Original Article

Is Ruxolitinib an Effective and Safe Therapy for Chronic Myeloproliferative Diseases?

Ruksolitinib Kronik Miyeloproliferatif Hastalık için Etkili ve Güvenli Bir Tedavi mi?

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ABSTRACT

Introduction: Polycythemia vera (PSV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) are BCR/ABL negative chronic myeloproliferative neoplasms (CMPNs). As a result of abnormal clonal proliferation of hematopoietic cells, these disorders have a higher risk of thrombosis, bleeding, leukemic transformation, and worsening in quality of life. While stem cell transplantation is the sole curative option for CMPNs, symptomatic therapies gain importance. The purpose of this study is to assess the results of patients with CMPNs treated with ruxolitinib at our center.

Methods: The data from eighteen patients (six patients with PSV and twelve patients with PMF) who were treated with ruxolitinib at our center between January 2013 and January 2022 were analyzed in this retrospective cohort study.

Results: Six PSV patients who received ruxolitinib were included in the study. Three patients with splenomegaly previous to ruxolitinib, had a response of spleen volume, median of 6 months. There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment.

Twelve patients with PMF used ruxolitinib were included in the study. Spleen volume response was observed in six patients (50%) at a median follow-up of 12 months, while symptomatic response was observed in nine patients (75%) during a median of 15.5 months of ruxolitinib treatment. Any thrombolytic or cardiovascular complications were observed.

Discussion and Conclusion: Ruxolitinib is an appropriate and safe treatment option for patients who are not candidates for hematopoietic stem cell transplantation.

Keywords: ruxolitinib, myelofibrosis, Polycythemia vera, JAK2 V617F, spleen

ÖZET

Giriş ve Amaç: Polisitemi vera (PSV), esansiyel trombositoz (ET) ve primer miyelofibroz (PMF), BCR/ABL negatif olan kronik miyeloproliferatif hastalıklardır (KMPH). Bu hastalıklarda hematopoietik hücrelerde anormal klonal proliferasyon sonucu artmış tromboz, kanama, lösemik transformasyon riski yanı sıra hayat kalitesinde bozulmalar görülmektedir. Hastalıkların tedavisinde kök hücre nakli tek küratif seçenek iken semptomatik tedaviler ön plana çıkmaktadır. Bu çalışmada amaç, merkezimizde ruksolitinib ile tedavi edilen KMPH hastalarının sonuçlarını değerlendirmektir.

Yöntem ve Gereçler: Bu retrospektif kohort çalışmada Ocak 2013 ile Ocak 2022 tarihleri arasında merkezimizde ruksolitinib ile tedavi edilen 18 hastanın (altı hasta PSV ve on iki hasta PMF) verileri analiz edildi.

Bulgular: Ruksolitinib alan altı PSV hastası çalışmaya alındı. Ruksolitinib öncesinde splenomegalisi olan üç hastada, ortanca 6 aylık tedavi süresince dalak hacmi yanıtı gözlendi. Ortanca 6 aylık (2-52

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aralığında) ruksolitinib tedavisi boyunca hematolojik veya hematolojik olmayan yan etkiler, trombolitik veya kardiyovasküler komplikasyonlar veya lösemik transformasyon görülmedi.
PMF tanısı ile ruksolitinib kullanan on iki hasta çalışmaya dahil edildi. Altı hastada (%50) ortanca 12 aylık takipte dalak hacmi yanıtı gözlenirken, dokuz hastada (%75) medyan 15,5 aylık ruksolitinib tedavisi sırasında semptomatik yanıt alındığı gözlendi. Trombolitik veya kardiyovasküler komplikasyon gözlenmedi.
Tartışma ve Sonuç: Hematopoietik kök hücre nakli için aday olmayan hastalarda ruksolitinib uygun ve güvenli bir tedavi seçeneğidir.

Anahtar Kelimeler: ruksolitinib, myelofibrozis, Polisitemia vera, JAK2 V617F, dalak

Introduction

Polycythemia vera (PSV), essential thrombocytosis (ET), and primer myelofibrosis (PMF) are chronic myeloproliferative diseases (MPN) that are BCR/ABL negative. Polycythemia vera is a BCR/ABL negative chronic MPN characterized by abnormal clonal proliferation of hematopoietic cells, which results in elevated peripheral blood cells, increased thrombotic and hemorrhagic events, and the possibility of disease progression to PMF or acute myeloid leukemia (AML) [1]. Hydroxyurea (HU) is the first line of cytoreductive treatment [2]. If a patient is intolerant or non-responsive to HU and experiences an unexpected side effect, ruxolitinib is considered a second-line treatment [2]. The RESPONSE and RESPONSE-2 clinical trials demonstrated ruxolitinib's safety and efficacy in PSV patients [3, 4].

Primary myelofibrosis is a type of MPN characterized by bone marrow fibrosis, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Among the MPNs, PMF has the worst prognosis, with patients at risk of early death from disease progression, leukemic transformation, thrombohemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Agents such as HU and ruxolitinib are used to treat symptoms and splenomegaly in patients who are not candidates for hematopoietic stem cell transplantation (HSCT). The first-line treatment for MF-related splenomegaly is HU [5]. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials demonstrated the safety and efficacy of ruxolitinib.

Ruxolitinib is recommended as a second-line treatment for PSV and PMF at our institution. We aimed to evaluate the characteristics and outcomes of MPN patients treated with ruxolitinib at our institution.

Methods

This retrospective cohort study examined data from patients with PSV and PMF treated at our center between January 2013 and January 2022, were analyzed. We evaluated the eighteen patients (six with PSV and twelve with PMF) who were treated with ruxolitinib. Manual file records and electronic medical record systems were used to obtain clinical information from patients. The demographics, comorbidities, disease diagnosis date, disease type, disease risk groups, therapy and response, last control date, and survival status of all patients were documented. The 2016 WHO classification was used for diagnosis [6].

The local human research ethics committee approved this study. All procedures performed in studies involving human participants were under the national research committee’s ethicalstandards and with the 1964 Helsinki Declaration and its later amendments or comparableethical standards. The study was carried out with the permission of the Ethics Committee of Ankara Onology hospital (24.08.2022 /Decision number: 2022.08/1981).

Table 1. Characteristics of patients with PSV who were treated with ruxolitinib

Parameters	N =6, (%)
Age, median (range min-max), years	63 (59-72)
Gender (M/F)	2 (33.3) / 4 (66.7)
JAK2 V617F, allele burden, median (range min-max), %	35 (20-67)
Splenomegaly	3 (50)
Duration between the initiation of ruxolitinib treatment and the diagnosis of the disease, median (min-max), months	30.5 (8-74)
Duration of ruxolitinib therapy, median (min-max), months	6 (2-52)
Disease duration, median (min-max), months	55 (10-82)

PSV; polycythemia vera, M; male, F; female

Statistical Analysis

The SPSS software (Version 25.0; Armonk, NY: IBM Corp.) was used for statistical analysis. The numerical variables were presented as medians (min-max), while the categorical variables were presented as ratios. Disease duration was calculated as the time defined as the period between the date of PSV or PMF diagnosis and the date of last follow-up or death from any cause.

Results

Polycythemia vera

Between January 2000 and January 2022, 80 PSV patients were diagnosed, but only six of them received ruxolitinib treatment and were included in the study. The average age of the patients was 63 years (range 59-73 years). JAK2 V617F and cytogenetic abnormalities were tested in all patients. The JAK2 V617F mutation was found in all the patients, and the median allele load was 37%. (range 20-67%). They didn't have any cytogenetic abnormalities or extra mutations like calreticulin (CALR) or myeloproliferative leukemia (MPL).

In the bone marrow examination, four patients (66%) had grade 2/3 fibrosis. Half of the patients had splenomegaly at the time of presentation. Table 1 summarizes the characteristics of PSV patients treated with ruxolitinib.

In the six patients treated with ruxolitinib as a second-line treatment, the median duration was 30.5 (range 8-74) months between starting ruxolitinib and disease diagnosis. The reasons for changing to ruxolitinib as a second-line treatment were oral ulcers (two patients) after HU, symptomatic splenomegaly (two patients), and HU-intolerant patients (two patients).

There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment. After a median of 6 months, three patients with splenomegaly prior to ruxolitinib had normal spleen volume (range 3-12 months). Only one patient had transformed myelofibrosis after 14 months of ruxolitinib treatment.

Myelofibrosis

Between January 2000 and January 2022, twelve patients were diagnosed with PMF and treated with ruxolitinib. The patients' median age was 68 years (range 25-80 years), with eight (66.7%) females. All cases were evaluated for JAK2 V617F, CALR, and MPL mutations as well as cytogenetic abnormalities.

Table 2. Characteristics of patients with PMF who were treated with ruxolitinib

Parameters	N = 12, (%)
Age, median (range min-max), years	68 (25-80)
Gender (M/F)	4 (33.3) / 8 (66.7)
Genetic mutations, JAK2 V617F mutation CALR mutation MPL mutation Triple negative	 8 (66.7) 1 (8.3) 0 2 (16.7)
JAK2 V617F, allele burden, median (range min-max), %	80 (22-91)
Bone marrow fibrosis, Grade 2/3 Grade 3/3	 10 (83.3) 2 (16.7)
Risk stratification, median (min-max) MIPSS-70 DIPSS-plus	 5 (2-7) 1 (0-1)
Splenomegaly	12 (100)
Duration between starting ruxolitinib and disease diagnosis, median (min-max), months	16.5 (8-74)
Duration of ruxolitinib therapy, median (min-max), months	12.5 (5-60)
Disease duration, median (min-max), months	48.5 (7-214)

PMF; primary myelofibrosis, M; male, F; female, CALR; Calreticulin, MPL; myeloproliferative leukemia

The JAK2 V617F mutation was found in eight patients (66.7%), with a median allele load of 80% (range 22-91%). Two (16.7%) of the patients had triple-negative disease. None of them had any cytogenetic abnormalities. Technical difficulties limited the evaluation of high molecular risk (HMR) mutations. In risk stratification, the median MIPSS-70 was 5 (2-7), while the DIPSS-plus was 1 (0-1). Four patients experienced ET and one had PSV before being diagnosed with PML. At the time of presentation, all the patients had splenomegaly. Table 2 summarizes the characteristics of PMF patients treated with ruxolitinib.

Because of HU resistance, nine (75%) patients received ruxolitinib as a second-line treatment. Ruxolitinib was used as first-line therapy in three patients. The median time between initiating ruxolitinib and disease diagnosis was 16.5 (range 8-74) months. Six patients (50%) had a response to decreased spleen volume (median 12 (6-24) months) and nine patients (75%) had a symptomatic response during a median of 15.5 (range 5-60) months of ruxolitinib treatment.

Three patients (25%) discontinued treatment; one suffered skin ulcers, one had disease progression with increased spleen volume, and one had AML transformation. One patient had thrombocytopenia during a median of 12.5 (range 5-60) months of ruxolitinib treatment, which was resolved by lowering the ruxolitinib dose. There were no thrombolytic or cardiovascular complications to report. Only one female patient transformed AML after 13 months of treatment with ruxolitinib. The patient had a long disease

duration (191 months), post-ET PMF, grade 2/3 fibrosis in the bone marrow, a negative JAK2 mutation, and a positive CALR mutation. Two patients died during therapy from unrelated causes of the disease.

Discussion

Polycythemia vera (PSV) is a condition characterized by clonal proliferation of hematopoietic cells, which results in elevated red blood cells, increased thrombotic events, and can progress to fibrosis or leukemia. The treatment's goal is to avoid thrombotic events and fibrotic/leukemic change while also improving quality of life. Ruxolitinib is used as a second-line treatment in HU-intolerant or nonresponder patients. Ruxolitinib was found to be safe and effective in PSV patients with and without splenomegaly in the RESPONSE and RESPONSE 2 clinical trials.

In our study, six patients with PSV who were intolerant or refractory to HU were treated with ruxolitinib. Three patients who had splenomegaly before ruxolitinib had normal spleen volume after a median of 6 months (range 3-12 months).

The RESPONSE study compared ruxolitinib to the best available treatment (BAT) in HU refractor/intolerant patients [3]. The trial results showed that ruxolitinib was superior to BAT in both hematocrit level control and lowering spleen volume [3]. Hematological and non-hematological adverse effects are comparable between the two arms of the trial; however, thrombotic events are more prevalent in the BAT arm [3]. Our patients with or without splenomegaly, received well-tolerated ruxolitinib treatment. During the median of 5.5 months (range 2-52 months) of ruxolitinib treatments, we did not observe any hematological or non-hematological side effects, thrombolytic and cardiovascular complications, or leukemic transformation. Only one female patient transformed myelofibrosis after 14 months of treatment with ruxolitinib. The patient had a long duration of disease (80 months) and splenomegaly, grade ⅔ fibrosis in the bone marrow, and a high JAK2 allele load.

Splenomegaly is found in 30-35% of PSV patients at the time of diagnosis, and it is considered to be associated with progressive disease [2]. These splenomegaly patients are more prone to develop myelofibrosis and AML [2]. Grade 2-3/3 bone marrow fibrosis is reported in 20-51% of PSV patients [7, 8], and these patients are more likely to progress to myelofibrosis [9]. Tefferi et al. demonstrated that the persistence of leukocytosis, fibrosis in the bone marrow at the time of diagnosis, and more than 50% JAK2 allele burden increase the probability of myelofibrosis transformation [10].

The RELIEF study demonstrated that ruxolitinib therapy reduced symptoms in PSV patients [11]. One of our study's shortcomings was that we did not evaluate patients' symptoms. The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. A meta-analysis reported that patients on ruxolitinib therapy had fewer thrombotic events, but the difference was not statistically significant [12].

Myelofibrosis is a form of MPN characterized by fibrosis of the bone marrow, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Patients with PMF suffer an increased risk of death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials established the safety and efficacy of ruxolitinib in patients with PMF [13, 14].

In our study, twelve patients were diagnosed with PMF and treated with ruxolitinib (nine patients as second-line and three patients as first-line). In the COMFORT-I trial, ruxolitinib was found to be more effective than placebo at 24 weeks in reducing spleen volume and improving the overall symptom

score [13]. In the COMFORT-2 trial, ruxolitinib was compared to the best available therapy in high-risk PMF patients; spleen volume reduction was better in the ruxolitinib arm (28% vs. 5%) [14]. During a median of 15.5 months of ruxolitinib treatment, 50% of our patients had a response to decreasing spleen volume, and 75% had a clinical response. Three patients (25%) discontinued treatment; two developed skin ulcers; and one patient had disease progression with increased spleen volume.

The JAK2 V617F mutation was reported in more than half of PMF patients, which is similar to our findings [15]. Another study from our center showed that 25% of all PMF patients had JAK2 mutations [16]. Triple-negative PMF is detected in 8-10% of patients [15], while in our study, we found triple-negative PMF in 16.7% of patients, and we only included patients receiving ruxolitinib. If we investigate all PMF patients, the percentage may be similar to the literature.

The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. AML transformation occurs in 3.9% of PMF patients, with the majority of them previously treated with alkylating drugs [17]. High levels of circulating blast (>3%) and thrombocytopenia (<100.000/mm^3) are independent risk factors for AML transformation [18]. In our study, one patient (8.3%) developed AML and was treated with HU before ruxolitinib; she had thrombocytopenia but no more than 3% circulating blast.

Therefore, PSV and PMF are diseases that can be treated with ruxolitinib. It is highly effective in relieving symptoms and reducing splenomegaly. In this study, we observed that ruxolitinib was well-tolerated, effective, and had few side effects. The effect of ruxolitinib on AML transformation and thromboembolic events is unclear; a larger series is required. For patients who are not candidates for HSCT, ruxolitinib is an appropriate and safe treatment option.

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Original Article

Is The COVID-19 Pandemic Reason, Shortage Result? A Survey Study on Drug Shortages in Turkish Oncology Clinics

COVID-19 Pandemi Nedeni, Kıtlık Sonucu mu? Türk Onkoloji Kliniklerinde İlaç Eksikliği Üzerine Bir Araştırma Çalışması

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ABSTRACT

Aim: The rapid development of the drug industry led to a great spectrum of medical treatment, especially in oncology practice. The prescribed drug alternations increased three times in the United States. Also, the increased drug numbers led to drug shortages, which doubled during this period in the oncology era. In this study, we try to evaluate the oncology clinics' drug supply last year in the eyes of oncology practitioners

Methods: We conducted an online questionnaire via Google Forms on the drug shortages which are faced last year by oncologists in Turkey. Our study is a cross-sectional study.The SPSS 25 software was used for statistical analysis

Results: Eighty-nine percent of the participants declared they had a drug shortage last year. The most affected drug groups were chemotherapeutics (61,4%), biologic agents (anti-VEGF, anti-EGFR agents, etc.) (56,8%), immunologic drugs (available anti-PD1 drugs) (54,5%), and supportive medicines (Folinic acid, GCSF, etc.) (42%). 61 percent of the oncologists referred their patients to other clinics to get over the drug shortage. The most common reasons were supply problems (70%), drug company-related concerns due to exchange rates (68%), hospital budget problems (48%), and bureaucratic procedures (47%). There was a significant difference between drug shortage and participants' hospitals. Also, the shortage has significantly lasted longer in university hospitals.

Conclusion: Our study showed an extensive drug shortage in oncology clinics last year independent of drug types. University hospitals had reported worse results compared with other organizations. There is an urgent need for further evaluation of drug shortages and the availability of oncologic drugs and the prognostic effect of this phenomenon..

Key words: COVID-19, Pandemic, Drug shortages, Oncology

ÖZET

Amaç: İlaç endüstrisinin hızlı gelişimi, özellikle onkoloji pratiğinde geniş bir tıbbi tedavi yelpazesine yol açmıştır. Amerika Birleşik Devletleri'nde 2005 ile 2011 yılları arasında reçete edilen ilaç değişimleri üç kat arttı. Ayrıca artan ilaç sayıları, onkoloji çağında bu dönemde ikiye katlanan ilaç kıtlığına yol açtı. Bu çalışmada onkoloji pratisyenlerinin gözünden onkoloji kliniklerinin geçen yılki ilaç arzını değerlendirmeye çalıştık.

Yöntemler: Türkiye'de onkologların geçtiğimiz yıl yaşadığı ilaç kıtlığı ile ilgili Google Forms üzerinden online bir anket gerçekleştirdik. Çalışmamız kesitsel bir çalışmadır. İstatistiksel analiz için SPSS 25 programı kullanıldı. Tanımlayıcı istatistikler frekans dağılımı olarak sunuldu Bu çalışmada, iki yönlü istatistiksel analizler yapıldı ve $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Katılımcıların yüzde seksen dokuzu geçen yıl ilaç sıkıntısı yaşadıklarını beyan ettiler. En çok etkilenen ilaç grupları kemoterapötikler (%61,4), biyolojik ajanlar (%56,8), immünolojik ilaçlar (%54,5) ve destekleyici ilaçlar (%42) idi. Onkologların yüzde 61'i hastalarını ilaç sıkıntısından kurtulmak için

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başka kliniklere yönlendiriyor. En sık nedenler tedarik sorunu (%70), döviz kurundan kaynaklanan ilaç firmaları kaygısı (%68), hastane bütçe sorunları (%48) ve bürokratik işlemler (%47) idi. İlaç sıkıntısı ile katılımcıların hastaneleri arasında anlamlı bir fark vardı. Ayrıca, üniversite hastanelerinde açık önemli ölçüde daha uzun sürmüştür

Sonuç: Çalışmamız, ilaç türlerinden bağımsız olarak geçen yıl onkoloji kliniklerinde yaygın bir ilaç sıkıntısı olduğunu gösterdi. Üniversite hastaneleri, diğer kuruluşlara kıyasla daha kötü sonuçlar bildirmişti. İlaç kıtlığının ve onkolojik ilaçların mevcudiyetinin ve bu fenomenin prognostik etkisinin daha fazla değerlendirilmesine acil bir ihtiyaç vardır.

Anahtar kelimeler: COVID-19, Pandemi, İlaç kıtlığı, Onkoloji

Introduction

The rapid development of the drug industry led to a great spectrum of medical treatment, especially in oncology practice. The prescribed drug alternations increased three-fold between 2005 and 2011 in the United States. Also, the increased drug numbers led to drug shortages, which doubled during this period in the oncology era [1]. The shortages in oncology practice may be related to serious damage to patient survival altered dosing, treatment gaps, and inferior protocols. Specific precautions were exercised in this era [2]. Although some studies tried to elucidate this area, the consequences of drug shortages are still inconclusive. Most of the studies are based on specific drugs or hospitals. Some studies tried to explain the situation with surveys [3,4].

After the start of the COVID-19 pandemic, multiple problems occurred in cancer treatment, consisting of increased workload, decreased supply of medical professionals, and materials with increased patient problems. Multiple studies showed the changes in oncology practice during the time of the COVID-19 pandemic. Increased workload, and decreased patient adherence due to COVID-19 fear and social regulations. [5,8]. The economic problems of countries and states are also evaluated during the pandemic and may be one of the problems leading to drug shortages [9]. During the pandemic period, drug shortages are foreseen with the overwhelming healthcare system. The breakdown of the supply-demand chain is speculated to have a great impact on medical drugs [10].

In this study, we try to evaluate the oncology clinics' drug supply last year in from the perspective of oncology practitioners.

Materials and Methods

We conducted an online questionnaire via Google Forms on the drug shortages which are faced last year by oncologists in Turkey. Of more than seven hundred, 95 oncologists answered the survey. Two follow-up emails and reminders were sent in 2 weeks to increase the number of responders and the study was completed. The survey was voluntary.

The survey had 3 questions about the position, experience, and work conditions of the participants. The questionnaire was consisting of fifteen questions to determine drug types had a shortage, time, reasons, solutions, and the most affected diagnosis in terms of effect and complications. Also, the difference between current optimal medical treatments and available practice was questioned. (see Supplemental Appendix 1 in the online version)

The SPSS 25 software was used for statistical analysis. Descriptive statistics were presented as frequency distribution and percentage. The chi-square or Fisher’s Exact tests were used to compare independent categorical variables. In this study, two-way statistical analyses were performed, and $p<0.05$ was considered statistically significant.

Table 1: The features of the study population

Age (years)	30-40	41-50	51-60	61-70	
n (%)	39 (41,1)	34 (35,8)	17 (17,9)	5 (5,3)	
Experience(years)	5 or less	6-10	11-20	21-30	
n (%)	25 (26,3)	26 (27,4)	27 (28,4)	17 (17,9)	
Affiliation	State H.	University H.	E & R Hospital	Private H.	City H.
n (%)	3 (3,2)	39 (41,1)	19 (20)	27 (28,4)	7 (7,4)
Academic Position	Fellow	Specialist/Assistant Professor	Associated Professor	Professor	
n (%)	19 (20)	21 (22,1)	28 (29,5)	27 (28,4)	

H.: Hospital; E&R: Education and Research;

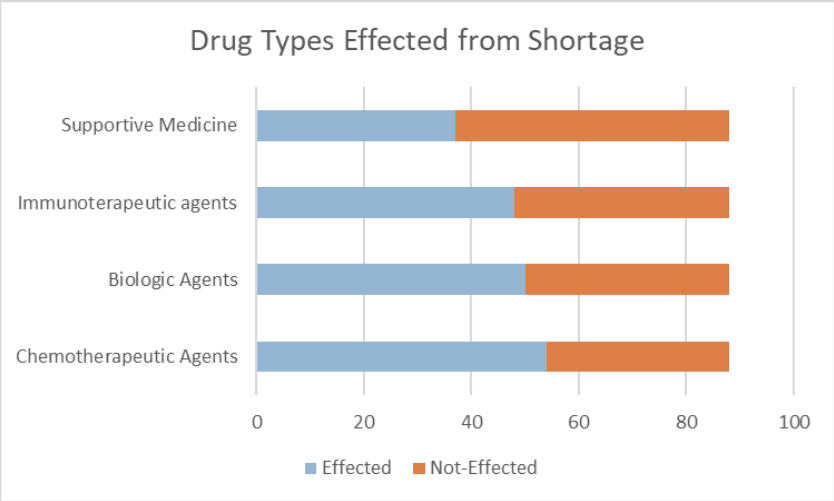

Figure-1: The drug types had shortage according to oncologists

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations. (Date & Number:01.07.2022 & 2022/8). An informed consent form was obtained from all patients.

Results

Ninety-five oncologists were included in the study. Forty-one percent of the participants were aged between 30 and 40. The three groups were stratified by experience, had roughly the same number of participants, and did not differ significantly. (5 or less; 6 to 10 and 11-20 years) The most frequent academic positions were associated professors and professors with nearly thirty percent. Approximately forty percent of the oncologists were working in a university followed by private hospitals with 28 percent. (Table-1)

Eighty-nine percent of the participants declared they had a drug shortage last year. The most affected drug groups were chemotherapeutics (61,4%), biologic agents (anti-VEGF, anti-EGFR agents, etc.) (56,8%), immunologic drugs (available anti-PD1 drugs) (54,5%), and supportive medicines (Folinic acid, GCSF, etc.) (42%). Sixty-one percent of the oncologists referred their patients to other clinics to get over the drug

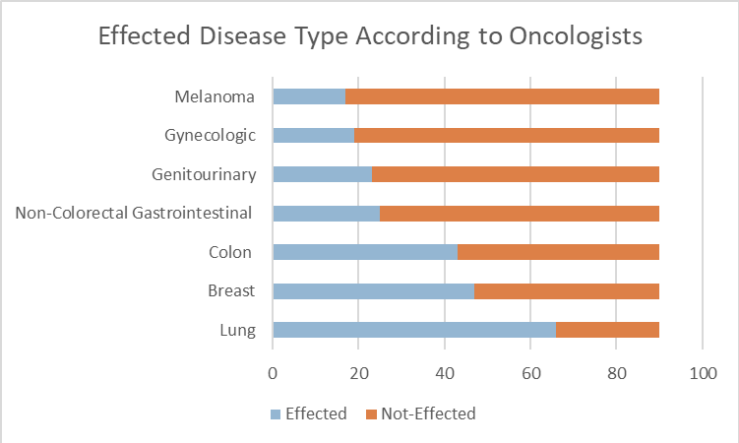

Figure-2: Most affected diseases from shortage according to oncologists

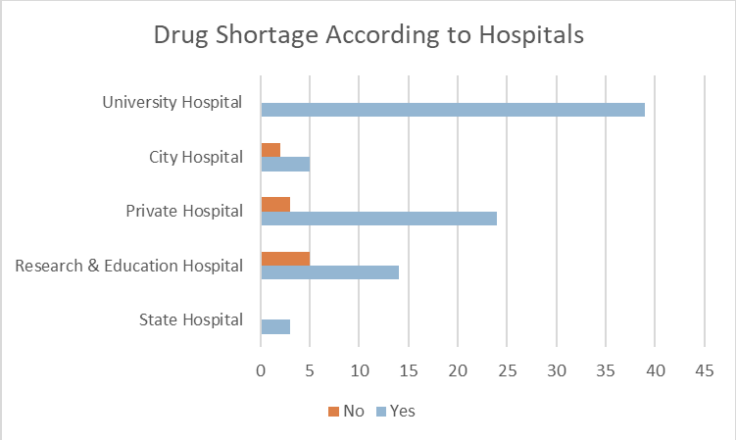

Figure-3: Drug shortage rates according to hospital types

shortage. (Figure-1) Nearly half of the participants selected alternative treatment options and 17 percent had to choose inferior treatments. Eighty-three percent of the study population declared the drug shortage lasted three months. The most common reasons were supply problems (70%), drug company-related concerns due to exchange rates (68%), hospital budget problems (48%), and bureaucratic procedures (47%).

Two-thirds of the oncologists thought that the survival of the patients was affected negatively, and nearly fifty percent were concerned about increased complication rates. Leading patient groups affected by shortages were lung, breast, and colon cancer patients respectively. (73,3%; 52,2%; 47,8%)

Ninety percent of the participants did not think current optimal practice fit their daily practice and over ninety percent thought that most of the incompetence was in lung cancer. Seventy-five percent of the oncologists foreseen the difference in optimal treatment and daily practice in Turkey will increase.

There was a significant difference between drug shortage and participants' hospitals. (p=0,047) (Figure-2) Also the shortage has significantly lasted longer in university hospitals. (p= 0,013) (Figure-3)

Discussion

This study showed there was a high-rate drug shortage in Turkey in oncology practice last year. Although the most affected drug types were chemotherapeutic agents, biologic and immunotherapy drugs have high rates of shortages. Our study represented nearly ten percent of the Turkish Oncology Society. Also, most of the participants had an academic

degree which may be related to control of the department in terms of drug recipients of the unit.

Turkish oncology association tried to take preventive causations via publishing guidelines like many other associations. No specific precautions were exercised for preventing drug shortages during this period by authorities [11]. Some studies showed minimal effect on outcomes of chemo-therapeutic agents' shortages. Most of the drugs that had shortages in studies were Fluorouracil, doxorubicin, and cytarabine [3,12]. However, it is stated that there may be a shortage of cisplatin and carboplatin recently. For this, it is emphasized that medical oncologists should be in constant communication globally and the importance of early detection [13]. In another study, an increase occurs in the shortage of sedative analgesics during the covid-19 pandemic. This phenomenon may also influence the cancer treatment especially in ICUs and operation rooms [14]. Although tocilizumab was used in a case study to prevent the limitations of mechanical ventilators and other drugs used in the treatment of covid, it caused an increase in the drug limitation in rheumatoid arthritis [15]. Although we did not perform a drug specification, it is possible to have the same drug shortages in Turkey. was limited data on shortages of biological and immunotherapy drugs used in oncology. We only know about There the BCG shortage in bladder cancer in the COVID-19 Era [16]. Although a shortage cannot be determined for these groups of drugs, most of the immuno-therapeutic agents have limitations in several countries due to their costs including Turkey. Prior studies evaluated nationwide or hospital-based drug shortages. Reasons and potential solutions for unavailability of agents evaluated [3,17]. On the other side, some studies evaluate the effect of drug shortages on patients. The alternative strategies were discussed with patients by oncologists, physicians, and pharmacists [18]. Although we don't know the attitudes of patient relations in our study, high rates of referral of patients to other hospitals may be related to informing patients about drug shortages.

Our study showed that oncologists are concerned about increased toxicity with unfamiliar drug utility or alternative treatment. Also, a study showed increased toxicity of alternative drug combinations due to altered doses or lack of knowledge about unfamiliar drugs [12]. The drug shortages are affecting both oncology and hematology as well as the adult and pediatric population [19,20]. Our study only showed results of adult solid organ malignities as Turkish oncologists are mainly responsible for treating this population excluding a few multi-disciplinary facilities. Also, a few centers that are treating oncology patients, including pulmonary medicine and gynecology clinics cannot be assessed by our survey study. This group of practitioners is very small and doesn't have the permission of using several targeted therapies which makes their evaluation inconclusive.

Different from other studies we also named another issue, which originated from different hospital types. University hospitals in Turkey are known to have low funds compared to private and ministry of Health-funded hospitals. The possible results of long and deep drug shortages in university hospitals may be related to this reason. To our knowledge, this is the first study evaluating the drug shortage in the oncology area in the pandemic era.

The data in this study are presented based on the statements of the oncologists participating in the study and are not official data. Inclusion of the subjective opinions of the authors is one of the limitations of our study. Although the study was a cross-sectional survey yet it could only evaluate the last year which was the second year of the pandemic. In addition, the

lack of any previous survey or analytical study evaluating the oncological drug shortage in Turkey was the reason why our study could not compare with the shortage situation in the pre-pandemic period. The COVID-19 pandemic had multiple effects on the Turkish health care system, especially via economic end-points. We found high rates of drug shortage by survey, but this might be related to low survey response rates of physicians who had not faced drug shortages.

Our study showed an extensive drug shortage of over fifty percent in oncology clinics last year independent of drug types. University hospitals had reported worse results compared with other organizations and may need more attention for drug supply. There is an urgent need for further evaluation of drug shortages and the availability of oncologic drugs and the prognostic effect of this phenomenon. The oncologists think the shortage of oncologic drugs will be a long lasting problem and optimal treatment may not be delivered in near future in Turkey.

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Original Article

The Prognostic Value of the Preoperative Geriatric Nutritional Risk Index in Elderly Colon Cancer Patients Underwent Curative Resection

Küratif Rezeksiyon Yapılan Yaşlı Kolon Kanseri Hastalarında Preoperatif Geriatrik Beslenme Risk Indeksinin Prognostik Değeri

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ABSTRACT

Introduction: The aim of this retrospective study was to assess the prognostic significance of the geriatric nutritional risk index (GNRI) for elderly patients diagnosed with early-stage colon cancer.

Materials and Methods: Medical records of 114 elderly patients diagnosed with colon cancer who underwent curative surgery and received chemotherapy were analyzed. The calculation of the GNRI was derived from the measurement of serum albumin levels and the assessment of body weight. Patients were divided into two nutritional risk categories: low-GNRI (GNRI: <98), and high-GNRI (GNRI: ≥98) and compared.

Results: The 5-year overall survival (OS) rate of the low-GNRI group was significantly lower than that of the high-GNRI group (65.7% vs. 91.1%, p= 0.002). There was also a statistically significant difference in the 5-year recurrence-free survival (RFS) rate of the two groups (66.7% vs. 90.8%, p <0.001). The multivariate Cox regression analysis identified tumor sidedness (p= 0.038) and GNRI (p = 0.042) as independent prognostic factors for only OS.

Conclusion: The GNRI is an easily applicable and valuable prognostic factor for OS in elderly patients diagnosed with early-stage colon cancer. The current investigation indicates that a low-GNRI was correlated with poor OS.

Key words: Colon cancer, elderly, nutrition, prognosis

ÖZET

Giriş: Bu çalışmanın amacı, erken evre kolon kanseri tanısı almış yaşlı hastalarda geriatrik beslenme risk indeksinin (GNRI) prognostik önemini retrospektif olarak değerlendirmektir.

Gereç ve Yöntem: Küratif cerrahi uygulanan ve kemoterapi alan kolon kanseri tanılı 114 yaşlı hastanın tıbbi kayıtları incelendi. GNRI, serum albümin düzeyi ve vücut ağırlığı kullanılarak hesaplandı. Hastalar düşük GNRI (GNRI: <98) ve yüksek GNRI (GNRI: ≥98) kategorilerine ayrılarak kıyaslandı.

Bulgular: Düşük GNRI grubunun 5 yıllık genel sağkalım oranı, yüksek GNRI grubundan anlamlı derecede düşüktü (%65.7'ye karşılık %91.1, p= 0.002). İki grubun 5 yıllık nükssüz sağkalım oranlarında da istatistiksel olarak anlamlı bir fark vardı (%66,7'ye karşı %90,8, p <0,001). Yapılan çok değişkenli Cox regresyon analizi, yalnızca tümör tarafı (p= 0.038) ve GNRI'yi (p = 0.042) genel sağ kalım için bağımsız prognostik faktörler olarak tanımladı.

Sonuç: GNRI, erken evre kolon kanseri tanısı almış yaşlı hastalarda genel sağ kalım için kolay uygulanabilir ve değerli bir prognostik faktördür. Araştırmamız, düşük bir GNRI'nin azalmış genel sağ kalım ile ilişkili olduğunu göstermektedir.

Anahtar kelimeler: Beslenme, kolon kanseri, prognoz, yaşlı

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Introduction

Malnutrition occurs frequently among cancer patients, and according to several studies, nutritional status is significantly associated with colon cancer patient survival [1-3]. There are numerous nutrition-related tools, such as body weight, prognostic nutritional index (PNI), and controlling nutritional status (CONUT) score [4-7]. The geriatric nutritional risk index (GNRI), measured by the serum albumin level and the ideal body weight, is a simple screening tool to evaluate nutritional-related risk. It was first defined by Bouillanne et al. to estimate the risk of morbidity and mortality in elderly patients [8]. It has also been reported that a lower GNRI can predict longer hospitalization and long-term mortality in elderly patients diagnosed with chronic kidney disease, congestive heart failure and sepsis [9-13]. Regarding the clinical significance of GNRI in cancer patients, there are many studies that revealed the prognostic role of GNRI in various cancers, including gastric, head and neck, pancreatic and lung cancer [14-17]. A few studies have been conducted to investigate the correlation between the GNRI and the outcomes of survival and recurrence in patients diagnosed with colon cancer.

In our study, we aimed to determine whether GNRI is an accurate prognostic factor for recurrence free survival (RFS) and overall survival (OS) in elderly patients with early-stage colon cancer patients who underwent curative resection and received chemo-therapy.

Methods

Patients and data

The data of 480 patients diagnosed and followed with colon cancer at a tertiary cancer center between 2011 and 2019 were analyzed. A total of 204 patients were excluded from the study because they were younger than 65 years of age and stage IV, while 71 patients were excluded because of not receiving chemotherapy. Ninety-one patients with Stage I were excluded because they did not attend their follow-ups regularly and therefore the dates of recurrence and death could not be reached. Finally, the data from 114 patients were analyzed. We excluded patients who died within the first month of the operation due to post-operative complications and who had co-morbidities (i.e. chronic renal failure, liver failure, nephrotic syndrome) causing hypoalbuminemia.

Medical records revealed clinical and pathological information including age, gender, time of operation, preoperative body weight, height and albumin level, tumor sidedness, tumor invasion depth, lymph node metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), differentiation type, and recurrence time. The American Joint Committee on Cancer Tumor Node Metastasis (TNM) classification system was utilized for staging [18].

Preoperative weight and height data of the patients were collected, and body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). GNRI was calculated as: GNRI = 1.489 x serum albumin (g/l) + 41.7 x current body weight/ideal body weight. As previous studies reported, patients were divided into two nutritional risk categories: low-GNRI (GNRI: <98), and high-GNRI (GNRI: ≥98) [19, 20]. Patients with a high-GNRI were considered high risk for malnutrition, while patients in the low-GNRI category were considered low risk.

Statistical Analyses

The continuous variables were reported as means and standard deviations (SD). Using Student's t-test, the means were compared. The chi-square test or Fisher's exact test was used to compare groups whose categorical variables were calculated as numbers and

Table 1. Clinicopathological features of the patients according to GNRI groups

Features		GNRI≥ 98 (n= 79, %)	GNRI< 98 (n= 35, %)	p-value
Age		67 (65-76)	68 (65-84)	
Gender	Male	45 (57%)	19 (54.3%)	0.474
	Female	34 (43%)	16 (45.7%)	
Diabetes mellitus	No	64 (81%)	25 (71.4%)	0.642
	Yes	15 (19%)	10 (28.6%)	
BMI	<25	10 (11.5%)	7 (25.9%)	0.068
	≥25	77 (88.5%)	20 (74.1%)	
Tumor sidedness	Right	14 (51.9%)	24 (27.6%)	0.02
	Left	13 (48.1%)	63 (72.4%)	
TNM Stage	II	43(54.4%)	16 (45.7%)	0.256
	III	36(45.6%)	19 (54.3%)	
T stage	T1/T2	5 (6.3%)	1 (2.9%)	0.400
	T3/T4	74 (93.7%)	34 (97.1%)	
LN metastases	No	43 (54.4%)	16 (45.7%)	0.256
	Yes	36 (45.6%)	19 (54.3%)	
Differentiation	Well	17 (21.5%)	5 (14.3%)	0.472
	Moderate/poor	59 (74.9%)	29 (82.9%)	
PNI	No	58 (73.4%)	23 (65.7%)	0.703
	Yes	12 (15.2%)	7 (20%)	
LVI	No	49 (62%)	18 (51.4%)	0.244
	Yes	27 (34.2%)	13 (37.1%)	
Perforation/obstruction	No	64 (81%)	30 (85.7%)	0.374
	Yes	15 (19%)	5 (14.1%)	

Abbreviations: BMI: Body mass index; GNRI: Geriatric nutritional risk index; LVI:Lymphovascular invasion; LN:Lymph node; PNI: Perineural invasion

percentages. Overall survival (OS) was defined as the interval between operation and death. The definition of recurrence-free survival (RFS) was the duration between colon cancer surgery and recurrence of the disease. Survival curves were calculated using the Kaplan-Meier method. The log-rank test was applied to determine the differences between the curves. The hazard ratios (HRs) were derived using Cox regression analyses. All variables with a p value <0.05 in the univariate analysis were included in multivariate Cox regression analysis. P value< 0.05 was regarded as statistically significant, and 95% confidence interval (CI) was determined. SPSS software (version 27.0) was utilized for all statistical analyses.

Ethics Committee Approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the institutional ethics committee (date: July 11, 2023, no: 952070b3-f214-466b-bea8-c8bb6ed6700a) and conducted in accordance with the related privacy statements and applicable regulatory requirements.

Results

Basic characteristics and pathological features

The median age of the 114 patients was 67 (range 65-84) years; 64 (56.1%) patients were male. The number of patients with T1/T2 was 6 (5.3%), while 108 (94.7%) of the patients

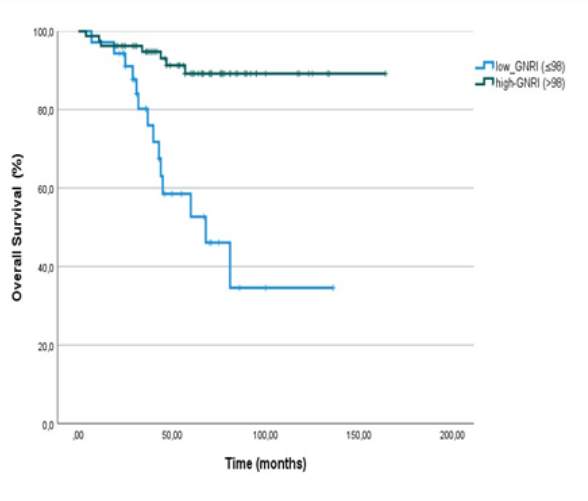

Figure 1. Kaplan Meier analyses of overall survival according to GNRI.

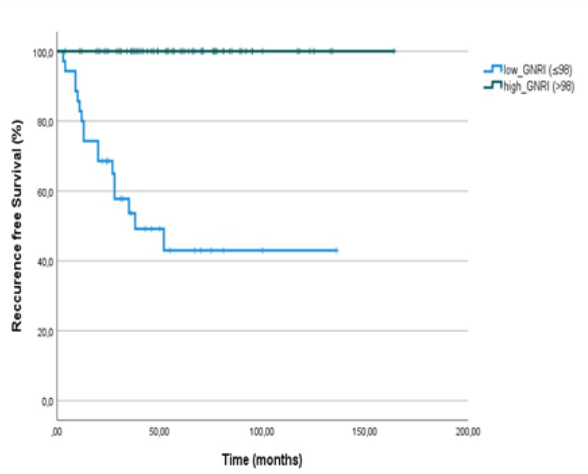

Figure 2. Kaplan Meier analyses of recurrence free survival according to GNRI.

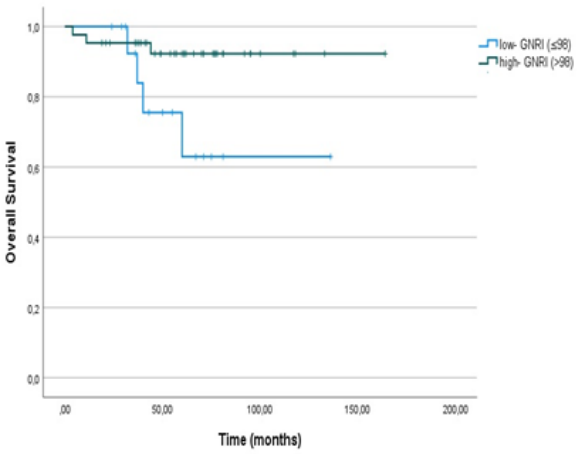

Figure 3. Estimates of overall survival by Kaplan-Meier according to the GNRI for stage 2 patients.

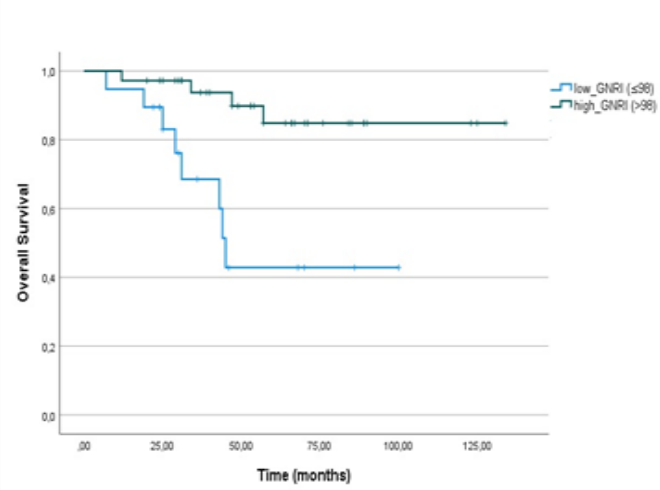

Figure 4. Estimates of overall survival by Kaplan-Meier according to the GNRI for stage 3 patients.

were staged as T3/T4. The number of patients with lymph node metastasis was 55 (48.2%). There were 59 (51.8%) patients with stage II, and 55 (48.2%) with stage III.

The mean GNRI was 103.5±11.9. Thirty-five (30.7%) of the patients had low-GNRI (GNRI≤ 98), and 79 (69.3%) had high-GNRI (GNRI> 98). Clinicopathological features of the patients according to GNRI groups were shown in Table 1. When the clinico-pathological features of the patients were compared according to the GNRI groups, only a significant correlation was found between tumor sidedness and GNRI. A total of 23.7% of left-sided tumors were categorized as low-GNRI, while 76.3% of them were in the high-GNRI group (p=0.02).

Survival analyses

The 5-year OS rate of the low-GNRI group was significantly lower than that of the high-GNRI group (65.7% vs. 91.1%, p=0.002; Figure 1). There was also a statistically significant difference in the 5-year RFS rate of the two groups (66.7% vs. 90.8%, p <0.001; Figure 2). Additionally, an assessment was conducted to determine the prognostic significance of the GNRI in relation to the

Table 2. Univariate and multivariate analyses of the factors associated with overall survival.

Variables		Univariate		Multivariate	
		95% CI	p-value	95% CI	p-value
Age	<75	1			
	≥75	1.235 (0.364-4.196)	0.735		
Gender	Female	1			
	Male	1.602 (0.662- 4.162)	0.296		
Tumor depth	T1-T2	1			
	T3-T4	2.003 (0.830 -4.835)	0.122		
Stage	2	1			
	3	2.022 (0.837-4.884)	0.118		
BMI	≥22	1			
	<22	1.765 (0.411-7.579)	0.445		
GNRI	High	1			
	Low	2.789 (1.172-6.637)	0.020	2.476 (1.031-5.942)	0.042
Tumor sidedness	Left	1			
	Right	2.797 (1.177-6.647)	0.020	2.528 (1.054-6.061)	0.038
Differentiation	Well/moderate	1			
	Poor	2.792 (0.645-12.083)	0.169		
LVI	No	1			
	Yes	1.084 (0.437-2.690)	0.862		
PNI	No	1			
	Yes	1.396 (0.468-4.162)	0.550		
Diabetes mellitus	No	1			
	Yes	1.951 (0.807-4.716)	0.138		
Obstruction/perforation	No	1			
	Yes	1.338 (0.450-3.980)	0.601		

Abbreviations: BMI: Body mass index; GNRI: Geriatric nutritional risk index; LVI:Lymphovascular invasion; PNI: Perineural invasion

stage of the tumor. In stage II, the 5-year OS rate was 86.7% in the group with a low-GNRI, while it was 88.6% in the group with a high-GNRI (p = 0.577; Figure 3). The 5-year OS rate in stage III patients was 58.3% in the group with low-GNRI, whereas it was 83.7% in the group with high-GNRI (p= 0.073; Figure 4).

Prognostic factors for OS

In the univariate analysis of factors related to OS, the HR for a low-GNRI was 2.789 (95% CI 1.172-6.637, p= 0.020). The other factor that was significantly correlated with OS was right tumor sidedness (p= 0.020). Gender, age, T stage, lymph node metastases, TNM stage, low-BMI, diabetes, presence of LVI, PNI and poor differentiation were not significantly associated with OS. The multivariate Cox regression analysis identified only tumor sidedness (p= 0.038) and GNRI (p= 0.042) as independent prognostic factors for OS (Table 2).

Prognostic factors for RFS

In the univariate analysis of prognostic factors related to RFS, GNRI was the only indicator that was correlated with RFS (HR: 4.265; %95 CI:1.641-11.087; p= 0.04). The other factors such as tumor sidedness, gender, age, T stage, lymph node metastases, TNM stage, low-BMI, diabetes, presence of LVI, PNI and poor differentiation were not significantly associated with RFS.

Discussion

Our study showed that the GNRI measured in the preoperative period in patients with early-stage colon cancer is prognostic in terms of OS and RFS. Although it has been previously shown that GNRI is prognostic for survival in several malignancies such as gastric, pancreatic, and lung cancer, there are few studies investigating the prognostic importance of GNRI in terms of survival in early-stage colon cancer patients. One of them was performed with 329 colorectal cancer

patients [20]. In this study, low-GNRI was reported to be associated with OS ($p< 0.001$) and was found to be an independent prognostic marker in multivariate analysis ($p=0.042$). The main difference between this study and ours is that there was no statistical relationship between low-GNRI and RFS in study performed by Doi et al. In our study, low-GNRI was both related to poor OS and poor RFS. The cut-off value of 98 for low-GNRI was similar as ours.

In addition, in our study high-GNRI group had a higher incidence of left colon cancer compared to the low-GNRI group and the association between GNRI and tumor sidedness was statistically significant. In recent studies about tumor sidedness demonstrated that right colon cancer was more aggressive than left colon cancer [21, 22]. Our study confirms these recent studies. Therefore, the association between high GNRI and left sidedness may depend on tumor biology. For this suggestion, more studies are needed at the molecular level.

The prognosis of colon cancer patients with low-GNRI is generally poorer, thus emphasizing the significance of improving nutritional status to improve survival. There are different markers such as prealbumin level and sarcopenia in the evaluation of nutritional status. But these markers are expensive and difficult to perform in elderly patients. Thus, GNRI can show nutritional status alone in elderly colon cancer patients as an easy and accessible marker that can be calculated by routine biochemistry. Several studies reported the impact of nutritional support on the prognosis of colon cancer patients and demonstrated the correlation between the use of oral nutritional supplements and reduced weight loss as well as a lower incidence of postoperative infection among colon cancer patients [23, 24]. Furthermore, it was observed that dietary factors play a significant role in the etiology of colon cancer [25, 26]. Nevertheless, the effects of these dietary treatments on the long-term prognosis of patients with colon cancer remain uncertain. Therefore, more research is needed to examine the potential of nutritional support in increasing the survival of individuals diagnosed with colon cancer. In this regard, GNRI can serve as a valuable tool for assessing patients who may benefit from nutritional support and for assessing the impact of such nutritional supports.

One of the limitations of our study is the lack of assessment regarding the association between GNRI and postoperative complications. This is because we were unable to access postoperative period information during the analysis of retrospective data. Secondly, there is no consensus regarding the GNRI cut-off value, which makes its practical use a challenge. Thirdly, we only included the stage II and III patients who were treated with CAPEOX or capecitabine monotherapy. Whether or not the patients could complete their chemotherapy regimens could not be reached because of retrospective data analysis. Therefore, survival analysis according to chemotherapy type and duration, and the relationship between survival and GNRI groups according to chemotherapy types could not be examined. Finally, we only assessed GNRI as a prognostic marker. Evaluating and comparing GNRI with other prognostic factors such as PNI, CONUT and sarcopenia could more effectively demonstrate the prognostic value of GNRI. Although several markers, such as CONUT, PNI have been evaluated in terms of their association with survival in colon cancer patients, it is still unclear which marker is the most effective. Prospective studies with a large number of patients are needed to compare these markers.

In conclusion, this study provides evidence that the GNRI serves as a basic and important prognostic indicator in elderly patients diagnosed with early-stage colon cancer. A low GNRI may be a prognostic indicator of poor OS and RFS.

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Original Article

Definitive Chemoradiotherapy versus Neoadjuvant Chemoradiotherapy Followed by Surgery in Locally Advanced Esophageal Cancer: A Retrospective Evaluation of Clinical Data of Two Centers

Lokal İleri Özofagus Kanserinde Definitif Kemoradyoterapi ile Neoadjuvant Kemoradyoterapiyi Takiben Cerrahinin Karşılaştırılması: İki Merkezin Klinik Verilerinin Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study is to investigate the results of neoadjuvant chemoradiotherapy /radiotherapy (neo-CRT/RT)+surgery and definitive chemoradiotherapy (def-CRT) approaches in locally advanced esophageal cancer

Methods: Between January 2012 and December 2021, in two centers, patients who received def-CRT or neo-CRT/RT with the diagnosis of locally advanced esophageal cancer, were retrospectively analyzed. Cases were evaluated for treatment response, overall survival (OS), disease-free survival (DFS), and local recurrence (LR).

Results: In total, fifty cases were included. The median follow-up was 10 months (range 2-26). In the def-CRT group; OS at one year, and two years were 67 % and 32 %, respectively; DFS at one year, and two years were 62 % and 32 % respectively. In the neo-CRT group; OS at one year was 81 % and DFS at one year was 73 %. In the follow-up time, LR was 12.1% in def-CRT and 11.8% in the neo-CRT group. For two treatment arms, there were no significant differences in OS (p=0.404), DFS (p=0.593) and LR (p=0.670). The neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

Conclusion: Considering the morbidity and mortality of surgery, def-CRT may be an alternative to neoadjuvant-surgical treatment in selected cases whose treatment response is considered a complete response. In these patients, waiting until recurrence and then salvage surgery can be considered.

Key words: Esophageal cancer, chemoradiotherapy, esophagectomy

ÖZET

Amaç: Lokal ileri özofagus kanserinde neoadjuvan kemoradyoterapi/radyoterapi (neo-KRT/RT)+cerrahi ve definitif kemoradyoterapi (def-KRT) yaklaşımlarının sonuçlarını araştırmaktır

Yöntemler: Ocak 2012 ile Aralık 2021 tarihleri arasında iki merkezde lokal ileri özofagus kanseri tanısı ile def-KRT veya neo-KRT/RT alan hastalar retrospektif olarak incelendi. Olgular tedavi yanıtı, genel sağkalım, hastalıksız sağkalım ve lokal nüks açısından değerlendirildi.

Bulgular: Toplamda elli vaka çalışmaya dahil edildi. Medyan takip süresi 10 (2-26) ay'dı. Def-KRT grubunda; Bir yıllık ve iki yıllık genel sağkalım sırasıyla %67 ve %32; bir yıllık ve iki yıllık hastalıksız sağkalım sırasıyla %62 ve %32 idi. Neo-KRT grubunda; bir yıllık genel sağkalım %81 ve bir yıllık hastalıksız %73 idi. Takip süresince lokal nüks oranı, def-KRT grubunda %12.1 ve neo-KRT grubunda %11.8 idi. İki tedavi kolu arasında, genel sağkalım (p=0,404), hastalıksız sağkalım (p=0,593) ve lokal

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nüks (p=0,670) açısından anlamlı fark yoktu. Neo-KRT grubu ameliyat zamanına göre değerlendirildiğinde, 8 haftadan sonra ameliyat edilen hastalarda istatistiksel anlamlılığa ulaşılamasa da daha fazla mortalite saptandı..
Sonuç: Cerrahinin morbidite ve mortalitesi göz önüne alındığında, tedaviye yanıtı tam yanıt olarak kabul edilen seçilmiş olgularda def-KRT, neoadjuvan+cerrahi tedaviye bir alternatif olabilir. Bu hastalarda nükse kadar bekleyip ardından salvaj cerrahi düşünülebilir.

Anahtar kelimeler: Özofagus kanseri, kemoradyoterapi, özofajektomi

Introduction

Esophageal cancer (EC) is one of the most common types of cancer worldwide. It was estimated over 600 thousand new cases and over 500 thousand deaths according to 2020 data [1]. The two major histopathological subtypes of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). The incidence of both subtypes differs by geographic region: SCC has a high prevalence in East Asia, East and Southern Africa, and Southern Europe; AC is more common in North America and other parts of Europe [2]. Although the 5-year overall survival is 20% [3], better outcomes can be seen in patients with early-stage disease [4]. Early-stage disease is usually treated with endoscopic resection [5]. Although esophagectomy remains the mainstay of surgical treatment, it has high morbidity and mortality rates [6]. EC is often diagnosed in advanced stages where surgery alone cannot cure it. Therefore, curative treatment options in advanced disease are neoadjuvant chemoradiotherapy (neo-CRT) followed by surgery or definitive chemoradiotherapy (def-CRT) [7].

Def-CRT is seen as an alternative to surgery with an increasing proportion of resectable diseases, especially in patients who are not suitable for surgery [8,9]. In neo-CRT, it is aimed to reduce both the tumor burden and the extent of the planned surgery, as well as the risk of distant metastasis (through the elimination of potential micrometastases) [8]. In advanced disease, multimodal therapy is needed to reduce relapse rates and achieve higher local control and survival rates [9]. A multidisciplinary approach is needed to determine the appropriate treatment option for each patient.

There are limited data comparing def-CRT to neo-CRT with esophagectomy in patients with esophageal carcinoma. This study aims to evaluate treatment response and survival according to def-CRT and neo-CRT+surgical approaches in patients with locally advanced esophageal cancer.

Materıal and Methods

We retrospectively analyzed the data of patients diagnosed with locally advanced esophageal cancer who underwent def-CRT or neo-CRT+ surgery in the Radiation Oncology Department of two centers. Between 2012 and 2021, in total, 50 patients were included in this study.

This study was conducted by considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. The study was approved by XXX University Ethical Committee for non-invasive investigations (Date: 30.11.2021, Decision No: E-71522473-050.01.04-83316-513).

The patients were evaluated in terms of treatment options by the multidisciplinary tumor board. Clinical staging of all patients was performed with PET-CT. The AJCC-2017 staging system [10] was used for clinical staging. Patients with T2-4 and/or node positive, M0 esophageal cancer were included in the study. Eastern Cooperative Oncology

Group Performance Status Scale (ECOG PS) was used to assess the performance status of patients [11] and patients with ECOG PS 0, 1 or 2 were included. Demographic characteristics, clinical and pathological data of the patients, the purpose of treatment, doses, and areas of radiotherapy (RT), response to treatment, overall survival (OS), disease-free survival (DFS), and local recurrence (LR) were recorded.

For RT planning; CT scans of the patients were taken in a 2.5 mm section thickness, in the supine position, and using a wing board. The target volume was determined by fusing PET-CT images and planning CT images. The median dose of RT for the primary tumor and lymphatic region was 5040 cGy (4140-6000 cGy) in median 28 fractions (range 23-30). RT was performed for all patients using the Intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT) technique.

Post-treatment response rates of patients were evaluated by radiological imaging and/or endoscopic examination. Response Evaluation Criteria in Solid Tumors (RECIST 1.0) are used for evaluation of response [12]. Accordingly, patients were evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Statistical analysis

Patient characteristics were compared with a chi-square test. The median ages of the patients were compared with Mann-Whitney U test. The survival analysis was performed by the actuarial Kaplan-Meier method and differences between the curves were analyzed using the log-rank test. OS was defined as the time from diagnosis to death or the date of last control for patients who were alive. DFS was defined as the time from diagnosis to recurrence of tumor or death. Statistical analysis was carried out using the SPSS 21.0 software package. $p < 0.05$ was considered statistically significant.

Results

Clinical Data and Tumor Characteristics

In total, fifty cases were included. The median age of patients was 60 (37-75) years. There was no significant difference in the distribution of age (p=0.500), gender (p=0.060), and ECOG PS (p=0.230). Patient characteristics are shown in Table 1.

Thirty-three patients (66%) were treated with def-RT/CRT and 17 patients received neo-CRT (34%). Carboplatin-paclitaxel combination was applied to 38 (83%) patients and cisplatin- 5-fluorouracil combination was used for eight (17%) patients as concomitant chemotherapy. Concomitant chemotherapy could not be applied to four patients who were scheduled for definitive treatment, due to their comorbidities.

Treatment Response

In all study groups; 18 patients (36%) had complete responses (CR), 13 patients (26%) had partial responses, and 12 patients (24%) had stable responses. Progressive disease was present in seven patients (14%).

In the def-CRT group; the CR was observed in nine patients (27.3%) after treatment. There was partial response in 10 patients (30.3%), stable response in seven patients (21.2%), and progressive disease in seven patients (21.2%). In the neo-CRT group, the median time between surgery and CRT was seven (3-17) weeks. According to the surgical specimen, 9 of 17 patients had a pathological complete response (pCR) and three patients had a partial response. In three patients, the radiological and pathological stages were the same. The treatment doses of these three patients were 41.4 Gy. The RT dose of patients with a CR was median of 50 Gy (45-50,4); for patients with downstaging was median of 50 Gy (45-56).

Table 1: Patient and tumor characteristics

		All patients (n=50)	Def-CRT and Def-RT (n=33)	Neo-CRT +Surgery (n=17)	p-value
Follow-up (months)	Median (Range)	10 (2-26)	10 (2-26)	9 (3-20)	0.400
Age	Median	60 (37-75)	60 (40-75)	61 (37-73)	0.500
	60≤	25 (50)	17 (51.5)	8 (47.1)	
	60>	25 (50)	16 (48.5)	9 (52.9)	
Gender	Female	26 (52)	14 (42.4)	12 (70.6)	0.060
	Male	24 (48)	19 (57.6)	5 (29.4)	
ECOG PS	0	37 (74)	22 (66.6)	15 (88.2)	0.230
	1	11 (22)	9 (27.3)	2 (11.8)	
	2	2 (4)	2 (6.1)		
Stage	IIB	24 (48)	14 (42.4)	10 (58.8)	
	IIIA	1 (2)	14 (42.4)	1 (5.9)	0.150
	IIIB	20 (40)	-	6 (35.3)	
	IVA	5 (10)	5 (15.2)		
Tumor Location	Upper esophagus	5 (10)	5 (15.1)	0 (0)	
	Middle esophagus	20 (40)	15 (45.5)	5 (29.4)	0.070
	Lower esophagus	25 (50)	13 (39.4)	12 (70.6)	
Histopathology	SCC	43 (86)	30 (90.9)	13 (76.5)	0.170
	AC	7 (14)	3 (9.1)	4 (23.5)	
Chemotherapy	Yes	46 (92)	29 (87.9)	17 (100)	0.180
	No	4 (8)	4 (12.1)	0 (0)	
Treatment Response	CR	18 (36)	9 (27.3)	9 (52.9)	
	PR	13 (26)	10 (30.3)	3 (17.6)	0.080
	SD	12 (24)	7 (21.2)	5 (29.4)	
	PD	7 (14)	7 (21.2)		
LR	Yes	6 (12)	4 (12.1)	2 (11.8)	0.674
	No	44 (88)	29(87.9)	15 (88.2)	
Distant Metastasis	Yes	9 (18)	7 (21.2)	3 (17.6)	0.539
	No	41 (82)	26 (78.8)	14 (82.4)	

SCC: Squamous cell carcinoma, AC: Adenocarcinoma, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease. LR: Local Recurrence.

Overall Survival /Disease-Free Survival

At a median follow-up of 10 months (2-26 months), overall survival (OS) at 1 year, and 2 years 70 % and 38 % were, respectively (Figure 1) and disease-free survival (DFS) at 1 year, and 2 years were 66 % and 30 % respectively (Figure 2).

In the Def-CRT group; At a median follow-up of 10 months (2-26 months), OS at 1 year, and 2 years were 67 % and 32 % respectively and DFS at 1 year, and 2 years were 62 % and 32 % respectively. In the neo-CRT group; At a median follow-up of 10 months (2-20 months), OS at 1 year was 81 % and DFS at 1 year was 73 %. There was no significant difference between the treatment groups for OS (p=0.593) and DFS (p=0.404).

This study showed that treatment option (def-CRT or neo-CRT+ surgery) (p=0.404), patients' gender (p=0.320), age of diagnosis (p=0.130), tumor histology (p=0.970), tumor location (p=0.740) and stage of diagnosis (p=0.110) had no significant impact on survival rate.

24 patients (%48) died. Although there was no significant difference between the treatment groups (p=0.513), OS was higher in the neo-CRT group. In the neo-CRT+ surgery group, five patients died due to surgery-related complications (%29) and two patients (%12) died due to distant metastases, and 1 (%6) patient died from pneumonia. In the def-CRT group, five patients (%15) died due to distant metastases, four patients (%12) died due to

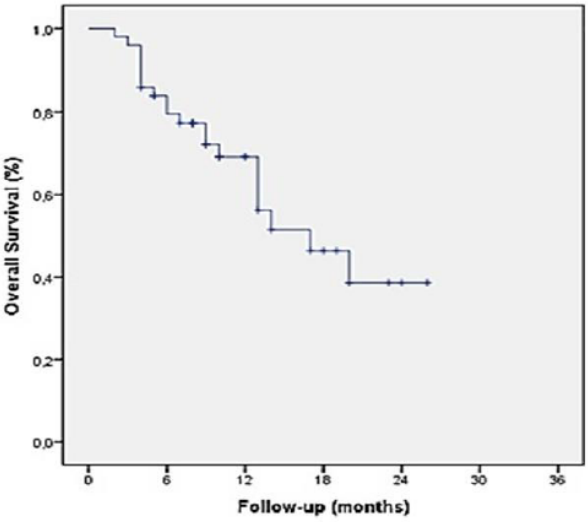

Figure 1. Overall survival at 1 year and 2 years

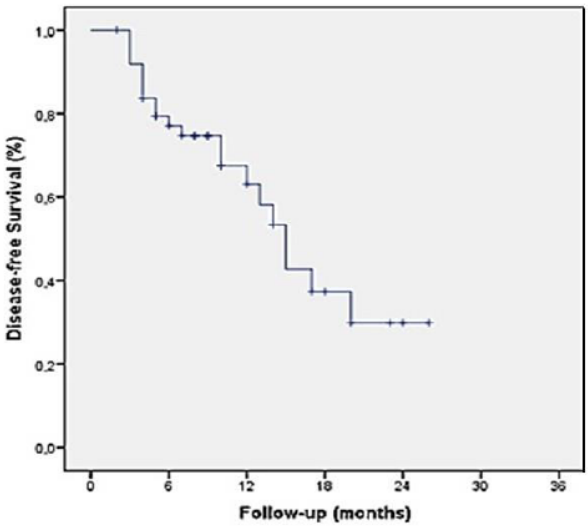

Figure 2. Disease-free survival at 1 year and 2 years

non-cancer reasons, and seven patients (%21) died due to primary disease after CRT.

Patterns of Failure

In the follow-up of the patients after the treatment, local recurrence (LR) was 12.1% in def-CRT and 11.8% in the neo-CRT group. There was no significant difference between the two treatment groups (p=0.670). In the follow-up of the patients, metastases developed in nine patients (18%) and there was no significant difference between the two treatment groups (p=0.539). Of the patients who developed distant metastases, four had lung metastases (44.5%), two had liver metastases (22.2%), two patients had lymph node metastases (22.2%), and one patient had brain metastases (11.1%).

Discussion

This retrospective study shows no significant difference in DFS and OS in patients with locally advanced EC when comparing def-CRT with neo-CRT followed by surgery. A preoperative chemoradiotherapy regimen that was based on carboplatin and paclitaxel was manageable and had a favorable safety profile. However, the neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

In a recently published systematic review and meta-analysis, patients with EC who received neo-CRT and esophagectomy had better survival than patients who received def-CRT [13]. However, in our study, in terms of OS, there was no significant difference between the two treatment groups. We also showed better at 1-year OS in the neo-CRT group (81% vs 67%), but not statistically significant, potentially due to follow-up time and/or sample size issues. In published two different studies of patients with locally advanced EC, for OS, there was no significant difference between patients who underwent def-CRT and surgery after neo-CRT [7,14]. The 2-year overall survival in patients who received neo-CRT followed by surgery and def-CRT were 69.1% and 40.0%, respectively [15]. Similarly, in our study, 2-year OS was 32 % in def-CRT. Since the longest follow-up period

was 20 months in the neoadjuvant group, 2-year survival could not be evaluated.

Dong Qian et al., more than 40% of patients with esophageal SCC had pCR after neo-CRT [14]. In other studies, The pCR of this approach ranges from 13 to 47% [15,16]. Similarly, in our cohort, 53% of the patients who received neoadjuvant therapy, had pCR. While increasing the pCR rate with neo-CRT was expected to have a positive effect on overall survival, no significant advantage in overall survival could be demonstrated despite the downstaging. Two separate studies have shown that surgical delay of >8 weeks doesn't lead to a favorable outcome in patients with esophageal cancer. These studies showed that an 8-week interval between neo-CRT and surgery is sufficient to produce a maximum RT response in patients with esophageal cancer, thus longer surgical delay may have adverse consequences for patients with a good response to neo-CRT [17,18]. In our study, CR was obtained in 29% of the patients in the surgical group. However, all patients who died from surgical complications had an interval of >8 weeks from CRT to surgery. Therefore, the positive effect of pathological complete response on overall survival may not have been observed in the neo-CRT group.

Carlo C. et al found that in patients with clinical CR after neo-CRT, waiting until relapse and then salvage surgery didn't adversely affect survival compared to patients treated with surgery [19]. We could not compare these two patient groups in our study. Because all patients in the neo-CRT group, underwent surgery regardless of clinical response to treatment. A case-control study showed that patients with CR had a better prognosis after CRT compared to surgery [20].

Kenji et al. compared def-CRT doses in patients with thoracic EC; CR rates in the 50.4 Gy and 60 Gy groups were 49.1% and 46.4%, respectively. Also, no significant difference was found between the two groups in terms of OS, and they revealed that 50.4 Gy was non-inferior compared to 60 Gy [21]. Similarly, in the INT 0123 study, doses of 50.4 and 64.8 Gy were compared in EC patients and it was shown that survival and local control results weren't better at higher doses [22]. In our study; in patients with CR and downstaging, the median dose was 50 Gy, and the lowest dose was 45 Gy. Treatment response was stable in both patients who received 41.4 Gy. Based on this, it can be interpreted that the treatment dose should be at least 45 Gy to get a treatment response, but to reach a meaningful result, it is necessary to compare the number of patients and the dosing schedule.

Marieke P. et al showed that the 1 and 3-year DFS were 67% and 43%, respectively, in a neo-CRT+surgery group, and 56% and 24%, respectively, in def-CRT group. DFS significantly shorter in the def-CRT group compared to resected patients [23]. Unlike this study, in our cohort 1 and 2-year DFS were 62% and 32%, respectively, in def-CRT group; and 1-year DFS was 73% in neo-CRT+surgery group. No significant difference was found between the two treatment arms. That reason may be due to the unequal distribution of patients in the groups and the relatively short follow-up period.

In our study, the cumulative LR incidence rate was found to be 12%. Considering the groups, it was 12.1% in def-CRT and 11.8% in neo-CRT group. Similarly, Lin J.W. et al found the 3-year cumulative incidence rate of LR was 13.3% of patients (15). In contrast to our study, Münch S. et al showed that in locally advanced EC patients treated with either def-CRT or neo-CRT+surgery group (38% vs. 10%), a higher rate of LR was seen in patients treated with def-CRT than in patients treated with neo-CRT+surgery [24]. Unlike that study, the reason why there was no difference in LR between the groups may be that all patients were N0 patients located in the thoracic and lower esophagus.

Some limitations of this study are that the study was designed retrospectively and the follow-up period was short. In addition, some imbalances in tumor parameters between patient groups (lymph node metastasis rate and tumor location) may affect the results and should be kept in mind. The small number of patients in our study didn't allow us to perform subgroup analysis. The results of clinical studies with larger patient groups will contribute to the creation of the most appropriate multidisciplinary strategy according to histological subtype, localization, stage, and post-CRT tumor response.

Conclusion

In this study, no significant difference was found between the two treatment groups in terms of OS, DFS, and LR. Def-CRT may be an alternative to neoadjuvant-surgical treatment, considering the morbidity and mortality of surgery in selected cases whose treatment response is considered CR. Salvage surgery may be considered after recurrence in these patients

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Case Report

Desmoid Fibromatosis of the Breast; A Case Report

Memenin Desmoid Fibromatozisi; Olgu Sunumu

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ABSTRACT

Desmoid-type fibromatosis of the breast is a rare, locally aggressive stromal tumor. This lesion is observed in 0.2% of all breast tumors, often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female). In this study, we report a case of a 57-year-old woman with breast fibromatosis, which has been mimicking breast carcinoma. On physical examination, there was an irregularly shaped mass lesion of approximately 3x2 cm fixed to the chest wall in the upper outer quadrant of the left breast. On mammography, an increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast. On ultrasound examination, a heterogeneous hypoechoic solid lesion with microcalcifications in places and 32x10mm in size with irregular borders and internal echoes were observed in the upper outer quadrant of the left breast. (BIRADS 4). Since the tru-cut biopsy could not differentiate between Fibromatosis-like Metaplastic Breast Carcinoma and Desmoid Fibromatosis, an excisional biopsy was performed under general anaesthesia. Wide local excision was performed due to positive surgical margins. In conclusion, desmoid-type fibromatosis has nonspecific physical examination findings and radiological imaging and is confused with malignancy. The primary treatment of this lesion is excision with a negative surgical margin

Keywords: Desmoid-type fibromatosis (DF), breast tumor, fibromatosis

ÖZET

Memenin desmoid tip fibromatozisi nadir görülen, lokal agresif bir stromal tümördür. Bu lezyon tüm meme tümörlerinin %0,2'sinde görülür, sıklıkla 25-45 yaşları arasında ortaya çıkar ve erkek: kadın oranı 1:2'dir. Bu olgu sunumunda, meme kanserini taklit eden meme fibromatozisi olan 57 yaşında bir kadın hastayı sunuyoruz. Fizik muayenede sol meme üst dış kadranda göğüs duvarına fikse yaklaşık 3x2 cm boyutlarında düzensiz şekilli kitle lezyonu izlendi. Mamografide sol meme dış orta kısmında fibroglandüler doku ile örtülü opaklıkta artış izlendi. Ultrason muayenesinde sol meme üst dış kadranda 32x10mm boyutlarında, sınırları düzensiz, iç ekosu olan, yer yer mikrokalsifikasyonlu, heterojen hipoekoik solid lezyon izlendi. (BIRADS 4). Tru-cut biyopside fibromatozis benzeri metaplastik meme karsinomu ile desmoid fibromatozis ayırt edilemediğinden genel anestezi altında eksizyonel biyopsi gerçekleştirildi. Pozitif cerrahi sınırlar nedeniyle geniş lokal eksizyon uygulandı. Sonuç olarak, desmoid tip fibromatosis nonspesifik fizik muayene bulguları ve radyolojik görüntüleme bulgularına sahiptir ve malignite ile karıştırılmaktadır. Bu lezyonun primer tedavisi negatif cerrahi sınır ile eksizyondur.

Anahtar kelimeler: desmoid fibromatozis, meme tümörü, fibromatozis

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Introduction

Desmoid-type fibromatosis of the breast is a rare, locally aggressive stromal tumor that occurs from musculoaponeurotic structures. It is a clonal fibroblastic proliferation that occurs in the deep soft tissues. Although it tends to be locally aggressive, distant metastases are not observed.[1] Desmoid-type fibromatosis is observed in 0.2% of all breast tumors.[2] This lesion often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female)[3]. We report a case of a 57-year-old woman with breast fibromatosis, which has been mimicking breast carcinoma.

Case Report

A 57-year-old female patient who developed a palpable left breast mass in several weeks was referred to our centre. She did not have any additional disease. The patient did not have a history of trauma or surgery in the left breast or a family history of cancer. On physical examination, there was an irregularly shaped mass lesion of approximately 3x2 cm fixed to the chest wall in the upper outer quadrant of the left breast. On mammography, an increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast, and the patient was recommended to be evaluated with ultrasound. (Figure 1)

On ultrasound examination, a heterogeneous hypoechoic solid lesion with micro-calcifications in places and 32x10mm in size with irregular borders and internal echoes was observed in the upper outer quadrant of the left breast. (BIRADS 4). Since the tru-cut biopsy could not differentiate between fibromatosis-like metaplastic breast carcinoma and desmoid fibromatosis, an excisional biopsy was performed under general anaesthesia.

In the pathological examination, the tumor consists of myofibroblastic cells forming intersecting long fascicles in the collagenized stroma with bland spindle nuclei, small nucleoli, and eosinophilic nuclei cytoplasm with indistinct borders. The tumor shows a highly infiltrative growth pattern into the surrounding breast tissue. One mitosis was observed in 10 HPF. No necrosis or cytological atypia was observed. There are haemorrhage foci and hemosiderin-laden macrophages within the tumor. Lymphoid aggregates were observed at the periphery of the tumor. The tumor was continuous with the anterior, base, superior, inferior, and lateral surgical margins. The medial surgical margin is intact. By immunohistochemistry, diffuse nuclear β-Catenin expression was observed. Focal Desmin, SMA, and Calponin expression were seen. Sparse cell staining was observed with S-100. PanCK, CK7, CD34 and p63 were negative. (Figure 2) The Ki67 proliferation index was 10%. Wide local excision was performed due to positive surgical margins.

Discussion

Desmoid-type fibromatosis is observed in 0.2% of all breast tumors.[2] This lesion often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female).[3] Although the etiology of the disease is not known, publications report that it is related to familial adenomatous polyposis, Gardner syndrome, surgical trauma, and silicone implants.[4] Our patient did not have any risk factors. It has nonspecific physical examination findings and radiological imaging and is confused with malignancy.

On physical examination, it often presents as a solitary, hard, and painless nodule. Nipple and cutaneous skin retraction and pectoral muscle fascia invasion can be observed.[5] In the study of Jörn Lorenzen et al., which is one of the largest series in the literature with 15 patients, a fixed mass was observed in 10 patients and a relatively soft mass in 4 patients. In addition, 4 patients had skin retraction. [2] In our case, there was a fixed

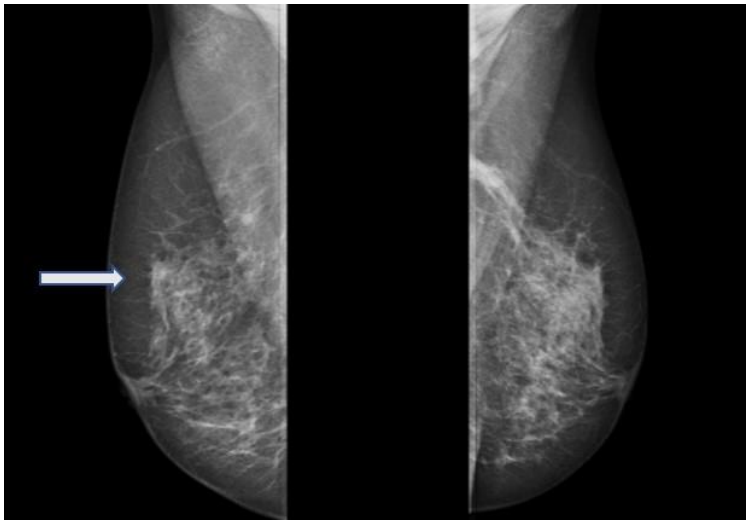

Figure-1. Left breast mammogram. An increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast.

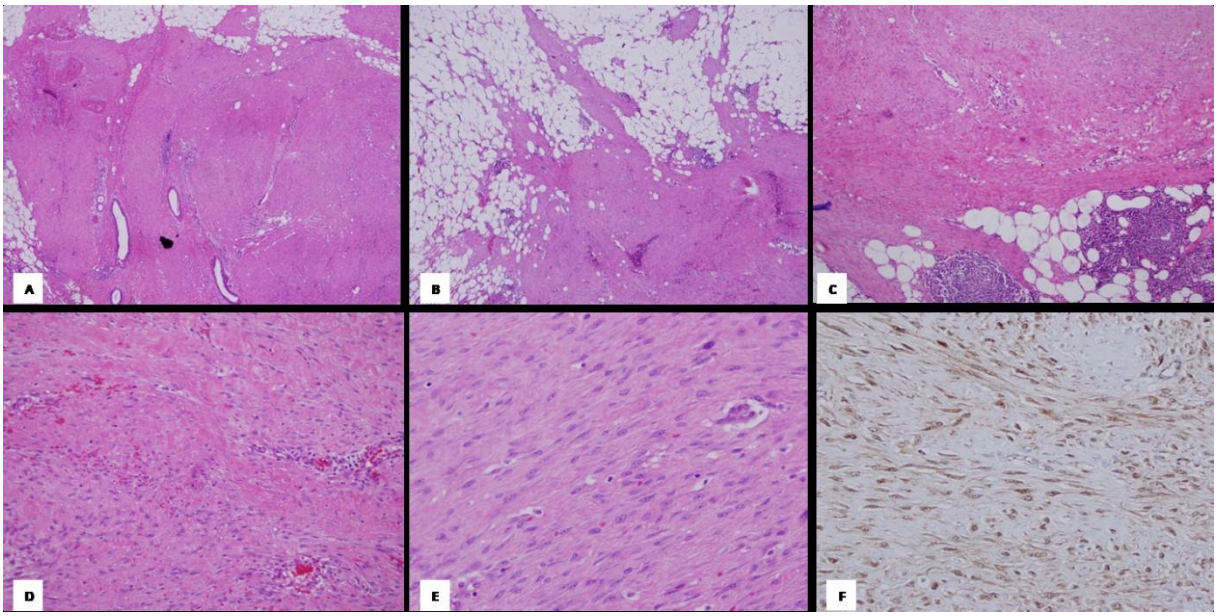

Figure-2. Tumor cells entrap normal breast ducts. B Spindle cells infiltrating the surrounding fat. C Lymphoid aggregates at the periphery of the tumor. D Collagenous stroma within the tumor. E Spindle cells appear bland with no mitotic activity. F Diffuse nuclear β-Catenin expression.

and hard palpable mass with irregular borders. In our case, there was an irregular, fixed, and hard palpable mass. However, there was no skin retraction as a deeply located mass invading the pectoral fascia was observed.

If we talk about radiological imaging, in the study of Michael R. Boland et al. (16 patients) and Jörn Lorenzen et al.; radial scars, architectural distortion, or a high-density mass appear as important mammographic findings. In our study, similar findings were observed in mammography. On ultrasound examination, the hypoechoic and irregular lesion was observed, which is consistent with the previous literature.[2, 6-10] Although there are studies suggesting MRI in the diagnosis and follow-up of desmoid fibromatosis, an excisional biopsy was performed without waiting for MRI because metaplastic carcinoma was suspected in our case.[11, 12]

Core biopsy is more valuable than fine-needle aspiration cytology. We also preferred the core biopsy first. Histopathological analyses play a critical role in the diagnosis. Diagnosis of low-grade spindle cell lesions in the breast is challenging because the differential diagnosis is broad and includes many rare lesions. The differential diagnosis includes fibromatosis-like metaplastic carcinoma, reactive spindle cell nodules, nodular fasciitis, inflammatory myofibroblastic tumor, myofibroblastoma, pseudoangiomatous stromal hyperplasia, phyllodes tumor, dermatofibrosarcoma protuberans, and spindle cell sarcomas. [13, 14] Desmoid fibromatosis is a locally aggressive mesenchymal neoplasm with infiltrative margins composed of a proliferation of uniform, cytologically bland fibroblasts, and myofibroblasts. Some histomorphologic clues to the diagnosis of desmoid fibromatosis include long fascicles of neoplastic spindle cells with entrapped benign breast glandular epithelial elements and peripheral lymphocytic aggregates. The spindle cells of desmoid fibromatosis express smooth muscle actin and show nuclear expression of Beta-Catenin, but lack cytokeratin expression. The most crucial lesion to distinguish from desmoid fibromatosis is fibromatosis-like metaplastic carcinoma. These tumors are composed of bland spindle cells resembling desmoid fibromatosis. A diagnosis of fibromatosis-like metaplastic carcinoma can be rendered based on any evidence of epithelial differentiation by histopathological or immunohistochemical analysis.[13, 15, 16] Due to tumor heterogeneity and focal cytokeratin expression, a definitive diagnosis can not be made in core biopsies. Broad macroscopic sampling and an immunohistochemical panel may be required to capture epithelial differentiation.

The primary treatment of desmoid-type fibromatosis is excision with a negative surgical margin. Wide (R0) microscopic margins resection is recommended. Positive (R1) microscopic margins can be accepted when cosmesis is problematic. There is no consensus about the indication of adjuvant radiotherapy after wide local excision. In addition, after R1 resection, there is no consensus between postoperative radiotherapy and reexcision, definitive radiotherapy can be given ın patients who cannot have surgery. It has been shown to provide sufficient local control. [17] On the other hand, a 'watch and wait' approach is also recommended in the current literature. This approach demonstrated a 60% 2-year progression-free survival similar to surgical treatment. This approach, at 3 to 6 months intervals for the first three years and then annually by MRI, consists of patient follow-up [11, 17]. Systemic treatment options for desmoid-type fibromatosis consist of non-steroidal anti-inflammatory drugs, anti-hormonal therapies, tyrosine kinase inhibitors, and conventional chemo-therapeutics.[18] Anti-hormonal agents (e.g.tamoxifen) have been frequently used alone or in combination with non-steroidal anti-inflammatory drugs. If the role of adjuvant chemotherapy is searched in the current literature, there are various regimens, including anthracycline-based regiments, sorafenib, imatinib, pazopanib, and vinblastine-methotrexate but no consensus. In addition, recent guidelines emphasize the importance of a multi-disciplinary approach. Re-excision was applied to the patient upon the decision of the multidisciplinary team council in our institution.

Conclusion

Desmoid-type fibromatosis of the breast is a rare stromal tumor. It has nonspecific physical examination findings and radiological imaging and is confused with malignancy. The primary treatment of desmoid-type fibromatosis is excision with a negative surgical margin.

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Case Report

Presentation of Metastatic Cholangiocellular Cancer with Orbital Metastasis

Metastatik Kolanjıoselüler Kanserin Orbital Metastaz ile Prezentasyonu

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ABSTRACT

Cholangiocarcinomas are cancers arising from epithelial cells of the intrahepatic and extrahepatic bile ducts. Most are locally advanced lesions when present. They usually present with jaundice, abdominal pain, and abnormal liver biochemical tests.

Proptosis developed in the right eye of a 49-year-old female patient who was diagnosed with carcinoma metastasis in the right femur and we examined for the primary one. Lacrimal gland biopsy of the patient was found to be compatible with cholangiocarcinoma metastasis. Neuroopthalmologic complications in cholangiocarcinoma are very rare and 10 cases have been reported in the literature.

Keywords: orbital metastasis, CNS metastasis, cholangiocarcinoma, exophthalmos

ÖZET

Kolanjiokarsinomlar intrahepatik ve ekstrahepatik safra kanallarının epitel hücrelerinden kaynaklanan kanserlerdir. Çoğu prezente olduğunda lokal olarak ilerlemiş lezyonlardır. Genellikle sarılık, abdominal ağrı ve anormal karaciğer biyokimyasal testleri ile prezente olurlar.

Sağ femurda karsinom metastazı saptanıp prımerıne yonelık tetkık ettiğimiz 49 yasındakı kadın hastanın sağ gözünde proptozis gelişti. Hastanın lakrimal bez biyopsisi kolanjıiokarsinom metastazı ile uyumlu saptandı. Kolanjiokarsinomda nörooptalmolojık komplikasyonlar oldukça nadir olup literatürde 10 vaka bildirimiştir.

Anahtar Kelimeler: orbital metastaz, SSS metastazı, kolanjiokarsinom, ekzoftalmus

Introduction

Metastaticorbital masses make up less than 5% of orbital tumors [1]. Most frequent metastatic cancers of the orbital are breast (52%), prostate (12%) and lung cancers (8%) [2]. Only ten cases of neuro-ophthalmologic and ocular presentations of cholangio-carcinoma have been reported in the literature [3-6].

Case Presentation

A 49-year-old female patient who admitted to orthopedics with low back and hip pain underwent a biopsy of the right femoral proximal after the bilateral T1A and T2A

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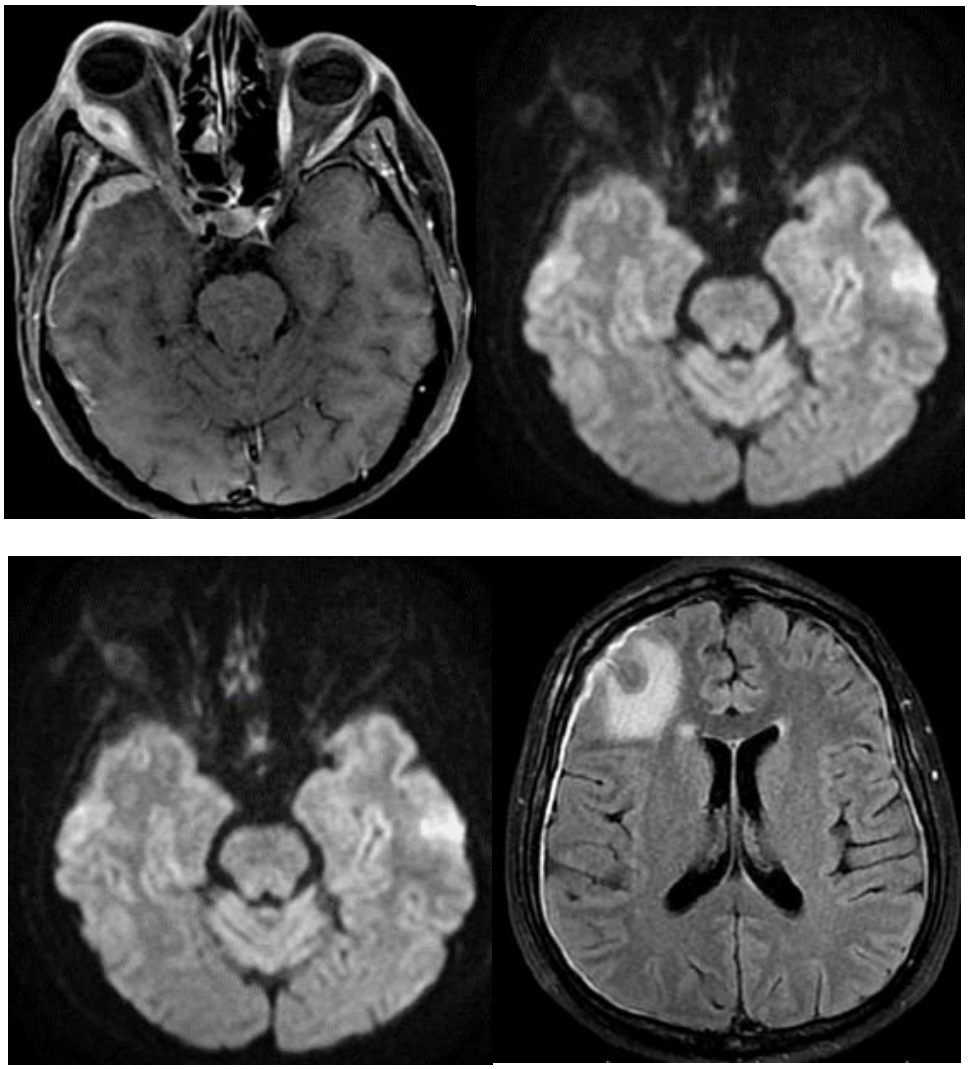

Figure 1a. In contrast T1 axial images, mass lesion in the right lateral rectus muscle, dural thickening and contrast involvement in the adjacent intracranial space and contrasting in subcutaneous plans are observed. 1b. Diffusion b 1000 MR images do not show diffusion limitation in the mass in the lateral rectus. 1c. In contrast axial FLAIR (c) and T1 weighted images (d), bilateral dural involvement as well as parenchymal extension and cerebral edema are seen to develop in the right frontal adjacent to dural involvement. 1d. In contrast axial FLAIR (c) and T1 weighted images (d), bilateral dural involvement as well as parenchymal extension and cerebral edema are seen to develop in the right frontal adjacent to dural involvement.

images in the patient's hip MRI showed diffused lesions suspected of metastasis on bone surfaces. As a result of the biopsy which revealed carcinoma metastasis, the patient admitted to the oncology outpatient clinic. In the computer tomography scans of the patient multiple metastatic mass lesions of 24x11 mm in size were detected in the liver parenchyma at the level of segment 7. A biopsy of the liver was performed on the patient. While waiting for the biopsy result, proptosis and a limitation of eye movement developed in the right eye of the patient. An orbital MR was performed on the patient. The patient's cranial and orbital MRI images are shown in figure 1a-1b-1c-1d. In the orbital and brain MRI images before and after contrast, soft tissue mass lesions in the lateral vicinity of the right orbita in the

right lateral rectus muscle which erase extraconal periorbital fat plans, with their central showing necrotic heterogeneous contrast involvement were observed. Exophthalmos was present in the ipsilateral glob.Pathologic contrast involvement was also seen in the subcutaneous soft tissue muscle plans in orbital neighborhood. In addition, irregular dural thickening and contrast were observed in the intracranial area adjacent to the right orbit, which was evaluated as dural involvement. In T1 and FLAIR images after contrast, dural involvement was observed not only in orbital proximity but also in the opposite cerebral hemisphere. Diffusion MRI images showed no restriction of diffusion in the lesions. With these findings, the lesions were primarily considered in favor of metastatic involvements. But in MRI images, because of ventilation losses in the right paranasal sinuses compatible with sinusitis and rapid progression of the patient's MRI findings, it was thought in the differential diagnosis, that the infection should be excluded and biopsy from the lacrimal gland was performed on the patient. While waiting for the biopsy result, empirical vancomsin, meropenem and amphotericin B were initiated.

The result of the liver biopsy of the patient was reported as cholangiocellular carcinoma.

The result of biopsy from the lacrimal gland was consistent with cholangiocellular carcinoma metastasis. Radiotherapy was planned for the eye and the whole brain of the patient. After radiotherapy, it was decided to start gemcitabine and cisplatin.

Discussion

The presentation of our case was not compatible with typical presentation of cholangiocarcinoma. Initially bone metastases were detected and metastasis of orbital and central nervous system developed during the examination process. CNS metastasis and orbital metastasis are rather rare in cholangiocarcinoma [7-9]. There are 26 CNS metastasis cases in the literature. The brain was reported as the site of metastasis in1.6% of patients with stage IV intrahepatic cholangiocarcinoma in a 2010-2015 review of US population. Orbital metastasis is also very rare and our case is the eleventh case in the literature. One case of a clival mass and sixth cranial nerve palsy, one case of metastasis to the medial rectus muscle and diplopia, two cases of metastasis to the occipital lobe and homonymous hemianopia, and one case of a hypercoagulable state-related stroke and homonymous hemianopia make up the five previously reported neuro-ophthalmologic presentations of cholangiocarcinoma[3]. A combination hepatocellular carcinoma/ cholangiocarcinoma that metastasized to the retina and vitreous was reported in one case, and there have also been two instances of cholangiocarcinoma that metastasized to the orbit and caused eye pain[5]. While, a case presenting with skin and orbital metastasis was reported in 2020 in Japan [10], in the same year metastatic cholangiocarcinoma presenting with 6th cranial nerve paralysis was reported from Miami [6].

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Original Article

Is Ruxolitinib an Effective and Safe Therapy for Chronic Myeloproliferative Diseases?

Ruksolitinib Kronik Miyeloproliferatif Hastalık için Etkili ve Güvenli Bir Tedavi mi?

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ABSTRACT

Introduction: Polycythemia vera (PSV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) are BCR/ABL negative chronic myeloproliferative neoplasms (CMPNs). As a result of abnormal clonal proliferation of hematopoietic cells, these disorders have a higher risk of thrombosis, bleeding, leukemic transformation, and worsening in quality of life. While stem cell transplantation is the sole curative option for CMPNs, symptomatic therapies gain importance. The purpose of this study is to assess the results of patients with CMPNs treated with ruxolitinib at our center.

Methods: The data from eighteen patients (six patients with PSV and twelve patients with PMF) who were treated with ruxolitinib at our center between January 2013 and January 2022 were analyzed in this retrospective cohort study.

Results: Six PSV patients who received ruxolitinib were included in the study. Three patients with splenomegaly previous to ruxolitinib, had a response of spleen volume, median of 6 months. There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment.

Twelve patients with PMF used ruxolitinib were included in the study. Spleen volume response was observed in six patients (50%) at a median follow-up of 12 months, while symptomatic response was observed in nine patients (75%) during a median of 15.5 months of ruxolitinib treatment. Any thrombolytic or cardiovascular complications were observed.

Discussion and Conclusion: Ruxolitinib is an appropriate and safe treatment option for patients who are not candidates for hematopoietic stem cell transplantation.

Keywords: ruxolitinib, myelofibrosis, Polycythemia vera, JAK2 V617F, spleen

ÖZET

Giriş ve Amaç: Polisitemi vera (PSV), esansiyel trombositoz (ET) ve primer miyelofibroz (PMF), BCR/ABL negatif olan kronik miyeloproliferatif hastalıklardır (KMPH). Bu hastalıklarda hematopoietik hücrelerde anormal klonal proliferasyon sonucu artmış tromboz, kanama, lösemik transformasyon riski yanı sıra hayat kalitesinde bozulmalar görülmektedir. Hastalıkların tedavisinde kök hücre nakli tek küratif seçenek iken semptomatik tedaviler ön plana çıkmaktadır. Bu çalışmada amaç, merkezimizde ruksolitinib ile tedavi edilen KMPH hastalarının sonuçlarını değerlendirmektir.

Yöntem ve Gereçler: Bu retrospektif kohort çalışmada Ocak 2013 ile Ocak 2022 tarihleri arasında merkezimizde ruksolitinib ile tedavi edilen 18 hastanın (altı hasta PSV ve on iki hasta PMF) verileri analiz edildi.

Bulgular: Ruksolitinib alan altı PSV hastası çalışmaya alındı. Ruksolitinib öncesinde splenomegalisi olan üç hastada, ortanca 6 aylık tedavi süresince dalak hacmi yanıtı gözlendi. Ortanca 6 aylık (2-52

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aralığında) ruksolitinib tedavisi boyunca hematolojik veya hematolojik olmayan yan etkiler, trombolitik veya kardiyovasküler komplikasyonlar veya lösemik transformasyon görülmedi.
PMF tanısı ile ruksolitinib kullanan on iki hasta çalışmaya dahil edildi. Altı hastada (%50) ortanca 12 aylık takipte dalak hacmi yanıtı gözlenirken, dokuz hastada (%75) medyan 15,5 aylık ruksolitinib tedavisi sırasında semptomatik yanıt alındığı gözlendi. Trombolitik veya kardiyovasküler komplikasyon gözlenmedi.
Tartışma ve Sonuç: Hematopoietik kök hücre nakli için aday olmayan hastalarda ruksolitinib uygun ve güvenli bir tedavi seçeneğidir.

Anahtar Kelimeler: ruksolitinib, myelofibrozis, Polisitemia vera, JAK2 V617F, dalak

Introduction

Polycythemia vera (PSV), essential thrombocytosis (ET), and primer myelofibrosis (PMF) are chronic myeloproliferative diseases (MPN) that are BCR/ABL negative. Polycythemia vera is a BCR/ABL negative chronic MPN characterized by abnormal clonal proliferation of hematopoietic cells, which results in elevated peripheral blood cells, increased thrombotic and hemorrhagic events, and the possibility of disease progression to PMF or acute myeloid leukemia (AML) [1]. Hydroxyurea (HU) is the first line of cytoreductive treatment [2]. If a patient is intolerant or non-responsive to HU and experiences an unexpected side effect, ruxolitinib is considered a second-line treatment [2]. The RESPONSE and RESPONSE-2 clinical trials demonstrated ruxolitinib's safety and efficacy in PSV patients [3, 4].

Primary myelofibrosis is a type of MPN characterized by bone marrow fibrosis, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Among the MPNs, PMF has the worst prognosis, with patients at risk of early death from disease progression, leukemic transformation, thrombohemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Agents such as HU and ruxolitinib are used to treat symptoms and splenomegaly in patients who are not candidates for hematopoietic stem cell transplantation (HSCT). The first-line treatment for MF-related splenomegaly is HU [5]. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials demonstrated the safety and efficacy of ruxolitinib.

Ruxolitinib is recommended as a second-line treatment for PSV and PMF at our institution. We aimed to evaluate the characteristics and outcomes of MPN patients treated with ruxolitinib at our institution.

Methods

This retrospective cohort study examined data from patients with PSV and PMF treated at our center between January 2013 and January 2022, were analyzed. We evaluated the eighteen patients (six with PSV and twelve with PMF) who were treated with ruxolitinib. Manual file records and electronic medical record systems were used to obtain clinical information from patients. The demographics, comorbidities, disease diagnosis date, disease type, disease risk groups, therapy and response, last control date, and survival status of all patients were documented. The 2016 WHO classification was used for diagnosis [6].

The local human research ethics committee approved this study. All procedures performed in studies involving human participants were under the national research committee’s ethicalstandards and with the 1964 Helsinki Declaration and its later amendments or comparableethical standards. The study was carried out with the permission of the Ethics Committee of Ankara Onology hospital (24.08.2022 /Decision number: 2022.08/1981).

Table 1. Characteristics of patients with PSV who were treated with ruxolitinib

Parameters	N =6, (%)
Age, median (range min-max), years	63 (59-72)
Gender (M/F)	2 (33.3) / 4 (66.7)
JAK2 V617F, allele burden, median (range min-max), %	35 (20-67)
Splenomegaly	3 (50)
Duration between the initiation of ruxolitinib treatment and the diagnosis of the disease, median (min-max), months	30.5 (8-74)
Duration of ruxolitinib therapy, median (min-max), months	6 (2-52)
Disease duration, median (min-max), months	55 (10-82)

PSV; polycythemia vera, M; male, F; female

Statistical Analysis

The SPSS software (Version 25.0; Armonk, NY: IBM Corp.) was used for statistical analysis. The numerical variables were presented as medians (min-max), while the categorical variables were presented as ratios. Disease duration was calculated as the time defined as the period between the date of PSV or PMF diagnosis and the date of last follow-up or death from any cause.

Results

Polycythemia vera

Between January 2000 and January 2022, 80 PSV patients were diagnosed, but only six of them received ruxolitinib treatment and were included in the study. The average age of the patients was 63 years (range 59-73 years). JAK2 V617F and cytogenetic abnormalities were tested in all patients. The JAK2 V617F mutation was found in all the patients, and the median allele load was 37%. (range 20-67%). They didn't have any cytogenetic abnormalities or extra mutations like calreticulin (CALR) or myeloproliferative leukemia (MPL).

In the bone marrow examination, four patients (66%) had grade 2/3 fibrosis. Half of the patients had splenomegaly at the time of presentation. Table 1 summarizes the characteristics of PSV patients treated with ruxolitinib.

In the six patients treated with ruxolitinib as a second-line treatment, the median duration was 30.5 (range 8-74) months between starting ruxolitinib and disease diagnosis. The reasons for changing to ruxolitinib as a second-line treatment were oral ulcers (two patients) after HU, symptomatic splenomegaly (two patients), and HU-intolerant patients (two patients).

There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment. After a median of 6 months, three patients with splenomegaly prior to ruxolitinib had normal spleen volume (range 3-12 months). Only one patient had transformed myelofibrosis after 14 months of ruxolitinib treatment.

Myelofibrosis

Between January 2000 and January 2022, twelve patients were diagnosed with PMF and treated with ruxolitinib. The patients' median age was 68 years (range 25-80 years), with eight (66.7%) females. All cases were evaluated for JAK2 V617F, CALR, and MPL mutations as well as cytogenetic abnormalities.

Table 2. Characteristics of patients with PMF who were treated with ruxolitinib

Parameters	N = 12, (%)
Age, median (range min-max), years	68 (25-80)
Gender (M/F)	4 (33.3) / 8 (66.7)
Genetic mutations, JAK2 V617F mutation CALR mutation MPL mutation Triple negative	 8 (66.7) 1 (8.3) 0 2 (16.7)
JAK2 V617F, allele burden, median (range min-max), %	80 (22-91)
Bone marrow fibrosis, Grade 2/3 Grade 3/3	 10 (83.3) 2 (16.7)
Risk stratification, median (min-max) MIPSS-70 DIPSS-plus	 5 (2-7) 1 (0-1)
Splenomegaly	12 (100)
Duration between starting ruxolitinib and disease diagnosis, median (min-max), months	16.5 (8-74)
Duration of ruxolitinib therapy, median (min-max), months	12.5 (5-60)
Disease duration, median (min-max), months	48.5 (7-214)

PMF; primary myelofibrosis, M; male, F; female, CALR; Calreticulin, MPL; myeloproliferative leukemia

The JAK2 V617F mutation was found in eight patients (66.7%), with a median allele load of 80% (range 22-91%). Two (16.7%) of the patients had triple-negative disease. None of them had any cytogenetic abnormalities. Technical difficulties limited the evaluation of high molecular risk (HMR) mutations. In risk stratification, the median MIPSS-70 was 5 (2-7), while the DIPSS-plus was 1 (0-1). Four patients experienced ET and one had PSV before being diagnosed with PML. At the time of presentation, all the patients had splenomegaly. Table 2 summarizes the characteristics of PMF patients treated with ruxolitinib.

Because of HU resistance, nine (75%) patients received ruxolitinib as a second-line treatment. Ruxolitinib was used as first-line therapy in three patients. The median time between initiating ruxolitinib and disease diagnosis was 16.5 (range 8-74) months. Six patients (50%) had a response to decreased spleen volume (median 12 (6-24) months) and nine patients (75%) had a symptomatic response during a median of 15.5 (range 5-60) months of ruxolitinib treatment.

Three patients (25%) discontinued treatment; one suffered skin ulcers, one had disease progression with increased spleen volume, and one had AML transformation. One patient had thrombocytopenia during a median of 12.5 (range 5-60) months of ruxolitinib treatment, which was resolved by lowering the ruxolitinib dose. There were no thrombolytic or cardiovascular complications to report. Only one female patient transformed AML after 13 months of treatment with ruxolitinib. The patient had a long disease

duration (191 months), post-ET PMF, grade 2/3 fibrosis in the bone marrow, a negative JAK2 mutation, and a positive CALR mutation. Two patients died during therapy from unrelated causes of the disease.

Discussion

Polycythemia vera (PSV) is a condition characterized by clonal proliferation of hematopoietic cells, which results in elevated red blood cells, increased thrombotic events, and can progress to fibrosis or leukemia. The treatment's goal is to avoid thrombotic events and fibrotic/leukemic change while also improving quality of life. Ruxolitinib is used as a second-line treatment in HU-intolerant or nonresponder patients. Ruxolitinib was found to be safe and effective in PSV patients with and without splenomegaly in the RESPONSE and RESPONSE 2 clinical trials.

In our study, six patients with PSV who were intolerant or refractory to HU were treated with ruxolitinib. Three patients who had splenomegaly before ruxolitinib had normal spleen volume after a median of 6 months (range 3-12 months).

The RESPONSE study compared ruxolitinib to the best available treatment (BAT) in HU refractor/intolerant patients [3]. The trial results showed that ruxolitinib was superior to BAT in both hematocrit level control and lowering spleen volume [3]. Hematological and non-hematological adverse effects are comparable between the two arms of the trial; however, thrombotic events are more prevalent in the BAT arm [3]. Our patients with or without splenomegaly, received well-tolerated ruxolitinib treatment. During the median of 5.5 months (range 2-52 months) of ruxolitinib treatments, we did not observe any hematological or non-hematological side effects, thrombolytic and cardiovascular complications, or leukemic transformation. Only one female patient transformed myelofibrosis after 14 months of treatment with ruxolitinib. The patient had a long duration of disease (80 months) and splenomegaly, grade ⅔ fibrosis in the bone marrow, and a high JAK2 allele load.

Splenomegaly is found in 30-35% of PSV patients at the time of diagnosis, and it is considered to be associated with progressive disease [2]. These splenomegaly patients are more prone to develop myelofibrosis and AML [2]. Grade 2-3/3 bone marrow fibrosis is reported in 20-51% of PSV patients [7, 8], and these patients are more likely to progress to myelofibrosis [9]. Tefferi et al. demonstrated that the persistence of leukocytosis, fibrosis in the bone marrow at the time of diagnosis, and more than 50% JAK2 allele burden increase the probability of myelofibrosis transformation [10].

The RELIEF study demonstrated that ruxolitinib therapy reduced symptoms in PSV patients [11]. One of our study's shortcomings was that we did not evaluate patients' symptoms. The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. A meta-analysis reported that patients on ruxolitinib therapy had fewer thrombotic events, but the difference was not statistically significant [12].

Myelofibrosis is a form of MPN characterized by fibrosis of the bone marrow, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Patients with PMF suffer an increased risk of death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials established the safety and efficacy of ruxolitinib in patients with PMF [13, 14].

In our study, twelve patients were diagnosed with PMF and treated with ruxolitinib (nine patients as second-line and three patients as first-line). In the COMFORT-I trial, ruxolitinib was found to be more effective than placebo at 24 weeks in reducing spleen volume and improving the overall symptom

score [13]. In the COMFORT-2 trial, ruxolitinib was compared to the best available therapy in high-risk PMF patients; spleen volume reduction was better in the ruxolitinib arm (28% vs. 5%) [14]. During a median of 15.5 months of ruxolitinib treatment, 50% of our patients had a response to decreasing spleen volume, and 75% had a clinical response. Three patients (25%) discontinued treatment; two developed skin ulcers; and one patient had disease progression with increased spleen volume.

The JAK2 V617F mutation was reported in more than half of PMF patients, which is similar to our findings [15]. Another study from our center showed that 25% of all PMF patients had JAK2 mutations [16]. Triple-negative PMF is detected in 8-10% of patients [15], while in our study, we found triple-negative PMF in 16.7% of patients, and we only included patients receiving ruxolitinib. If we investigate all PMF patients, the percentage may be similar to the literature.

The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. AML transformation occurs in 3.9% of PMF patients, with the majority of them previously treated with alkylating drugs [17]. High levels of circulating blast (>3%) and thrombocytopenia (<100.000/mm^3) are independent risk factors for AML transformation [18]. In our study, one patient (8.3%) developed AML and was treated with HU before ruxolitinib; she had thrombocytopenia but no more than 3% circulating blast.

Therefore, PSV and PMF are diseases that can be treated with ruxolitinib. It is highly effective in relieving symptoms and reducing splenomegaly. In this study, we observed that ruxolitinib was well-tolerated, effective, and had few side effects. The effect of ruxolitinib on AML transformation and thromboembolic events is unclear; a larger series is required. For patients who are not candidates for HSCT, ruxolitinib is an appropriate and safe treatment option.

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Original Article

Is The COVID-19 Pandemic Reason, Shortage Result? A Survey Study on Drug Shortages in Turkish Oncology Clinics

COVID-19 Pandemi Nedeni, Kıtlık Sonucu mu? Türk Onkoloji Kliniklerinde İlaç Eksikliği Üzerine Bir Araştırma Çalışması

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ABSTRACT

Aim: The rapid development of the drug industry led to a great spectrum of medical treatment, especially in oncology practice. The prescribed drug alternations increased three times in the United States. Also, the increased drug numbers led to drug shortages, which doubled during this period in the oncology era. In this study, we try to evaluate the oncology clinics' drug supply last year in the eyes of oncology practitioners

Methods: We conducted an online questionnaire via Google Forms on the drug shortages which are faced last year by oncologists in Turkey. Our study is a cross-sectional study.The SPSS 25 software was used for statistical analysis

Results: Eighty-nine percent of the participants declared they had a drug shortage last year. The most affected drug groups were chemotherapeutics (61,4%), biologic agents (anti-VEGF, anti-EGFR agents, etc.) (56,8%), immunologic drugs (available anti-PD1 drugs) (54,5%), and supportive medicines (Folinic acid, GCSF, etc.) (42%). 61 percent of the oncologists referred their patients to other clinics to get over the drug shortage. The most common reasons were supply problems (70%), drug company-related concerns due to exchange rates (68%), hospital budget problems (48%), and bureaucratic procedures (47%). There was a significant difference between drug shortage and participants' hospitals. Also, the shortage has significantly lasted longer in university hospitals.

Conclusion: Our study showed an extensive drug shortage in oncology clinics last year independent of drug types. University hospitals had reported worse results compared with other organizations. There is an urgent need for further evaluation of drug shortages and the availability of oncologic drugs and the prognostic effect of this phenomenon..

Key words: COVID-19, Pandemic, Drug shortages, Oncology

ÖZET

Amaç: İlaç endüstrisinin hızlı gelişimi, özellikle onkoloji pratiğinde geniş bir tıbbi tedavi yelpazesine yol açmıştır. Amerika Birleşik Devletleri'nde 2005 ile 2011 yılları arasında reçete edilen ilaç değişimleri üç kat arttı. Ayrıca artan ilaç sayıları, onkoloji çağında bu dönemde ikiye katlanan ilaç kıtlığına yol açtı. Bu çalışmada onkoloji pratisyenlerinin gözünden onkoloji kliniklerinin geçen yılki ilaç arzını değerlendirmeye çalıştık.

Yöntemler: Türkiye'de onkologların geçtiğimiz yıl yaşadığı ilaç kıtlığı ile ilgili Google Forms üzerinden online bir anket gerçekleştirdik. Çalışmamız kesitsel bir çalışmadır. İstatistiksel analiz için SPSS 25 programı kullanıldı. Tanımlayıcı istatistikler frekans dağılımı olarak sunuldu Bu çalışmada, iki yönlü istatistiksel analizler yapıldı ve $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Katılımcıların yüzde seksen dokuzu geçen yıl ilaç sıkıntısı yaşadıklarını beyan ettiler. En çok etkilenen ilaç grupları kemoterapötikler (%61,4), biyolojik ajanlar (%56,8), immünolojik ilaçlar (%54,5) ve destekleyici ilaçlar (%42) idi. Onkologların yüzde 61'i hastalarını ilaç sıkıntısından kurtulmak için

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başka kliniklere yönlendiriyor. En sık nedenler tedarik sorunu (%70), döviz kurundan kaynaklanan ilaç firmaları kaygısı (%68), hastane bütçe sorunları (%48) ve bürokratik işlemler (%47) idi. İlaç sıkıntısı ile katılımcıların hastaneleri arasında anlamlı bir fark vardı. Ayrıca, üniversite hastanelerinde açık önemli ölçüde daha uzun sürmüştür

Sonuç: Çalışmamız, ilaç türlerinden bağımsız olarak geçen yıl onkoloji kliniklerinde yaygın bir ilaç sıkıntısı olduğunu gösterdi. Üniversite hastaneleri, diğer kuruluşlara kıyasla daha kötü sonuçlar bildirmişti. İlaç kıtlığının ve onkolojik ilaçların mevcudiyetinin ve bu fenomenin prognostik etkisinin daha fazla değerlendirilmesine acil bir ihtiyaç vardır.

Anahtar kelimeler: COVID-19, Pandemi, İlaç kıtlığı, Onkoloji

Introduction

The rapid development of the drug industry led to a great spectrum of medical treatment, especially in oncology practice. The prescribed drug alternations increased three-fold between 2005 and 2011 in the United States. Also, the increased drug numbers led to drug shortages, which doubled during this period in the oncology era [1]. The shortages in oncology practice may be related to serious damage to patient survival altered dosing, treatment gaps, and inferior protocols. Specific precautions were exercised in this era [2]. Although some studies tried to elucidate this area, the consequences of drug shortages are still inconclusive. Most of the studies are based on specific drugs or hospitals. Some studies tried to explain the situation with surveys [3,4].

After the start of the COVID-19 pandemic, multiple problems occurred in cancer treatment, consisting of increased workload, decreased supply of medical professionals, and materials with increased patient problems. Multiple studies showed the changes in oncology practice during the time of the COVID-19 pandemic. Increased workload, and decreased patient adherence due to COVID-19 fear and social regulations. [5,8]. The economic problems of countries and states are also evaluated during the pandemic and may be one of the problems leading to drug shortages [9]. During the pandemic period, drug shortages are foreseen with the overwhelming healthcare system. The breakdown of the supply-demand chain is speculated to have a great impact on medical drugs [10].

In this study, we try to evaluate the oncology clinics' drug supply last year in from the perspective of oncology practitioners.

Materials and Methods

We conducted an online questionnaire via Google Forms on the drug shortages which are faced last year by oncologists in Turkey. Of more than seven hundred, 95 oncologists answered the survey. Two follow-up emails and reminders were sent in 2 weeks to increase the number of responders and the study was completed. The survey was voluntary.

The survey had 3 questions about the position, experience, and work conditions of the participants. The questionnaire was consisting of fifteen questions to determine drug types had a shortage, time, reasons, solutions, and the most affected diagnosis in terms of effect and complications. Also, the difference between current optimal medical treatments and available practice was questioned. (see Supplemental Appendix 1 in the online version)

The SPSS 25 software was used for statistical analysis. Descriptive statistics were presented as frequency distribution and percentage. The chi-square or Fisher’s Exact tests were used to compare independent categorical variables. In this study, two-way statistical analyses were performed, and $p<0.05$ was considered statistically significant.

Table 1: The features of the study population

Age (years)	30-40	41-50	51-60	61-70	
n (%)	39 (41,1)	34 (35,8)	17 (17,9)	5 (5,3)	
Experience(years)	5 or less	6-10	11-20	21-30	
n (%)	25 (26,3)	26 (27,4)	27 (28,4)	17 (17,9)	
Affiliation	State H.	University H.	E & R Hospital	Private H.	City H.
n (%)	3 (3,2)	39 (41,1)	19 (20)	27 (28,4)	7 (7,4)
Academic Position	Fellow	Specialist/Assistant Professor	Associated Professor	Professor	
n (%)	19 (20)	21 (22,1)	28 (29,5)	27 (28,4)	

H.: Hospital; E&R: Education and Research;

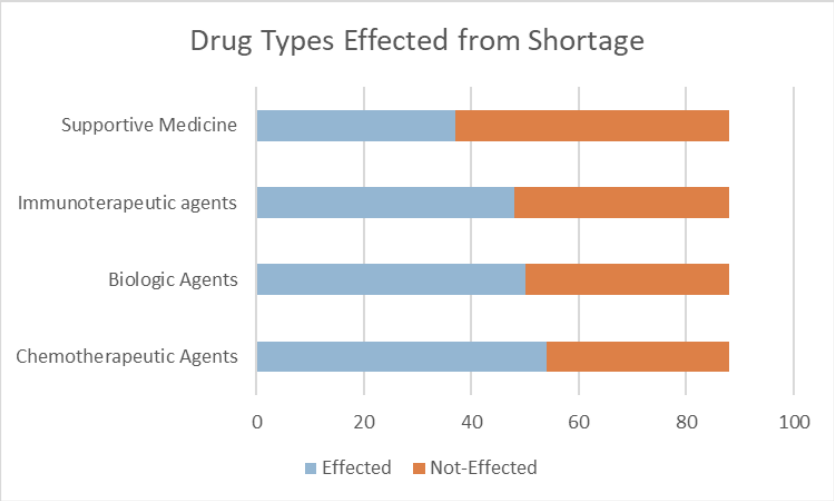

Figure-1: The drug types had shortage according to oncologists

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations. (Date & Number:01.07.2022 & 2022/8). An informed consent form was obtained from all patients.

Results

Ninety-five oncologists were included in the study. Forty-one percent of the participants were aged between 30 and 40. The three groups were stratified by experience, had roughly the same number of participants, and did not differ significantly. (5 or less; 6 to 10 and 11-20 years) The most frequent academic positions were associated professors and professors with nearly thirty percent. Approximately forty percent of the oncologists were working in a university followed by private hospitals with 28 percent. (Table-1)

Eighty-nine percent of the participants declared they had a drug shortage last year. The most affected drug groups were chemotherapeutics (61,4%), biologic agents (anti-VEGF, anti-EGFR agents, etc.) (56,8%), immunologic drugs (available anti-PD1 drugs) (54,5%), and supportive medicines (Folinic acid, GCSF, etc.) (42%). Sixty-one percent of the oncologists referred their patients to other clinics to get over the drug

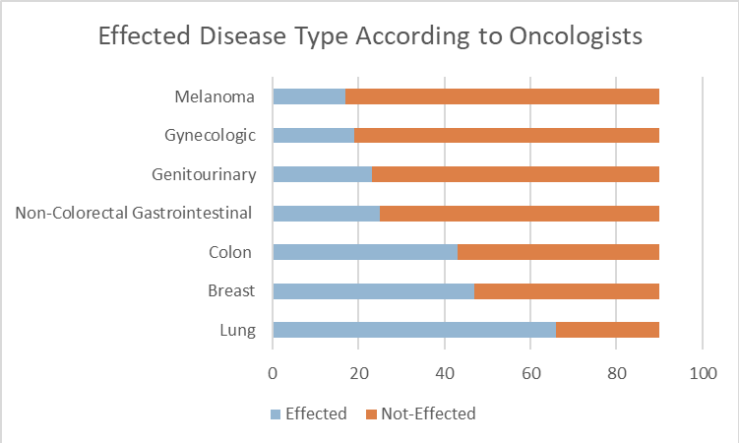

Figure-2: Most affected diseases from shortage according to oncologists

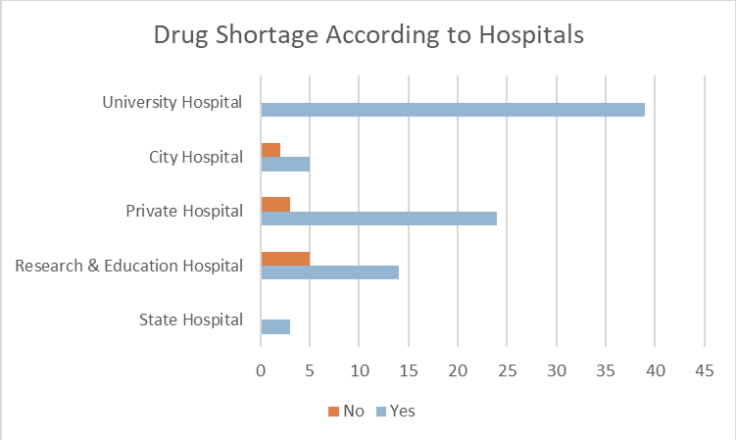

Figure-3: Drug shortage rates according to hospital types

shortage. (Figure-1) Nearly half of the participants selected alternative treatment options and 17 percent had to choose inferior treatments. Eighty-three percent of the study population declared the drug shortage lasted three months. The most common reasons were supply problems (70%), drug company-related concerns due to exchange rates (68%), hospital budget problems (48%), and bureaucratic procedures (47%).

Two-thirds of the oncologists thought that the survival of the patients was affected negatively, and nearly fifty percent were concerned about increased complication rates. Leading patient groups affected by shortages were lung, breast, and colon cancer patients respectively. (73,3%; 52,2%; 47,8%)

Ninety percent of the participants did not think current optimal practice fit their daily practice and over ninety percent thought that most of the incompetence was in lung cancer. Seventy-five percent of the oncologists foreseen the difference in optimal treatment and daily practice in Turkey will increase.

There was a significant difference between drug shortage and participants' hospitals. (p=0,047) (Figure-2) Also the shortage has significantly lasted longer in university hospitals. (p= 0,013) (Figure-3)

Discussion

This study showed there was a high-rate drug shortage in Turkey in oncology practice last year. Although the most affected drug types were chemotherapeutic agents, biologic and immunotherapy drugs have high rates of shortages. Our study represented nearly ten percent of the Turkish Oncology Society. Also, most of the participants had an academic

degree which may be related to control of the department in terms of drug recipients of the unit.

Turkish oncology association tried to take preventive causations via publishing guidelines like many other associations. No specific precautions were exercised for preventing drug shortages during this period by authorities [11]. Some studies showed minimal effect on outcomes of chemo-therapeutic agents' shortages. Most of the drugs that had shortages in studies were Fluorouracil, doxorubicin, and cytarabine [3,12]. However, it is stated that there may be a shortage of cisplatin and carboplatin recently. For this, it is emphasized that medical oncologists should be in constant communication globally and the importance of early detection [13]. In another study, an increase occurs in the shortage of sedative analgesics during the covid-19 pandemic. This phenomenon may also influence the cancer treatment especially in ICUs and operation rooms [14]. Although tocilizumab was used in a case study to prevent the limitations of mechanical ventilators and other drugs used in the treatment of covid, it caused an increase in the drug limitation in rheumatoid arthritis [15]. Although we did not perform a drug specification, it is possible to have the same drug shortages in Turkey. was limited data on shortages of biological and immunotherapy drugs used in oncology. We only know about There the BCG shortage in bladder cancer in the COVID-19 Era [16]. Although a shortage cannot be determined for these groups of drugs, most of the immuno-therapeutic agents have limitations in several countries due to their costs including Turkey. Prior studies evaluated nationwide or hospital-based drug shortages. Reasons and potential solutions for unavailability of agents evaluated [3,17]. On the other side, some studies evaluate the effect of drug shortages on patients. The alternative strategies were discussed with patients by oncologists, physicians, and pharmacists [18]. Although we don't know the attitudes of patient relations in our study, high rates of referral of patients to other hospitals may be related to informing patients about drug shortages.

Our study showed that oncologists are concerned about increased toxicity with unfamiliar drug utility or alternative treatment. Also, a study showed increased toxicity of alternative drug combinations due to altered doses or lack of knowledge about unfamiliar drugs [12]. The drug shortages are affecting both oncology and hematology as well as the adult and pediatric population [19,20]. Our study only showed results of adult solid organ malignities as Turkish oncologists are mainly responsible for treating this population excluding a few multi-disciplinary facilities. Also, a few centers that are treating oncology patients, including pulmonary medicine and gynecology clinics cannot be assessed by our survey study. This group of practitioners is very small and doesn't have the permission of using several targeted therapies which makes their evaluation inconclusive.

Different from other studies we also named another issue, which originated from different hospital types. University hospitals in Turkey are known to have low funds compared to private and ministry of Health-funded hospitals. The possible results of long and deep drug shortages in university hospitals may be related to this reason. To our knowledge, this is the first study evaluating the drug shortage in the oncology area in the pandemic era.

The data in this study are presented based on the statements of the oncologists participating in the study and are not official data. Inclusion of the subjective opinions of the authors is one of the limitations of our study. Although the study was a cross-sectional survey yet it could only evaluate the last year which was the second year of the pandemic. In addition, the

lack of any previous survey or analytical study evaluating the oncological drug shortage in Turkey was the reason why our study could not compare with the shortage situation in the pre-pandemic period. The COVID-19 pandemic had multiple effects on the Turkish health care system, especially via economic end-points. We found high rates of drug shortage by survey, but this might be related to low survey response rates of physicians who had not faced drug shortages.

Our study showed an extensive drug shortage of over fifty percent in oncology clinics last year independent of drug types. University hospitals had reported worse results compared with other organizations and may need more attention for drug supply. There is an urgent need for further evaluation of drug shortages and the availability of oncologic drugs and the prognostic effect of this phenomenon. The oncologists think the shortage of oncologic drugs will be a long lasting problem and optimal treatment may not be delivered in near future in Turkey.

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Original Article

The Prognostic Value of the Preoperative Geriatric Nutritional Risk Index in Elderly Colon Cancer Patients Underwent Curative Resection

Küratif Rezeksiyon Yapılan Yaşlı Kolon Kanseri Hastalarında Preoperatif Geriatrik Beslenme Risk Indeksinin Prognostik Değeri

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ABSTRACT

Introduction: The aim of this retrospective study was to assess the prognostic significance of the geriatric nutritional risk index (GNRI) for elderly patients diagnosed with early-stage colon cancer.

Materials and Methods: Medical records of 114 elderly patients diagnosed with colon cancer who underwent curative surgery and received chemotherapy were analyzed. The calculation of the GNRI was derived from the measurement of serum albumin levels and the assessment of body weight. Patients were divided into two nutritional risk categories: low-GNRI (GNRI: <98), and high-GNRI (GNRI: ≥98) and compared.

Results: The 5-year overall survival (OS) rate of the low-GNRI group was significantly lower than that of the high-GNRI group (65.7% vs. 91.1%, p= 0.002). There was also a statistically significant difference in the 5-year recurrence-free survival (RFS) rate of the two groups (66.7% vs. 90.8%, p <0.001). The multivariate Cox regression analysis identified tumor sidedness (p= 0.038) and GNRI (p = 0.042) as independent prognostic factors for only OS.

Conclusion: The GNRI is an easily applicable and valuable prognostic factor for OS in elderly patients diagnosed with early-stage colon cancer. The current investigation indicates that a low-GNRI was correlated with poor OS.

Key words: Colon cancer, elderly, nutrition, prognosis

ÖZET

Giriş: Bu çalışmanın amacı, erken evre kolon kanseri tanısı almış yaşlı hastalarda geriatrik beslenme risk indeksinin (GNRI) prognostik önemini retrospektif olarak değerlendirmektir.

Gereç ve Yöntem: Küratif cerrahi uygulanan ve kemoterapi alan kolon kanseri tanılı 114 yaşlı hastanın tıbbi kayıtları incelendi. GNRI, serum albümin düzeyi ve vücut ağırlığı kullanılarak hesaplandı. Hastalar düşük GNRI (GNRI: <98) ve yüksek GNRI (GNRI: ≥98) kategorilerine ayrılarak kıyaslandı.

Bulgular: Düşük GNRI grubunun 5 yıllık genel sağkalım oranı, yüksek GNRI grubundan anlamlı derecede düşüktü (%65.7'ye karşılık %91.1, p= 0.002). İki grubun 5 yıllık nükssüz sağkalım oranlarında da istatistiksel olarak anlamlı bir fark vardı (%66,7'ye karşı %90,8, p <0,001). Yapılan çok değişkenli Cox regresyon analizi, yalnızca tümör tarafı (p= 0.038) ve GNRI'yi (p = 0.042) genel sağ kalım için bağımsız prognostik faktörler olarak tanımladı.

Sonuç: GNRI, erken evre kolon kanseri tanısı almış yaşlı hastalarda genel sağ kalım için kolay uygulanabilir ve değerli bir prognostik faktördür. Araştırmamız, düşük bir GNRI'nin azalmış genel sağ kalım ile ilişkili olduğunu göstermektedir.

Anahtar kelimeler: Beslenme, kolon kanseri, prognoz, yaşlı

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Introduction

Malnutrition occurs frequently among cancer patients, and according to several studies, nutritional status is significantly associated with colon cancer patient survival [1-3]. There are numerous nutrition-related tools, such as body weight, prognostic nutritional index (PNI), and controlling nutritional status (CONUT) score [4-7]. The geriatric nutritional risk index (GNRI), measured by the serum albumin level and the ideal body weight, is a simple screening tool to evaluate nutritional-related risk. It was first defined by Bouillanne et al. to estimate the risk of morbidity and mortality in elderly patients [8]. It has also been reported that a lower GNRI can predict longer hospitalization and long-term mortality in elderly patients diagnosed with chronic kidney disease, congestive heart failure and sepsis [9-13]. Regarding the clinical significance of GNRI in cancer patients, there are many studies that revealed the prognostic role of GNRI in various cancers, including gastric, head and neck, pancreatic and lung cancer [14-17]. A few studies have been conducted to investigate the correlation between the GNRI and the outcomes of survival and recurrence in patients diagnosed with colon cancer.

In our study, we aimed to determine whether GNRI is an accurate prognostic factor for recurrence free survival (RFS) and overall survival (OS) in elderly patients with early-stage colon cancer patients who underwent curative resection and received chemo-therapy.

Methods

Patients and data

The data of 480 patients diagnosed and followed with colon cancer at a tertiary cancer center between 2011 and 2019 were analyzed. A total of 204 patients were excluded from the study because they were younger than 65 years of age and stage IV, while 71 patients were excluded because of not receiving chemotherapy. Ninety-one patients with Stage I were excluded because they did not attend their follow-ups regularly and therefore the dates of recurrence and death could not be reached. Finally, the data from 114 patients were analyzed. We excluded patients who died within the first month of the operation due to post-operative complications and who had co-morbidities (i.e. chronic renal failure, liver failure, nephrotic syndrome) causing hypoalbuminemia.

Medical records revealed clinical and pathological information including age, gender, time of operation, preoperative body weight, height and albumin level, tumor sidedness, tumor invasion depth, lymph node metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), differentiation type, and recurrence time. The American Joint Committee on Cancer Tumor Node Metastasis (TNM) classification system was utilized for staging [18].

Preoperative weight and height data of the patients were collected, and body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). GNRI was calculated as: GNRI = 1.489 x serum albumin (g/l) + 41.7 x current body weight/ideal body weight. As previous studies reported, patients were divided into two nutritional risk categories: low-GNRI (GNRI: <98), and high-GNRI (GNRI: ≥98) [19, 20]. Patients with a high-GNRI were considered high risk for malnutrition, while patients in the low-GNRI category were considered low risk.

Statistical Analyses

The continuous variables were reported as means and standard deviations (SD). Using Student's t-test, the means were compared. The chi-square test or Fisher's exact test was used to compare groups whose categorical variables were calculated as numbers and

Table 1. Clinicopathological features of the patients according to GNRI groups

Features		GNRI≥ 98 (n= 79, %)	GNRI< 98 (n= 35, %)	p-value
Age		67 (65-76)	68 (65-84)	
Gender	Male	45 (57%)	19 (54.3%)	0.474
	Female	34 (43%)	16 (45.7%)	
Diabetes mellitus	No	64 (81%)	25 (71.4%)	0.642
	Yes	15 (19%)	10 (28.6%)	
BMI	<25	10 (11.5%)	7 (25.9%)	0.068
	≥25	77 (88.5%)	20 (74.1%)	
Tumor sidedness	Right	14 (51.9%)	24 (27.6%)	0.02
	Left	13 (48.1%)	63 (72.4%)	
TNM Stage	II	43(54.4%)	16 (45.7%)	0.256
	III	36(45.6%)	19 (54.3%)	
T stage	T1/T2	5 (6.3%)	1 (2.9%)	0.400
	T3/T4	74 (93.7%)	34 (97.1%)	
LN metastases	No	43 (54.4%)	16 (45.7%)	0.256
	Yes	36 (45.6%)	19 (54.3%)	
Differentiation	Well	17 (21.5%)	5 (14.3%)	0.472
	Moderate/poor	59 (74.9%)	29 (82.9%)	
PNI	No	58 (73.4%)	23 (65.7%)	0.703
	Yes	12 (15.2%)	7 (20%)	
LVI	No	49 (62%)	18 (51.4%)	0.244
	Yes	27 (34.2%)	13 (37.1%)	
Perforation/obstruction	No	64 (81%)	30 (85.7%)	0.374
	Yes	15 (19%)	5 (14.1%)	

Abbreviations: BMI: Body mass index; GNRI: Geriatric nutritional risk index; LVI:Lymphovascular invasion; LN:Lymph node; PNI: Perineural invasion

percentages. Overall survival (OS) was defined as the interval between operation and death. The definition of recurrence-free survival (RFS) was the duration between colon cancer surgery and recurrence of the disease. Survival curves were calculated using the Kaplan-Meier method. The log-rank test was applied to determine the differences between the curves. The hazard ratios (HRs) were derived using Cox regression analyses. All variables with a p value <0.05 in the univariate analysis were included in multivariate Cox regression analysis. P value< 0.05 was regarded as statistically significant, and 95% confidence interval (CI) was determined. SPSS software (version 27.0) was utilized for all statistical analyses.

Ethics Committee Approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the institutional ethics committee (date: July 11, 2023, no: 952070b3-f214-466b-bea8-c8bb6ed6700a) and conducted in accordance with the related privacy statements and applicable regulatory requirements.

Results

Basic characteristics and pathological features

The median age of the 114 patients was 67 (range 65-84) years; 64 (56.1%) patients were male. The number of patients with T1/T2 was 6 (5.3%), while 108 (94.7%) of the patients

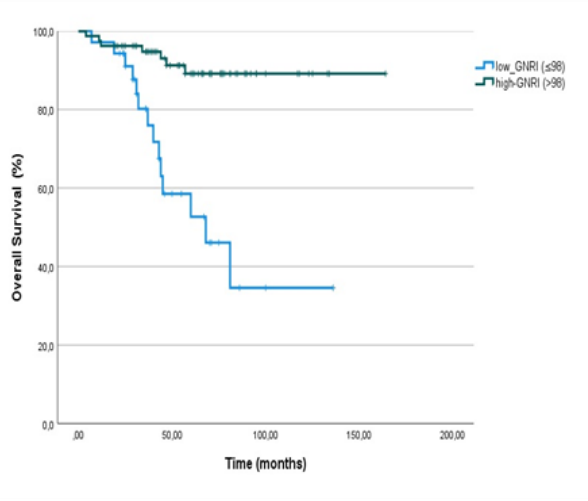

Figure 1. Kaplan Meier analyses of overall survival according to GNRI.

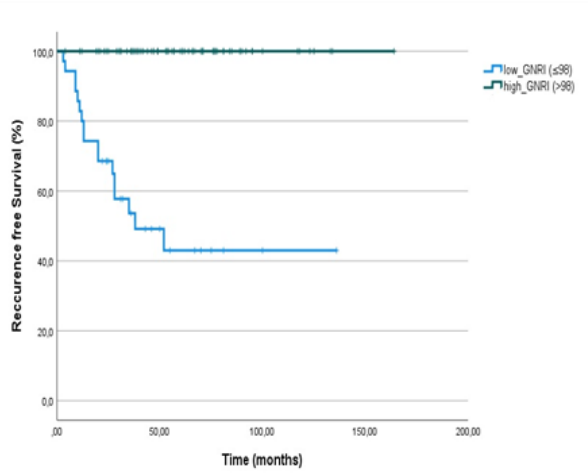

Figure 2. Kaplan Meier analyses of recurrence free survival according to GNRI.

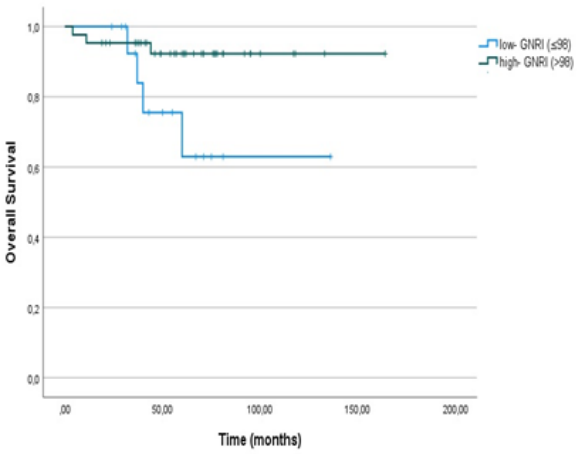

Figure 3. Estimates of overall survival by Kaplan-Meier according to the GNRI for stage 2 patients.

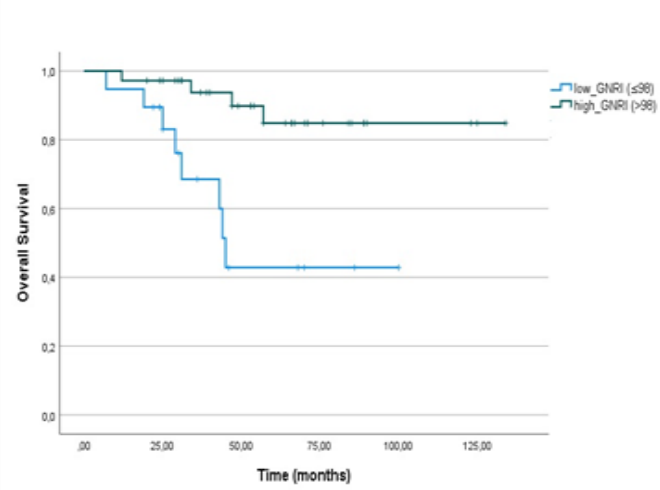

Figure 4. Estimates of overall survival by Kaplan-Meier according to the GNRI for stage 3 patients.

were staged as T3/T4. The number of patients with lymph node metastasis was 55 (48.2%). There were 59 (51.8%) patients with stage II, and 55 (48.2%) with stage III.

The mean GNRI was 103.5±11.9. Thirty-five (30.7%) of the patients had low-GNRI (GNRI≤ 98), and 79 (69.3%) had high-GNRI (GNRI> 98). Clinicopathological features of the patients according to GNRI groups were shown in Table 1. When the clinico-pathological features of the patients were compared according to the GNRI groups, only a significant correlation was found between tumor sidedness and GNRI. A total of 23.7% of left-sided tumors were categorized as low-GNRI, while 76.3% of them were in the high-GNRI group (p=0.02).

Survival analyses

The 5-year OS rate of the low-GNRI group was significantly lower than that of the high-GNRI group (65.7% vs. 91.1%, p=0.002; Figure 1). There was also a statistically significant difference in the 5-year RFS rate of the two groups (66.7% vs. 90.8%, p <0.001; Figure 2). Additionally, an assessment was conducted to determine the prognostic significance of the GNRI in relation to the

Table 2. Univariate and multivariate analyses of the factors associated with overall survival.

Variables		Univariate		Multivariate	
		95% CI	p-value	95% CI	p-value
Age	<75	1			
	≥75	1.235 (0.364-4.196)	0.735		
Gender	Female	1			
	Male	1.602 (0.662- 4.162)	0.296		
Tumor depth	T1-T2	1			
	T3-T4	2.003 (0.830 -4.835)	0.122		
Stage	2	1			
	3	2.022 (0.837-4.884)	0.118		
BMI	≥22	1			
	<22	1.765 (0.411-7.579)	0.445		
GNRI	High	1			
	Low	2.789 (1.172-6.637)	0.020	2.476 (1.031-5.942)	0.042
Tumor sidedness	Left	1			
	Right	2.797 (1.177-6.647)	0.020	2.528 (1.054-6.061)	0.038
Differentiation	Well/moderate	1			
	Poor	2.792 (0.645-12.083)	0.169		
LVI	No	1			
	Yes	1.084 (0.437-2.690)	0.862		
PNI	No	1			
	Yes	1.396 (0.468-4.162)	0.550		
Diabetes mellitus	No	1			
	Yes	1.951 (0.807-4.716)	0.138		
Obstruction/perforation	No	1			
	Yes	1.338 (0.450-3.980)	0.601		

Abbreviations: BMI: Body mass index; GNRI: Geriatric nutritional risk index; LVI:Lymphovascular invasion; PNI: Perineural invasion

stage of the tumor. In stage II, the 5-year OS rate was 86.7% in the group with a low-GNRI, while it was 88.6% in the group with a high-GNRI (p = 0.577; Figure 3). The 5-year OS rate in stage III patients was 58.3% in the group with low-GNRI, whereas it was 83.7% in the group with high-GNRI (p= 0.073; Figure 4).

Prognostic factors for OS

In the univariate analysis of factors related to OS, the HR for a low-GNRI was 2.789 (95% CI 1.172-6.637, p= 0.020). The other factor that was significantly correlated with OS was right tumor sidedness (p= 0.020). Gender, age, T stage, lymph node metastases, TNM stage, low-BMI, diabetes, presence of LVI, PNI and poor differentiation were not significantly associated with OS. The multivariate Cox regression analysis identified only tumor sidedness (p= 0.038) and GNRI (p= 0.042) as independent prognostic factors for OS (Table 2).

Prognostic factors for RFS

In the univariate analysis of prognostic factors related to RFS, GNRI was the only indicator that was correlated with RFS (HR: 4.265; %95 CI:1.641-11.087; p= 0.04). The other factors such as tumor sidedness, gender, age, T stage, lymph node metastases, TNM stage, low-BMI, diabetes, presence of LVI, PNI and poor differentiation were not significantly associated with RFS.

Discussion

Our study showed that the GNRI measured in the preoperative period in patients with early-stage colon cancer is prognostic in terms of OS and RFS. Although it has been previously shown that GNRI is prognostic for survival in several malignancies such as gastric, pancreatic, and lung cancer, there are few studies investigating the prognostic importance of GNRI in terms of survival in early-stage colon cancer patients. One of them was performed with 329 colorectal cancer

patients [20]. In this study, low-GNRI was reported to be associated with OS ($p< 0.001$) and was found to be an independent prognostic marker in multivariate analysis ($p=0.042$). The main difference between this study and ours is that there was no statistical relationship between low-GNRI and RFS in study performed by Doi et al. In our study, low-GNRI was both related to poor OS and poor RFS. The cut-off value of 98 for low-GNRI was similar as ours.

In addition, in our study high-GNRI group had a higher incidence of left colon cancer compared to the low-GNRI group and the association between GNRI and tumor sidedness was statistically significant. In recent studies about tumor sidedness demonstrated that right colon cancer was more aggressive than left colon cancer [21, 22]. Our study confirms these recent studies. Therefore, the association between high GNRI and left sidedness may depend on tumor biology. For this suggestion, more studies are needed at the molecular level.

The prognosis of colon cancer patients with low-GNRI is generally poorer, thus emphasizing the significance of improving nutritional status to improve survival. There are different markers such as prealbumin level and sarcopenia in the evaluation of nutritional status. But these markers are expensive and difficult to perform in elderly patients. Thus, GNRI can show nutritional status alone in elderly colon cancer patients as an easy and accessible marker that can be calculated by routine biochemistry. Several studies reported the impact of nutritional support on the prognosis of colon cancer patients and demonstrated the correlation between the use of oral nutritional supplements and reduced weight loss as well as a lower incidence of postoperative infection among colon cancer patients [23, 24]. Furthermore, it was observed that dietary factors play a significant role in the etiology of colon cancer [25, 26]. Nevertheless, the effects of these dietary treatments on the long-term prognosis of patients with colon cancer remain uncertain. Therefore, more research is needed to examine the potential of nutritional support in increasing the survival of individuals diagnosed with colon cancer. In this regard, GNRI can serve as a valuable tool for assessing patients who may benefit from nutritional support and for assessing the impact of such nutritional supports.

One of the limitations of our study is the lack of assessment regarding the association between GNRI and postoperative complications. This is because we were unable to access postoperative period information during the analysis of retrospective data. Secondly, there is no consensus regarding the GNRI cut-off value, which makes its practical use a challenge. Thirdly, we only included the stage II and III patients who were treated with CAPEOX or capecitabine monotherapy. Whether or not the patients could complete their chemotherapy regimens could not be reached because of retrospective data analysis. Therefore, survival analysis according to chemotherapy type and duration, and the relationship between survival and GNRI groups according to chemotherapy types could not be examined. Finally, we only assessed GNRI as a prognostic marker. Evaluating and comparing GNRI with other prognostic factors such as PNI, CONUT and sarcopenia could more effectively demonstrate the prognostic value of GNRI. Although several markers, such as CONUT, PNI have been evaluated in terms of their association with survival in colon cancer patients, it is still unclear which marker is the most effective. Prospective studies with a large number of patients are needed to compare these markers.

In conclusion, this study provides evidence that the GNRI serves as a basic and important prognostic indicator in elderly patients diagnosed with early-stage colon cancer. A low GNRI may be a prognostic indicator of poor OS and RFS.

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Original Article

Definitive Chemoradiotherapy versus Neoadjuvant Chemoradiotherapy Followed by Surgery in Locally Advanced Esophageal Cancer: A Retrospective Evaluation of Clinical Data of Two Centers

Lokal İleri Özofagus Kanserinde Definitif Kemoradyoterapi ile Neoadjuvant Kemoradyoterapiyi Takiben Cerrahinin Karşılaştırılması: İki Merkezin Klinik Verilerinin Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study is to investigate the results of neoadjuvant chemoradiotherapy /radiotherapy (neo-CRT/RT)+surgery and definitive chemoradiotherapy (def-CRT) approaches in locally advanced esophageal cancer

Methods: Between January 2012 and December 2021, in two centers, patients who received def-CRT or neo-CRT/RT with the diagnosis of locally advanced esophageal cancer, were retrospectively analyzed. Cases were evaluated for treatment response, overall survival (OS), disease-free survival (DFS), and local recurrence (LR).

Results: In total, fifty cases were included. The median follow-up was 10 months (range 2-26). In the def-CRT group; OS at one year, and two years were 67 % and 32 %, respectively; DFS at one year, and two years were 62 % and 32 % respectively. In the neo-CRT group; OS at one year was 81 % and DFS at one year was 73 %. In the follow-up time, LR was 12.1% in def-CRT and 11.8% in the neo-CRT group. For two treatment arms, there were no significant differences in OS (p=0.404), DFS (p=0.593) and LR (p=0.670). The neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

Conclusion: Considering the morbidity and mortality of surgery, def-CRT may be an alternative to neoadjuvant-surgical treatment in selected cases whose treatment response is considered a complete response. In these patients, waiting until recurrence and then salvage surgery can be considered.

Key words: Esophageal cancer, chemoradiotherapy, esophagectomy

ÖZET

Amaç: Lokal ileri özofagus kanserinde neoadjuvan kemoradyoterapi/radyoterapi (neo-KRT/RT)+cerrahi ve definitif kemoradyoterapi (def-KRT) yaklaşımlarının sonuçlarını araştırmaktır

Yöntemler: Ocak 2012 ile Aralık 2021 tarihleri arasında iki merkezde lokal ileri özofagus kanseri tanısı ile def-KRT veya neo-KRT/RT alan hastalar retrospektif olarak incelendi. Olgular tedavi yanıtı, genel sağkalım, hastalıksız sağkalım ve lokal nüks açısından değerlendirildi.

Bulgular: Toplamda elli vaka çalışmaya dahil edildi. Medyan takip süresi 10 (2-26) ay'dı. Def-KRT grubunda; Bir yıllık ve iki yıllık genel sağkalım sırasıyla %67 ve %32; bir yıllık ve iki yıllık hastalıksız sağkalım sırasıyla %62 ve %32 idi. Neo-KRT grubunda; bir yıllık genel sağkalım %81 ve bir yıllık hastalıksız %73 idi. Takip süresince lokal nüks oranı, def-KRT grubunda %12.1 ve neo-KRT grubunda %11.8 idi. İki tedavi kolu arasında, genel sağkalım (p=0,404), hastalıksız sağkalım (p=0,593) ve lokal

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nüks (p=0,670) açısından anlamlı fark yoktu. Neo-KRT grubu ameliyat zamanına göre değerlendirildiğinde, 8 haftadan sonra ameliyat edilen hastalarda istatistiksel anlamlılığa ulaşılamasa da daha fazla mortalite saptandı..
Sonuç: Cerrahinin morbidite ve mortalitesi göz önüne alındığında, tedaviye yanıtı tam yanıt olarak kabul edilen seçilmiş olgularda def-KRT, neoadjuvan+cerrahi tedaviye bir alternatif olabilir. Bu hastalarda nükse kadar bekleyip ardından salvaj cerrahi düşünülebilir.

Anahtar kelimeler: Özofagus kanseri, kemoradyoterapi, özofajektomi

Introduction

Esophageal cancer (EC) is one of the most common types of cancer worldwide. It was estimated over 600 thousand new cases and over 500 thousand deaths according to 2020 data [1]. The two major histopathological subtypes of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). The incidence of both subtypes differs by geographic region: SCC has a high prevalence in East Asia, East and Southern Africa, and Southern Europe; AC is more common in North America and other parts of Europe [2]. Although the 5-year overall survival is 20% [3], better outcomes can be seen in patients with early-stage disease [4]. Early-stage disease is usually treated with endoscopic resection [5]. Although esophagectomy remains the mainstay of surgical treatment, it has high morbidity and mortality rates [6]. EC is often diagnosed in advanced stages where surgery alone cannot cure it. Therefore, curative treatment options in advanced disease are neoadjuvant chemoradiotherapy (neo-CRT) followed by surgery or definitive chemoradiotherapy (def-CRT) [7].

Def-CRT is seen as an alternative to surgery with an increasing proportion of resectable diseases, especially in patients who are not suitable for surgery [8,9]. In neo-CRT, it is aimed to reduce both the tumor burden and the extent of the planned surgery, as well as the risk of distant metastasis (through the elimination of potential micrometastases) [8]. In advanced disease, multimodal therapy is needed to reduce relapse rates and achieve higher local control and survival rates [9]. A multidisciplinary approach is needed to determine the appropriate treatment option for each patient.

There are limited data comparing def-CRT to neo-CRT with esophagectomy in patients with esophageal carcinoma. This study aims to evaluate treatment response and survival according to def-CRT and neo-CRT+surgical approaches in patients with locally advanced esophageal cancer.

Materıal and Methods

We retrospectively analyzed the data of patients diagnosed with locally advanced esophageal cancer who underwent def-CRT or neo-CRT+ surgery in the Radiation Oncology Department of two centers. Between 2012 and 2021, in total, 50 patients were included in this study.

This study was conducted by considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. The study was approved by XXX University Ethical Committee for non-invasive investigations (Date: 30.11.2021, Decision No: E-71522473-050.01.04-83316-513).

The patients were evaluated in terms of treatment options by the multidisciplinary tumor board. Clinical staging of all patients was performed with PET-CT. The AJCC-2017 staging system [10] was used for clinical staging. Patients with T2-4 and/or node positive, M0 esophageal cancer were included in the study. Eastern Cooperative Oncology

Group Performance Status Scale (ECOG PS) was used to assess the performance status of patients [11] and patients with ECOG PS 0, 1 or 2 were included. Demographic characteristics, clinical and pathological data of the patients, the purpose of treatment, doses, and areas of radiotherapy (RT), response to treatment, overall survival (OS), disease-free survival (DFS), and local recurrence (LR) were recorded.

For RT planning; CT scans of the patients were taken in a 2.5 mm section thickness, in the supine position, and using a wing board. The target volume was determined by fusing PET-CT images and planning CT images. The median dose of RT for the primary tumor and lymphatic region was 5040 cGy (4140-6000 cGy) in median 28 fractions (range 23-30). RT was performed for all patients using the Intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT) technique.

Post-treatment response rates of patients were evaluated by radiological imaging and/or endoscopic examination. Response Evaluation Criteria in Solid Tumors (RECIST 1.0) are used for evaluation of response [12]. Accordingly, patients were evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Statistical analysis

Patient characteristics were compared with a chi-square test. The median ages of the patients were compared with Mann-Whitney U test. The survival analysis was performed by the actuarial Kaplan-Meier method and differences between the curves were analyzed using the log-rank test. OS was defined as the time from diagnosis to death or the date of last control for patients who were alive. DFS was defined as the time from diagnosis to recurrence of tumor or death. Statistical analysis was carried out using the SPSS 21.0 software package. $p < 0.05$ was considered statistically significant.

Results

Clinical Data and Tumor Characteristics

In total, fifty cases were included. The median age of patients was 60 (37-75) years. There was no significant difference in the distribution of age (p=0.500), gender (p=0.060), and ECOG PS (p=0.230). Patient characteristics are shown in Table 1.

Thirty-three patients (66%) were treated with def-RT/CRT and 17 patients received neo-CRT (34%). Carboplatin-paclitaxel combination was applied to 38 (83%) patients and cisplatin- 5-fluorouracil combination was used for eight (17%) patients as concomitant chemotherapy. Concomitant chemotherapy could not be applied to four patients who were scheduled for definitive treatment, due to their comorbidities.

Treatment Response

In all study groups; 18 patients (36%) had complete responses (CR), 13 patients (26%) had partial responses, and 12 patients (24%) had stable responses. Progressive disease was present in seven patients (14%).

In the def-CRT group; the CR was observed in nine patients (27.3%) after treatment. There was partial response in 10 patients (30.3%), stable response in seven patients (21.2%), and progressive disease in seven patients (21.2%). In the neo-CRT group, the median time between surgery and CRT was seven (3-17) weeks. According to the surgical specimen, 9 of 17 patients had a pathological complete response (pCR) and three patients had a partial response. In three patients, the radiological and pathological stages were the same. The treatment doses of these three patients were 41.4 Gy. The RT dose of patients with a CR was median of 50 Gy (45-50,4); for patients with downstaging was median of 50 Gy (45-56).

Table 1: Patient and tumor characteristics

		All patients (n=50)	Def-CRT and Def-RT (n=33)	Neo-CRT +Surgery (n=17)	p-value
Follow-up (months)	Median (Range)	10 (2-26)	10 (2-26)	9 (3-20)	0.400
Age	Median	60 (37-75)	60 (40-75)	61 (37-73)	0.500
	60≤	25 (50)	17 (51.5)	8 (47.1)	
	60>	25 (50)	16 (48.5)	9 (52.9)	
Gender	Female	26 (52)	14 (42.4)	12 (70.6)	0.060
	Male	24 (48)	19 (57.6)	5 (29.4)	
ECOG PS	0	37 (74)	22 (66.6)	15 (88.2)	0.230
	1	11 (22)	9 (27.3)	2 (11.8)	
	2	2 (4)	2 (6.1)		
Stage	IIB	24 (48)	14 (42.4)	10 (58.8)	
	IIIA	1 (2)	14 (42.4)	1 (5.9)	0.150
	IIIB	20 (40)	-	6 (35.3)	
	IVA	5 (10)	5 (15.2)		
Tumor Location	Upper esophagus	5 (10)	5 (15.1)	0 (0)	
	Middle esophagus	20 (40)	15 (45.5)	5 (29.4)	0.070
	Lower esophagus	25 (50)	13 (39.4)	12 (70.6)	
Histopathology	SCC	43 (86)	30 (90.9)	13 (76.5)	0.170
	AC	7 (14)	3 (9.1)	4 (23.5)	
Chemotherapy	Yes	46 (92)	29 (87.9)	17 (100)	0.180
	No	4 (8)	4 (12.1)	0 (0)	
Treatment Response	CR	18 (36)	9 (27.3)	9 (52.9)	
	PR	13 (26)	10 (30.3)	3 (17.6)	0.080
	SD	12 (24)	7 (21.2)	5 (29.4)	
	PD	7 (14)	7 (21.2)		
LR	Yes	6 (12)	4 (12.1)	2 (11.8)	0.674
	No	44 (88)	29(87.9)	15 (88.2)	
Distant Metastasis	Yes	9 (18)	7 (21.2)	3 (17.6)	0.539
	No	41 (82)	26 (78.8)	14 (82.4)	

SCC: Squamous cell carcinoma, AC: Adenocarcinoma, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease. LR: Local Recurrence.

Overall Survival /Disease-Free Survival

At a median follow-up of 10 months (2-26 months), overall survival (OS) at 1 year, and 2 years 70 % and 38 % were, respectively (Figure 1) and disease-free survival (DFS) at 1 year, and 2 years were 66 % and 30 % respectively (Figure 2).

In the Def-CRT group; At a median follow-up of 10 months (2-26 months), OS at 1 year, and 2 years were 67 % and 32 % respectively and DFS at 1 year, and 2 years were 62 % and 32 % respectively. In the neo-CRT group; At a median follow-up of 10 months (2-20 months), OS at 1 year was 81 % and DFS at 1 year was 73 %. There was no significant difference between the treatment groups for OS (p=0.593) and DFS (p=0.404).

This study showed that treatment option (def-CRT or neo-CRT+ surgery) (p=0.404), patients' gender (p=0.320), age of diagnosis (p=0.130), tumor histology (p=0.970), tumor location (p=0.740) and stage of diagnosis (p=0.110) had no significant impact on survival rate.

24 patients (%48) died. Although there was no significant difference between the treatment groups (p=0.513), OS was higher in the neo-CRT group. In the neo-CRT+ surgery group, five patients died due to surgery-related complications (%29) and two patients (%12) died due to distant metastases, and 1 (%6) patient died from pneumonia. In the def-CRT group, five patients (%15) died due to distant metastases, four patients (%12) died due to

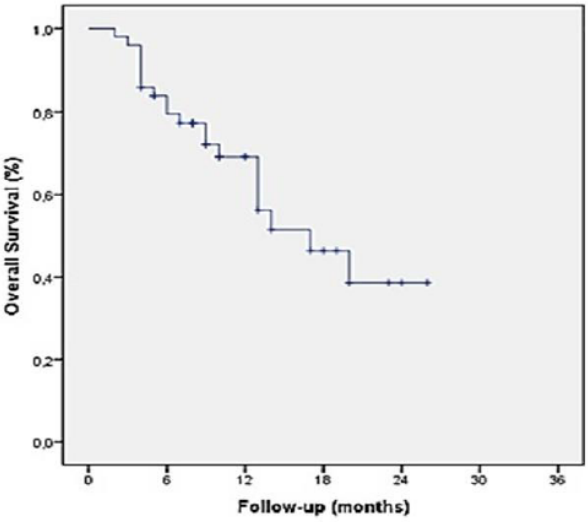

Figure 1. Overall survival at 1 year and 2 years

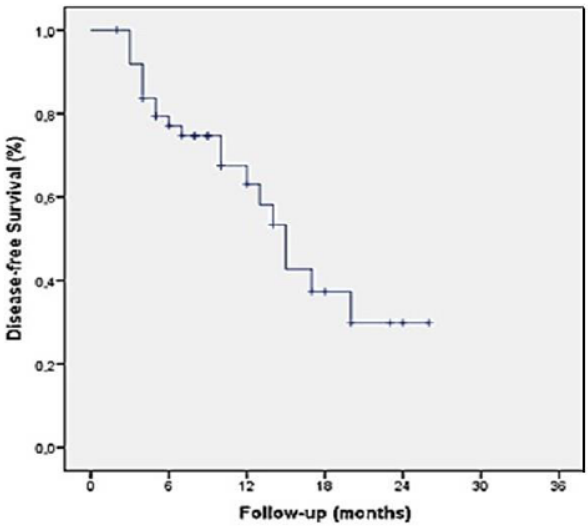

Figure 2. Disease-free survival at 1 year and 2 years

non-cancer reasons, and seven patients (%21) died due to primary disease after CRT.

Patterns of Failure

In the follow-up of the patients after the treatment, local recurrence (LR) was 12.1% in def-CRT and 11.8% in the neo-CRT group. There was no significant difference between the two treatment groups (p=0.670). In the follow-up of the patients, metastases developed in nine patients (18%) and there was no significant difference between the two treatment groups (p=0.539). Of the patients who developed distant metastases, four had lung metastases (44.5%), two had liver metastases (22.2%), two patients had lymph node metastases (22.2%), and one patient had brain metastases (11.1%).

Discussion

This retrospective study shows no significant difference in DFS and OS in patients with locally advanced EC when comparing def-CRT with neo-CRT followed by surgery. A preoperative chemoradiotherapy regimen that was based on carboplatin and paclitaxel was manageable and had a favorable safety profile. However, the neo-CRT group was evaluated according to the time of surgery, more mortality was found in patients who underwent surgery after 8 weeks, although statistical significance was not reached.

In a recently published systematic review and meta-analysis, patients with EC who received neo-CRT and esophagectomy had better survival than patients who received def-CRT [13]. However, in our study, in terms of OS, there was no significant difference between the two treatment groups. We also showed better at 1-year OS in the neo-CRT group (81% vs 67%), but not statistically significant, potentially due to follow-up time and/or sample size issues. In published two different studies of patients with locally advanced EC, for OS, there was no significant difference between patients who underwent def-CRT and surgery after neo-CRT [7,14]. The 2-year overall survival in patients who received neo-CRT followed by surgery and def-CRT were 69.1% and 40.0%, respectively [15]. Similarly, in our study, 2-year OS was 32 % in def-CRT. Since the longest follow-up period

was 20 months in the neoadjuvant group, 2-year survival could not be evaluated.

Dong Qian et al., more than 40% of patients with esophageal SCC had pCR after neo-CRT [14]. In other studies, The pCR of this approach ranges from 13 to 47% [15,16]. Similarly, in our cohort, 53% of the patients who received neoadjuvant therapy, had pCR. While increasing the pCR rate with neo-CRT was expected to have a positive effect on overall survival, no significant advantage in overall survival could be demonstrated despite the downstaging. Two separate studies have shown that surgical delay of >8 weeks doesn't lead to a favorable outcome in patients with esophageal cancer. These studies showed that an 8-week interval between neo-CRT and surgery is sufficient to produce a maximum RT response in patients with esophageal cancer, thus longer surgical delay may have adverse consequences for patients with a good response to neo-CRT [17,18]. In our study, CR was obtained in 29% of the patients in the surgical group. However, all patients who died from surgical complications had an interval of >8 weeks from CRT to surgery. Therefore, the positive effect of pathological complete response on overall survival may not have been observed in the neo-CRT group.

Carlo C. et al found that in patients with clinical CR after neo-CRT, waiting until relapse and then salvage surgery didn't adversely affect survival compared to patients treated with surgery [19]. We could not compare these two patient groups in our study. Because all patients in the neo-CRT group, underwent surgery regardless of clinical response to treatment. A case-control study showed that patients with CR had a better prognosis after CRT compared to surgery [20].

Kenji et al. compared def-CRT doses in patients with thoracic EC; CR rates in the 50.4 Gy and 60 Gy groups were 49.1% and 46.4%, respectively. Also, no significant difference was found between the two groups in terms of OS, and they revealed that 50.4 Gy was non-inferior compared to 60 Gy [21]. Similarly, in the INT 0123 study, doses of 50.4 and 64.8 Gy were compared in EC patients and it was shown that survival and local control results weren't better at higher doses [22]. In our study; in patients with CR and downstaging, the median dose was 50 Gy, and the lowest dose was 45 Gy. Treatment response was stable in both patients who received 41.4 Gy. Based on this, it can be interpreted that the treatment dose should be at least 45 Gy to get a treatment response, but to reach a meaningful result, it is necessary to compare the number of patients and the dosing schedule.

Marieke P. et al showed that the 1 and 3-year DFS were 67% and 43%, respectively, in a neo-CRT+surgery group, and 56% and 24%, respectively, in def-CRT group. DFS significantly shorter in the def-CRT group compared to resected patients [23]. Unlike this study, in our cohort 1 and 2-year DFS were 62% and 32%, respectively, in def-CRT group; and 1-year DFS was 73% in neo-CRT+surgery group. No significant difference was found between the two treatment arms. That reason may be due to the unequal distribution of patients in the groups and the relatively short follow-up period.

In our study, the cumulative LR incidence rate was found to be 12%. Considering the groups, it was 12.1% in def-CRT and 11.8% in neo-CRT group. Similarly, Lin J.W. et al found the 3-year cumulative incidence rate of LR was 13.3% of patients (15). In contrast to our study, Münch S. et al showed that in locally advanced EC patients treated with either def-CRT or neo-CRT+surgery group (38% vs. 10%), a higher rate of LR was seen in patients treated with def-CRT than in patients treated with neo-CRT+surgery [24]. Unlike that study, the reason why there was no difference in LR between the groups may be that all patients were N0 patients located in the thoracic and lower esophagus.

Some limitations of this study are that the study was designed retrospectively and the follow-up period was short. In addition, some imbalances in tumor parameters between patient groups (lymph node metastasis rate and tumor location) may affect the results and should be kept in mind. The small number of patients in our study didn't allow us to perform subgroup analysis. The results of clinical studies with larger patient groups will contribute to the creation of the most appropriate multidisciplinary strategy according to histological subtype, localization, stage, and post-CRT tumor response.

Conclusion

In this study, no significant difference was found between the two treatment groups in terms of OS, DFS, and LR. Def-CRT may be an alternative to neoadjuvant-surgical treatment, considering the morbidity and mortality of surgery in selected cases whose treatment response is considered CR. Salvage surgery may be considered after recurrence in these patients

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Case Report

Desmoid Fibromatosis of the Breast; A Case Report

Memenin Desmoid Fibromatozisi; Olgu Sunumu

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ABSTRACT

Desmoid-type fibromatosis of the breast is a rare, locally aggressive stromal tumor. This lesion is observed in 0.2% of all breast tumors, often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female). In this study, we report a case of a 57-year-old woman with breast fibromatosis, which has been mimicking breast carcinoma. On physical examination, there was an irregularly shaped mass lesion of approximately 3x2 cm fixed to the chest wall in the upper outer quadrant of the left breast. On mammography, an increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast. On ultrasound examination, a heterogeneous hypoechoic solid lesion with microcalcifications in places and 32x10mm in size with irregular borders and internal echoes were observed in the upper outer quadrant of the left breast. (BIRADS 4). Since the tru-cut biopsy could not differentiate between Fibromatosis-like Metaplastic Breast Carcinoma and Desmoid Fibromatosis, an excisional biopsy was performed under general anaesthesia. Wide local excision was performed due to positive surgical margins. In conclusion, desmoid-type fibromatosis has nonspecific physical examination findings and radiological imaging and is confused with malignancy. The primary treatment of this lesion is excision with a negative surgical margin

Keywords: Desmoid-type fibromatosis (DF), breast tumor, fibromatosis

ÖZET

Memenin desmoid tip fibromatozisi nadir görülen, lokal agresif bir stromal tümördür. Bu lezyon tüm meme tümörlerinin %0,2'sinde görülür, sıklıkla 25-45 yaşları arasında ortaya çıkar ve erkek: kadın oranı 1:2'dir. Bu olgu sunumunda, meme kanserini taklit eden meme fibromatozisi olan 57 yaşında bir kadın hastayı sunuyoruz. Fizik muayenede sol meme üst dış kadranda göğüs duvarına fikse yaklaşık 3x2 cm boyutlarında düzensiz şekilli kitle lezyonu izlendi. Mamografide sol meme dış orta kısmında fibroglandüler doku ile örtülü opaklıkta artış izlendi. Ultrason muayenesinde sol meme üst dış kadranda 32x10mm boyutlarında, sınırları düzensiz, iç ekosu olan, yer yer mikrokalsifikasyonlu, heterojen hipoekoik solid lezyon izlendi. (BIRADS 4). Tru-cut biyopside fibromatozis benzeri metaplastik meme karsinomu ile desmoid fibromatozis ayırt edilemediğinden genel anestezi altında eksizyonel biyopsi gerçekleştirildi. Pozitif cerrahi sınırlar nedeniyle geniş lokal eksizyon uygulandı. Sonuç olarak, desmoid tip fibromatosis nonspesifik fizik muayene bulguları ve radyolojik görüntüleme bulgularına sahiptir ve malignite ile karıştırılmaktadır. Bu lezyonun primer tedavisi negatif cerrahi sınır ile eksizyondur.

Anahtar kelimeler: desmoid fibromatozis, meme tümörü, fibromatozis

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Introduction

Desmoid-type fibromatosis of the breast is a rare, locally aggressive stromal tumor that occurs from musculoaponeurotic structures. It is a clonal fibroblastic proliferation that occurs in the deep soft tissues. Although it tends to be locally aggressive, distant metastases are not observed.[1] Desmoid-type fibromatosis is observed in 0.2% of all breast tumors.[2] This lesion often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female)[3]. We report a case of a 57-year-old woman with breast fibromatosis, which has been mimicking breast carcinoma.

Case Report

A 57-year-old female patient who developed a palpable left breast mass in several weeks was referred to our centre. She did not have any additional disease. The patient did not have a history of trauma or surgery in the left breast or a family history of cancer. On physical examination, there was an irregularly shaped mass lesion of approximately 3x2 cm fixed to the chest wall in the upper outer quadrant of the left breast. On mammography, an increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast, and the patient was recommended to be evaluated with ultrasound. (Figure 1)

On ultrasound examination, a heterogeneous hypoechoic solid lesion with micro-calcifications in places and 32x10mm in size with irregular borders and internal echoes was observed in the upper outer quadrant of the left breast. (BIRADS 4). Since the tru-cut biopsy could not differentiate between fibromatosis-like metaplastic breast carcinoma and desmoid fibromatosis, an excisional biopsy was performed under general anaesthesia.

In the pathological examination, the tumor consists of myofibroblastic cells forming intersecting long fascicles in the collagenized stroma with bland spindle nuclei, small nucleoli, and eosinophilic nuclei cytoplasm with indistinct borders. The tumor shows a highly infiltrative growth pattern into the surrounding breast tissue. One mitosis was observed in 10 HPF. No necrosis or cytological atypia was observed. There are haemorrhage foci and hemosiderin-laden macrophages within the tumor. Lymphoid aggregates were observed at the periphery of the tumor. The tumor was continuous with the anterior, base, superior, inferior, and lateral surgical margins. The medial surgical margin is intact. By immunohistochemistry, diffuse nuclear β-Catenin expression was observed. Focal Desmin, SMA, and Calponin expression were seen. Sparse cell staining was observed with S-100. PanCK, CK7, CD34 and p63 were negative. (Figure 2) The Ki67 proliferation index was 10%. Wide local excision was performed due to positive surgical margins.

Discussion

Desmoid-type fibromatosis is observed in 0.2% of all breast tumors.[2] This lesion often occurs between the ages of 25 and 45 and the sex ratio is 1:2 (male: female).[3] Although the etiology of the disease is not known, publications report that it is related to familial adenomatous polyposis, Gardner syndrome, surgical trauma, and silicone implants.[4] Our patient did not have any risk factors. It has nonspecific physical examination findings and radiological imaging and is confused with malignancy.

On physical examination, it often presents as a solitary, hard, and painless nodule. Nipple and cutaneous skin retraction and pectoral muscle fascia invasion can be observed.[5] In the study of Jörn Lorenzen et al., which is one of the largest series in the literature with 15 patients, a fixed mass was observed in 10 patients and a relatively soft mass in 4 patients. In addition, 4 patients had skin retraction. [2] In our case, there was a fixed

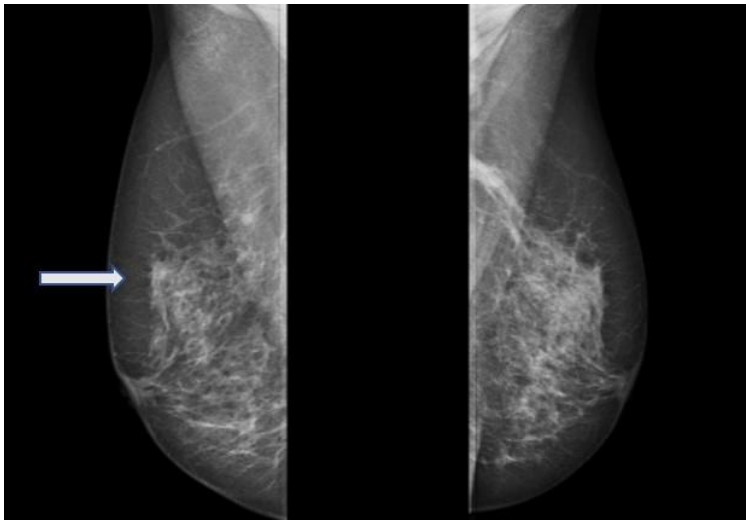

Figure-1. Left breast mammogram. An increase in opacity covered by fibroglandular tissue was observed in the outer middle part of the left breast.

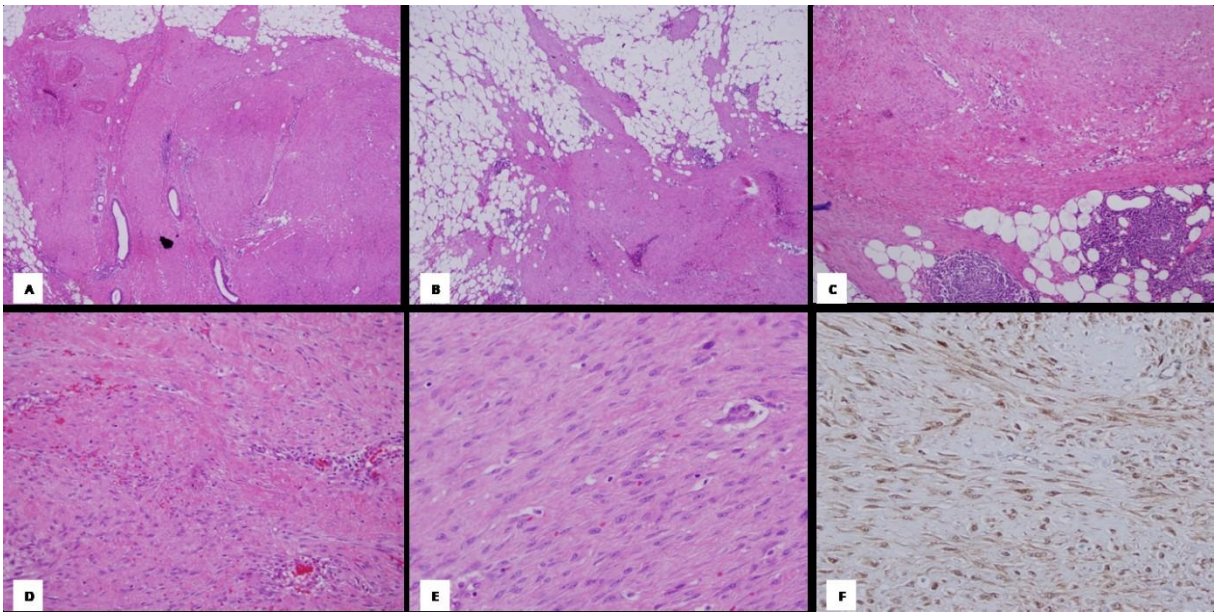

Figure-2. Tumor cells entrap normal breast ducts. B Spindle cells infiltrating the surrounding fat. C Lymphoid aggregates at the periphery of the tumor. D Collagenous stroma within the tumor. E Spindle cells appear bland with no mitotic activity. F Diffuse nuclear β-Catenin expression.

and hard palpable mass with irregular borders. In our case, there was an irregular, fixed, and hard palpable mass. However, there was no skin retraction as a deeply located mass invading the pectoral fascia was observed.

If we talk about radiological imaging, in the study of Michael R. Boland et al. (16 patients) and Jörn Lorenzen et al.; radial scars, architectural distortion, or a high-density mass appear as important mammographic findings. In our study, similar findings were observed in mammography. On ultrasound examination, the hypoechoic and irregular lesion was observed, which is consistent with the previous literature.[2, 6-10] Although there are studies suggesting MRI in the diagnosis and follow-up of desmoid fibromatosis, an excisional biopsy was performed without waiting for MRI because metaplastic carcinoma was suspected in our case.[11, 12]

Core biopsy is more valuable than fine-needle aspiration cytology. We also preferred the core biopsy first. Histopathological analyses play a critical role in the diagnosis. Diagnosis of low-grade spindle cell lesions in the breast is challenging because the differential diagnosis is broad and includes many rare lesions. The differential diagnosis includes fibromatosis-like metaplastic carcinoma, reactive spindle cell nodules, nodular fasciitis, inflammatory myofibroblastic tumor, myofibroblastoma, pseudoangiomatous stromal hyperplasia, phyllodes tumor, dermatofibrosarcoma protuberans, and spindle cell sarcomas. [13, 14] Desmoid fibromatosis is a locally aggressive mesenchymal neoplasm with infiltrative margins composed of a proliferation of uniform, cytologically bland fibroblasts, and myofibroblasts. Some histomorphologic clues to the diagnosis of desmoid fibromatosis include long fascicles of neoplastic spindle cells with entrapped benign breast glandular epithelial elements and peripheral lymphocytic aggregates. The spindle cells of desmoid fibromatosis express smooth muscle actin and show nuclear expression of Beta-Catenin, but lack cytokeratin expression. The most crucial lesion to distinguish from desmoid fibromatosis is fibromatosis-like metaplastic carcinoma. These tumors are composed of bland spindle cells resembling desmoid fibromatosis. A diagnosis of fibromatosis-like metaplastic carcinoma can be rendered based on any evidence of epithelial differentiation by histopathological or immunohistochemical analysis.[13, 15, 16] Due to tumor heterogeneity and focal cytokeratin expression, a definitive diagnosis can not be made in core biopsies. Broad macroscopic sampling and an immunohistochemical panel may be required to capture epithelial differentiation.

The primary treatment of desmoid-type fibromatosis is excision with a negative surgical margin. Wide (R0) microscopic margins resection is recommended. Positive (R1) microscopic margins can be accepted when cosmesis is problematic. There is no consensus about the indication of adjuvant radiotherapy after wide local excision. In addition, after R1 resection, there is no consensus between postoperative radiotherapy and reexcision, definitive radiotherapy can be given ın patients who cannot have surgery. It has been shown to provide sufficient local control. [17] On the other hand, a 'watch and wait' approach is also recommended in the current literature. This approach demonstrated a 60% 2-year progression-free survival similar to surgical treatment. This approach, at 3 to 6 months intervals for the first three years and then annually by MRI, consists of patient follow-up [11, 17]. Systemic treatment options for desmoid-type fibromatosis consist of non-steroidal anti-inflammatory drugs, anti-hormonal therapies, tyrosine kinase inhibitors, and conventional chemo-therapeutics.[18] Anti-hormonal agents (e.g.tamoxifen) have been frequently used alone or in combination with non-steroidal anti-inflammatory drugs. If the role of adjuvant chemotherapy is searched in the current literature, there are various regimens, including anthracycline-based regiments, sorafenib, imatinib, pazopanib, and vinblastine-methotrexate but no consensus. In addition, recent guidelines emphasize the importance of a multi-disciplinary approach. Re-excision was applied to the patient upon the decision of the multidisciplinary team council in our institution.

Conclusion

Desmoid-type fibromatosis of the breast is a rare stromal tumor. It has nonspecific physical examination findings and radiological imaging and is confused with malignancy. The primary treatment of desmoid-type fibromatosis is excision with a negative surgical margin.

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Case Report

Presentation of Metastatic Cholangiocellular Cancer with Orbital Metastasis

Metastatik Kolanjıoselüler Kanserin Orbital Metastaz ile Prezentasyonu

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ABSTRACT

Cholangiocarcinomas are cancers arising from epithelial cells of the intrahepatic and extrahepatic bile ducts. Most are locally advanced lesions when present. They usually present with jaundice, abdominal pain, and abnormal liver biochemical tests.

Proptosis developed in the right eye of a 49-year-old female patient who was diagnosed with carcinoma metastasis in the right femur and we examined for the primary one. Lacrimal gland biopsy of the patient was found to be compatible with cholangiocarcinoma metastasis. Neuroopthalmologic complications in cholangiocarcinoma are very rare and 10 cases have been reported in the literature.

Keywords: orbital metastasis, CNS metastasis, cholangiocarcinoma, exophthalmos

ÖZET

Kolanjiokarsinomlar intrahepatik ve ekstrahepatik safra kanallarının epitel hücrelerinden kaynaklanan kanserlerdir. Çoğu prezente olduğunda lokal olarak ilerlemiş lezyonlardır. Genellikle sarılık, abdominal ağrı ve anormal karaciğer biyokimyasal testleri ile prezente olurlar.

Sağ femurda karsinom metastazı saptanıp prımerıne yonelık tetkık ettiğimiz 49 yasındakı kadın hastanın sağ gözünde proptozis gelişti. Hastanın lakrimal bez biyopsisi kolanjıiokarsinom metastazı ile uyumlu saptandı. Kolanjiokarsinomda nörooptalmolojık komplikasyonlar oldukça nadir olup literatürde 10 vaka bildirimiştir.

Anahtar Kelimeler: orbital metastaz, SSS metastazı, kolanjiokarsinom, ekzoftalmus

Introduction

Metastaticorbital masses make up less than 5% of orbital tumors [1]. Most frequent metastatic cancers of the orbital are breast (52%), prostate (12%) and lung cancers (8%) [2]. Only ten cases of neuro-ophthalmologic and ocular presentations of cholangio-carcinoma have been reported in the literature [3-6].

Case Presentation

A 49-year-old female patient who admitted to orthopedics with low back and hip pain underwent a biopsy of the right femoral proximal after the bilateral T1A and T2A

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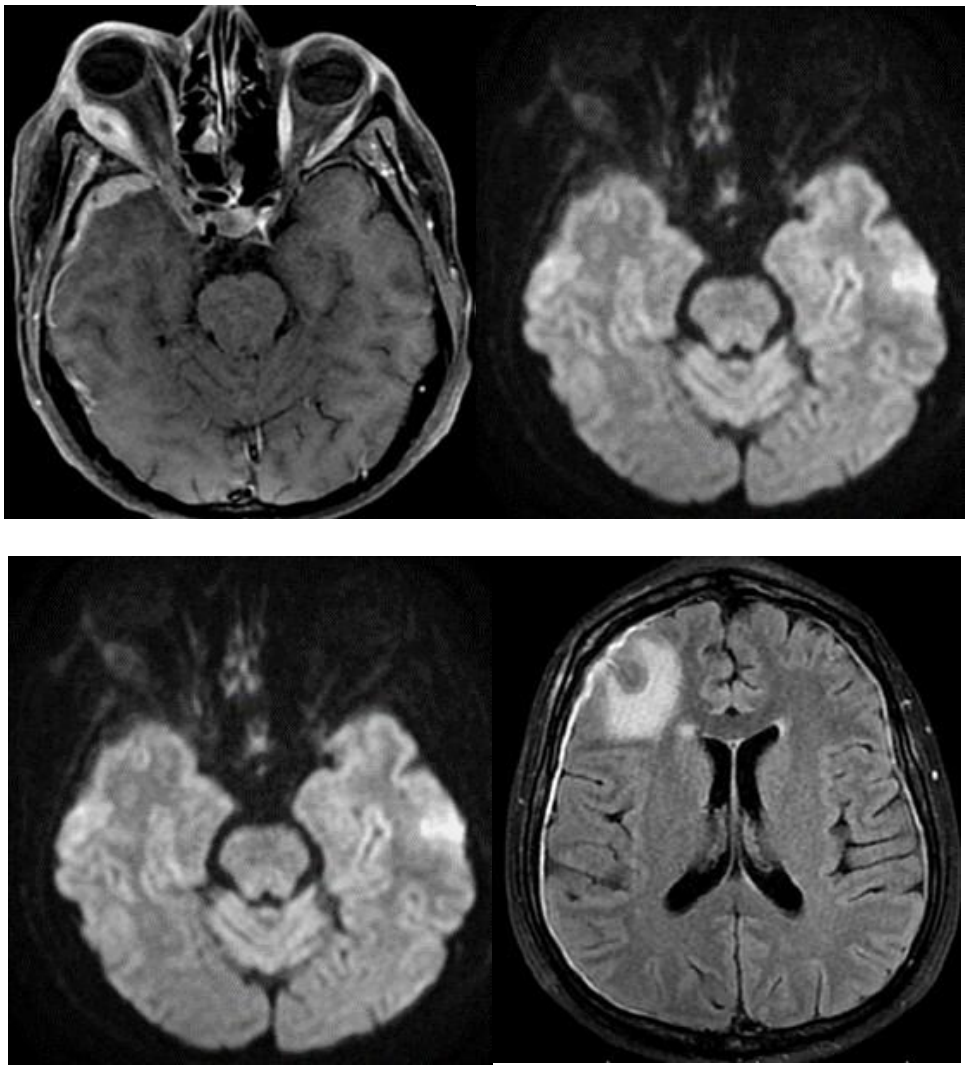

Figure 1a. In contrast T1 axial images, mass lesion in the right lateral rectus muscle, dural thickening and contrast involvement in the adjacent intracranial space and contrasting in subcutaneous plans are observed. 1b. Diffusion b 1000 MR images do not show diffusion limitation in the mass in the lateral rectus. 1c. In contrast axial FLAIR (c) and T1 weighted images (d), bilateral dural involvement as well as parenchymal extension and cerebral edema are seen to develop in the right frontal adjacent to dural involvement. 1d. In contrast axial FLAIR (c) and T1 weighted images (d), bilateral dural involvement as well as parenchymal extension and cerebral edema are seen to develop in the right frontal adjacent to dural involvement.

images in the patient's hip MRI showed diffused lesions suspected of metastasis on bone surfaces. As a result of the biopsy which revealed carcinoma metastasis, the patient admitted to the oncology outpatient clinic. In the computer tomography scans of the patient multiple metastatic mass lesions of 24x11 mm in size were detected in the liver parenchyma at the level of segment 7. A biopsy of the liver was performed on the patient. While waiting for the biopsy result, proptosis and a limitation of eye movement developed in the right eye of the patient. An orbital MR was performed on the patient. The patient's cranial and orbital MRI images are shown in figure 1a-1b-1c-1d. In the orbital and brain MRI images before and after contrast, soft tissue mass lesions in the lateral vicinity of the right orbita in the

right lateral rectus muscle which erase extraconal periorbital fat plans, with their central showing necrotic heterogeneous contrast involvement were observed. Exophthalmos was present in the ipsilateral glob.Pathologic contrast involvement was also seen in the subcutaneous soft tissue muscle plans in orbital neighborhood. In addition, irregular dural thickening and contrast were observed in the intracranial area adjacent to the right orbit, which was evaluated as dural involvement. In T1 and FLAIR images after contrast, dural involvement was observed not only in orbital proximity but also in the opposite cerebral hemisphere. Diffusion MRI images showed no restriction of diffusion in the lesions. With these findings, the lesions were primarily considered in favor of metastatic involvements. But in MRI images, because of ventilation losses in the right paranasal sinuses compatible with sinusitis and rapid progression of the patient's MRI findings, it was thought in the differential diagnosis, that the infection should be excluded and biopsy from the lacrimal gland was performed on the patient. While waiting for the biopsy result, empirical vancomsin, meropenem and amphotericin B were initiated.

The result of the liver biopsy of the patient was reported as cholangiocellular carcinoma.

The result of biopsy from the lacrimal gland was consistent with cholangiocellular carcinoma metastasis. Radiotherapy was planned for the eye and the whole brain of the patient. After radiotherapy, it was decided to start gemcitabine and cisplatin.

Discussion

The presentation of our case was not compatible with typical presentation of cholangiocarcinoma. Initially bone metastases were detected and metastasis of orbital and central nervous system developed during the examination process. CNS metastasis and orbital metastasis are rather rare in cholangiocarcinoma [7-9]. There are 26 CNS metastasis cases in the literature. The brain was reported as the site of metastasis in1.6% of patients with stage IV intrahepatic cholangiocarcinoma in a 2010-2015 review of US population. Orbital metastasis is also very rare and our case is the eleventh case in the literature. One case of a clival mass and sixth cranial nerve palsy, one case of metastasis to the medial rectus muscle and diplopia, two cases of metastasis to the occipital lobe and homonymous hemianopia, and one case of a hypercoagulable state-related stroke and homonymous hemianopia make up the five previously reported neuro-ophthalmologic presentations of cholangiocarcinoma[3]. A combination hepatocellular carcinoma/ cholangiocarcinoma that metastasized to the retina and vitreous was reported in one case, and there have also been two instances of cholangiocarcinoma that metastasized to the orbit and caused eye pain[5]. While, a case presenting with skin and orbital metastasis was reported in 2020 in Japan [10], in the same year metastatic cholangiocarcinoma presenting with 6th cranial nerve paralysis was reported from Miami [6].

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