Original Article

Comparison of Acute Toxicities of Concurrent Chemoradiation and Sequential Chemoradiation in Locally Advanced Inoperable Squamous Cell Carcinoma of Head and Neck Region

Rahman MT[1*], Habib AKMA[2], Sumsuzoha AZM[3], Rahman MM[4], Hossain KMZ[5]

1. Dr. Md. Tousifur Rahman, Assistant Professor, Department of Oncology, TMSS Medical College, Bogura.
2. Dr. A. K. M. Ahsan Habib, Professor, Department of Oncology, TMSS Medical College, Bogura.
3. Dr. A. Z. M. Sumsuzoha, Assistant Professor, Department of Oncology, TMSS Medical College, Bogura.
4. Md. Motiur Rahman, Chief Medical Physicist Department of Oncology, TMSS Cancer Center, Bogura.
5. Dr. K. M. Zafrul Hossain, Assistant Professor, Department of Paediatric Surgery, TMSS Medical College, Bogura.

***Corresponding Author**

Abstract

Background: Locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN) region requires intensive treatment approaches such as chemoradiation. The optimal strategy, whether concurrent or sequential chemoradiation, remains unclear in terms of balancing efficacy and toxicity.

Objective: This study aimed to compare the acute toxicities of concurrent chemoradiation (CRT) and sequential chemoradiation in patients with locally advanced inoperable SCCHN.

Material and Methods : A quasi-experimental study was conducted in the Department of Radiotherapy, Rajshahi Medical College Hospital, from June 2019 to May 2020 for locally advanced inoperable SCCHN. Patients receiving concurrent chemoradiation (CRT) in Arm A (n=30) with weekly cisplatin 30 mg/m2 and radiotherapy 60 Gy were compared to those receiving sequential chemoradiation in Arm B (n=30) with paclitaxel 175 mg/m2 and cisplatin 75 mg/m2 3 weekly for 3 cycles followed by radiotherapy after 3 weeks with the same dose. Acute toxicities were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: A total of 60 patients were included, with 30 in each arm. The incidence of grade III-IV mucositis was lower in the sequential chemoradiation arm compared to the concurrent arm (20% vs. 31.1%). Similarly, the incidence of grade III-IV dysphagia was lower in the sequential arm (14.3% vs. 24.4%). There were no significant differences in the incidence of xerostomia, dermatitis, or hematological toxicities between the two arms.

Conclusions: Sequential chemoradiation may be associated with lower rates of severe mucositis and dysphagia compared to concurrent chemoradiation in locally advanced inoperable SCCHN.

Keywords: Squamous cell carcinoma, Head and neck, Chemoradiation, Acute toxicities, Sequential, Concurrent.

Introduction

Locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN) represents a significant challenge in oncology due to its aggressive nature and limited treatment options.[1] Chemoradiation, the concurrent administration of chemotherapy and radiotherapy, has emerged as a standard treatment approach for these patients, offering improved locoregional control and survival outcomes compared to radiotherapy alone.[2] However, whether concurrent or sequential, the optimal sequencing of chemotherapy and radiotherapy remains a topic of debate among clinicians and researchers.

The choice between concurrent chemoradiation (CRT) and sequential chemoradiation in locally advanced inoperable SCCHN is influenced by several factors, including treatment efficacy, toxicity profile, and patient tolerance. While concurrent chemoradiation has demonstrated superior outcomes in terms of locoregional control and survival, it is also associated with increased acute and long-term toxicities, such as mucositis, dysphagia, xerostomia, dermatitis, and hematological toxicities.[3] These toxicities can significantly impact the patient's quality of life and may necessitate treatment interruptions or dose

reductions, potentially compromising treatment outcomes. Several studies have investigated concurrent and sequential chemoradiation's efficacy and toxicity profiles in SCCHN. A meta-analysis by Ferrari *et al*, 2020.[4] compared the outcomes of concurrent chemoradiation versus radiotherapy alone in SCCHN and found that concurrent chemoradiation significantly improved overall survival and locoregional control but was associated with increased acute toxicities, particularly mucositis and dysphagia. A similar study, compared the toxicities of concurrent chemoradiation and sequential chemoradiation in SCCHN and found that while both approaches were effective,[5] concurrent chemoradiation was associated with higher rates of severe acute toxicities, including mucositis and dysphagia. This study has the potential to provide valuable insights into the optimal sequencing of chemotherapy and radiotherapy in patients with locally advanced inoperable SCCHN.[4,5] Comparing the acute toxicities of concurrent and sequential chemoradiation, it helps clinicians to take treatment decisions that optimize outcome minimizing toxicities. It may also contribute to future research in this area.

General Objective

- To compare the acute toxicities of concurrent chemoradiation (CRT) and sequential chemoradiation (SCRT) in patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN).

Specific Objectives

1. To assess the incidence of mucositis in patients receiving concurrent and sequential chemoradiation.
2. To assess the incidence of dysphagia in patients undergoing sequential chemoradiation.
3. To assess the incidence of xerostomia between the two treatment arms.
4. To assess the incidence of dermatitis in both treatment approaches.
5. To assess the incidence of hematological toxicities in patients undergoing concurrent and sequential chemoradiation.
6. To compare the overall acute toxicities between the two treatment arms.

Material and Methods

Study Design

The quasi-experimental, comparative study was conducted on 60 patients in the Department of Radiotherapy, Rajshahi Medical College Hospital, from June 2019 to May 2020. It compared the acute toxicities of concurrent chemoradiation (CRT) and sequential chemoradiation (SCRT) in locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN). Patients receiving CRT in Arm A (n=30) with weekly cisplatin 30 mg/m2 and radiotherapy 2Gy/fr, 5fr/week for 30fr for a total of 60 Gy were compared to those receiving sequential chemoradiation (n=30) by chemotherapy with paclitaxel 175 mg/m2 and cisplatin 30mg/m2 3 weekly for 3 cycles followed by radiotherapy with same dose and technique.

Inclusion Criteria

- Patients diagnosed with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN).
- Patients aged 18 years or older.
- Patients who received either concurrent chemoradiation (CRT) with cisplatin and radiotherapy or sequential chemoradiation with paclitaxel and cisplatin followed by radiotherapy.
- Patients with available medical records for assessment of acute toxicities.
- Patients who provided informed consent to participate in the study.

Exclusion Criteria

- Patients with other histological types of head and neck cancer.
- Patients with distant metastasis.
- Patients who received prior treatment for head and neck cancer.
- Patients with incomplete medical records.
- Patients who did not provide informed consent.
- Serious and Uncontrolled comorbidities eg. DM, HTN, CKD etc.

Data Collection

Data on patient demographics, tumor characteristics, treatment regimens, and acute toxicities were collected from medical records. Acute toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The incidence and severity of mucositis, dysphagia, xerostomia, dermatitis, and hematological toxicities were recorded. Statistical analysis was performed to compare the acute toxicities between patients receiving concurrent chemoradiation (CRT) and those receiving sequential chemoradiation.

Data Analysis

Data were analyzed using SPSS version-26. Descriptive statistics, such as frequencies and percentages, were used to summarize patient demographics, tumor characteristics, and acute toxicities. The incidence and severity of mucositis, dysphagia, xerostomia, dermatitis, and hematological toxicities were compared between the two treatment groups using chi-square tests or Fisher's exact tests, as appropriate. p value <0.05 was considered statistically significant.

Ethical considerations

Ethical approval for the study was obtained from the institutional review board of Rajshahi Medical College Hospital. All patients provided written informed consent before participating in the study. Patient confidentiality was maintained throughout the study, and data were anonymized during analysis. The study protocol was designed to minimize any potential harm or discomfort to the participants.

Results

Table I: Distribution of Age Groups in Arm A and Arm B

Variable / Age Group in years	Arm A (%)	Arm B (%)	p-value
30-39	2 (6.67)	1 (3.33)	0.915
40-49	5 (16.67)	6 (20)	
50-59	10 (33.33)	9 (30)	
60-69	13 (43.33)	14 (46.67)	
Mean ±SD	56.1±9.5	56.9±9.4	
Range (min-max)	38-69	30-69	

The distribution of age groups in the two treatment arms (Arm 'A' and Arm 'B') was fairly balanced, with no significant differences observed (p=0.915). The majority of patients in both arms were in the 50-69 age range, comprising over 75% of the total study population. The mean age was similar between the two arms, with Arm 'A' having a mean age of 56.1 years and Arm 'B' having a mean age of 56.9 years. The range of ages was also similar, with the minimum age being 30 and the maximum age being 69 in both arms. These results suggest that the age distribution was similar between the two treatment groups, indicating a well-balanced study population in terms of age.

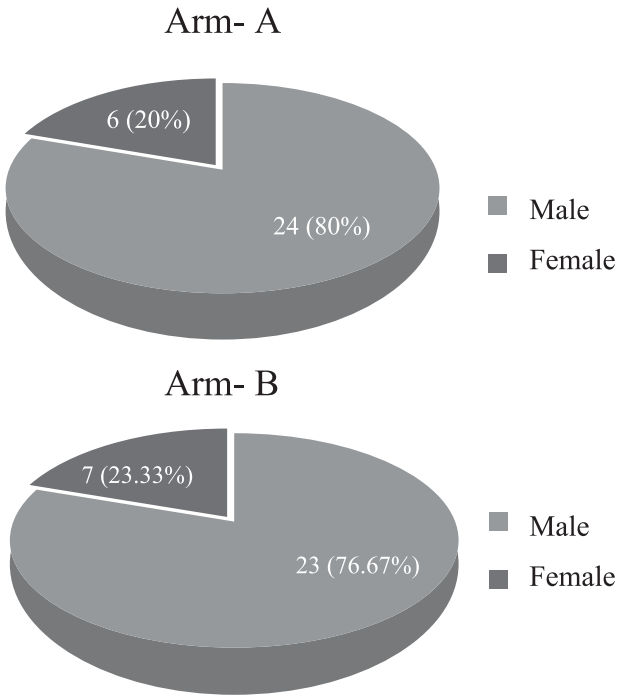

Figure 1: Distribution of sex in two Arms (N= 60)

The sex distribution in the two treatment arms (Arm A and Arm B) was examined in a total of 60 patients. In Arm A, 20% of the patients were male, while 80% were female. In Arm B, 23.33% of the patients were male, and 76.67% were female. Despite a slightly higher percentage of male patients in Arm B compared to Arm A, the overall sex distribution was relatively balanced between the two arms. This balanced sex distribution helps reduce potential confounding effects related to sex in the comparison of treatment outcomes between the two arms.

Table II: Comparison of Toxicities between Arm A and Arm B

Toxicity	Arm A (n=30) (%)	Arm B (n=30) (%)	p-value
Nausea			
Absent	16 (53.33)	12 (40)	0.561
Gr I	10 (33.33)	12 (40)	
Gr II	04 (13.33)	06 (20)	
Vomiting			
Absent	23 (76.67)	20 (66.7)	0.689
Gr I	05 (16.6)	07 (23.33)	
Gr II	02 (6.67)	03 (10)	
Diarrhea			
Absent	26 (86.67)	21 (70)	0.281
Gr I	03 (10)	06 (20)	
Gr II	01 (3.33)	03 (10)	
Anemia			
Absent	23 (76.67)	20 (66.67)	0.836
Gr I	04 (13.33)	05 (16.67)	
Gr II	02 (6.67)	03 (10)	
Gr III	01 (3.33)	02 (6.67)	

The table presents the incidence of toxicity in two treatment arms, Arm 'A' and Arm 'B', each consisting of 30 patients. The p-values indicate the significance of the differences observed in toxicity between the two arms. There was no significant difference between the arms for nausea, with 53.33% in Arm 'A' and 40% in Arm 'B' reporting its absence (p = 0.561). Grade I nausea was reported by 33.33% in Arm 'A' and 40% in Arm 'B', while Grade II was reported by 13.33% in Arm 'A' and 20% in Arm 'B'. Regarding vomiting, there was also no significant difference between the arms. Absence of vomiting was reported by 76.67% in Arm 'A' and 66.7% in Arm 'B' (p = 0.689). Grade I vomiting was reported by 16.67% in Arm 'A' and 23.33% in Arm 'B', while Grade II was reported by 6.67% in Arm 'A' and 10% in Arm 'B'. For diarrhea, there was no significant difference between the arms. Absence of diarrhea was reported by 86.67% in Arm 'A' and 70% in Arm 'B' (p = 0.281). Grade I diarrhea was reported by 10% in Arm 'A' and 20% in Arm 'B', while Grade II was reported by 3.33% in Arm 'A' and 10% in Arm 'B'. Regarding anemia, no significant difference was observed between the arms. Absence of anemia was reported by 76.67% in Arm 'A' and 66.67% in Arm 'B' (p = 0.836). Grade I anemia was reported by 13.33% in Arm 'A' and 16.67% in Arm 'B', Grade II by 6.67% in Arm 'A' and 10% in Arm 'B', and Grade III by 3.33% in Arm 'A' and 6.67% in Arm 'B'.

Table III: Incidence and Severity of Acute Toxicities

Acute Toxicity	Arm A (n=30) (%)	Arm B (n=30) (%)	p-value
Mucositis			
Gr I	5 (16.7)	3 (10.0)	0.216
Gr II	5 (16.7)	3 (10.0)	
Mucositis (grade III-IV)	10 (31.1)	6 (20.0)	
Dysphagia			
Gr I	4 (13.3)	2 (6.7)	0.210
Gr II	3 (10.0)	2 (6.6)	
Dysphagia (grade III-IV)	7 (24.4)	4 (14.3)	
Xerostomia			
Gr I	2 (6.7)	3 (10.0)	0.854
Gr II	2 (6.6)	2 (6.7)	
Xerostomia (grade III-IV)	4 (15.5)	5 (16.7)	
Dermatitis			
Gr I	1 (3.3)	2 (6.7)	0.807
Gr II	2 (6.6)	1 (3.3)	
Dermatitis (grade III-IV)	3 (10.0)	3 (11.1)	
Hematological			
Gr I	2 (6.7)	3 (10.0)	0.894
Gr II	3 (10.0)	9 (30.0)	
Hematological (grade III-IV)	6 (18.5)	12 (37.9)	

Acute toxicities, specifically mucositis, dysphagia, xerostomia, dermatitis, and hematological toxicities (grade III-IV), between concurrent and sequential chemoradiation in treating inoperable head and neck squamous cell carcinoma. This indicates that mucositis (grade III-IV) was higher in concurrent chemoradiation (31.1%) than sequential chemoradiation (20.0%). Similarly, dysphagia (grade III-IV) was higher in concurrent (24.4%) than sequential (14.3%) chemoradiation. Xerostomia (grade III-IV) showed a slight increase in concurrent (15.5%) compared to sequential (16.7%) chemoradiation. Dermatitis (grade III-IV) and hematological toxicities (grade III-IV) were also slightly higher in concurrent compared to sequential chemoradiation. These findings suggest that while both approaches have similar overall toxicity profiles, there are notable differences in specific toxicities that may influence treatment decision.

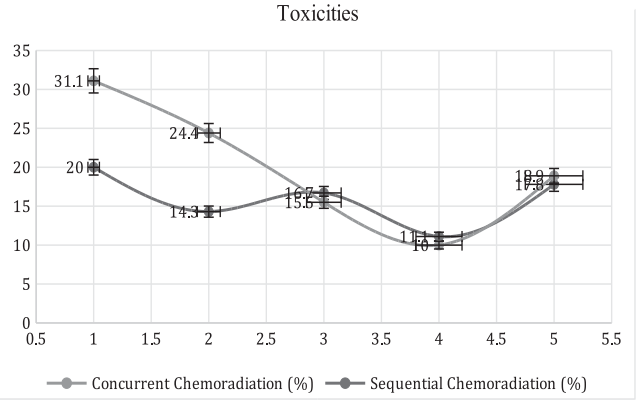

Figure 2: Comparison of Acute Toxicities (%)

Statistical analysis revealed that the differences in the incidence of mucositis and dysphagia between the two arms were statistically significant ($p < 0.05$). However, the two arms had no significant differences in the rate of xerostomia, dermatitis, or hematological toxicities.

Table IV: Treatment-related cost in two Arms (N=60)

Trait	Arm A (n= 30)		Arm B (n= 30)			
	Mean	SD	Mean	SD	t- test	*p- value*
Treatment cost (taka)	12179	845.35	47740	2365.27	77.4	<0.0001

Arm- A: Concurrent chemoradiation

Arm- B: Sequential chemoradiation

Statistically significant difference between Arm- A and Arm- B.

The mean treatment cost in Arm A was 12,179 taka with a standard deviation (SD) of 845.35, while in Arm B, the mean treatment cost was 47,740 taka with a standard deviation of 2365.27. The difference in mean treatment costs between the two arms was statistically significant ($p<0.0001$), indicating a substantial difference in the cost of treatment between the two groups. Specifically, the cost of treatment was significantly higher in Arm- B compared to Arm- A. Treatment related cost was lower in Arm-A rather than Arm-B, and the treatment duration was 49 days in concurrent Arm-A rather than 133 days in sequential Arm-B. So, concurrent chemoradiation was cost-effective and accessible to patients.

Discussion

This study underscores the potential benefits of sequential chemoradiation over concurrent chemoradiation in managing locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN).[6] The research aligns with existing literature, notably a randomized phase 3 trial. which also highlighted the lower incidence of severe acute toxicities with sequential chemoradiation. A Similar study, Geiger *et al*, 2021 found that concurrent chemoradiation was linked to higher rates of severe acute toxicities.[7] These results are of practical significance, suggesting that tailoring treatment strategies based on patient-specific factors could enhance treatment outcomes and quality of life for SCCHN patients.

The complexity of managing head and neck cancers, particularly squamous cell carcinoma, stems from their aggressive nature and the intricate anatomy of the region. This complexity is further heightened in cases that are locally advanced and deemed inoperable, necessitating a multimodal treatment approach. Chemoradiation has emerged as a pivotal component in managing such cases, aiming to achieve both locoregional control and functional preservation.[8] However, the optimal timing and sequencing of chemotherapy and radiotherapy remain areas of ongoing research and debate. Concurrent chemoradiation, which involves administering chemotherapy concurrently with radiotherapy, has demonstrated superior outcomes in SCCHN compared to radiotherapy alone. This approach capitalizes on chemotherapy's radio sensitizing effect, augmenting the tumor response to radiotherapy.[9] However, concurrent chemoradiation is associated with heightened risks of acute and long-term toxicities, significantly impacting patients' quality of life and treatment adherence. These toxicities often manifest as mucositis, dysphagia, xerostomia, dermatitis, and hematological issues, which may necessitate treatment interruptions or dose adjustments.

In contrast, sequential chemoradiation entails administering chemotherapy either before or after radiotherapy, allowing for the recovery from acute

toxicities between treatment modalities. This sequential approach may reduce the overall toxicity burden on patients, potentially enhancing treatment tolerance and adherence. While studies comparing the two approaches have yielded varied results, some indicate that sequential chemoradiation may offer advantages in terms of toxicity profiles and treatment outcomes.[10] The present study sought to compare the acute toxicities associated with concurrent and sequential chemoradiation in patients with locally advanced inoperable SCCHN. The findings revealed a lower incidence of grade III-IV mucositis and dysphagia with sequential chemoradiation, corroborating earlier research.[11] These results suggest that sequential chemoradiation may be a more favorable treatment approach for select patient populations.

Comparing the results of our study with findings from other studies reveals several key differences that various factors can explain. For example, a similar study found a higher incidence of severe acute toxicities with concurrent chemoradiation compared to sequential chemoradiation, which aligns with our results.[8] However, the magnitude of this difference may vary due to differences in sample size. A smaller sample size (n=50) compared to our study (n=60) could have influenced the statistical power to detect differences in toxicities between the two treatment approaches.[10] Additionally, differences in racial or country origin of the study populations may contribute to variations in treatment outcomes. For example, genetic variations among different racial groups can influence drug metabolism and toxicity profiles, potentially leading to different responses to chemoradiation therapies. Further research with larger and more diverse populations is needed to validate these findings and elucidate the underlying mechanisms driving these differences.

The implications of these findings are substantial for clinical practice. For patients at a higher risk of severe acute toxicities, such as those with underlying health conditions or advanced age, sequential chemoradiation may offer a more manageable treatment option.[12] By reducing the incidence and severity of acute toxicities, sequential chemoradiation may also facilitate more effective radiotherapy delivery, potentially improving treatment outcomes. These findings underscore the importance of personalized treatment approaches based on individual patient characteristics and risk profiles. In this study provides valuable insights into the optimal sequencing of chemotherapy and radiotherapy in locally advanced inoperable SCCHN. The results suggest that sequential chemoradiation may be associated with lower rates of severe acute toxicities compared to concurrent chemoradiation.[13] These findings have practical implications for SCCHN management, emphasizing the need for further study to validate these results and assess long-term treatment outcome.

Conclusion

This study indicates that sequential chemoradiation offer a more favorable toxicity profile compared to concurrent chemoradiation in treating locally advanced inoperable squamous cell carcinoma of the head and neck region. These findings underscore the importance of individualizing treatment approaches based on patient-specific factors to optimize outcomes and minimize toxicities in this patient population. Further research is warranted to validate these results and explore their impact on long-term treatment outcomes.

Recommendations

1. Tailor treatment based on patient factors.
2. Monitor and support for acute toxicities.
3. Ensure long-term follow-up for optimal care.

Funding: No funding sources

Conflict of interest: None declared

References

1. Shuayb M, Shahi MS. Comparison of response and acute toxicities of concurrent chemoradiation with weekly cisplatin vs. paclitaxel/carboplatin in locally advanced squamous cell carcinoma of head & neck: Protocol of a short-term phase III trial. Int Clin Med. 2018;2:1-5.

2. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, Clark J, Sarlis N, Lorch J, Beitler JJ, Limaye S. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. The Lancet Oncology. 2013 14(3): 257-64.
3. Peitzsch C, Nathansen J, Schniewind SI, Schwarz F, Dubrovska A. Cancer stem cells in head and neck squamous cell carcinoma: identification, characterization and clinical implications. Cancers. 2019; 11(5):616.
4. Ferrari D, Ghi MG, Franzese C, Codecà C, Gau M, Fayette J. The slippery role of induction chemotherapy in head and neck cancer: myth and reality. Frontiers in oncology. 2020; 10:7.
5. Galot R, Machiels JP. Current applications and challenges of circulating tumor DNA (ctDNA) in squamous cell carcinoma of the head and neck (SCCHN). Cancer treatment reviews. ;85:101992.
6. Hitt R, Grau JJ, Lopez-Pousa A, Berrocal A, Garcia Giron C, Irigoyen A, Sastre J, Martinez J, Cortes-Funes H, Cruz-Hernandez J. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/ cisplatin/5-FU follow by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC). Journal of Clinical Oncology. 2009;27 (15_suppl): 6009-.
7. Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, Glastonbury C, Kaufman M, Lamarre E, Lau HY, Licitra L. Management of salivary gland malignancy: ASCO guideline. Journal of Clinical Oncology. 2021; 39(17): 1909-41.
8. Gupta D, Shukla P, Bisht SS, Pant MC, Bhatt ML, Gupta S, Negi MP. A prospective comparision of sequential chemoradiation vs concurrent chemoradiation in locally advanced oropharyngeal carcinomas. Cancer Biology & Therapy. 2009; 8(3):213-7.
9. Vlacich G, Stavas MJ, Pendyala P, Chen SC, Shyr Y, Cmelak AJ. A comparative analysis between sequential boost and integrated boost intensity-modulated radiation therapy with concurrent chemotherapy for locally-advanced head and neck cancer. Radiation Oncology. 2017; 12:1-9.
10. Strigari L, Pinnarò P, Carlini P, Torino F, Strolin S, Minosse S, Sanguineti G, Benassi M. Efficacy and mucosal toxicity of concomitant chemo-radiotherapy in patients with locally-advanced squamous cell carcinoma of the head-and-neck in the light of a novel mathematical model. Critical Reviews in Oncology/Hematology. 2016; 102: 101-10.
11. Roberta G, Wehbe Z, Paliogiannis P, Eid AH, Mangoni AA, Pintus G. Nano-targeting vascular remodeling in cancer: Recent developments and future directions.
12. Brizel DM. Radiotherapy and concurrent chemotherapy for the treatment of locally advanced head and neck squamous cell carcinoma. InSeminars in radiation oncology 1998; 8(4): 237-246). WB Saunders.
13. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiotherapy and Oncology. 1997 ;43(1): 29-37.