DOI:10.31557/APJCC.2025.10.1.27

RESEARCH ARTICLE

A Comparative Analysis between Sequential Boost and Simultaneous Integrated Boost Volumetric Modulated Arc Therapy in Head and Neck Cancer Patients

Divya Sharma, H S Kumar, Neeti Sharma, Shweta Mohata

Department of Radiation Oncology, Sardar Patel Medical College, Bikaner, Rajasthan, India.

Abstract

Background: In head and neck cancer radical VMAT can be delivered by two techniques: Sequential Boost (SEQ) and Simultaneous Integrated Boost (SIB). Our aim is to compare SEQ and SIB planning techniques of VMAT in patients of Head and Neck Squamous Cell Carcinoma (HNSCC) in terms of acute toxicities and disease response. **Materials and Methods:** A prospective randomized comparative study was conducted at ATRCTRI, S.P. Medical college Bikaner from January 2023 to December 2024. A total of 60 patients of locally advanced HNSCC of stage II- IVA planned for radical chemoradiation were enrolled into two arms equally between SEQ-VMAT and SIB-VMAT. Concurrent Chemotherapy was given with weekly cisplatin (40 mg/m^2). Acute toxicity evaluation was done at end of the treatment. Response evaluation was done as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at the 3- and 6-months post treatment. **Results:** Acute toxicities at the end of the treatment, mucositis, dysphagia, and xerostomia are comparable in both arms, SIB has statistically significant dermatitis. At 3 months of follow up, 76 % patients in SIB arm and 70% patients in SEQ arms had complete response, 5 in SIB and 6 in SEQ patients had partial response, 2 in SIB arm and 3 patients in SEQ arm had progressive disease. At 6 months of follow up, all the patients in both arms who achieved PR by 3rd month had stable disease and 1 patient in SIB arm who had PD achieved PR. All responses were statistically nonsignificant. **Conclusion:** SIB-VMAT and SEQ-VMAT are comparable in terms of overall response. Whereas SEQ-VMAT appears better in terms of acute toxicities but SIB-VMAT was more convenient as it has 6 weeks treatment compare to SEQ (7-week treatment) and no re-planning is required in SIB arm.

Keywords: SIB-VMAT, SEQ-VMAT, HNSCC, RECIST

Asian Pac J Cancer Care, **10 (1)**, 27-32

Submission Date: 07/09/2024 Acceptance Date: 11/14/2024

Introduction

Cancers is listed among the leading cause of morbidity and mortality worldwide, with approximately 19.97 million new cases and 9.94 million cancers related deaths in 2022 and 53.50 million prevalent cases in all age groups [1].The International Agency for Research on Cancer (IARC) estimates that globally, 1 in 5 people develop cancer during their lifetime, and 1 in 8 men and 1 in11 women die from the disease [2]. The ten most common cancer accounts for more than 60% of the newly diagnosed cancer cases and more than 70% of the cancer deaths. On the Indian scenario, 1.41 million new cancer cases were estimated, India as a single country (of the 185 countries) contributing to 10.43% of the global cancer burden; mortality figures were 9.16,827 contributing to 7.05% of global cancer deaths and 32,58,518 prevalent cases in 2022. Incidence rate of cancer was higher in females with 7,22,138 and 6,91,178 in males in same year [1]. The aim of radiation therapy is better control of the tumor volume with less toxicity to nearby tissues. By using 3D-Conformal Radiotherapy irradiation of the tumor was done more accurately with better sparing of nearby normal tissues OAR (organ at risk). After introduction of intensity-modulated radiotherapy (IMRT), even more conformity and higher

Corresponding Author:
Dr. Divya Sharma
Department of Radiation Oncology, Sardar Patel Medical College, Bikaner, Rajasthan, India.
Email: divya21.mbbs@gmail.com

dose to target volumes and less dose to the organs at risk achieved [3, 4]. VMAT can be given by sequential boost volumetric modulated arc therapy (SEQ-VMAT) technique or simultaneous integrated boost volumetric modulated arc therapy (SIB-VMAT) technique. SEQ-VMAT can be given in two phases with shrinking field approach, in first phase gross tumor, positive nodes and the elective nodal region with clinical target volume (CTV) are irradiated and in second only primary tumor is irradiated. SIB-VMAT dose distribution is most conformal. By Using iso effect radiobiological relationships in SIB-VMAT fractionation approaches are designed in such a way that dose levels to the primary, regional disease and electively treated volumes are appropriately adjusted, each receiving different dose/fx [5].

Materials and Methods

This prospective randomized study was conducted in Department of Radiation Oncology, S P medical college Bikaner, Rajasthan. The study was done from January 2023 to December 2023 with follow-up of 3 and 6 months. After taking informed consent total of 60 patients of biopsy proven squamous cell carcinoma of head and neck region were taken in the study.

Inclusion criteria

Histopathological proven primary HNSCC of either sex, who had ECOG PS 0-2 included in the study.

Exclusion criteria

Patients with severe co-morbidities, pregnant and lactating women, those who had received prior radiotherapy and postoperative patients were excluded from the study.

Study Population

Newly diagnosed patients with histologically confirmed Squamous Cell Carcinoma of locally advanced head and neck cancer, attending Department of Radiation Oncology, SP Medical college, Bikaner. The cases were randomly distributed among Group A who received Simultaneous Integrated Boost (SIB-VMAT) and Group B who received Sequential Boost (SEQ-VMAT).

Study Design

Hospital based, Prospective Randomized, Comparative study. 95% confidence level, 80% power of study. Patients of either sex above the age of 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to two were randomized into two arms, and treated with either SEQ-VMAT or SIB-VMAT. Pre-treatment evaluation including nutritional evaluation was done prior to treatment as per National Comprehensive Cancer Network Guidelines (NCCN) [6]. Assessment of disease extension and staging was done by American Joint Committee of Cancer (AJCC) criteria along with clinical examination, Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) scan when required [7].

Treatment planning

Immobilization was done in the supine position with head-shoulder four clamp thermoplastic mould to undergo CT simulation with slice thickness of 3 mm. Target volume delineation was done as per International Committee for Radiological Units (ICRU) 83 guidelines [8]. Gross Tumor Volume (GTV) is defined as the gross extent of the target tumor shown on CT /MRI or PET scan also included all involved (positive) lymph nodes. Based on the primary tumor and positive node, Clinical Target Volume High Risk (CTV-HR), CTV- Intermediate Risk (CTV-IR) and CT Low Risk (CTV-LR) were contoured. The dose constraints to Organ at Risk (OAR) were prescribed using Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [9].

Dose delivery

Dose delivery was, for SEQ VMAT a total dose of 70 Gy in 35 fractions in two phases with 2Gy/fr. For SIB VMAT tumor and involved nodal volumes received 66 Gy with 2.2 Gy per fraction as above and prophylactic nodal level received 1.8 Gy per fraction to 54 Gy in 30 fractions.

Chemotherapy

Patient received weekly Cisplatin with dose of 40 mg/m^2 along with radiations for effective treatment.

Assessment of Toxicities

Toxicities scored according to the CTCAE Criteria version 4.03(Common Terminology Criteria for Adverse Events) for Acute toxicities in both groups of patients.

Assessment of Tumour Response

Response evaluation done at 3 months and 6 months after completion of treatment in both arms based on clinical examination, ENT evaluation CECT/MRI Scan of Head and Neck findings in each patient. Patients then categorized as per RECIST Criteria version1.1 (Response Evaluation Criteria in Solid Tumors) [10].

Data Analysis

Data was coded and recorded in MS Excel Software. primer 6.0 was used for data analysis. $P<0.05$ was taken as the cut-off for statistical significance.

Results

In our study we compared SIB-VMAT to SEQ-VMAT technique in head and neck cancer patients. In which we took patients between 18 to 70 years of age and most of the patients belong to ECOG PS 1. The most common age of presentation for all head and neck cancers is at the 4th and 5th decade of life. This study population had a range in age of 18- 70 years. Most patients were from rural background. Of the total population, 14 (24%) patients presented with an ECOG performance score of 0, 41 (69%) patients presented with ECOG performance score 1 and the remaining 5 (9%) had an ECOG score of 2. In a developing country like India, head and neck cancers are among the most common type of malignancy

Table 1. Baseline Patient Characteristics between SIB-VMAT and SEQ-VMAT Arms

Characteristics	SIB-VMAT (n = 30)	SEQ-VMAT (n = 30)	p-value
Mean age (yr.)	47.17	47.07	0.979
Gender			0.656
Male	24 (80)	25 (84)	
Female	6 (20)	5 (17)	
History of tobacco consumption	26 (87)	28 (93)	0.343
Co-morbidity			0.476
Diabetes	2 (6)	5 (16)	
Hypertension	4 (14)	4 (14)	
No comorbidity	24 (80)	21 (70)	
ECOG PS			0.943
0	5 (16)	9 (30)	
1	22 (74)	19 (64)	
2	3 (10)	2 (6)	
AJCC staging			0.887
II	2 (6)	3 (10)	
III	17 (57)	16 (53)	
IV A	11 (37)	11 (37)	
Primary site			
Oral cavity	2 (6)	1 (3)	0.643
Oropharynx	14 (46)	13 (43)	
Larynx	4 (13)	5 (16)	
Hypopharynx	10 (33)	11 (36)	
6 cycles weekly chemotherapy received	22 (74)	21 (70)	0.946

with most patients presenting in locally advanced stage. In this study patients were of stage II 5 (8%), stage III 33 (55%) and stage IV 22(37%) (Table 1).

Acute toxicity assessment

In SEQ-VMAT arm at the end of treatment 18 (60%), 10 (33%), 3 (10%) of total patients developed grade 1, grade 2, and grade 3 dermatitis, respectively and in SIB arm 7 (24%), 19 (63%), 4 (13%) Patients had grade 1, 2 and 3 dermatitis respectively. All the differences in SIB-VMAT and SEQ-VMAT for dermatitis are statically significant. (p= 0.001 and 0.039 for grade 1 and 2) (Table 2). There were also no statically significant differences in incidence of other toxicities i.e. mucositis, dysphagia, xerostomia and other treatment compliance parameters like weight-loss, incidence of hospitalization for supportive management and requirement of nasogastric tube intubation for feeding (Table 2). Twenty (67%) patients versus Twenty-two patients (74%) developed grade 2 mucositis in SEQ-VMAT and SIB-VMAT arms, respectively (p = 0.858). There was no significant difference in incidence of grade 2 oral mucositis between both the arms (Table 2). The patients in SIB-VMAT arm had better treatment-compliance compared to SEQ-VMAT arm. In SIB-VMAT arm, 17 (56%) and in SEQ arm 18 (60%) developed xerostomia, respectively (p = 0.998). There was no significant difference in incidence of xerostomia between both the arms. Eight patients (27%) in SIB-VMAT arm and Nine patients (30%) in SEQ-VMAT arm required nasogastric intubation (p = 0.908) (Table 2), more no of patients in SEQ-VMAT arm needed nasogastric tube compared to SIB-VMAT but that was not statistically significant. Out of 60 patients total 27 patients (47%) required admission in the hospital for supportive treatment and management of dysphagia, mucositis. Fourteen patients (47%) in SIB-VMAT arm versus 13 patients (43%) in SEQ-VMAT arm required admission in the hospital (p = 0.967) (Table 2), more number of patients in SIB-VMAT arm required hospitalization compared to SEQ-VMAT but not statistically significant.

Objective response

In this study, we treated patients with curative intent. At 3 months of follow up 76 % patients in SIB arm and 70% patients in SEQ arms had complete response, 5 in SIB and 6 patients in SEQ arm had partial response, 2 in SIB and 3 patients in SEQ had progressive disease (Table 3). At 6 months of follow up, all the patients in both arms who achieved PR by 3rd month had stable disease and 1 patient in SIB arm who had PD achieved PR. All responses were statistically nonsignificant. In our study we used cisplatin as concurrent chemotherapy and many also received induction chemotherapy and that was well tolerated by most of the patients some of them had grade 1, 2 hematological toxicities and grade 1 non-hematological toxicities. In SIB arm 8 patients did not complete all 6 cycles and in SEQ arm 9 patients did not complete.

Table 2. Acute Toxicity Comparison between SIB-VMAT and SEQ-VMAT Arm

Toxicity	SIB-VMAT (n = 30)	SEQ-VMAT (n = 30)	p-value
Mucositis			0.858
Grade 1	0 (0)	3 (10)	
Grade 2	22 (74)	20 (67)	
Grade 3	8 (26)	7(23)	
Dysphagia			0.345
Grade 1	1 (3)	3 (10)	
Grade 2	21 (70)	20 (67)	
Grade 3	8 (27)	7 (23)	
Xerostomia			0.998
Present	17 (56)	18 (60)	
Absent	13 (43)	12 (40)	
Dermatitis			0.001
Grade 1	7 (23)	18 (60)	
Grade 2	19 (64)	10 (30)	
Grade 3	4 (13)	3 (10)	
Hospitalization for supportive treatment	14 (46)	13 (43)	0.876

Table 3. Objective Response between SEQ-VMAT Arm and SIB-VMAT Arm

Response	SIB Group (n=30)		SEQ Group (n=30)	
Complete Response	23	76%	21	70%
Partial Response	5	20%	6	23%
Progressive Diseases	2	6%	3	7%
Total	30	100%	30	100%

Discussion

Use of VMAT for curative definitive treatment of head and neck cancer patients has resulted in move from sequential boost technique to simultaneous integrated boost radiation planning. This shift was due to early dosimetry studies suggested improved dose distribution, initial ease of designing one plan in SIB versus two or more in SEQ, and mostly of using the SIB technique in Cooperative Group studies [11, 12].

In our study we shifted from SIB to SEQ-VMAT for head and neck cancer patients based on our clinical observation that patients who are treating with SIB had experienced more acute skin and pharyngeal toxicity than SEQ arm. This is the study comparing VMAT techniques that include head and neck subsites and were consecutively treated using similar chemotherapy and dose-volume constraints. Active and good treatment-compliance is very crucial and important management planning. Treatment interruptions and prolonged radiation treatment time are associated with poor treatment results. Langendijk et al. [13], in a study, concluded that overall treatment time is an important prognostic factor for oral cancers. The authors observed the locoregional control decreased about 9% with each extra week in prolongation of overall treatment time [13]. In our study, patients in SIB-VMAT arm showed better treatment-compliance and had less interruption in radiation treatment as compared to SEQ-VMAT arm but it was not statistically significant. In SIB-VMAT arm, mean treatment-interruption (gap in radiotherapy) was 4.2 days whereas in SEQ-VMAT arm it was 6.5 days (p = 0.102). Interruption was due to toxicities and managed conservatively by using of topical anesthetics, analgesics, and opioids. Nutrition and hydration were maintained by iv fluids and multivitamin drips. Patients were asked to do gargles 6 to 7 times a day with baking soda to manage mucositis and keeping hygiene and not use of oil, cream on RT area. Acute toxicity (mucositis) was resulted in decrease oral intake and was further managed by iv fluids. Dysphagia was also managed by nasogastric tube insertion in the between treatment. The severity of dermatitis (more so than dysphagia and mucositis) can vary depending on factors independent of treatment volumes and disease. Observed improvement in dermatitis and dysphagia seen clinically with SEQ boost is due to decreasing radiation exposure to the lower neck and pharyngeal constrictors from 7 week to 5 weeks. The addition of concurrent chemotherapy to definitive radiation for head and neck cancer is well known to increase toxicity compared to radiation alone [14-16]. Concurrent chemotherapy regimens are variable, but historically mostly have been cisplatin based. In our study we used cisplatin as concurrent chemotherapy that was well tolerated by most of the patients some of them had grade 1, 2 hematological toxicities and grade 1 non-hematological toxicities. In SIB arm 8 patients did not complete all 6 cycles and in SEQ arm 9 patients did not complete. Vlacich et al [17] did a comparative,

retrospective study of SIB-IMRT versus SEQ-IMRT in 209 patients of locally advanced head neck cancer, there were no significant differences in local, regional, or distant recurrence-free survival. In addition, there were no significant differences in relative weight loss, the rate of gastrostomy tube placement, or prolonged PEG tube dependence. Rates of grade 3 or 4 dysphagia (82% vs 55%) and dermatitis (78% vs 58%) were higher significantly in the SIB group (P<0.001 and P<0.012). Moreover, a greater percentage of the SIB cohort did not receive the total prescribed dose due to acute toxicity (7% versus 0). Although in this study a higher rate of grade 3 and 4 radiation dermatitis and dysphagia were observed in the SIB-IMRT group, however this did not translate into differences in late toxicity and there was no difference in weight loss or gastrostomy tube placement. These results are comparable to our study with similar tumor control rate and toxicity between both the treatment technique. Grade 1 and 2 dermatitis are more in SIB and are statistically significant. In a population-based propensity score-based analysis, Yao-Hung Kuo et al compared SIB-IMRT and SEQ-IMRT in 200 patients of carcinoma oropharynx and hypopharynx patients. The HR of death between SIB-IMRT and SEQ-IMRT was 1.23 (95% confidence interval 0.84-1.80, P=.29). The results were similar for other disease outcome or subgroups. The authors concluded that the survival outcome is comparable between both the techniques. Our study also suggests similar treatment outcomes between the both arms. Songthong et al. reported on their phase II/III trial comparing SIB and sequential boost IMRT in 112 patients with nasopharyngeal carcinoma and found no significant difference in short-term treatment outcomes or acute toxicities [18]. In contrast, our study shows rates of grade 1 and 2 acute toxicity (dermatitis) more in SIB arm compare to SEQ arm but overall response is similar to the above study (no significant difference in both arms regarding treatment outcome). Scorsetti M et al., reported their early clinical experience in radiotherapy of different sites of head and neck cancer treated by volumetric modulated arcs [19]. Like present study, percutaneous gastrostomy or feeding tube was not required in any of the patients. The most common acute grade 3 toxicities in this study were reported as mucositis (28%), dermatitis (14%) and dysphagia (7%). Whereas in present study, the most common grade 1, 2 acute toxicities are more in SIB arm. Jiang L et al. did meta-analysis of total seven studies to compare the result and severe acute side effects between SIB IMRT and SEQ-IMRT [20]. In study of total 1049 patients' author did not find any significant difference in overall and progression free survival. Similarly, the present study shows no significant difference in the tumor response. The present study needs longer follow-up to compare overall survival and recurrence free survival. In our study, SIB VMAT shows higher incidence of statistically significant acute dermatitis grade 2 compared to SEQ. Other toxicities are comparable in both arms. As the main aim of radiotherapy treatment is to provide the best tumor control in the target and nontarget lesions. Like other studies, in this study no significant difference was observed in the overall response to treatment. Both arms have equivalent dose prescription to the target volumes in terms of biological effective dose.

In conclusion, a prospective randomized study was conducted at ATRCTRI, S P medical college Bikaner Rajasthan. A total of 60 patients (30 patients in each arm) of biopsy proven squamous cell carcinoma of head and neck cancer of stage II- IVA with ECOG score 0 – 2 were included and treated with curative intent using SIB-VMAT (ARM A) and SEQ-VMAT (ARM B) to compare response, toxicities for individual technique. For SEQ VMAT the tumor, involved nodes and prophylactic nodal volumes all received 54 Gy at 2 Gy per fraction in first phase followed by Gross tumor and involved nodal volumes receiving an additional 12-16 Gy at 2 Gy per fraction for a total dose of 66-70 Gy in 33-35 fractions in two phases. For SIB VMAT tumor and involved nodal volumes received 66 Gy with 2.2 Gy per fraction as above and prophylactic nodal level received 1.8 Gy per fraction to 54 Gy in 30 fractions. At 3 months of follow up 76 % patients in SIB arm and 70% patients in SEQ arms had complete response, 5 in SIB and 6 patients in SEQ arm had partial response, 2 in SIB and 3 patients in SEQ had progressive disease. (Table 2) At 6 months of follow up, all the patients in both arms who achieved PR by 3rd month had stable disease and 1 patient in SIB arm who had PD achieved PR. All responses were statistically nonsignificant. In terms of acute toxicities at the end of the treatment, mucositis, dysphagia, and xerostomia are comparable in both arms but SIB has more grade 1, 2 statistically significant dermatitis.

To conclude both SEQ-VMAT and SIB-VMAT are equivalent in terms of survival, incidence of mucositis, dysphagia, xerostomia, and hematological toxicities. Although higher rate of statistically significant grade 1, 2 radiation induced dermatitis was observed with the SIB-VMAT compared to SEQ-VMAT. SIB-VMAT has additional advantage of no additional planning hence less time consuming and more convenient and total treatment is also less in SIB (6 weeks) compare to SEQ (7 weeks). However more such studies with larger sample size and longer follow up are required for conclusive results.

Acknowledgments

Statement of Transparency and Principals

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229-263. https://doi.org/10.3322/caac.21834
2. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO global oncology. 2020 07;6:1063-1075. https://doi.org/10.1200/GO.20.00122
3. Veen J, Nuyts S. Can Intensity-Modulated-Radiotherapy Reduce Toxicity in Head and Neck Squamous Cell Carcinoma?. Cancers. 2017 Oct 06;9(10):135. https://doi.org/10.3390/cancers9100135
4. Tubiana M, Eschwège F. Conformal radiotherapy and intensity-modulated radiotherapy--clinical data. Acta Oncologica (Stockholm, Sweden). 2000;39(5):555-567. https://doi.org/10.1080/028418600750013249
5. Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. Radiobiological considerations in the design of fractionation strategies for intensity-modulated radiation therapy of head and neck cancers. International Journal of Radiation Oncology, Biology, Physics. 2000 02 01;46(3):619-630. https://doi.org/10.1016/s0360-3016(99)00438-1
6. Guidelines With Evidence Blocks [Internet]. NCCN. 2021 [cited 9 November 2021]. Available from: https://www.nccn.org/guidelines/guidelines-with-evidence-blocks.
7. AJCC Cancer Staging Handbook: TNM Classification of Malignant Tumors; SpringerLink; https://link.springer.com/book/9783319406176..
8. The International Commission on Radiation Units and Measurements. Journal of the ICRU. 2010;10(1): Report 83..
9. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK, Yorke ED. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. International Journal of Radiation Oncology, Biology, Physics. 2010 03 01;76(3 Suppl):S3-9. https://doi.org/10.1016/j.ijrobp.2009.09.040
10. Eisenhauer E, Verweij J. New response evaluation criteria in solid tumors: RECIST GUIDELINE VERSION 1.1. European Journal of Cancer Supplements. 2009;7(2):5.
11. Eisbruch A, Harris J, Garden AS, Chao CKS, Straube W, Harari PM, Sanguineti G, Jones CU, Bosch WR, Ang KK. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). International Journal of Radiation Oncology, Biology, Physics. 2010 04;76(5):1333-1338. https://doi.org/10.1016/j.ijrobp.2009.04.011
12. Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, Bosch W, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2009 08 01;27(22):3684-3690. https://doi.org/10.1200/JCO.2008.19.9109
13. Langendijk JA, Jong MA, Leemans CR, Bree R, Smeele LE, Doornaert P, Slotman BJ. Postoperative radiotherapy in squamous cell carcinoma of the oral cavity: the importance of the overall treatment time. International Journal of Radiation Oncology, Biology, Physics. 2003 Nov 01;57(3):693-700. https://doi.org/10.1016/s0360-3016(03)00624-2
14. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Oudinot P, Bertrand P. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. Journal of the National Cancer Institute. 1999 Dec 15;91(24):2081-2086. https://doi.org/10.1093/jnci/91.24.2081
15. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, Glisson B, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. The New England Journal of Medicine. 2003 Nov 27;349(22):2091-2098. https://doi.org/10.1056/NEJMoa031317
16. Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, Schuller DE, Forastiere AA. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2003 01 01;21(1):92-98. https://doi.org/10.1200/JCO.2003.01.008
17. Vlacich G, Diaz R, Thorpe SW, Murphy BA, Kirby W, Sinard RJ, Shakhtour B, et al. Intensity-modulated radiation therapy with concurrent carboplatin and paclitaxel for locally advanced head and neck cancer: toxicities and efficacy. The Oncologist. 2012;17(5):673-681. https://doi.org/10.1634/theoncologist.2011-0396
18. Songthong AP, Kannarunimit D, Chakkabat C, Lertbutsayanukul C. A randomized phase II/III study of adverse events between sequential (SEQ) versus simultaneous integrated boost (SIB) intensity modulated radiation therapy (IMRT) in nasopharyngeal carcinoma; preliminary result on acute adverse events. Radiation Oncology (London, England). 2015 08 08;10:166. https://doi.org/10.1186/s13014-015-0472-y
19. Scorsetti M, Fogliata A, Castiglioni S, Bressi C, Bignardi M, Navarria P, Mancosu P, et al. Early clinical experience with volumetric modulated arc therapy in head and neck cancer patients. Radiation Oncology (London, England). 2010 Oct 15;5:93. https://doi.org/10.1186/1748-717X-5-93
20. Jiang L, Zhang Y, Yang Z, Liang F, Wu J, Wang R. A comparison of clinical outcomes between simultaneous integrated boost (SIB) versus sequential boost (SEQ) intensity modulated radiation therapy (IMRT) for head and neck cancer: A meta-analysis. Medicine. 2019 08;98(34):e16942. https://doi.org/10.1097/MD.0000000000016942