# The Effect of Age on the Quality of Life in Head and Neck Cancer Patients Treated with Radiotherapy

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**ABSTRACT**

We investigated the effect of age on the quality of life (QoL) of 310 patients with head and neck cancer (HNC) who received radiotherapy (RT) and chemoradiotherapy treatments for the head and neck region. The EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires (version 3.0) were completed by each patient at 4 different time-points (between the start of RT and 6 months after the completion of RT). A total of 189 patients (61%) aged < 65 years were included in Group I and 121 (49%) aged ≥ 65 years in Group II. As per the RTOG acute toxicity criteria, the scores for skin toxicity (p= 0.005), mucosal toxicity (p= 0.041), neutropenia (p= 0.043), and weight loss (p= 0.007) were found to be higher for Group I than for Group II. The global health status (p= 0.002), role functioning (p< 0.001), physical function score (p< 0.001), cognitive function score (p< 0.001), fatigue (p< 0.001), pain (p =0.014), and dyspnea (p= 0.002) symptom scores were negatively affected in Group II as per the module-C30 questionnaire. No statistically significant differences were noted in the module-H&N35 scores for either age group. Elderly patients, who were considered to be more fragile due to the presence of comorbid diseases, were observed to tolerate the RT side-effects better than younger patients. The reason for this could be that older patients received less combined modality treatment and neck radiotherapy than younger patients. However, we also determined that some QoL scores of the elderly patients remained negatively affected.

**Keywords:** Head and Neck Cancers, Radiotherapy, Chemoradiotherapy, Quality of Life

## INTRODUCTION

Head and neck cancers (HNC) are the sixth-most common type of cancer worldwide, with 900.000 new cases diagnosed annually.[1] Although these cancers are generally diagnosed at an early stage, they are considered difficult to treat. However, improvements in the treatment methods in the last 20 years have resulted in longer survival times after diagnosis. The overall 5-year survival rate for HNC squamous cell carcinoma increased from 54.7% in 1992-1996 to 65.9% in 2002-2006.[2] For the years 2010-2016, this rate was reported to be 70.8%.[3]

Radiotherapy (RT) and chemoradiotherapy (CRT) are the most frequently used methods of treatment in HNCs, both with and without surgery. Because the mucosal surfaces in the head and neck region are sensitive to RT, it can cause serious side-effects that can disrupt the patient's nutrition during or after the treatment. With impaired nutrition, the quality of life (QoL) of patients is also negatively affected by RT or CRT. Treatment of HNCs may also lead to significant loss of critical functions such as in vision, swallowing, in the sense of speech, taste, hearing, the use of facial expressions, and breathing.

Therefore, it is important to determine the effects of treatments and other factors (such as patient age) on QoL. More than 60% of the patients with HNC possess functional problems such as with speech and swallowing and psychological problems such as depression. Therefore, QoL measurement is important to meet the needs of patients.[4,5]

In elderly patients, the gradual weakening of the body functions with age is a natural process. With age, people become more fragile due to the presence of comorbid diseases such as hypertension and coronary heart diseases etc. Therefore, careful evaluation should be performed before starting RT or CRT for elderly cancer patients. Comprehensive geriatric evaluation in elderly patients can facilitate better examination of the patient's functional reserve to make optimal treatment decisions. This evaluation can also improve the functions and nutritional status of the head and neck regions.[6] Therefore, extensive evaluation of elderly patients should include QoL measurements.

In our study conducted in 2013, we investigated the effect of RT on QoL by using the module-H&N35 questionnaire in patients with HNC.[7] In the present study, we investigated the effectiveness of patient age on QoL by expanding the patient group and adding the module-C30 questionnaire for patients with HNC who received RT and CRT treatment in the head and neck region.

## PATIENTS AND METHODS

The medical records of 310 patients diagnosed with HNC and who attended the Radiation Oncology Department at the Cumhuriyet University Faculty of Medicine between February 2007 and December 2018 were retrospectively analyzed. The patients who did not have distant metastases and who received adjuvant or definitive RT or CRT treatment for their neck cancers were enrolled in this study. Patients with distant metastasis who received palliative RT or second-series RT were excluded. The subjects were stratified into 2 groups: Group I consisted of patients aged < 65 years and Group II consisted of those aged ≥ 65 years.

The disease staging was determined according to the TNM staging system, as developed by the International Union Against Cancer and the American Joint Committee on Cancer, 2017 (8th edition).[8]

### Radiotherapy

RT was performed using linear accelerators (Varian DHX device) and TomoTherapy with standard fractionation. The Eclipse (ver. 8.6; Varian Medical Systems, Inc., Palo Alto, CA, USA) was used as the 3DCRT planning software program. The VoLO planning system (Tomo HD VoLO planning system, Accuray Inc. Madison, WI, USA) was used for the intensity-modulated RT (IMRT). RT was applied in the conventional fraction (1.8-2 Gy daily) as a total of 54-70 Gy or SIB method as a total of 54-70 Gy. RT in malignant melanoma was applied at the rate of 2.5 Gy/day, as a total of 50 Gy.

The acute side-effects of RT were evaluated with reference to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria.[9] The side-effects were evaluated once a week during RT.

The study was approved by the Institutional Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Review Board (requirement for ethics committee approval was waived off as this was a retrospective study; Decision number: 2020-05/630) and was conducted in accordance with the ethical standards stated by the 1964 Declaration of Helsinki.

### Chemotherapy

Weekly cisplatin (40 mg/m$^2$) or high-dose cisplatin (100 mg/m$^2$ D1, D22, and D43) was used in CRT. DCF (docetaxel 75 mg/m$^2$ D1, cisplatin 75 mg/m$^2$ D1, and 5 fluorouracil 750 mg/m$^2$ D1-5; repeat every 3 weeks) or CF (cisplatin 80 mg/m$^2$ D1 and 5 fluorouracil 1.000 mg/m$^2$ D1-4; repeat cycle every 4 weeks) regimens were administered as induction or adjuvant chemotherapy

### QoL Scale

The European Organization for Research and Treatment of Cancer's Life Questionnaire Core-30 (EORTC QLQ-C30; version 3.0) and the ques-

tionnaire module to be used in QoL assessments in HNC (EORTC QLQ-H&N35; version 3.0) were completed at 4 different time-points by each patient, namely, at the start of RT (T1), the end of RT (T2), 1 month after completion of RT (T3), and 6 months after completion of RT (T4).

The components of the module-C30, a 30-item questionnaire, included global health status, 5 functional scales (i.e., physical, role functioning, cognitive, emotional, and social), and 9 symptom scales/items (i.e., fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The patients' responses were scored according to the module-C30 scoring guide.[10] The scores for the symptom components were linearly transformed on a scale of 0 - 100. A high score for the functional scale represented a relatively high level of functioning, while a high score for the symptom scale represented greater severity of the symptoms or the financial impact.[10,11]

The module-H&N35 was developed as an additional survey form to module-C-30 in order to better evaluate the QoL of patients with HNC. This module comprises of 35 questions on the symptoms and side-effects of treatment, social function, and body image/sexuality. This module incorporates 7 multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. There are also 11 single items, namely, teeth problems, opening mouth, dry mouth, sticky saliva, cough problems, feeling ill, painkiller use, nutritional supplement use, feeding tube use, weight loss, and weight gain. The scoring approach for the module-H&N35 is identical in principle to that of the symptom scales/single items of the module-C30. It became valid after working in a large population of HNC in the Europe and the United States of America.[12]

**Statistical Analysis**

All data were analyzed by using the SPSS version 22 (IBM Corp., Armonk, New York, USA) statistics program. The medians and frequencies were calculated for the patient demographics. The questionnaire scores were compared across the 4

time-points using repeated-measures analysis of variance. The effect of age on the changes in QoL over a period of time was analyzed using 2-way repeated-measures analysis of variance. $p \leq 0.05$ was considered to indicate statistical significance.

**RESULTS**

A total of 189 (61%) patients were included in Group I and 121 (39%) in Group II. The demographic characteristics and treatment protocols of the group patients are shown in Table 1. According to this table, there was a statistically significant difference between the groups in terms of comorbidity, localization of primary disease, disease stage, and treatments (except for surgery).

RTOG based on the age in acute toxicity findings; In groups I and II, grade 1-2 skin toxicity was recorded in 141 (75%) and 91 (75%) patients and grade 3-4 skin toxicity was recorded in 26 (14%) and 5 (4%) patients, respectively, albeit statistically significant differences were noted between the groups (p= 0.005).

In groups I and II, grade 1-2 mucositis was recorded in 94 (50%) and 58 (48%) patients and grade 3-4 mucositis was recorded in 43 (23%) and 17 (14%) patients, respectively, and the difference was statistically significant (p= 0.041). Grade 1-2 neutropenia was noted in 27 (14%) and 8 (7%) patients and grade 3-4 neutropenia was noted in 1 (1%) and 3 (2%) patients; the difference was statistically significant (p= 0.043). The loss of 5% of the patient's weight during the treatment was recorded in 70 (37%) patients in Group I and in 27 (22%) patients in Group II, and the difference was statistically significant (p= 0.007). In other acute toxicity findings, no statistically significant finding was noted between the 2 groups.

Table 2 summarizes the comparisons of the module-C30 questionnaire scores at the 4 different time-points with age. The questionnaire response rates were 100% (n= 310) at T1, 99% (n= 308) at T2, 68% (n= 212) at T3, and 38% (n= 119) at T4. As per the module-C30 questionnaire, the global health status, physical functions, role functioning, fatigue, pain, and the scores of cognitive functions and dyspnea symptoms were negatively affected in the Group II patients. As per the results of the mod-

**Table 1.** Demographic characteristics and treatments of patients by age.

| No of patients (%) | Group I (< 65 ages) n= 189 (61) | Group II (≥ 65 ages) n= 121 (39) | p value |
|---|---|---|---|
| **Gender** | | | |
| Male | 152 (80) | 88 (73) | 0.075 |
| Female | 37 (20) | 33 (27) | |
| **Comorbidity** | 46 (24) | 81 (67) | < 0.001 |
| **Primary disease** | | | |
| Nasopharyngeal + paranasal sinus | 46 (24) | 9 (7) | < 0.001 |
| Oral cavity + oropharynx | 27 (14) | 35 (29) | |
| Larynx + hypopharynx | 82 (44) | 42 (35) | |
| Salivary gland | 14 (7) | 9 (7) | |
| Skin | 13 (7) | 18 (15) | |
| Other | 7 (4) | 8 (7) | |
| **Pathology** | | | |
| Squamous cell carcinoma | 154 (81) | 92 (76) | 0.324 |
| Basal cell carcinoma | 6 (3) | 6 (5) | |
| Malign melanoma | 5 (3) | 2 (2) | |
| Mucoepidermoid carcinoma | 6 (3) | 5 (4) | |
| Adenoid cystic carcinoma | 5 (3) | 4 (3) | |
| Other | 13 (7) | 9 (10) | |
| **Stage** | | | |
| Insitu | 2 (1) | – | 0.023 |
| Stage I | 22 (11) | 27 (23) | |
| Stage II | 39 (21) | 32 (27) | |
| Stage III | 64 (34) | 30 (25) | |
| Stage IVA | 62 (33) | 30 (25) | |
| **Treatments** | | | |
| Surgery | 82 (43) | 55 (45) | 0.405 |
| RT* | 84 (45) | 84 (70) | < 0.001 |
| CRT** | 101 (55) | 36 (30) | < 0.001 |
| Induction chemotherapy | 25 (13) | 4 (3) | 0.002 |
| Adjuvant chemotherapy | 36 (19) | 8 (7) | 0.001 |
| **Treatments** | | | |
| Single | 33 (17) | 35 (29) | 0.013 |
| Combine | 156 (83) | 86 (71) | |
| **RT fields** | | | |
| Tumor and/or bed | 44 (24) | 46 (38) | 0.005 |
| Tumor and/or bed+neck lymphatics | 141 (76) | 74 (62) | |
| RT dose (mean±SD) Gy | 63.8±0.60 | 60±1.16 | 0.012 |

Group I: < 65 ages, Group II: ≥ 65 ages
* RT: Radiotherapy, ** CRT: Chemoradiotherapy

ule-C30 questionnaire, statistically significantly affected QoL scale curves are depicted in Figure 1 (Physical function score curve of functional scales) and Figure 2 (Dyspnea score curve of symptom scales). The comparison of Group I and II patients showed no statistically significant difference for any of the other scores.

The Module-H&N35 questionnaire scores of the patients were compared at the 4 different time-points with age. The questionnaire response rates were 51% (n= 157) at T1, 51% (n= 157) at T2, 32% (n= 98) at T3, and 31% (n= 96) at T4. No statistically significant difference was noted in the module- H&N35 scores for both the age groups.

**Table 2.** Comparisons of the EORTC QLQ-C30 questionnaire scores at the four time points according to age

| EORTC QLQ-C30 | T1 | T2 | T3 | T4 | p |
|---|---|---|---|---|---|
| No of patients (%) | 310 (100) | 308 (99) | 212 (68) | 119 (38) | |
| **Global health status** | | | | | |
| Group I | 77±17 | 68±20 | 77±19 | 81±23 | **0.002** |
| Group II | 67±27 | 59±19 | 60±16 | 68±25 | |
| **Functional Scale** | | | | | |
| Physical | | | | | |
| Group I | 84±17 | 72±21 | 80±21 | 86±20 | **< 0.001** |
| Group II | 62±32 | 50±27 | 52±27 | 58±26 | |
| Role functioning | | | | | |
| Group I | 87±23 | 72±23 | 76±25 | 82±24 | **< 0.001** |
| Group II | 67±34 | 56±29 | 55±28 | 53±26 | |
| Emotional | | | | | |
| Group I | 79±21 | 73±22 | 78±21 | 83±22 | 0.413 |
| Group II | 77±21 | 74±21 | 75±20 | 75±23 | |
| Cognitive | | | | | |
| Group I | 84±17 | 84±15 | 89±15 | 86±18 | **< 0.001** |
| Group II | 76±20 | 72±25 | 76±20 | 71±21 | |
| Social | | | | | |
| Group I | 80±24 | 75±25 | 85±22 | 88±21 | 0.229 |
| Group II | 81±24 | 72±24 | 75±26 | 78±25 | |
| **Symptom scale** | | | | | |
| Fatigue | | | | | |
| Group I | 18±19 | 34±23 | 24±22 | 17±22 | **< 0.001** |
| Group II | 33±26 | 44±22 | 41±27 | 36±26 | |
| Nause | | | | | |
| Group I | 1±5 | 14±24 | 7±18 | 4±15 | 0.448 |
| Group II | 1±5 | 9±13 | 7±14 | 3±8 | |
| Pain | | | | | |
| Group I | 11±15 | 25±25 | 11±17 | 12±22 | **0.014** |
| Group II | 25±27 | 30±25 | 23±19 | 17±17 | |
| Dyspnea | | | | | |
| Group I | 10±19 | 11±20 | 7±16 | 8±16 | **0.002** |
| Group II | 25±27 | 19±27 | 22±28 | 19±30 | |
| Insomnia | | | | | |
| Group I | 16±23 | 26±30 | 16±24 | 13±23 | 0.295 |
| Group II | 27±30 | 24±26 | 21±30 | 19±27 | |
| Appetite loss | | | | | |
| Group I | 8±21 | 33±34 | 17±25 | 12±24 | 0.248 |
| Group II | 9±18 | 36±27 | 27±29 | 17±27 | |
| Constipation | | | | | |
| Group I | 5±12 | 2±10 | 1±6 | 2±13 | 0.459 |
| Group II | 5±12 | 5±11 | 1±7 | 6±17 | |
| Diarrhea | | | | | |
| Group I | 2±7 | 2±10 | 1±6 | 2±13 | 0.148 |
| Group II | 2±7 | 5±11 | 1±7 | 6±17 | |
| Financial problems | | | | | |
| Group I | 21±29 | 32±29 | 22±28 | 20±28 | 0.585 |
| Group II | 19±24 | 22±26 | 21±24 | 21±26 | |

Results are denoted as mean ± standard deviation. Group I: < 65 ages, Group II: ≥ 65 ages.
T1: start of radiotherapy; T2: end of radiotherapy; T3: 1 month after completion of radiotherapy; T4: 6 months after completion of radiotherapy
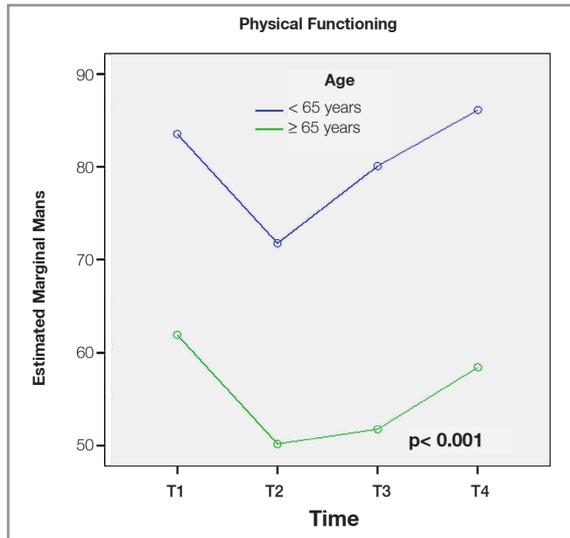
**Figure 1.** Curves of functional scales that were statistically significantly affected by age in the EORTC QLQ-C30 questionnaire
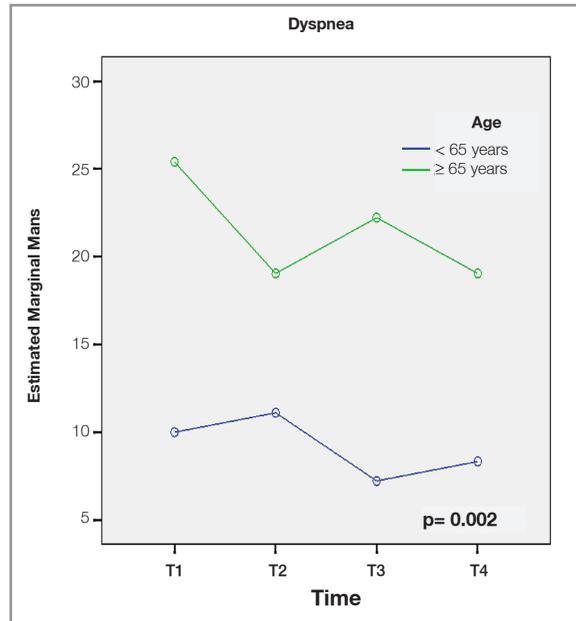


**Figure 2.** Curves of symptom scales that were statistically significantly affected by age in the EORTC QLQ-C30 questionnaire

## DISCUSSION

The population of most developed countries is rapidly aging. Furthermore, there has been a significant increase in the total cancer rates in the past decade in these countries. Especially after the age of 50 years, an increase in the incidences of HNC has been reported.[13] It has also been reported that 22.3% of the patients with HNC diagnosed between 2001 and 2008 in the cancer registry data in Slovenia were of age > 70 years.[14] In 2014, approximately 42,400 new cases of oral and pharyngeal cancer were identified in the United States of America, of which 50% were reported to occur in patients aged ≥ 65 years.[15] According to the cancer registry center data in Scotland in 1994, Muir et al. reported that 24% of the HNC patients were of age > 70 years.[16] In our study, the rate of elderly (aged ≥ 65 years) HNC patients was 39%.

Several studies in the past have compared the side-effects of treatments among older and younger patients. It therefore seems reasonable to expect to see more RT or CRT side-effects in elderly patients with reduced body function and comorbid diseases. Pignon et al. showed that, based on the results of 1,307 HNC patients who underwent RT, no difference was noted between the age groups in terms of grade 1-2 acute mucosal toxicity and weight loss. In contrast, grade 3-4 functional acute mucosal toxicity was more severe in elderly patients than in younger patients.[17] Schofield et al. researched toxicity in 98 patients with HNC of age ≥ 80 years who received curative RT. They found that the rates of acute objective mucosal toxicity were similar to that of younger patients.[18] Merlano et al. examined 317 patients diagnosed with HNC. They noted that the side-effects such as grade 3-4 stomatitis, diarrhea, thrombosis, weight loss, total parenteral nutrition, parenteral, and enteral nutrition requirement, grade 3-4 neutropenia, and grade 3-4 anemia due to CRT were similar between the young and old patients. However, they reported that the incidence of infection and pneumonia were significantly more in elderly patients.[19] Yücel et al. reported no significant difference between younger and older patients for acute side-effects such as skin reactions, mucositis, pharyngeal, laryngeal, salivary gland toxicity, neutropenia, thrombocytopenia, and anemia due to definitive RT in a study of 67 HNC patients among 423 different cancer patients.[20] In our study, treatment-related side-effects such as skin toxicity, mucosal toxicity, neutropenia, and weight loss were observed more frequently in Group I. In our study, the reason for the less acute

treatment side-effects among the elderly patients may be related to the fact that older patients received less combined modality treatment and neck RT than the younger patients.

Among cancer patients, almost all treatments affected the patients' QoL. However, not only the treatments may contribute to the deterioration of the patients' QoL but also some factors related to the patients' themselves (e.g., age and the presence of comorbid disease). Several studies have reported that the QoL of elderly patients with HNC suitable for therapeutic treatment was comparable to that of younger patients, as assessed by the module-C30 and H&N35 questionnaires.[21-23] However, on the contrary, some studies have shown that the global QoL score is low in HNC patients, especially among elderly women, as assessed by the module-C30 and H&N35 questionnaires. These studies reported that female patients with older larynx tumors had more substantial problems.[24,25] Van der Schroeff et al. evaluated 24 elderly (≥ 70 years) and 33 relatively young (45-60 years) HNC patients by using the module-C30 and H&N35 questionnaires with global QoL assessments and found that, even after 6 years of RT and CRT, there was no significant difference in the QoL scores between the older and younger patients.[21] Derks et al. evaluated 78 elderly (aged ≥ 70 years) and 105 young (aged 45-60 years) HNC patients by using the module-C30 and H&N35 questionnaires before and at 3, 6, and 12 months after RT and CRT. In elderly patients, a significantly worse score was noted with respect to the scale of physical function before treatment. Initially, none of the other variables differed significantly between the 2 groups. In the third month, physical function remained the only score that differed significantly between the age groups. With respect to the score regarding teeth problems, elderly patients reported more issues, albeit the difference was not statistically significant. In the sixth month, younger patients experienced more pain, and, in the elderly patients, the score on physical function was still weak, which was statistically significant. A year later, the incidences of nausea and vomiting were significantly more in younger patients. However, no significant differences were found for other variables.[23]

Silveira et al. evaluated the QoL of HNC patients according to the age (115 patients aged ≥ 65 years and 174 patients aged 45-60 years). The researchers noted that the physical, cognitive, and emotional functional scores were statistically significantly lower in the elderly patients than in the younger patients.[25] Hammerlid et al. evaluated 117 patients aged ≥ 65 years and 180 patients aged < 65 years using the module-C30 and H&N35 questionnaires and after RT and CRT at 6 different time-points. For emotional and social function, the scores were better for the elderly patients than for those aged < 65 years, although they noted that the scores were worse in the elderly patients for physical functions, constipation, dyspnea, financial impact, sexuality, teeth problems, dry mouth, and cough.[26] Similar to that in the study of Silveira et al., we noted that the global health status, physical function, role functioning, fatigue, pain, and the scores of cognitive functions and dyspnea symptom as per the module-C30 questionnaire were statistically significantly more negative in patients aged ≥ 65 years than in the younger patients. In addition, data analyses revealed that all elderly patients' scores were worse at the baseline when compared with the younger patients' scores. This can be considered normal for elderly patients with higher comorbid disease rates, as detected in our study. This observation may explain the noted vulnerability in the elderly patients.

Silveira et al. noted worse scores in the elderly patients with laryngeal cancer for swallowing, speech problems, social eating, social contact, sexuality, and teeth problems. In oral cancers, except for teeth problems in older patients, the scores for other variables were not different from those of the younger patients. For pharynx cancer, no significant difference was noted between the older and younger cancer patients, albeit that the scores of older cancer patients were slightly better. The scores for speech, opening the mouth, coughing, and feeling ill have been reported to be quite low in younger patients.[25] In the study by Hammerlid et al. the score for speech problems were worse in the older patients as assessed by the module-HN35 questionnaire at the baseline. At the 12th month, greater problems with sexuality and sticky saliva and greater deterioration in scores of some of the symptoms (e.g., for sensations, sexuality, and di-

etary supplement use) were recorded in the older patients than in the younger ones. However, the authors also noted that younger patients experienced a greater increase in the incidence of dry mouth.[26] In our previous study published in 2013, the HNC patients aged < 65 years (58 patients) and those aged ≥ 65 years (24 patients) were evaluated by using the module-H&N35 questionnaire before, at the middle of, at the end of, and after 1 and 6 months of RT and CRT treatments. With respect to the scores, weight gain was more common in the elderly patients; however, weight loss and reduced sexuality were more common in the younger patients. Other symptom scores were not statistically significant.[7] In the present study, no statistically significant difference was noted in the module- H&N35 scores in both the age groups. Lower prevalence of side-effects in the elderly patients may explain the lack of significant difference in the module- H&N35 scores between the groups.

The limitations of the present study include that some patients did not complete all the questionnaires at 4 different time-points and that the QoL of the patients was not evaluated 6 months after the RT.

## Conclusion

RT was observed to have negative effects on the global health status, physical function, role functioning, fatigue, pain, and scores of cognitive function and dyspnea symptom on the module-C30 scale for elderly patients. However, this negative effect was not observed on the module- H&N35 scale and treatment toxicity. As the combined modality treatment and neck RT are more common in young patients, the module- H&N35 scale scores were equal between the young and elderly patients. With respect to the decision-making process, patients should be evaluated in a multidisciplinary environment, and their performance status, presence of comorbidity, cognitive function, nutritional status, and socioeconomic conditions should also be considered. When RT treatment is individualized, it can be applied effectively and safely to elderly patients. However, in order to increase the QoL, appropriate factors should be monitored closely at regular intervals, and relevant steps should be taken to minimize the complications of treatment through early intervention and supportive treatments.

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