ScienceForecast
A digital science library

Research Article
Published: 15 Jan, 2019

Journal of Cancer Research Forecast

Early Side Effects of Radiotherapy for Head and Neck Tumors

Soydemir GP and Tiken EE*

Health Sciences University Bakırköy, Dr. Sadi Konuk Education and Research Hospital, Turkey

Abstract

Objective: The objective of this study is to evaluate early side effects of adjuvant or definitive radiotherapy and/or chemoradiotherapy in patients diagnosed with squamous cell head and neck tumor and treated in our clinic.

Materials and Methods: The early side effects in the patients who were treated between February 2017 and April 2018 were retrospectively evaluated. A total of 51 patients diagnosed with head and neck cancer were included in the study. Definitive RT was applied to 19 patients and adjuvant RT was applied to 24 patients due to recurrence in 6 patients, and metastasis in 2 patients. Radiation therapy was applied to tumor/tumor lodge ± lymphatics at a dose of 54-70 Gy. The early side effects observed in the patients were noted and evaluated.

Results: The most common location of tumor in the patients included in the study was larynx (56%). 12 (23.5%) patients were in the early stage of disease and 39 (76.4%) patients were in stage 3-4. 30 (61.22%) patients underwent surgery. 17 (34.6%) patients received adjuvant CRT, 13 (26.5%) received adjuvant RT, 14 (28.5%) received definitive CRT and 5 (10.2%) received definitive RT. Of the patients who applied for treatment, 2 (3.9%) received palliative RT due to metastatic disease. Considering the correlation between early stage side effects and dose, no significant difference was found between a dose below and above 66Gy, age, gender, and side effects. Only hematological toxicity was significantly higher in the chemotherapy group.

Conclusion: RT/CRT is a long-term, organ-protective treatment method with high toxicity. Our study was consistent with the literature in terms of early side effects. Recognizing and treating early side effects increases the patient compliance and therefore the effectiveness of the treatment.

Keywords: Head and neck tumors; Concurrent chemoradiotherapy; Side effects

OPEN ACCESS

**Correspondence:*
Gülşen Pınar Soydemir, Health Sciences University Bakırköy, Dr. Sadi Konuk Education and Research Hospital Bakırköy, İstanbul, Turkey.
Tel: 05336540226/ 02124147171
E-mail: gulpin3528@hotmail.com

Received Date: 23 Nov 2018
Accepted Date: 11 Jan 2019
Published Date: 15 Jan 2019

Citation: Soydemir GP, Tiken EE. Early Side Effects of Radiotherapy for Head and Neck Tumors. J Cancer Res Forecast. 2019; 2(1): 1015.

ISSN 2690-4179

Introduction

Each year, 550,000 patients around the world are diagnosed with head and neck tumor (HNT), and 300,000 of these lose their lives. 90% of all HNTs are squamous cell carcinoma (SCC), and head and neck SCCs are the sixth most common among all cancers [1].

The most common HNTs are oral cavity, larynx and hypopharynx cancers. The disease is highly associated with living standards. Its incidence increases with increased alcohol and/or cigarette consumption. There is a 60% Human Papilloma Virus (HPV) positivity in patients with HNTs [2].

A multidisciplinary approach is important for deciding on the treatment. The selection of treatment is based on tumor localization, histopathological features and patient-related factors. Approximately one third of patients are in the early stage. Surgery or RT is preferred in early-stage T1-2N0 diseases. There is no difference between these two methods in terms of survival [3]. Early-stage disease is treated with a high cure rate, and 5-year survival rates are 70-90%.

Local advanced, stage 3-4, SCC head and neck tumors are high-risk in terms of regional recurrence and distant metastasis. Combined treatment modalities, surgery and/or radiotherapy (RT) following postoperative or definitive chemoradiotherapy (CRT) or induction CT have been shown to increase local control and survival [4,5].

In this study, we evaluated early side effects observed in patients with squamous cell HNT, who were treated with adjuvant or definitive RT and/or CRT in our clinic.

Materials and Methods

This study was approved by the ethics committee of Health Sciences University Bakırköy Dr.

Table 1: Patient properties CRT: Chemoradiotherapy; RT: Radiotherapy.

		n	%
Gender	**Female**	11	21.6
	Male	40	78.4
Tumor Location	**Larynx**	28	56
	Oral cavity	4	8
	Hipopharynx	4	8
	Other	19	28
Stage	**Stage 1-2**	12	23.5
	Stage 3-4	39	76.4
Application Status	**Definitive**	43	84.31
	Nuks	6	11.76
	Metastatic	2	3.92
Operation	**Yes**	30	61.22
	No	19	38.78
Radiotheraphy	**Adjuvant CRT**	17	34.6
	Adjuvant RT	13	26.5
	Definitive RT	14	28.5
	Definitive CRT	5	10.2
Concomitant chemotherapy	**No**	18	36.73
	Yes	31	63.27

Table 2: Early Side Effect.

	Grade	n(%)
Skin Reaction	1	2(3.9)
	2	25(49)
	3	24(47.1)
	4	0
Mucositis	1	2(3.9)
	2	6(11.8)
	3	42(82.4)
	4	1(2)
Esophagitis	0	1(2)
	1	4(7.8)
	2	12(23.5)
	3	34(66.7)
Haematological toxicity	0	6(11.8)
	1	29(56.9)
	2	13(25.5)
	3	3(5.9)

Sadi Konuk education and Research Hospital under no 2017/422.

A total of 51 patients diagnosed with head and neck cancer, who were treated in our clinic between February 2017 and April 2018, were included in the study. Definitive RT was applied to 19 patients and adjuvant RT was applied to 24 patients due to recurrence in 6 patients, and metastasis in 2 patients.

Patient recruitment criteria were as follows; patients being diagnosed with HNT, aged 18 to 80 years, oriented and cooperative. In the study, the criteria for administering adjuvant radiotherapy and/or chemotherapy were T3-T4 stage tumors, lymph node involvement,

Table 3: Side effect - gender correlation.

		Female	Male	
		n (%)	n (%)	p
RTOG	2.00	5 (45.45)	20 (52.63)	0.675**
Skin Reaction	3.00	6 (54.55)	18 (47.37)	
RTOG	2.00	3 (30)	3 (7.89)	0.095*
Mucositis	3.00	7 (70)	35 (92.11)	
RTOG	2.00	3 (30)	9 (25)	0.706*
Esophagitis	3.00	7 (70)	27 (75)	
RTOG	2.00	1 (100)	12 (80)	1.000*
Haematological toxicity	3.00	0 (0)	3 (20)	

**Fisher's exact test; ** Pearson chi-square test.*

surgical margin positivity/proximity, extra capsular extension (ECE) and other histopathological risk factors (lymphovascular invasion (LVI), perineural invasion (PNI), etc.).

During the evaluation process prior to RT, Positron Emission Tomography (PET) images were taken with the help of patient's history, physical examination, Magnetic Resonance (MR) and/or Computed Tomography (CT). Blood biochemistry and complete blood count were evaluated for all patients at the beginning of treatment. Laboratory tests were repeated weekly throughout the treatment.

For immobilization prior to RT, each patient underwent a special thermoplastic mask fixation in the supine position. The section thickness for tomography images was taken as 2.5mm. The planning CT images of the patients were fused with pretreatment MRI and/or PET CT images and lymphatic areas and tumor loops were determined according to RTOG head and neck atlas based on the disease indication.

Using Monte-Carlo planning analysis with 6 MV photon energy, volumetric arc therapy (VMAT) plans were made at a linear accelerator device (LINAC) (ELEKTA) for RT. In a total of five fractions per week with a daily fraction dose of 2Gy, a RT dose of 54Gy was administered to prophylactic neck lymphatics, 60Gy to involved neck lymphatics, and 66-70 Gy to tumor and/or tumor lodge. During the treatment, the patients were included in the treatment by performing cone-beam CT every other day.

Concomitant chemotherapy with RT was performed in 32 (62.7%) patients. Of these patients, 29 (56.8%) received cisplatin, 2 (3.9%) received carboplatin weekly and 1 (1.9%) received cetuximab weekly. 20 (68.9%) patients received cisplatin CT at a dose of 75-100 mg/m^2 every 3 weeks, and 9 (31%) patients received it at a dose of 40 mg/m^2 per week.

The patients were examined weekly during RT and every 3 months after the first 6 weeks following RT. Side effects observed within 90 days from the onset of RT were considered to be early side effects, whereas those observed 90 days after RT were considered to be late side effects. The scoring of side effects was based on American Radiotherapy Oncology Group criteria (https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity_grading/RTOG).

Statistical method

In our study, the RT and CT methods and early side effects (mucositis, esophagitis, hematologic) were compared. Pearson chi-square test was used for comparisons. Statistical significance value

(p) <0.05 was considered significant. General characteristics of patients were noted. Frequency percentage values were calculated for categorical variables. Mean standard deviation and median values were given for continuous variables. The data were analyzed using NCSS 11 (Number Cruncher Statistical System, 2017 statistical software) and Excel 2016.

Results

The median age of the patients was 59.3 ± 12.1 years. Of a total of 51 patients, 11 (21.6%) were female and 40 (78.4%) male. The most common tumor location in the patients included in the study was larynx (56%) followed by oral cavity and hypopharynx. 12 (23.5%) patients were in the early stage of disease and 39 (76.4%) patients were in stage 3-4. In the evaluation of pathological findings of the operated patients, it was seen that 21 (41%) patients were PNI-negative and 6 (11.7%) patients were PNI-positive. 16 (31.3%) patients were ECE-negative and 8 (15.6%) patients were ECE-positive. 14 (27.4%) patients were LVI-negative and 11 (21.5%) patients were LVI-positive. Surgical margins were close or positive in 13 (25.5%) patients.

30 (61.22%) patients underwent surgery. 17 (34.6%) received adjuvant CRT, 13 (26.5%) received adjuvant RT, 14 (28.5%) received definitive CRT and 5 (10.2%) received definitive RT. Of the patients who applied for treatment, 2 (3.9%) patients received palliative RT due to metastatic disease. Characteristics of all patients are shown in Table 1.

Radiation therapy was applied to tumor/tumor lodge ± lymphatics at a dose of 54-70 Gy. Concomitant chemotherapy with RT was performed in 32 (62.7%) patients. Of these patients, 29 (56.8%) received cisplatin, 2 (3.9%) received carboplatin and 1 (1.9%) received cetuximab. 20 (68.9%) patients received cisplatin CT at a dose of 75-100 mg/m^2 every 3 weeks, and 9 (31%) patients received it at a dose of 40 mg/m^2 per week.

The mean follow-up period for side effect analysis was found to be 8.4 months. The side effects on skin, oral mucosa and esophagus were noted for acute toxicity. A complete blood count was also recorded to determine the hematological toxicity of the patients. 82% of the patients had grade 3 mucositis, 11% had grade 2 mucositis, and 66.7% had grade 3 esophagitis, 23.5% had grade 2 esophagitis. The distribution of early side effects is given in Table 2. No correlation was found between age, gender, adverse effects and weight loss (Table 3,4,5).

The most common dermatitis grade was grade 3 which was observed in 24 (47.1%) patients. 77.8% of grade 3 mucositis side effects were observed in the patients who received a dose of ≤ 66Gy, while 90.9% were observed in the patients who received a dose of >66Gy (0.027*). 59.3% of grade 3 esophagitis side effects were observed in the patients who received a dose of ≤ 66Gy, while 77.3% were observed in the patients who received >66Gy. Considering the correlation between early side effects and dose, no significant difference was found between a dose below and above 66 Gy and non-mucositis side effects (Table 6).

Only hematological toxicity was significantly higher in the chemotherapy group. Hematological side effects were observed in 19 patients who received a high-dose cisplatin CT every 3 weeks. Only 3 patients in this group had grade 3 early hematological toxicity. When all side effects were examined, grade 4 side effects were only observed in one patient (Table 7).

Table 4: Side effect - age correlation.

		< 50 age	≥50 age	
		N (%)	N (%)	p
RTOG	2.00	5 (55.56)	20 (50)	1.000*
Skin Reaction	3.00	4 (44.44)	20 (50)	
RTOG	2.00	3 (33.33)	3 (7.69)	0.071*
Mucositis	3.00	6 (66.67)	36 (92.31)	
RTOG	2.00	2 (33.33)	10 (25)	0.644*
Esophagitis	3.00	4 (66.67)	30 (75)	
RTOG	2.00	1 (100)	12 (80)	1.000*
Haematological toxicity	3.00	0 (0)	3 (20)	

** Fisher's exact test.*

Table 5: Weight loss – gender and age correlation.

	Weight loss	
	Average±SD	p
	Median (min-max)	
Gender		
Female (n=11)	5.64±2.84	0.835*
	5- (2-11)	
Male (n=40)	5.75±3.39	
	5- (0-15)	
Age		
< 50 age (n=9)	5.89±4.62	0.891*
	5- (0-15)	
≥50 age (n=42)	5.69±2.96	
	5- (0-15)	

**Mann Whitney U test.*

Table 6: Radiation dose and side effect correlation.

		Planning Radiation Dose		
		≤66 Gy	>66Gy	p
Skin Reaction	1	0 (0.0)	1 (4.5)	0.464*
	2	15 (55.6)	9 (40.9)	
	3	12 (44.4)	12 (54.5)	
Mucositis	**1**	**0 (0.0)**	**1 (4.5)**	**0.027***
	2	**6 (22.2)**	**0 (0.0)**	
	3	**21 (77.8)**	**20 (90.9)**	
	4	**0 (0.0)**	**1 (4.5)**	
Esophagitis	0	1 (3.7)	0 (0.0)	0.618*
	1	2 (7.4)	1 (4.5)	
	2	8 (29.6)	4 (18.2)	
	3	16 (59.3)	17 (77.3)	
Haematological toxicity	0	5 (18.5)	1 (4.5)	0.168*
	1	17 (63.0)	11 (50.0)	
	2	4 (14.8)	8 (36.4)	
	3	1 (3.7)	2 (9.1)	

**Fisher's exact test.*

Discussion

Local treatment modalities such as surgery and/or radiotherapy can be preferred alone for definitive treatment in early-stage diseases

Table 7: Concomitant Chemotheraphy and side effect correlation.

		Concomitant Chemotherapy		
		No	Yes	p
Skin Reaction	1	1 (5.0)	1 (3.2)	0.786*
	2	11 (55.0)	14 (45.2)	
	3	8 (40.0)	16 (51.6)	
Mucositis	1	1 (5.0)	1 (3.2)	0.190*
	2	4 (20.0)	2 (6.5)	
	3	14 (70.0)	28 (90.3)	
	4	1 (5.0)	0 (0.0)	
Esophagitis	0	1 (5.0)	0 (0.0)	0.059*
	1	3 (15.0)	1 (3.2)	
	2	2 (10.0)	10 (32.3)	
	3	14 (70.0)	20 (64.5)	
Haematological toxicity	0	5 (25.0)	1 (3.2)	**0.002***
	1	14 (70.0)	15 (48.4)	
	2	1 (5.0)	12 (38.7)	
	3	0 (0.0)	3 (9.7)	

**Fisher's exact testi.*

[6]. In addition, concomitant CRT can be the most appropriate approach when surgical intervention is restricted due to anatomical location of the tumor [7].

Two-thirds of patients with SCC head and neck cancer are in locally advanced stage at the time of admission. In this group of diseases, local recurrence develops in 50-60% of the cases, and distant metastasis is observed in 20-30% of the cases [8-10]. Surgery and adjuvant radiotherapy +/-chemotherapy is accepted as standard therapy in locally advanced resectable diseases. Randomized studies and meta-analyses have shown that there have been increases in local regional disease control, organ preservation and survival rates with chemoradiotherapy [11,12]. It is aimed to increase local control rates and gain survival advantage with different treatment approaches in locally advanced stage patients. 79.4% of the patients included in the study had stage 3-4 disease. 24 of the patients who had locally advanced disease received post-operative RT/CRT and 15 patients received definitive CRT. In our study, 23.5% of patients had early stage disease. Adjuvant RT was administered to 8 early-stage patients and 4 patients received definite RT or CRT.

In the treatment of head and neck cancers, it is aimed to achieve a disease-free survival and a functional life in which organs under risk are protected as much as possible. One of the main objectives is to increase local control with new technologies, therefore providing survival advantage and protecting patients from early and late side effects.

It is known that CRT increases the risk of mucositis, hematological suppression, dermatitis and infection [13]. It is important to perform necessary treatments for side effects for achieving the patient compliance with treatment. In the study conducted by Atasoy et al. [4] examining the patients with locally advanced head and neck cancer, a side effect of grade 3 and above was observed in 61.5% of the patients. Adelstein et al. [14] reported in their study that the rate of side effects of grade 3 and above was 89%. In our study, 82% of patients had grade 3 mucositis, 11% had grade 2 mucositis, and 66.7% had grade 3 esophagitis, and 23.5% had grade 2 esophagitis. 77.8% of grade 3 mucositis side effects were observed in the patients who received a dose of ≤ 66Gy, while 90.9% were observed in the patients who received a dose of >66 Gy (0.027*). 59.3% of grade 3 esophagitis side effects were observed in the patients who received a dose of ≤ 66 Gy, while 77.3% were observed in the patients who received >66Gy.

Side effect rates are lower in chemotherapy administrations performed with a low weekly dose. In our study, grade 3 hematological side effects were observed the most in the group that received CT every 3 weeks.

In the RT of head and neck cancers, nutrition problems are common due to early side effects. As a result, severe weight losses are observed, which have an adverse effect on the continuity of treatment. The rate of grade 2-3 weight loss was reported to be 29.1% by Atasoy et al., 6.4% in the Study INT 0099, 32% by Lee et al., 74% by Chan et al. and 12% by Wee et el. [4,15-18] In our study, the mean weight loss during the RT period was 5.8kg (0-15 kg), and 8 patients had a grade 2-3 weight loss.

In conclusion, in the treatment of head and neck cancers, it is aimed to achieve a disease-free survival and a functional life in which organs under risk are protected as much as possible. RT/CRT is a long-term, organ-protective treatment method with high toxicity. The data obtained in the evaluation of side effects experienced by patients with HNT during the RT/CRT process in our clinic were found to be consistent with the literature. The evaluation of responses for the treatment efficacy was planned to be conducted in the future. Our study is consistent with the literature in terms of early side effects. Recognizing and treating early side effects increases the patient compliance and therefore the effectiveness of the treatment.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017; 67: 7-30.
2. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide : A Systematic Review Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 2005; 14: 467-475.
3. Demiröz C, Özşahin EM. Skuamöz Hücreli Baş Boyun Kanserinde Kemoradyoterapi. Uludağ Üniversitesi Tıp Fakültesi Derg. 2011; 37: 61-65.
4. Atasoy BM, Dane F, Sari M, Akgün Z, Yumuk PF, Turhal NS, et al. Lokal ileri evre skuamöz hücreli baş ve boyun kanserinde sisplatinle eş zamanli kemoradyoterapi: Yan etki ve uygulanabilirlik analizi. Turk Onkol Derg. 2008; 23: 1-11.
5. Bernier J, Cooper JS, Pajak TF, vanGlabbeke M, Bourhis JFA, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005; 27: 843-850.
6. Agrawal N, Ha PK. Management of Early-Stage Laryngeal Cancer. Otolaryngol Clin North Am. 2008; 41: 757-769.
7. Scher RL, Esclamado RM. Organ and Function Preservation: The Role of Surgery as the Optimal Primary Modality or as Salvage After Chemoradiation Failure. Semin Radiat Oncol. 2009; 19: 17-23.
8. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. N Engl J Med. 2001; 345: 1890-1900.
9. Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, et al. National Cancer Database report on cancer of the head and neck: 10-Year update. Head Neck. 2009; 31: 748-758.

10. Posner MR, Haddad RI, Wirth L, Norris CM, Goguen LA, Mahadevan A, et al. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. Semin Oncol. 2004; 31: 778-785.

11. Pignon J-P, le Maître A, Bourhis J, MACH-NC Collaborative Group. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys. 2007; 69: S112-114.

12. Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998; 338: 1798-1804.

13. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354: 567-578.

14. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. 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. J Clin Oncol. 2003; 21: 92-98.

15. Al-Sarraf M. Treatment of locally advanced head and neck cancer: historical and critical review. Cancer Control. 2002; 9: 387-399.

16. Lee AWM, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al. Preliminary Results of a Randomized Study on Therapeutic Gain by Concurrent Chemotherapy for Regionally-Advanced Nasopharyngeal Carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol. 2005; 23: 6966-6975.

17. Chan ATC, Teo PML, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent Chemotherapy-Radiotherapy Compared With Radiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma: Progression-Free Survival Analysis of a Phase III Randomized Trial. J Clin Oncol. 2002; 20: 2038-2044.

18. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized Trial of Radiotherapy Versus Concurrent Chemoradiotherapy Followed by Adjuvant Chemotherapy in Patients With American Joint Committee on Cancer/International Union Against Cancer Stage III and IV Nasopharyngeal Cancer of the Endemic Variety. J Clin Oncol. 2005; 23: 6730-6738.