

Evaluation of oral manifestations and head and neck lymphadenopathy in newly diagnosed acute leukemia patients

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Abstract

Objectives: To determine the frequency of head and neck lymphadenopathy (LAP) and intraoral findings (non-dental/dental) in patients with newly diagnosed acute leukemia (AL).

Subjects and methods: Twenty-eight (52.8%) females and 25 (47.2%) males in a total of 53 patients with newly diagnosed AL with a mean age of 46 years were included in the study. Personal information, the type of AL (AML [acute myelogenous leukemia]/ALL [acute lymphocytic leukemia]), and hematological findings (anemia, neutropenia, and thrombocytopenia) were obtained from medical records. One of two calibrated oral diagnosis and maxillofacial radiology specialists performed extraoral (head and neck LAPs) and intraoral (non-dental and dental) clinical examinations. The Chi-square (χ^2) test was used to evaluate categorical variables.

Results: LAP was observed in 22.6% and intraoral findings in 30.2% of the patients. LAP was most commonly observed in the neck and none in the parotid glands. The most intraoral findings were gingival/mucosal bleeding and oral petechiae/ecchymosis. While there was no statistical difference between AML and ALL patients in terms of LAP ($p > .05$), intraoral findings were observed more in patients with AML ($p < .05$). Only two (3.8%) patients had dental findings. With a slight difference, intraoral findings were more with thrombocytopenia and LAP with neutropenia.

Conclusion: In AL, especially non-dental intraoral findings are common. The fact that dentists working in the oral cavity are often the first specialists to encounter the oral manifestations of AL imposes an important role in early diagnosis and treatment.

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KEYWORDS

acute leukemia, intraoral finding, lymphadenopathy

1 | INTRODUCTION

Leukemia is a general term for a group of malignant hematological disorders originating from hematopoietic stem cells and characterized by the unregulated proliferation of neoplastic cells.¹ In the early and even pre-diagnosed stages of leukemia, patients may exhibit fever, fatigue, persistent and recurrent infections, hematoma, pallor, petechiae, and bleeding from the skin and mucous membranes, including the oral mucosa.^{2,3}

Leukemia is classified based on clinical behavior (acute or chronic) and the primary hematopoietic cell line affected (myeloid or lymphoid).³ Thus, the two principal diagnostic categories (type) of acute leukemia (AL) are acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL). Although the oral manifestations arise in both acute and chronic forms, they are more common in AL.⁴ As in many systemic diseases, oral manifestations can be observed in patients with AL and may even be the early symptoms/signs of the disease in some cases.⁵⁻⁷ Oral manifestations may occur because of direct infiltration of proliferative neoplastic leukemic cells or their effect on non-neoplastic hematopoietic cells. In addition, they can be observed secondary to underlying anemia, thrombocytopenia, and neutropenia, which accompany AL.^{7,8} Compared to other body structures, the determination of oral manifestations is easier for patients and clinicians because of the visibility of the mouth. These occur mainly in soft tissues as, gingiva (the highest rate), lips, hard and/or soft palate, and tongue.^{9,10} Typical oral manifestations of AL are gingival enlargement, mucosal ulceration, spontaneous gingival bleeding, petechiae/ecchymosis, mucosal pallor, and bacterial, viral, and fungal infections.^{4,11-14} In the head and neck region, cervical and submandibular lymphadenopathy (LAP) may be observed as an extraoral finding with AL.¹⁵ In previous studies, the frequency of intraoral findings and head and neck LAP were reported in the range of 20–69%, in patients with AL.^{1,9,15,16}

The oral lesions encountered in routine dental practice are rarely associated with AL. The rarity of the situation poses a disadvantage as it pushes dentists into inertia. Delayed diagnosis of AL due to the failure to refer patients to a hematologist in cases of suspicious intraoral findings and head and neck LAP may affect the prognosis. This undesirable situation can lead to reduced lifespan and even fatal consequences. Additionally, delaying the treatment of

oral lesions of AL may increase the frequency and severity of related complications.¹⁷

Current papers regarding the oral manifestations of leukemia mainly include case reports or retrospective studies based on medical records. Individual cases may exhibit clinical findings that vary from patient to patient and depending on the type of leukemia, so they are far from drawing a comprehensive and general framework of the disease. It can be mentioned that the oral health of leukemia patients generally worsens in the advancing processes, depending on the chemotherapy and prognosis of the disease. The number of studies examining the pre-treatment oral health status of patients with newly diagnosed AL by clinical examination is limited. The lack of sufficient data on oral manifestations, which can be the first symptoms/signs of AL, is of vital importance for early diagnosis and affects the prognosis.

This study aimed to determine the frequency of the head and neck LAP and intraoral findings in patients with newly diagnosed AL. The relationship between these findings and AML/ALL, anemia, neutropenia, and thrombocytopenia were also investigated.

2 | SUBJECTS AND METHODS

A total of 53 patients (28 [52.8%] females, 25 [47.2%] males) who were newly diagnosed with AL according to WHO classification³ and whose medical treatment has not been started yet were included in the study. The age range of the patients was between 18 and 87 with a mean age of 46.

Personal information, the type of AL (AML/ALL), hematological findings (anemia, neutropenia, and thrombocytopenia), extraoral (head and neck LAP) and intraoral (non-dental and dental) clinical examination findings of the patient were recorded in a form prepared considering previous studies (Table 1).^{1,14}

An extraoral examination was performed to determine whether there was LAP in the head and neck region. During the extraoral examination, submandibular, neck, submental and parotid lymph nodes were examined by palpation for the presence of LAP. No radiological evaluation was performed to evaluate LAP. The intraoral examination was performed with the help of dental examination equipment visually. In intraoral examination, the presence of non-dental and dental findings was investigated. The non-dental findings investigated were gingival bleeding,

TABLE 1 The form in which patient information were recorded and the distribution of the patients, *n* (%) (*n* = 53).

Personal information		
1. Age: Min; 18, Max; 87, Mean; 46.0		
		<i>n</i> (%)
2. Sex	Female	28 (52.8)
	Male	25 (47.2)
3. Type of acute leukemia	AML	33 (62.3)
	ALL	20 (37.7)
4. Hematological findings		
4. 1. Anemia	Yes	46 (86.8)
	No	7 (13.2)
4. 2. Neutropenia	Yes	22 (41.5)
	No	31 (58.5)
4. 3. Thrombocytopenia	Yes	38 (71.7)
	No	4 (28.3)
5. LAP in the head and neck region	Yes	12 (22.6)
	No	41 (77.4)
5. 1. Submandibular	Yes	5 (9.4)
	No	48 (90.6)
5. 2. Neck	Yes	8 (15.1)
	No	45 (84.9)
5. 3. Submental	Yes	1 (1.9)
	No	52 (98.1)
5. 4. Parotid	Yes	0 (0)
	No	53 (100)
Intraoral findings	Yes	16 (30.2)
	No	37 (69.8)
6. Non-dental findings		
6. 1. Gingival bleeding	Yes	12 (22.6)
	No	41 (77.4)
6. 2. Gingival enlargement	Yes	6 (11.3)
	No	47 (88.7)
6. 3. Oral petechiae/ecchymosis	Yes	12 (22.6)
	No	41 (77.4)
6. 4. Oral ulceration	Yes	5 (9.4)
	No	48 (90.6)
6. 5. Oral viral infection	Yes	1 (1.9)
	No	52 (98.1)
6. 6. Oral fungal infection	Yes	1 (1.9)
	No	52 (98.1)
7. Dental findings		
7. 1. Dental abscess	Yes	2 (3.8)
	No	51 (96.2)
7. 2. Fistula	Yes	2 (3.8)
	No	51 (96.2)
7. 2. Fistula	Yes	0 (0)
	No	53 (100)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; LAP, lymphadenopathy.

Highlights of the Study

- The most common intraoral findings in acute leukemia (AL) are those associated with bleeding, such as gingival/mucosal bleeding and petechiae/ecchymosis.
- More intraoral findings (non-dental) are observed in acute myelogenous leukemia (AML) than in acute lymphocytic leukemia (ALL).
- It can be mentioned that dental findings do not increase with acute leukemia (AL).

progressive gingival enlargement of the interdental papillae as well as the marginal and attached gingival, oral petechiae/ecchymosis, oral ulceration, viral, and fungal infections. The ulcers were diagnosed by visual examination. Ulcers suspected to be viral or fungal in origin were confirmed by cytological tests from the medical records. The dental findings investigated were dental abscess and fistula.^{1,14} Personal information, the type of AL, and hematological findings were obtained from medical records. Within the scope of the study, one of two oral diagnosis and maxillofacial radiology specialists, who had at least 4 years of experience and were calibrated before starting the study, performed extraoral and intraoral clinical examinations of the patients. Examinations were performed in the patients' rooms of the hematology clinic under standardized conditions with a headlight, a mirror, and a dental explorer.¹⁴ The reason for examining the patient urgently in the hematology clinic instead of being referred to a dental clinic was because of the possible nature of the progressive process of AL. Additionally, there was a possibility that the hematological treatments being applied in the period until the patient's referral to a dental clinic could trigger new oral manifestations. Patients with suspected dental problems were referred to full-fledged dental centers for a detailed intraoral and radiographic evaluation after the medically stable condition in terms of leukemia.

2.1 | Statistical analysis

IBM-SPSS (International Business Machines-Software Package for Social Sciences) package program (version 25) (SPSS Inc., Chicago, Illinois, USA) was used to summarize and analyze the data. Frequency tables and descriptive statistics summarized the data of the patients. The necessary statistical analysis was made using the Chi-square (χ^2) test for evaluating the comparisons between two

TABLE 2 Distribution of the findings according to sex.

Variables		Female (n, %)	Male (n, %)	Total (n, %)
AML		14 (26.4)	19 (35.8)	33 (62.3)
ALL		14 (26.4)	6 (11.3)	20 (37.7)
Anemia		26 (49.1)	20 (37.7)	46 (86.8)
Neutropenia		10 (18.9)	12 (22.6)	22 (41.5)
Thrombocytopenia		23 (43.4)	15 (28.3)	38 (71.7)
Head and neck LAP	Submandibular LAP	3 (5.7)	2 (3.8)	5 (9.4)
	Neck LAP	6 (11.3)	2 (3.8)	8 (15.1)
	Submental LAP	1 (1.9)	0 (0.0)	1 (1.9)
	Parotid LAP	0 (0.0)	0 (0.0)	0 (0.0)
	Total	10 (18.9)	2 (3.8)	12 (22.6)
Intraoral finding	Gingival bleeding	5 (9.4)	7 (13.2)	12 (22.6)
	Gingival enlargement	3 (5.7)	3 (5.7)	6 (11.4)
	Oral petechiae/ecchymosis	5 (9.4)	7 (13.2)	12 (22.6)
	Oral ulceration	2 (3.8)	3 (5.7)	5 (9.4)
	Oral viral infection	1 (1.9)	0 (0.0)	1 (1.9)
	Oral fungal infection	0 (0.0)	1 (1.9)	1 (1.9)
	Dental abscess	1 (1.9)	1 (1.9)	2 (3.8)
	Fistula	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (13.2)	9 (17.0)	16 (30.2)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; LAP, lymphadenopathy.

variables. A less than .05 *p* value was taken as statistically significant.

3 | RESULTS

Of the 53 AL patients examined, 12 (22.6%) had 14 LAPs (1.2 per patient), 16 (30.2%) had 39 intraoral findings (2.4 per patient), and 6 (11.3%) had both LAP and intraoral findings (Table 1). The frequency of patients with LAP and intraoral findings were close to each other. However, unlike LAP, as multiple intraoral findings were observed in the same patient, the frequency of intraoral findings was twice that of LAP.

Anemia (86.8%) and thrombocytopenia (71.7%) were observed more frequently than neutropenia (41.5%). The neck LAP was the most common and parotid LAP was never observed. The most frequently observed intraoral findings were gingival bleeding and oral petechiae/ecchymosis, and the fistula was never been observed (Table 1).

The distribution of the hematological and clinical examination findings according to sex is given in Table 2.

Generally, the distribution of the findings was in balance between the sexes. However, in females, ALL and thrombocytopenia were slightly common and LAP was much more common.

The distribution of patients with LAP and intraoral findings according to the type of AL and hematological findings is given in Table 3.

According to the data in Table 3, approximately one-quarter of both AML and ALL patients had at least one LAP. Regionally, the most observed LAP in patients with ALL was the neck (20%), and the submandibular (12.1%) and neck (12.1%) in patients with AML. However, in terms of LAP, there was no statistically significant difference between AML and ALL patients ($p = .748 > .05$). While approximately half of the patients with AML had at least one intraoral finding, this rate was only 5% in patients with ALL. The difference between the frequency of intraoral findings of patients with AML and ALL was statistically significant ($p = .002 < .05$). The frequencies of intraoral findings with AML patients were higher for almost all parameters examined.

The frequencies of both intraoral findings and LAP were similar in patients with anemia (47.8%), neutropenia (45.5%), and thrombocytopenia (57.6%). However, albeit slightly, the intraoral findings were observed more frequently with thrombocytopenia and the LAP with neutropenia.

The mean age and the distribution of intraoral findings according to the sex, type of AL, and hematological findings of patients are given in Table 4. This table is based on the frequency of findings not patients.

TABLE 3 Distribution of patients with LAP and intraoral findings according to the type of AL and hematologic findings.

Variables	AML (n, %)	ALL (n, %)	Total (n, %)	Anemia (n, %)	Neutropenia (n, %)	Thrombocytopenia (n, %)
Absence of LAP	26 (78.8)	15 (75.0)	41 (77.4)	35 (76.1)	16 (72.7)	28 (73.7)
Submandibular LAP	4 (12.1)	1 (5.00)	5 (9.4)	5 (10.9)	5 (22.7)	4 (10.5)
Neck LAP	4 (12.1)	4 (20.0)	8 (15.0)	7 (15.2)	3 (13.6)	6 (15.8)
Submental LAP	1 (3.0)	0 (0.0)	1 (1.9)	1 (2.2)	0 (0.0)	1 (2.6)
Parotid LAP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Absence of intraoral finding	18 (54.5)	19 (95.0)	37 (69.8)	31 (67.4)	16 (72.7)	24 (63.2)
Gingival bleeding	11 (33.3)	1 (5.0)	12 (22.6)	11 (23.9)	3 (13.6)	10 (26.3)
Gingival enlargement	6 (18.2)	0 (0.0)	6 (11.3)	5 (10.9)	2 (9.1)	4 (10.5)
Oral petechiae/ecchymosis	11 (33.3)	1 (5.0)	12 (22.6)	11 (23.9)	4 (18.2)	10 (26.3)
Oral ulceration	5 (15.2)	0 (0.0)	5 (9.4)	5 (10.9)	3 (13.6)	3 (7.9)
Oral viral infection	1 (3.0)	0 (0.0)	1 (1.9)	1 (2.2)	0 (0.0)	1 (2.6)
Oral fungal infection	1 (3.0)	0 (0.0)	1 (1.9)	1 (2.2)	0 (0.0)	0 (0.0)
Dental abscess	2 (6.1)	0 (0.0)	2 (3.8)	2 (4.4)	2 (9.1)	2 (5.2)
Fistula	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AL, acute leukemia; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; LAP, lymphadenopathy.

TABLE 4 Mean age and distribution of the intraoral findings according to sex, type of AL, and hematological findings.

Variables		Non-dental finding (n, %)	Dental finding (n, %)	Total
Mean age		45.5	53.0	46.0
Sex	Female	7 (25.0)	1 (3.6)	11 (39.3)
	Male	9 (36.0)	1 (4.0)	12 (48.0)
Type of acute leukemia	AML	15 (45.5)	2 (6.1)	22 (66.7)
	ALL	1 (5.0)	0 (0.0)	1 (5.0)
Hematological findings	Anemia	15 (32.6)	2 (4.3)	22 (47.8)
	Neutropenia	6 (27.3)	2 (9.1)	10 (45.5)
	Thrombocytopenia	14 (36.8)	2 (5.3)	19 (57.6)

Abbreviations: AL, acute leukemia; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia.

For all parameters examined, non-dental findings were always the most frequently observed. According to Tables 3 and 4, the intraoral findings were observed in only one patient (5%) with ALL who had two findings and in 15 (45.5%) patients with AML with 22 findings. Dental findings were found only in two patients, one female and one male, both with AML and both with pancytopenia.

4 | DISCUSSION

Because of its typical oral manifestations, many specialists working in the oral cavity (e.g., dentistry) have studied AL. Dentists should be educated to be vigilant about the oral manifestations of leukemia because they should have comprehensive knowledge and awareness.¹⁸ In some cases, the

oral manifestations may be the initial symptoms/signs of undiagnosed AL, extensive knowledge about them can be vital. It has been claimed that dentists contribute to the diagnosis of AML in approximately 25% of patients.¹⁴

In this study, 22.6% of the patients had head and neck LAP and 30.2% had intraoral findings. The most observed LAP was in the neck region (15.1%), and the most observed intraoral findings were gingival bleeding and oral petechiae/ecchymosis (22.6%). Although no significant difference was observed between patients with AML and ALL in terms of LAP, the frequency of intraoral findings in patients with AML was much higher than in patients with ALL (45.5% > 5%). It can also be mentioned that anemia, neutropenia, or thrombocytopenia did not significantly affect the frequency of LAP and intraoral findings. The number of studies examining the head and neck LAP

in patients with AL is limited. Stafford et al. observed LAP in more than half of the patients with AL, especially in ALL type.⁴ Lynch et al., who investigated submandibular and neck LAP in patients with AL, reported the frequency as 44.4%.¹⁵ Hou et al., who examined patients with AL by dividing them into two types (ALL and AML), reported head and neck LAP in patients with ALL more than with AML (71.4% > 45%).⁹ There are many case reports in the literature that reported submandibular LAP^{6,11,19–23} and/or cervical LAP^{6,11,18,24–27} in the head and neck region in AL patients. The relatively lower frequency of LAP in this study compared to previous studies may be related to the inclusion of only newly diagnosed AL patients. In the literature, it is not clearly stated at what stage of the disease the LAP examination is performed on AL patients.

Studies conducted on this subject previously have reported similar results to those found in this study in terms of intraoral findings. The first studies reached by the authors of this study were conducted by Roath et al. (1964) and Lynch et al. (1967).^{15,16} Roath et al. observed intraoral findings in 19.5% of 580 patients with AL, while Lynch et al. in 58% of 58 patients, mostly with oral petechiae/ecchymosis (35.6%).^{15,16} In earlier studies, conducted between 1934 and 1957, which were not reached, but mentioned in Lynch's study, the frequency of oral manifestations (in most studies these were not fully defined) in patients with AL was reported between 24% and 80%.¹⁵ Takagi et al. reported gingival bleeding as the most common intraoral finding (50%) among 16 patients with AL.²⁸ Stafford et al. recorded oral findings in just over a quarter of patients with AL in the initial physical examination carried out, more commonly in the AML type.⁴ They reported gingival bleeding as the most common intraoral finding in both AML and ALL types.⁴ Hou et al. reported gingival bleeding was the most common intraoral finding in patients with AL (43.2% in AML and 28.6% in ALL).⁹ Oral ulceration, gingival enlargement, and petechiae were, respectively, less. Watson et al. reported that 30.8% of 263 newly diagnosed patients with AL who were examined clinically had at least one intraoral finding.¹ The most intraoral findings reported were gingival bleeding (29.6%) and petechiae (24.7%).¹ Additionally, the researchers noted that gingival enlargement was more common in patients with AML than in patients with ALL (%7.4 > %2.6).¹ Busjan et al., who examined 39 newly diagnosed AL patients clinically and compared their intraoral findings with the control group, reported that the frequency of oral mucosal lesions was 62% (most common hyperplasia) in the study group, and did not detect any mucosal lesions in the control group.¹⁴ They stated that intraoral findings were more frequent in patients with AML than in patients with ALL (69% > 46%).¹⁴ In a literature review in which 33 cases

of leukemia with intraoral manifestations were examined and 30 of them were AL patients, it was reported that AML was considerably higher than ALL (72.72% > 18.18%). They reported that oral findings were also observed in soft tissues rather than hard tissues (72.72% > 18.18%). The most common location of oral findings was reported as gingival tissue (63.63%). Dental mobility has been reported as the most common finding in patients with hard tissues affected.¹⁰ A poor periodontal health condition may develop in patients with leukemia, which is incompatible with existing dental plaque or oral hygiene. Therefore, it has been stated that findings such as gingival enlargement and bleeding may be related to leukemic infiltration or to the exaggerated periodontal inflammatory response in these patients.⁹ In this study, non-dental intraoral findings were observed in approximately one-third of all AL patients, in line with the findings of previous studies. Additionally, consistent with previous studies, the frequency of intraoral findings was higher in patients with AML compared to patients with ALL, and gingival bleeding and oral petechiae/ecchymosis were the most observed intraoral findings. Although gingival hyperplasia is considered almost pathognomonic for AL in the literature, it was observed only in 11.3% of patients with AL in this study, and all of them were patients with AML. The reason for the difference in the frequency of intraoral findings compared with previous studies may be due to the difference in the method. In many studies, not only newly diagnosed patients with AL were included. Additionally, instead of an oral clinical examination performed by a dentist, the intraoral findings' data were obtained from medical records that were recorded by medical doctors who do not routinely work in the oral cavity. The results of intraoral findings may not have been fully reflected in any previous studies due to the difference in the time of intraoral examination and the kind of specialist performing the procedure.

In patients with AL, early (in the newly diagnosed stage) intraoral findings may be associated with pancytopenia. In particular, petechiae, ecchymosis, and especially gingival bleeding, are findings associated with thrombocytopenia.^{9,15,18} Some researchers do not completely agree with this view. Firkin and Moore claimed that there was no definite correlation between the severity of thrombocytopenia and gingival bleeding and stated that other factors may play a role.²⁹ It has been reported that important additional factors such as defects in platelets or qualitative differences in platelet function, abnormalities in coagulation, hypofibrinogenemia, deficiency in coagulation factors, and increased fibrinolytic activity can trigger bleeding.^{28,30–32} In the literature review of Quispe et al., in which they reviewed the case reports of leukemia patients with oral manifestations, anemia

was the most common (63.63%), while thrombocytopenia was the second (59.09%).¹⁰ In this study, gingival bleeding and oral petechiae/ecchymosis associated with thrombocytopenia and consequent bleeding were the most frequently observed intraoral findings.

Among studies investigating oral manifestations in patients with AL, the number of studies that include dental (odontogenic) examination findings was rare. Watson et al. reported at least one or more clinical dental findings or symptoms in more than 40% of patients with AL.¹ They examined dental abscess, dental pain, tooth percussion sensitivity, tooth mobility, visible caries, poor oral hygiene, and third-molar-related issues.¹ Busjan et al. reported a high caries prevalence and increased periodontal inflammation in patients with AL, particularly in patients with AML.¹⁴ In this study, attention was paid to the limited dental findings that can only be investigated by visual clinical examination. Probably because of this limitation, dental findings were observed only in two patients. This can be interpreted as no specific dental disease accompanying AL. Keeping the scope of dental findings wide without a control group of healthy individuals, the findings observed in the general population can be presented as if they are specific to AL.

5 | CONCLUSION

The findings of this study showed that approximately one-third of newly diagnosed AL patients had at least one intraoral finding, particularly associated with bleeding dysfunction. These intraoral findings were most commonly observed in patients with AML. LAPs were rare and they did not show a tendency among the AL types. It cannot be said that any of the anemia, neutropenia and thrombocytopenia observed in AL patients are more associated with intraoral findings and LAP than the others. Dental findings were found very rare at a level that can lead to the judgment that AL did have not any dental component. The high rate of intraoral findings imposes an important role on dentists in the early diagnosis of AL.

AUTHOR CONTRIBUTIONS

Umut Pamukcu, Ilkay Peker, Mehmet Sinan Dal, and Fevzi Altuntas designed the study. Umut Pamukcu, Ilkay Peker, Samet Yaman, Burcu Aslan Candir, Ersin Bozan, and Sema Secilmis collected the data. Sibel Acik Kemaloglu did the statistical analysis of the data. Umut Pamukcu wrote the manuscript. Ilkay Peker, Mehmet Sinan Dal, and Fevzi Altuntas reviewed and edited the manuscript for intellectual content and provided critical comments. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

The Clinical Research Ethics Committee of XXX Oncology Training and Research Hospital approved the ethical approval of the study (Approval number: 2021-11/1482). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from participants (or their parent/legal guardian/next of kin) who participated in the study.

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