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ORIGINAL ARTICLE

The Effect of Nutrition on Prognosis in Patients with Head and Neck Tumors Receiving Organ Preserving Treatment Turkish Radiation Oncology Integrative Group Study (TROD 12-06)

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OBJECTIVE

Head and neck cancer (HNC) is one of the cancer types with the highest prevalence of malnutrition and, therefore, sarcopenia. In this study, we evaluated whether nutritional support can prevent weight loss and sarcopenia among patients who undergo RT/CRT.

METHODS

A total of 94 head and neck cancer patients who received 5-week RT or CRT with concomitant nutritional support were included in this study. For each patient, before treatment and at the end of the 5th week of treatment, C3-level paravertebral muscles were contoured through planning systems. Patient demographics, PNI, NRI, and NRS-2002 scores, as well as height, weight, and body mass index, were also evaluated.

RESULTS

At the end of 5 weeks, there was a significant loss in the patients' weight z-score and BMI ($p<0.001$ and $p<0.001$, respectively). The decrease in C3-level paravertebral muscle volume of patients with high PNI values was also observed to be high between the 1st and 5th weeks ($p=0.037$), and there was no connection between NRI and muscle volume ($p=0.301$). No correlation was observed between the patients' weight z-score, BMI, and PNI or NRI values between the 1st and 5th weeks ($p>0.066$ and $p>0.210$, respectively). A significant decrease was observed in C3-level paravertebral muscle volume over a 5-week period ($p<0.001$).

CONCLUSION

In our study, nutritional intervention did not prevent patients from losing weight and caused decreases in BMI, regardless of head and neck cancer type, stage, and risk score, during the 5-week follow-up. There was no correlation between the nutritional risk score (NRS), the prognostic nutritional index (PNI), and muscle volume. Even on occasions when BMI has not changed, occult sarcopenia and muscle loss should not be overlooked. However, more accurate results will be obtained with a longer-term follow-up.

Keywords: Chemoradiotherapy; clinical nutrition; head and neck cancers; prognostic nutritional index.

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INTRODUCTION

Head and neck cancer (HNC) is one of the cancer types with the highest prevalence of malnutrition, due to the compromising impact of lifestyle habits adopted prior to diagnosis, as well as the location of the tumor on food intake and nutritional status, beside the hyper-catabolic characteristics of cancer itself and radiotherapy (RT) or chemoradiotherapy (CRT)-related side effects.[1–4]

As has been known for years, radiotherapy has an important place in the treatment of head and neck cancers. Although treatment for early-stage (stage I-II) head and neck cancers is often surgery alone or definitive RT-CRT, the standard treatment for more advanced-stage resectable diseases consists of combined surgery and chemoradiotherapy. While malignancy is intended to be kept under control with the treatments applied, treatment-related complications cause malnutrition and ultimately sarcopenia in patients.

Head and neck cancer patients often experience malnutrition during treatment.[5] In clinical practice, malnutrition is defined as weight loss of >5% in 1 month or >10% in 6 months.[6] It has been found that malnutrition develops in 30–50% of patients during radiotherapy, in which the oropharynx and hypopharynx are particularly susceptible.[7,8] Dysphagia and odynophagia are frequently observed due to edema and mucosal toxicities associated with radiotherapy. In addition, cytokines such as TNF released from malignant tissues cause a decrease in appetite. These situations result in oral intake disorders and muscle and weight loss.

Compared to conventional fractionation, other fractionation schemes may improve tumor control, but both the addition of chemotherapy and fractionation changes may increase acute radiation toxicities. Previous surgeries also frequently cause an increase in acute radiotherapy morbidities.[5]

Oral intake disorders disrupt and prolong the treatment process and, therefore, the hospital stay.[9] It has been observed that deterioration in the treatment process causes low clinical response, poor prognosis, low functional performance, decreased quality of life, and increased mortality.[9–11] This study aims to identify the effects of nutritional management on anthropometry and cancer prognosis in head and neck cancer patients.

MATERIALS AND METHODS

Data were collected from 5 centers across Türkiye and a total of 94 head and neck cancer patients between March 10, 2022, and September 15, 2022. For each patient, before treatment and at the end of the 5th week of treatment, C3-level paravertebral muscles were contoured through planning systems to measure the surface area, as previously described in the literature.[12] If there was muscle loss at the end of the 5th week, the percentage of loss was recorded.

Medical nutritional products were started as supplements along with treatment for each patient. Nutritional risk index is calculated as (NRI) = 1.519 × serum albumin level (g/l) + 41.7 × (present/ideal body weight). Prognostic nutritional index is calculated as PNI = (10 × serum albumin [g/dL]) + (0.005 × lymphocytes/µL). PNI and NRI values were compared with 5-week BMI and weight z-score changes. Height and body weight of each patient were measured before treatment and at the end of the 5th week of treatment, and BMI was calculated based on these values. For each patient, the ideal body weight in kg was calculated using the formulas 50 + (0.91 × [height in cm − 152.4]) for men and 45.5 + (0.91 × [height in cm − 152.4]) for women.

Nutritional risk score is scored as: Normal nutritional status (0); >5% weight loss in 3 months or food intake in the past week below 50–75% of normal requirements (1); weight loss >5% in 2 months or BMI 18.5–20.5 + impaired general condition or nutritional intake in the past week 25–50% of normal requirements (2); weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 + impaired general condition or nutritional intake in the past week below 0–25% of normal needs (3).

NRS-2002 score was calculated before treatment and at the end of the 5th week by adding the nutritional score + severity of disease score and +1 if the patient's age is 70 years or older.

Height, weight, body mass index (BMI), and C3-level paravertebral muscle volume measured at baseline were compared with week 5 measurements for the entire patient group with a nutritional risk score (NRS)≥3. BMI and muscle volume 5-week changes were compared separately under tumor response, tumor response and location subgroups, in addition to the whole group. Statistical significance was considered p<0.05.

RESULTS

Demographic information is given in Table 1a. At the end of 5 weeks, there was a significant loss in the patients' weight z-score and BMI (p<0.001 and p<0.001, respectively) (Table 1b, Fig. 1a, b). A decrease in the number of overweight and obese patients according to

Table 1a Demographic information

Demographics	**Female**		**Male**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
Gender (%)	16	17.0	78	83.0	94	100
Age, median (IQR)	62	20	62	15	62.0	16

Table 1b The relationship between nutritional index and the amount of anthropometric change and comparison of 5th week anthropometry and paravertebral muscle volume measurements under all and NRS≥3 subgroups

Nutritional indices	**Descriptives**	**Change of weight over 5 weeks z-score correlation p value**	**Change of BMI over 5 weeks correlation p value**	**Change of muscle volume over 5 weeks correlation p value**
PNI, mean (SD)	50.6 (7.22)	0.094	0.066	0.037
NRI, median (IQR)	53.3 (13.3)	0.210	0.275	0.301
Anthropometrics	**Patients with NRS≥3**	**p value**	**Total**	**p value**
Admission weight (kg), mean (SD)	73.1 (16.3)	<0.001	73.2 (14.5)	<0.001
5th week weight (kg), mean (SD)	65.1 (14.3)		67.6 (13.4)	
Admission weight z-score, median (IQR)	0.38 (1.32)	<0.001	0.6 (1.33)	<0.001
5th week weight z-score, median (IQR)	-0.18 (1.31)		0.1 (1.39)	
Admission BMI, median (IQR)	24.1 (5.5)	<0.001	25.0 (6.19)	<0.001
5th week BMI, median (IQR)	21.6 (5.95)		22.9 (6.28)	
C3 Paravertebral muscle volume (cm^2), mean (SD)	36.3 (11.21)	<0.001	36.7 (11.07)	<0.001
5th week C3 Paravertebral muscle volume (cm^2), mean (SD)	29.9 (9.70)		31.6 (8.93)	
Admission height (cm), mean (SD)	168.9 (8.17)	NA	168.6 (7.37)	NA

Table 1c Distribution of patients at 5th week with admission according to BMI weight status thresholds

BMI[31]	**Weight status[31]**	**Patient number at admission (%)**	**Patient number at 5th week**
<18.5	Underweight	1 (1.1)	6 (6.4)
18.5–24.9	Healthy weight	43 (45.7)	55 (58.5)
25.0–29.9	Overweight	30 (31.9)	24 (25.5)
>29.9	Obesity	20 (21.3)	9 (9.6)

IQR: Interquartile range; PNI: Prognostic nutritional index; SD: Standard deviation; NRI: Nutritional risk index; NRS: Nutritional risk score; BMI: Body mass index

BMI due to undesirable weight loss was observed, at 6.4% and 11.7%, respectively (Table 1c). The decrease in C3-level paravertebral muscle volume of patients with high PNI values (values greater than 49.75) was also observed to be high between the 1st and 5th weeks (p=0.037), and there was no connection between NRI and muscle volume (p=0.301).

Apart from this, no correlation was observed between the patients' weight z-score, BMI, and PNI or NRI values between the 1st and 5th weeks (p>0.066 and p>0.210, respectively) (Table 1b). Additionally, a significant decrease was observed in C3-level paravertebral muscle volume over a 5-week period (p<0.001) (Table 1b and Fig. 1c). There was no difference in BMI improvement between patients with NRS≥3 and the whole group (p=0.485).

When tumor location, response, and stage subgroups were examined separately, a significant BMI decrease was observed in all of them at 5 weeks (p<0.036 for all variables) (Table 2). The decrease in muscle volume was not seen only in stage 2 cancer patients and in patients with tumors originat-

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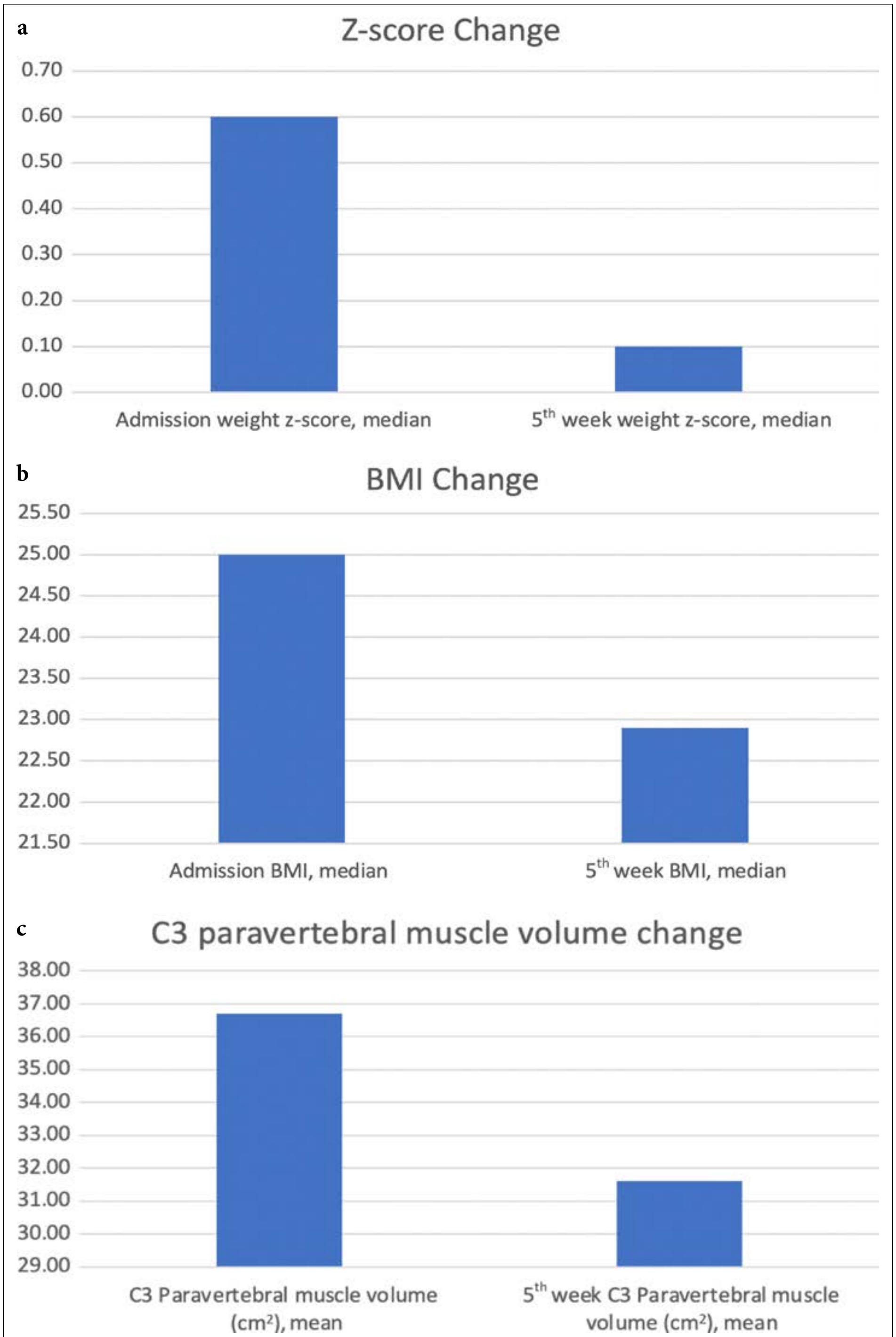

Fig. 1. (a) Application and 5th week weight z-score measurement averages. (b) Application and 5th week BMI measurement averages. (c) Admission and 5th week C3 paravertebral muscle volume measurement averages.
BMI: Body mass index.

ing from the oral cavity and oropharynx (p=0.196, p=0.695, and p=0.889, respectively). A significant decrease in muscle volume was observed in other patients (p<0.025) (Table 2). No correlation was found between the amount of BMI change and the type of nutrition (p=0.063).

Table 2 Statistical comparison of tumor response, tumor stage and location subgroups with anthropometry and C3 paravertebral muscle volume measurements measured at 5 weeks

Tumor response	Overall frequency (%)	Admission BMI, mean (SD)	5th week BMI, mean (SD)	BMI over 5 weeks p value	C3 paravertebral muscle volume (cm^2), mean (SD)	5th week C3 paravertebral muscle volume (cm^2), mean (SD)	C3 paravertebral muscle volume over 5 weeks p value
CR	27 (63.8)	25.7 (4.83)	23.5 (3.77)	<0.001	39.1 (11.5)	30.7 (8.65)	<0.001
PR	60 (28.7)	25.8 (4.21)	23.9 (4.36)	<0.001	35.4 (11.0)	31.5 (9.10)	0.001
SD	4 (4.3)	25.6 (8.18)	23.9 (8.20)	Insufficient sample	33.2 (7.23)	36.9 (9.45)	Insufficient sample
PD	3 (3.2)	22.7 (0.49)	20.5 (1.05)	Insufficient sample	41.2 (10.35)	39.7 (11.90)	Insufficient sample
Tumor stage							
1	3 (3.2)	26.1 (7.20)	25.1 (6.73)	Insufficient sample	39.1 (10.72)	30.5 (12.55)	Insufficient sample
2	14 (14.9)	28.1 (3.96)	26.8 (4.02)	0.006	38.6 (10.60)	35.0 (6.77)	0.196
3	43 (45.7)	24.6 (4.15)	22.8 (4.16)	<0.001	35.0 (10.29)	32.0 (10.16)	0.002
4	34 (36.2)	26.1 (4.67)	23.5 (3.99)	<0.001	37.9 (12.23)	29.8 (7.58)	<0.001
Total	94 (100)						
Tumor location							
Larynx	40 (42.6)	25.8 (4.67)	23.3 (4.68)	<0.001	37.3 (10.05)	33.4 (7.38)	0.003
Nasopharynx	18 (19.1)	26.7 (4.39)	24.1 (4.08)	<0.001	42.5 (12.57)	31.4 (10.07)	0.001
Oral cavity	12 (12.8)	26.6 (5.22)	24.5 (4.37)	0.006	31.1 (11.65)	28.4 (12.45)	0.695
Oropharynx	8 (8.5)	22.4 (3.65)	21.2 (3.13)	0.036	30.0 (7.55)	30.1 (7.79)	0.889
Other	8 (8.5)	25.3 (3.64)	23.3 (4.68)	0.003	36.4 (9.73)	30.5 (8.78)	0.011
Hypopharynx	6 (6.4)						
Tongue	2 (2.1)						

BMI: Body mass index; SD: Standard deviation; CR: Complete response; PR: Partial response; PD: Progressive disease

DISCUSSION

Malnutrition negatively impacts quality of life and treatment toxicities, and it has been estimated that up to 10–20% of cancer patients die due to consequences of malnutrition rather than the tumor itself. Thus, nutrition plays a crucial role in multimodal cancer care.[13] Many head and neck cancer patients have a history of heavy alcohol and smoking consumption, malnutrition, and a low performance score.[11,14] The nutritional status of patients is worsened by the local and systemic effects of the tumor (tumor cachexia, tumor compression), pain experienced during the recovery period after surgical treatment, difficulty in chewing and swallowing, problems in jaw movements (trismus), edema, and related difficulties in chewing and swallowing. Conditions such as nausea and vomiting, which are observed with high incidence in these patients, also cause impaired oral intake and weight loss.[15]

Problems caused by oral intake disorders and malnutrition in cancer patients include: decreased physical function and performance status, low immune status and increased infections, more severe (grade III/IV) late RT toxicity, decreased treatment effectiveness due to interruption in treatment (RT/KRT), low chemotherapy response rate, increased hospitalizations, decreased quality of life (QoL), and increased mortality rates.

Radiation-induced loss of the basal cells in the epithelium of the oral mucosa results in oral mucositis, and radiation-induced inflammation of salivary glands leads to xerostomia, which are other major causes of oral intake disorders and weight loss. The first recommendation for patients undergoing RT should be to carefully maintain their oral hygiene to minimize the clinical risks related to xerostomia. Preventive strategies such as regular tooth brushing are suggested,

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and rinsing with antimicrobials such as chlorhexidine and povidone iodine is only recommended if there is oral infection.[16]

Pharmacological agents such as pilocarpine and bethanechol are widely used to stimulate saliva secretion. Corticosteroids can also be considered to increase the appetite of anorectic cancer patients with advanced disease for a restricted period (1–3 weeks), but side effects should be carefully monitored. Other pharmacological agents such as prokinetic agents, non-steroidal anti-inflammatory drugs, and progestins can also be considered.[13]

The ESPEN guideline recommends nutritional intervention to increase oral intake in cancer patients who are able to eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake (nutrition impact symptoms), and offering oral nutritional supplements.[13] Although, in our study, we could not prove any benefit from oral nutritional supplements.

Langius et al.[17] reported that weight loss before and during radiotherapy is an important prognostic factor for 5-year disease-specific survival in HNC patients. Weight loss is a common occurrence during RT. Lees et al.,[18] in a study on this subject, found weight loss in 57% of patients during the treatment process. An average weight loss of 6.5 kg was detected in patients, which corresponds to 10% of body weight. Johnston et al.,[19] in his study, evaluated body weight in 31 patients with localized head and neck cancer before, during, and after treatment. It was found that 68% of 31 patients lost more than 5% of their initial weight within 1 month after the end of treatment. An average of 10% weight loss was observed in patients, ranging from 5.4% to 18.9%. In this study, similar to ours, initial anthropometric measurements, serum albumin, lymphocyte count, as well as creatinine and creatinine/height ratio, were not predictive for weight loss.

From the study by Munshi et al.,[5] a total dose of >60 Gy was found to be significant for acute toxicities and weight loss. Additionally, a low initial Karnofsky performance score (KPS; $p<0.001$) and the use of chemoradiation ($p<0.001$) were found to be significant. With increasing dose, more acute morbidity is observed, and the duration of treatment is prolonged. However, this correlation was not shown in our study because total dose and fractionation schemes were not evaluated.

Current ESPEN guidelines suggest that, to detect nutritional disturbances at an early stage, patients should be regularly evaluated for nutritional intake, weight change, and body mass index (BMI). They also suggest that patients' daily calorie needs should be assumed to be similar to those of healthy subjects, generally ranging between 25 and 30 kcal/kg/day.[13] They further recommend maintaining or increasing physical activity levels in cancer patients to support muscle mass, physical function, and metabolic patterns. In our study, we observed a statistically meaningful decrease in both BMI and lean muscle weight.

The NRI index was first described by Buzby et al.[20] to score the severity of postoperative complications. It combines two nutritional indicators (albumin and weight loss). By extension, it has been used as an index of malnutrition in hospitalized adults. Since its introduction, it has been applied in several medical specialties, mainly in the field of oncology.[21,22] It has been recently shown that NRI has a better prognostic value than both BMI and albumin.[23] In our study, the mean NRI was 53.3, and no correlation was found between NRI and skeletal muscle mass loss.

In addition, in this study, we evaluated the PNI in patients, which is a simple, economical, and useful parameter calculated using albumin concentration and lymphocyte count. The PNI was originally derived to assess the nutritional and immunological status of patients undergoing gastrointestinal surgery.[24] Recently, the use of PNI in patients with brain tumors (especially glioblastoma) has been investigated to help predict prognosis early and guide optimal therapeutic decisions. Studies have generally focused on the effect of preoperative PNI on OS.[24–29] In our study, the mean PNI value was 50.6, and no correlation was found between PNI and skeletal muscle mass loss.

In a similar study to ours, Akmansu et al.[30] evaluated the effect of immunonutrition on PNI in high-grade glioma patients in adjuvant settings. Retrospectively, data from 30 consecutive brain tumor patients who received brain chemoradiotherapy with immunonutrition support were evaluated. There was no statistically significant difference between mean albumin values before and after adjuvant treatment, but a statistically significant difference was found between mean lymphocyte counts. In the study, despite the negative effects of intensive chemoradiotherapy treatments on PNI parameters, no decrease was observed in PNI. Even a minimal increase was detected, and it was found that immunonutrition support has positive effects on PNI and albumin levels in brain tumor patients who undergo postoperative radiotherapy/chemoradiotherapy. The authors concluded that low PNI, which may be an indicator of hematological and nutritional toxicity predicted by brain chemoradiotherapy, can be prevented by immunonutrition support.

In another study by Akmansu et al.,[32] the utility of GLIM criteria in relation to NRS-2002 scores in diagnosing malnutrition in head and neck cancer patients receiving anti-cancer treatment with concomitant nutritional support was evaluated. Similar to our study, a total of 32 HNC patients who received 5-week RT or CRT with concomitant nutritional support were evaluated for anthropometrics, SMM at the level of the third cervical vertebra, and the evaluation of nutritional status using NRS-2002 and GLIM criteria. It was found that, at the end of the 5th week, the number of malnourished patients increased according to GLIM criteria, and a significant decrease was noted in body weight, BMI, calf circumference, and cross-sectional muscle area at the level of C3, while NRS-2002 scores significantly increased despite nutritional support. No significant correlation was observed between the NRS-2002 scores or the GLIM stages and skeletal muscle mass parameters. Diagnosis of stage 1 and stage 2 GLIM on the first day or 5th week was associated with significantly higher first-day and 5th-week NRS-2002 scores compared to the non-malnourished group, indicating the feasibility of GLIM criteria in identifying malnourished patients who would benefit from clinical nutrition before anti-cancer treatment, as well as those with severe malnutrition and increased risk of adverse patient outcomes.

CONCLUSION

In our study, nutritional intervention did not prevent patients from losing weight and caused decreases in BMI, regardless of head and neck cancer type, stage, and risk score, during the 5-week follow-up. Since 53.2% of the study cohort consisted of overweight and obese patients, improvement based on BMI and weight z-score in the study occurred due to weight loss. As a result of the 5-week follow-up, there was no correlation between the nutritional risk score (NRS) and the prognostic nutritional index (PNI) and muscle volume. Even on occasions when BMI has not changed, occult sarcopenia and muscle loss should not be overlooked. However, more accurate results will be obtained with a longer-term follow-up.

Ethics Committee Approval: The study was approved by the Trakya University Faculty of Medicine Non-interventional Scientific Research Ethics Committee (no: 03/27, date: 14/02/2022).

Authorship contributions: Concept – M.A.; Design – S.Y.S.; Supervision – M.A.; Materials – S.Y.S.; Data collection and/or processing – F.D.; Data analysis and/or interpretation – N.G.; Literature search – V.Y.Ç.; Writing – H.E.C.; Critical review – M.A.

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Turk J Oncol 2025;40(1):43–50
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