dimensional Conformal Radiation Therapy(3DCRT))was also used in selected cases] was used to restrict the spinal cord dose to below 45 Gy and fields including the primary tumor with a 2-3 cm cranio-caudal and 1-1.5 cm circumferential margin were used to a total dose of 63 Gy (35 fractions). The field borders were modified as per clinical requirements.

2.3 CHEMOTHERAPY

All patients were planned for concurrent chemotherapy. However, out of total 105 patients, 64 (61%) patients received weekly regimen of concurrent Paclitaxel 50 mg/m^2 plus Carboplatin AUC 2 and 12 (11.4%) patients received weekly concurrent Cisplatin 40 mg/m^2 while Chemotherapy was not administered in 29 (27.6%) patients due to co-morbidities. A total of 4-6 cycles of concurrent chemotherapy were administered.

2.4 FOLLOW UP

All patients were examined weekly to monitor treatment related toxicities and general conditions. After completion of treatment, follow up was done at the interval of 2-3 months in the outdoor department. Follow up included clinical examination and endoscopic evaluation. Computed Tomography (CT) scan of chest and upper abdomen was also done to assess the local control of the disease.
Patient suspected of having metastatic disease on follow up were subjected to an appropriate investigations and were managed accordingly.

2.5 STATISTICAL ANALYSIS

Statistical analysis of data was done using Statistical Packages for Social Sciences (SPSS) and Disease Free Survival (DFS) was calculated using Kaplan-Meier Plot method.

3. RESULTS

A total of 105 patients were included in this study. All patients received a total dose of 63Gy radiation. Out of 105 patients, 76 patients received concurrent chemotherapy while 29 patients did not received chemotherapy due to one or more co-morbidities. Patient and tumor characteristics are listed in (Table 2).

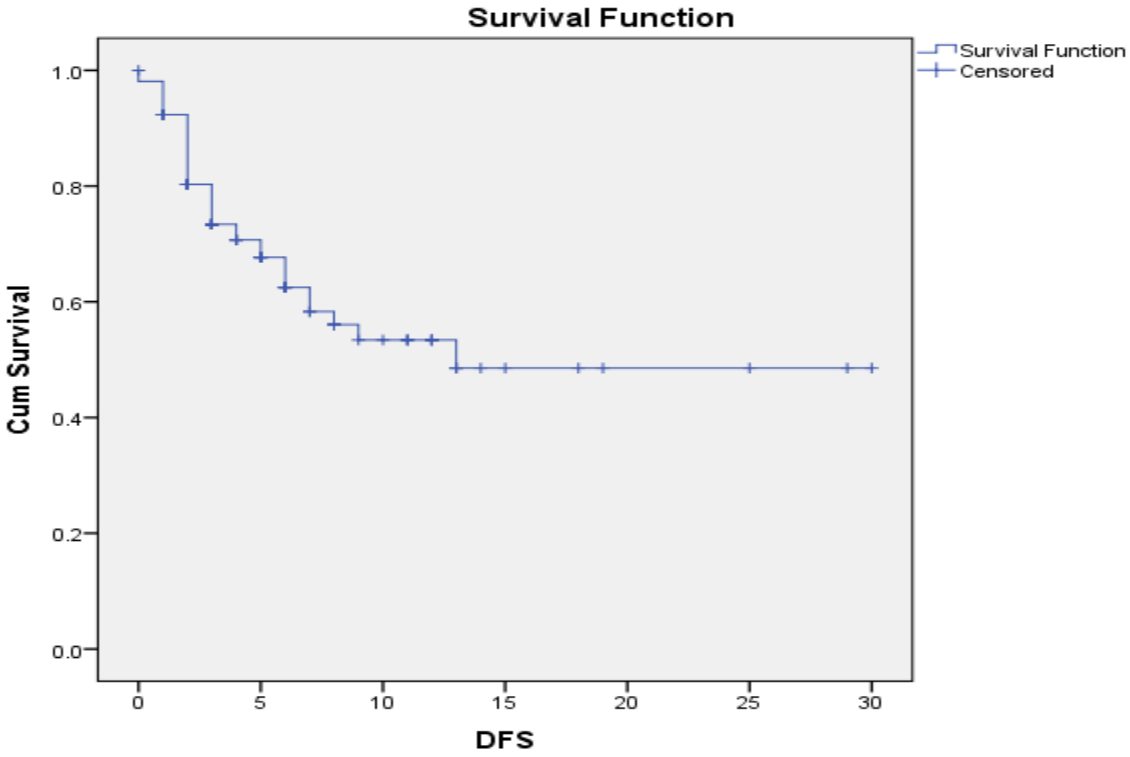
TABLE 2: PATIENT CHARACTERISTICS

AGE (YEARS)	FREQUENCY	PERCENTAGE
<45	5	4.8
≥45	100	95.2
Total	105	100.0
GENDER		
M	67	63.8
F	38	36.2
Total	105	100.0
RURAL/URBAN		
Rural	83	79
Urban	22	21
Total	105	100.0
TUMOR SIZE		
<5	37	35.2
≥5	68	64.8
Total	105	100.0
TUMOR LOCATION		
Cervical Thoracic Esophagus	1	1
Upper Thoracic Esophagus	39	37.1
Middle Thoracic Esophagus	60	57.1
Lower Thoracic Esophagus	5	4.8
Total	105	100.0
HISTOPATHOLOGICAL EXAMINATION (HPE)		
Well Differentiated Squamous Cell Carcinoma (WDSCC)	19	18.1
Moderately Differentiated Squamous Cell Carcinoma (MDSCC)	79	75.2
Poorly Differentiated Squamous Cell Carcinoma (PDSCC)	7	6.7
Total	105	100.0
STAGE		
IIIA	43	41
IIIB	35	33.3
IVA	27	25.7
Total	105	100.0
CHEMOTHERAPY		
Paclitaxel And Carboplatin	64	61.0
Cisplatin	12	11.4
No chemotherapy	29	27.6
Total	105	100.0
CLINICAL RESPONSE AT 1ST FOLLOW UP		
Complete Response	89	84.8
Partial Response	10	9.5
Progressive Disease	6	5.7
Total	105	100.0

At first follow up, 89 (84.8%) patients showed complete response, 10 (9.5%) showed partial response and 6 (5.7%) showed progressive disease. Treatment related toxicities were assessed. None of the patient developed > Grade 2 toxicity.

Further, follow up data showed that median disease free survival was 13 months with estimated mean was 16.98 months (Std. Error =1.683, CI =13.682-20.279). Kaplan – Meier plot of DFS is shown in figure-1. From the figure-1, we can conclude that the rate of survival is decreasing rapidly before the median DFS and the rate of survival is constant after the median DFS.

FIGURE-1: KAPLAN-MEIER PLOT OF DISASE FREE SURVIVAL (DFS)



4. INTERPRETATION (FIGURE-1)

N(Total Cases)	105
N of Events (Dead)	38
Censored N(Alive & Loss to Follow Up)	67(63.8%)

MEAN	
Estimates (in Months)	16.98
Standard Error (S.E)	1.683
Interval (Lower Bound)	13.682
Interval (Upper Bound)	20.279

MEDIAN	
Estimates (in Months)	13
Standard Error (S.E)	0
Interval (Lower Bound)	0
Interval (Upper Bound)	0

Here, Median DFS=13. From the figure-1, We can conclude that the rate of survival is decreasing rapidly before the Median DFS and after 13 months the rate of survival is constant after the Median DFS.

5. DISCUSSIONS

In NCCN EC guidelines [14] recommend the radiation dose of 50 or 50.4 Gy for definitive chemo-radiotherapy, radiation dose escalation in the treatment of EC should be studied further. In the recent meta-analysis of trials [24] comparing high-

dose (≥ 60 Gy) versus standard-dose (50.4 Gy) radiation for patients with EC, the high-dose group demonstrated a significant improvement in Local-Regional Failure (LRF) (OR 2.199, 95% CI 1.487-3.253; P<0.001), two-year local-regional control (LRC) (OR 0.478, 95% CI 0.309-0.740; P=0.001), two-year OS (HR 0.744, 95% CI 0.657-0.843; P<0.001) and five-year OS (HR 0.683, 95% CI 0.561-0.831; P<0.001) rates relative to the standard-dose group. In addition, there was no difference in grade ≥ 3 radiation-related toxicities and treatment-related deaths between the groups. Results of other trial also indicated that there was a significant benefit in favor of high dose radiotherapy.

Although the survival rate has been slowly improving likely because of multimodal treatment and improved supportive care, the survival rate remains modest at 20% at 5 years. Considering the high local failure rates after 50 Gy [19] for patients that are not going for surgery, we think that high dose radiation with concurrent chemotherapy should be the optimal treatment for these patients. Surgery might be preserved for salvage treatment if there is residual disease after high dose radiation in selected cases. Therefore, many Institutes practice high dose (> 60 Gy) radiation with concurrent chemotherapy as weekly regimen of Cisplatin or Paclitaxel plus Carboplatin for the definitive treatment of EC.

In the present study, we evaluated the clinical outcomes of high dose radiotherapy (63 Gy) with or without concurrent chemotherapy in EC patients. The present data showed a modest median disease free survival of 13 months.

In the State Cancer Institute, Doctors also practice high dose (63 Gy) radiation with concurrent chemotherapy for patients in whom surgery is not considered as an option. This study also strengthens the use of high dose radiation with acceptable toxicity. Although, median DFS in the current study was 13 months only in consistent with the poor survival of EC, higher complete response rate at first follow up and good symptomatic improvement with high dose radiation support the current practice.This study was retrospective in nature.

6. CONCLUSIONS

The high dose radiation (63 Gy) with concurrent chemotherapy as weekly regimen of Cisplatin or Paclitaxel plus Carboplatin is an effective definitive treatment of Stage I – IVA EC with acceptable toxicity.

7. FINANCIAL SUPPORT AND SPONSORSHIP

Nil

8. CONFLICT OF INTEREST

Nil

9. REFERENCES:

1. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer,127, 3029-3030.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
3. National Cancer Registry Programme Report (ICMR) (2020). Five Year Report of Population Based Cancer Registries: 2012-2016, Bangalore, India.
4. Testa U, Castelli G, Pelosi E. Esophageal cancer: Genomic and molecular characterization, stem cell compartment and clonal evolution. Medicinis. 2017,4,67.
5. Song Q, Jiang D, Wang H, Huang J, Liu Y, Xu C, Hou Y. Chromosomal and Genomic Variations in Esophageal Squamous Cell Carcinoma: A Review of Technologies, Applications, and Prospections. J Cancer 2017; 8(13):2492-2500.
6. Taylor PR, Abnet CC, Dawsey SM. Squamous dysplasia--the precursor lesion for esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2013;22(4):540-552.
7. Siewert JR, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease?.Semin Radiat Oncol. 2007;17(1):38-44.
8. Hou X, Wen J, Ren Z, et al. Non-coding RNAs: New biomarkers and therapeutic targets for esophageal cancer. Oncotarget. 2017;8:43571–43578.
9. Wong RK, Malthaner RA, Zuraw L, et al. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. Int J Radiat Oncol Biol Phys 2003;55:930-42.
10. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemo radiation for oesophageal cancer- a standard care in patients with non-metastatic oesophageal cancer. Clin Oncol (R Coll Radiol) 2011; 23:182-8.
11. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999; 281:1623-1627.
12. Jang et al. Multimodality Approaches for the Curative Treatment of Esophageal Cancer. J Natl ComprCancNetw2015; 13:229-238.
13. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (RTOG 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20:1167-74.
14. NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 2.2020. Available at: NCCN.org.
15. Fletcher GH. Clinical dose-response curves of human malignant epithelial tumours. Br J Radiol. 1973;46(541):1–12.
16. Tong DK, Law S, Kwong DL, Chan KW, Lam AK, Wong KH. Histological regression of squamous esophageal carcinoma assessed by percentage of residual viable cells after neoadjuvant chemoradiation is an important prognostic factor. Ann Surg Oncol. 2010;17(8):2184–2192.

17. Song T, Liang X, Fang M, Wu S. High-dose versus conventional-dose irradiation in cisplatin-based definitive concurrent chemoradiotherapy for esophageal cancer: a systematic review and pooled analysis. Expert Rev Anticancer Ther. 2015;15(10):1157–1169.
18. He L, Allen PK, Potter A, et al. Re-evaluating the optimal radiation dose for definitive chemoradiotherapy for esophageal squamous cell carcinoma. J Thorac Oncol. 2014;9(9):1398-1405.
19. Zhang Z, Liao Z, Jin J, et al. Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 2005; 61:656-64.
20. Yang-Gun Suh, Lee IJ, Koom WS et al. High-dose Versus Standard-dose Radiotherapy with Concurrent Chemotherapy in Stages II-III Esophageal Cancer. Jpn J Clin Oncol 2014; 44(6)534-540.
21. Kim HJ, Suh YG, Lee YC, et al. Dose-Response Relationship between Radiation Dose and Loco-regional Control in Patients with Stage II-III Esophageal Cancer Treated with Definitive Chemoradiotherapy. Cancer Res Treat. 2017; 49 (3):669-677.
22. Chen CY, Li CC, Chien CR. Does higher radiation dose lead to better outcome for non-operated localized esophageal squamous cell carcinoma patients who received concurrent chemoradiotherapy? A population based propensity-score matched analysis. Radiother Oncol. 2016; 120 (1):136-139.
23. Wolf MC, Zehentmayr F, Schmidt M, Hölzel D, Belka C. Treatment strategies for oesophageal cancer - time-trends and long term outcome data from a large tertiary referral centre. Radiat Oncol. 2012; 7: 60.
24. Xiao L, Czito BG, Pang Q, et al. Do Higher Radiation Doses with Concurrent Chemotherapy in the Definitive Treatment of Esophageal Cancer Improve Outcomes? A Meta-Analysis and Systematic Review. J Cancer. 2020; 11(15):4605-4613