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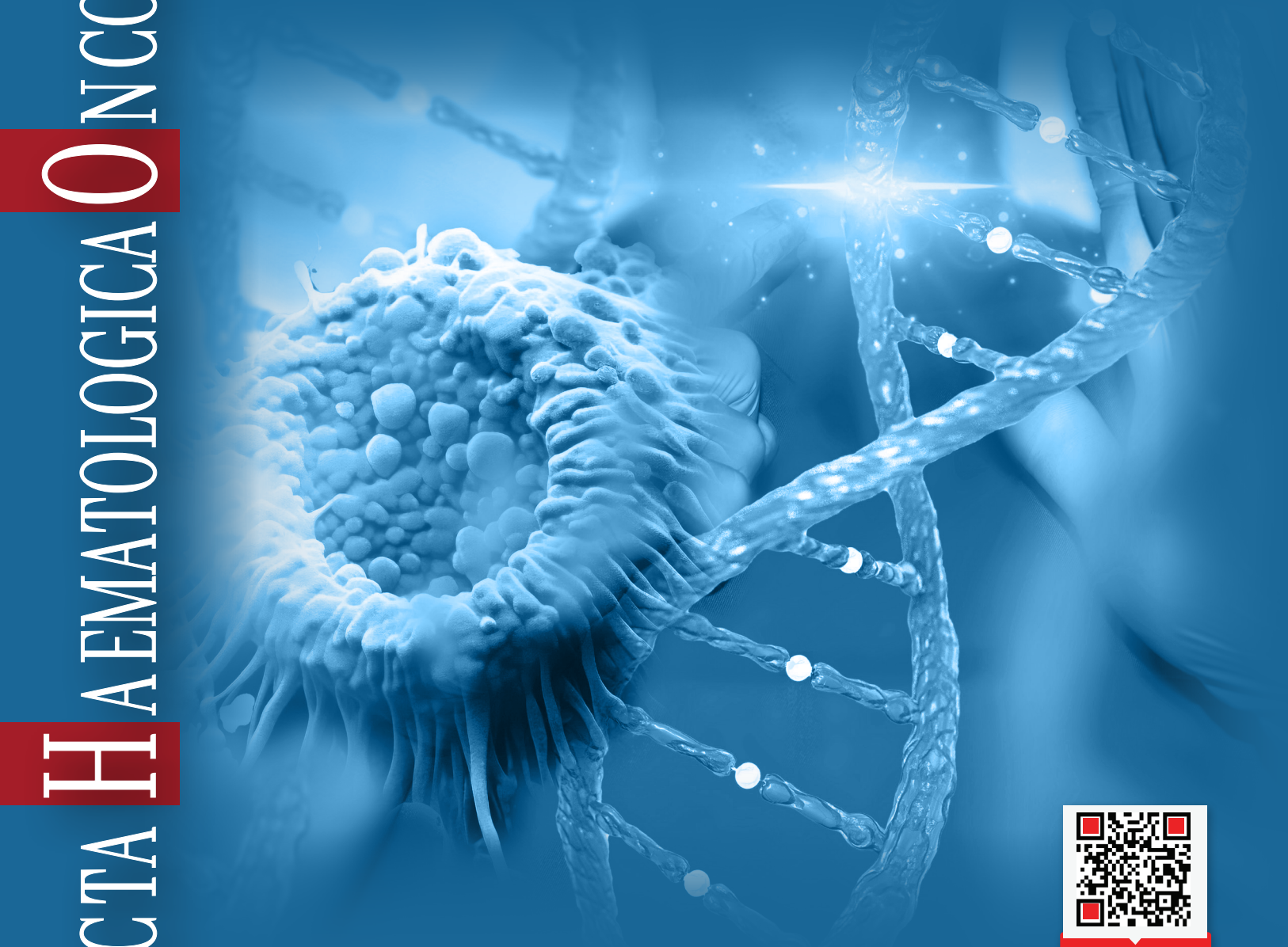

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VOLUME 58 / ISSUE 1

CONTENTS

Review

1 **Immunotherapy in Early and Locally Advanced Stage Non-small Cell Lung Cancer**
Abdülkadir Koçanoğlu, Yakup Düzköprü, Serdar Karakaya; Ankara, Aksaray, Türkiye

Original Articles

8 **Clinicopathological and Demographics Analysis of Testicular Tumors: A Single-center Experience**
Yakup Düzköprü, Abdülkadir Koçanoğlu, Serkan Gülcü, Berna Öksüzoğlu; Ankara, Türkiye

12 **Evaluation of the Effect of Radiotherapy Timing on Toxicity in HER2-Positive Breast Cancer Receiving Trastuzumab Emtansine During the Adjuvant Period**
İlknur Deliktaş Onur, Oğuzcan Kınıkoğlu, Gözde Kavgacı, Ömer Faruk Kuzu, Tuğba Başoğlu, Öztürk Ateş, Cengiz Karaçin; Ankara, İstanbul, Türkiye

16 **Does Wilms Tumour-1 Gene Mutation Affect Treatment Options and Response in Acute Myeloid Leukaemia?**
Seda Yılmaz, Tuğba Zorlu, Salih Cırık, Emine Hidayet, Ali Durdu, Nazik Okumuş, Abdulkadir Baştürk; Konya, Ankara, Türkiye

21 **Artificial Intelligence Chatbot as a Companion for Cancer Patients About Most Common Questions: Analysis of Readability and Quality**
Efe Cem Erdat, Elif Berna Köksoy, Güngör Utkan; Ankara, Türkiye

28 **The Effect of Video Streaming with Virtual Reality on Anxiety and Physiological Parameters During Chemotherapy Treatment in Hematologic Malignancy Patients**
Emine Korkmaz, Serdal Korkmaz; Kırşehir, Kayseri, Türkiye

36 **Is Hemoglobin, Albumin, Lymphocyte, and Platelet Score a Prognostic Indicator in Metastatic Squamous Cell Lung Cancer?**
Özlem Doğan, Yakup Düzköprü, Eyyüp Çavdar, Tülay Eren; Adıyaman, Aksaray, Ankara, Türkiye

40 **Impact of Metastasectomy on Survival Outcomes in Colorectal Cancer: A Single Center Retrospective Study**
Oğuzcan Kınıkoğlu, Yunus Emre Altıntaş, Goncagül Akdağ, Sedat Yıldırım, Hacer Şahika Yıldız, Akif Doğan, Uğur Özkerim, Sıla Öksüz, Alper Topal, Deniz Işık, Tuğba Başoğlu, Heves Sürmeli, Seval Ay, Hatice Odabaş, Nedim Turan; İstanbul, Tokat, Türkiye

46 **Molecular and Hematological Characterization of α-Thalassemia in Denizli Province**
Derya Karaer, Tuba Uğurlu Er, Nevin Alayvaz Aslan, Taner Durak; Denizli, Türkiye

Case Reports

51 **Two Rare Clinical Spectrums in a Hodgkin Lymphoma Patient: Super-acute Tumor Lysis Syndrome and Syndrome of Inappropriate Antidiuretic Hormone**
Rafiye Çiftçiler, Zahir Hasan, Hasan Önner; Konya, Türkiye

55 **Malar Fat Pad Flap for the Reconstruction of the Orbit: Case Report**
Moath Zuhour, Mehmet Dadacı, Selçuk Kendir; Konya, Ankara, Türkiye

58 **Acquired Hemophilia Developing After Whipple Operation**
Nebi Acar, İsmail Hasırcı; Kocaeli, Konya, Türkiye

AHOT Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Turc 2025;58(1):1-7

Review

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Immunotherapy in Early and Locally Advanced Stage Non-small Cell Lung Cancer

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ABSTRACT

Non-small cell lung cancer (NSCLC) is important for public health as it is one of the major causes of cancer-related deaths worldwide. The use of immunotherapy in NSCLC is becoming increasingly widespread. Immunotherapies are currently used in metastatic stages, as well as in earlier stages, in light of new studies. In our article, we aimed to summarize and compare neoadjuvant, perioperative, and adjuvant immunotherapy studies and their results in patients diagnosed with early and locally advanced NSCLC. Although there are no studies comparing neoadjuvant, perioperative, or adjuvant immunotherapy head-to-head, which treatment strategy is superior is one of the most important problems we encounter in clinical practice. Studies have shown that good results are obtained from both perioperative and neoadjuvant immunotherapy in patients who develop a pathological complete response (pCR). However, in patients without a pCR, the results indicate that perioperative immunotherapy is superior to neoadjuvant immunotherapy. Biomarkers such as circulating tumor DNA and baseline four-gene inflammatory score will be used to facilitate follow-up of patients and individualize treatment strategies in the future. Nowadays, perioperative immunotherapy and chemotherapy studies come to the fore for patients diagnosed with operable or potentially operable NSCLC. For inoperable locally advanced NSCLC, adjuvant immunotherapy is a valuable option after definitive chemoradiotherapy.

Keywords: Lung cancers, immunotherapy, neoadjuvant, perioperative, adjuvant

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases [1]. The primary treatment for NSCLC is surgery if possible. However, disease recurrence is observed in 45-55% of operable patients [2]. These high recurrence rates increase the importance of neoadjuvant and adjuvant therapies.

After studies conducted with adjuvant cisplatin-based doublet chemotherapies yielded different results, the LACE meta-analysis published in 1995 evaluated the data of 4584 patients from 5 studies. The overall survival (OS) benefit was found to be 5.4% and the disease-free survival (DFS) benefit was 5.8% [3]. Subsequently, a large meta-analysis was performed with data from 13 studies in neoadjuvant therapy. As a result of this meta-analysis, it was shown that platinum-based doublet chemotherapy was superior to surgery in terms of OS when given neoadjuvant [4]. Another large meta-analysis, neoadjuvant chemotherapy was compared with adjuvant chemotherapy. It was observed that the benefit obtained from chemotherapy was the same in terms of OS in neoadjuvant and adjuvant settings [5]. In light of these studies, there has been no change regarding neoadjuvant and adjuvant treatment of NSCLC for many years.

As immune checkpoint inhibitors (ICIs) were observed to significantly prolong survival data in the metastatic stage, the use of immunotherapy in studies shifted towards adjuvant, neoadjuvant and perioperative periods [6]. ICIs are IgG type

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antibodies that act by showing an antagonistic effect against programmed death 1/programmed death ligand 1 (PD-1/PD-L1) or cytotoxic T-lymphocyte-associated protein 4. While ICIs can be used alone, it is known that they provide additional immunomodulatory activity when used with chemotherapy [7]. Chemotherapy causes tumor cells to die and thus release tumor-derived antigens into the microenvironment. This situation increases the immune response to the tumor and the effectiveness of ICIs [8]. Based on these data, ICIs were first used as adjuvants in the postoperative period. Subsequently, the effectiveness of its use in combination with chemotherapy was evaluated through neoadjuvant and perioperative studies. As an outcome, it emerged as a potent option in an essential field for NSCLC treatment [9].

The advantages of giving immunotherapy to an unoperated patient include strong antigenic effect because the primary tumor is still in place and the lymphatic system has not been changed by surgery yet. Tumor antigens are usually presented to cytotoxic T cells in the lymph nodes. From here, cytotoxic T cells and memory T cells spread throughout the body. While the T cell clones formed against the tumor are responsible for the effectiveness of immunotherapy on tumor tissue and micrometastases, memory T cells ensure that this effect is maintained. Neoadjuvant and perioperative immunotherapy are thought to provide benefits by increasing the strength of this immune activity [10,11].

The survival benefit of definitive concurrent or sequential chemoradiotherapy (CRT) in patients with inoperable locally advanced NSCLC is limited. The 5-year OS in stage 3A, stage 3B and stage 3C patients was 36%, 26% and 13%, respectively [12]. It has been shown that the use of maintenance immunotherapy after CRT in patients who have received definitive treatment provides significant improvements in these survival data [13]. It is certain that neoadjuvant, perioperative, or post-CRT maintenance immunotherapy options will be discussed in these patient groups that we currently consider unresectable.

Adjuvant Immunoterapy

While the recurrence rate in patients who undergo surgery is approximately 45% in stage 1B, it can reach up to 70% in stage 3 patients. For this reason, adjuvant treatment is essential in operated NSCLC. However, it is known that cisplatin-based adjuvant chemotherapy has a very modest OS contribution [3]. It has been shown that adding adjuvant immunotherapy to standard chemotherapy provides a significant contribution to OS. The main advantage of preferring adjuvant treatment is surgical removal of the primary tumor without delay. It is known that in neoadjuvant studies, at least 20% of patients cannot undergo surgery at all [14]. Adjuvant treatment can be started at more flexible times during the postoperative period. For these reasons, patients can tolerate the treatment more easily [15,16]. Adjuvant chemo-immunotherapy hypothetically eliminates micrometastases and circulating tumor cells at a time when tumor burden is reduced by surgery [17]. There may be longer recovery times following surgery. Thus, an effective treatment strategy can be developed [18].

Many adjuvant ICI studies have been designed to prove the hypothetical benefits mentioned above. IMpower-010 is one of them. IMpower-010 is a phase 3, open-label, randomized study. 1280 patients with R0 resection, stage 1B (≥4 cm)-stage 3A (TNM 7th edition) and ECOG performance score 0-1 were included in the study, and 1005 patients were randomized. Patients were divided into two arms: one receiving 16 cycles of atezolizumab 1200 mg, and the other receiving best supportive care after standard cisplatin-based adjuvant chemotherapy. IMpower-010 is important because it is the first adjuvant immunotherapy study that has been shown to demonstrate improvement in DFS. While evaluating the data, we focused on patients with stage 2-3A. Patients were stratified according to PD-L1 status. Five-year follow-up results were published in 2024. DFS contribution is especially evident in the PD-L1 ≥1% group. In the intent-to-treat (ITT) population (stage 1B-3A), median DFS was 65.6 months in the atezolizumab arm and 47.8 months in the control arm. Hazard ratio (HR): 0.85 [95% confidence irterval (CI): 0.71-1.01], p value: 0.07. In all randomized patients in stage 2-3A, median DFS was 57.4 months/40.8 months; HR: 0.83 (95% CI: 0.69-1.00). In patients with PD-L1 ≥1%, median DFS was 68.5 months versus 37.3 months and HR: 0.70 (95% CI: 0.55-0.91). In patients with PD-L1 ≥50%, DFS was not reached (NR)/41.1 months. HR: 0.48 (95% CI: 0.32-0.72). Although there was a numerical difference between the two groups in the general population, there was no statistically significant difference. However, it was seen that there was a significant DFS difference starting from the PD-L1 ≥1% group, and it was more evident among PD-L1 ≥50% patients. Median OS was NR in the atezolizumab arm in PD-L1 ≥1%, patients, while it was 87.1 months in the control arm. HR: 0.77 (95% CI: 0.56-1.06). However, in PD-L1 ≥50% patients, the median OS was NR/87.1 months, with an HR of 0.47 (95% CI: 0.28-0.77). Grade 3 or higher side effects were seen in 22% of atezolizumab patients, and 12% were observed in the opposite arm. Of note, a significant difference in OS was only achieved in patients with PD-L1 ≥50% [19,20].

Another significant adjuvant ICIs study is KEYNOTE-091/PEARLS. The phase 3 randomized study included 1177 patients who underwent surgery for NSCLC, stage 1B-3A. Adjuvant pembrolizumab was started within 3-12 weeks after adjuvant platinum-based chemotherapy. Patients who started pembrolizumab by week 12 after surgery and did not receive adjuvant chemotherapy were included in the study. One arm received pembrolizumab every 21 days for 18 cycles, while the other arm received placebo. No crossover was allowed. Median DFS was 53.6 months in the immunotherapy arm and 42 months in the placebo arm. HR: 0.76 (95% CI: 0.60-0.89). In patients with PD-L1 1-49%, the HR was 0.67 (95% CI: 0.48-0.92) in terms of DFS. Unexpectedly, no statistically significant difference was seen between the two arms in patients with PD-L1 ≥50% (HR: 0.82). The median was NR in either arm. However, the pembrolizumab arm demonstrated numerically superior results compared to the placebo arm. In the subgroups, patients receiving ICIs without adjuvant chemotherapy, stage 3 patients, and patients with squamous cell carcinoma pathology were seen to have worse outcomes.

The median was also NR OS in the study. There was a significant benefit in terms of DFS in the ITT population and PD-L1 1-49% patients, but the lack of a statistically significant difference in patients with PD-L1 ≥50% presents a contrast. The reason for this discrepancy may be the difference in patient populations between the IMpower-010 study and the KEYNOTE-091/PEARLS study. At the same time, this may be because, in KEYNOTE-091/PEARLS, there were patients who received adjuvant ICIs without receiving adjuvant chemotherapy, and the rate of stage 3A patients was higher. Additionally, the immaturity of some data may have caused this discrepancy [21].

The adjuvant BR-31 study included patients with stage 1B-3A NSCLC. The study was designed as a Phase 3, double-blind study. Patients who received adjuvant platinum-based doublet therapies after surgery were then given durvalumab or placebo for 1 year. No significant difference in DFS was found between the two arms in patients with PD-L1 ≥1% and PD-L1 ≥25% [22]. In addition to the current studies, the adjuvant ANVIL study of nivolumab and the MERMAID 1 and 2 durvalumab studies are still ongoing [23-25]. Adjuvant ICI trials are summarized in Table 1.

Neoadjuvant and Perıoperative Immunoterapy

There is no clinical study comparing neoadjuvant ICIs with adjuvant ICIs in patients with NSCLC. However, the OpACIN study conducted in patients with stage 3 malignant melanoma showed a stronger immune response and greater T cell expansion with immunotherapy given in the neoadjuvant period [26,27]. It is known that immunotherapy given in the neoadjuvant period while the primary tumor remains in situ creates a stronger immune response. It is thought that this response creates a more permanent effect against circulating tumor cells and micrometastases [28]. Since the patient's performance status was better before the operation, treatment compliance was observed to be higher. In addition, another advantage of neoadjuvant ICIs includes the R0 resection rates and increased surgical success associated with the reduction in tumor size [29,30].

The concepts of pathological complete response (pCR) and major pathological response (MPR), which are thought to contribute to survival, are frequently used in neoadjuvant or perioperative, ICI studies. In pathological evaluation, no remaining viable tumor cells were defined as pCR, and ≤10% remaining viable cells were defined as MPR [31].

The most well-known study planned solely as a neoadjuvant study is CheckMate 816. Stage 1B-3A EGFR and ALK negative patients diagnosed with NSCLC were included in the study. One arm received 3 cycles of neoadjuvant nivolumab and chemotherapy every 21 days, while the control arm received 3 cycles of chemotherapy alone. The primary endpoints were pCR and event-free survival (EFS), and the secondary endpoints were MPR and OS. After neoadjuvant treatment, definitive surgery could be performed in 83.2% of the patients in the nivolumab + chemotherapy arm, while this rate was 77.8% in the control arm. Surgery could not be performed in 15.6% of the patients in the nivolumab + chemotherapy arm. When the reasons for not being able to undergo surgery in these patients were examined, it was observed that 6.7% of the patients could not be operated on due to disease progression, 1.1% due to treatment side effects, and 7.7% due to other reasons. Other reasons were the refusal of surgery by patients and the performance status or lung capacity of patients not being suitable for surgery. Median surgery time was 185 minutes in the experimental arm and 213.5 minutes in the control arm. A complete response was achieved in 24% of patients in the nivolumab + chemotherapy arm, while the complete response rate was 2.2% in the control arm. Again, MPR was 36.9% in the nivolumab + chemotherapy arm and 8.8% in the control arm. No significant difference was found only in terms of pCR in never smokers. The nivolumab + chemotherapy arm was superior in all other subgroups, such as PD-L1, age, and pathological type. Median EFS was 31.6 months in the experimental arm and 20.8 months in the control arm, with a HR of 0.63. When examined according to stage, the greatest EFS contribution was in stage 3A patients, with an HR of HR: 0.54. In stage 1B and 2, the contribution to EFS was not statistically significant. Non-squamous histology was associated with a better clinical outcome. While there was a significant contribution to EFS in the PD-L1 ≥1% group (HR: 0.41), there was no statistically significant difference in the PD-L1 <1% group. OS data is not available yet [32].

Table 1. Characteristics of adjuvant immunotherapy trials

Adjuvant trial	Phase	Stage	N	Treatment	Primary endpoint	HR in terms of DFS		
						ITT	PD-L1 ≥1%	PD-L1 ≥50%
IMpower-010	3	1B-3A	1280	CT + atezolizumab/ placebo	DFS	0.85 (95% CI: 0.71-1.01)	0.70 (95% CI: 0.55-0.91)	0.48 (95% CI: 0.32-0.72)
KEYNOTE-091/ PEARLS	3	1B-3A	1177	CT + pembrolizumab/ placebo	DFS	0.76 (95% CI: 0.60-0.89)	PD-L1 1-49% 0.67 (95% CI: 0.48-0.92)	0.82 (95% CI: 0.54-1.20)
Adjuvant BR-31	3	1B-3A	1219	CT + durvalumab/ placebo	DFS	0.89 (p=0.21)	0.99 (p=0.93)	-
ANVIL	3	1B-3A	903	CT + nivolumab/ placebo	DFS, OS	-	-	-

HR: Hazard ratio, DFS: Disease free survival, OS: Overall survival, CT: Chemotherapy, ITT: Intent-to-treat population, N: Sample size, PD-L1: Programmed death 1/programmed death ligand 1, CI: Confidence interval

The CheckMate 816 study included an exploratory arm in which 3 courses of neoadjuvant nivolumab plus ipilimumab were administered, while 3 courses of neoadjuvant chemotherapy were given in the control arm. Chemotherapy or radiotherapy was allowed in the adjuvant phase. These data were published in 2025. Two hundred and twenty-one patients were randomized 1:1. Median EFS was determined as 54.8 months in the nivolumab plus ipilimumab arm and 20.9 months in the control arm. The relationship between EFS and baseline four-gene inflammatory score (calculated by *STAT1, LAG3, CD8A, CD274,* genes) was examined. While there was no relationship between the baseline four-gene inflammatory score and EFS in patients who developed MPR, it was seen that, patients who developed pCR and had higher scores had significantly better EFS (HR: 0.45). pCR was observed as 20.4% in the nivolumab plus ipilimumab arm and 4.6% in the control arm. The MPR was 28.3% in the ICIs arm and 14.8% in the contralateral arm. OS data are immature, but 3-year OS data are 73% in the ICIs arm and 61% in the control arm. Grade 3-4 drug-related adverse events were seen in 14% of the ICIs arm and 36% of the control arm. Recurrence rates after definitive surgery were 23% and 44%, respectively. Recurrence rates with brain metastases were 2% and 13% [33].

LungMate 002 is a phase 2 neoadjuvant immunotherapy study, conducted with 50 patients with stage 2-3 disease. Toripalimab and chemotherapy was given for 2 to 4 cycles. After the operation, 27.8% of the patients achieved pCR and 55.6% achieved MPR [34]. In addition, TD-FOREKNOW is a phase 2 neoadjuvant immunotherapy study. It was conducted with 88 patients, with stage 3A and 3B disease. One arm received 3 cycles of camrelizumab plus chemotherapy and the other arm received 3 cycles of chemotherapy. The sentence needs to be rewritten for logical consistency and clarity, such as: 'After the procedure, the patients were monitored in the recovery room'. After the operation, pCR was 32.6% compared to 8.9%, and MPR was 65.1% compared to 15.6%, demonstrating the superiority of the (immunotherapy + chemotherapy) arm. In terms of EFS, HR: 0.13 was achieved in patients with pCR, while HR: 0.84 was achieved in patients without pCR [35].

NADIM II is a phase 2, perioperative immunotherapy study. Stage 3A and 3B; 86 patients were randomized 2:1. One arm received 3 cycles of nivolumab + carboplatin + paclitaxel, and the other arm received only carboplatin + paclitaxel. Postoperatively, nivolumab was continued every 28 days for 6 months in the immunotherapy arm. pCR was 37% in the immunotherapy arm and 7% in the control arm. The MPR was 57% compared to 14%, indicating a significant difference between the two groups. Downstaging occurred in 69.8% of the patients in the immunotherapy arm. The median PFS was NR in the immunotherapy arm, while it was 18.3 months in the control arm (HR: 0.47). 93% of the immunotherapy arm underwent surgery, while only 69% of the control arm underwent surgery. PFS and OS have been linked to baseline and changes in levels of ctDNA [36,37].

KEYNOTE-671 is a randomized, double-blind, phase 3 study. Seven hundred and eighty six patients with stage 2-3B NSCLC were randomized 1:1. The experimental arm received 4 cycles of neoadjuvant pembrolizumab + chemotherapy every 21 days. The control arm received 4 cycles of placebo + chemotherapy. The experimental arm received 13 cycles of postoperative pembrolizumab every 21 days. The primary endpoints of the study were EFS and OS. The secondary endpoints were pCR and MPR. The median EFS was NR in the pembrolizumab arm. The median EFS was 17 months in the placebo arm. HR: 0.58 (95% CI: 0.46-0.72) and p value: 0.00001. There was no statistically significant difference in EFS between patients with PD-L1 <1 and never smokers. In other subgroups, the ICI arm was significantly superior to the control arm. In terms of OS, the pembrolizumab arm did NR the median. In the placebo arm, the median OS was 45.5 months. HR: 0.73 (95% CI: 0.54-0.99) and p value: 0.02124. pCR was seen in 18.1% of patients in the ICI arm and 4% in the control arm. MPR was 30.2% vs 11%. In terms of EFS, the HR was 0.33 in patients with pCR, while the HR was 0.69 in patients without pCR. Regarding EFS, patients with MPR had an HR of 0.54, whereas those without MPR had an HR of 0.73 [38].

CheckMate 77T is a perioperative immunotherapy study that included patients with stage 2A (>4 cm)-3B NSCLC. Four hundred and sixty one patients without anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) mutations, ECOG 0-1, were randomized 1:1 in the study. Patients were stratified according to their histological diagnosis and PD-L1 status. The ICI arm received 4 cycles of nivolumab and chemotherapy every 21 days, while the control arm received 4 cycles of placebo and chemotherapy. Among the patients who underwent surgery afterwards, nivolumab was continued for 1 year in the ICI arm. The primary endpoint was defined as EFS. The secondary endpoints were pCR and MPR. While 78% of the patients in the ICI arm underwent definitive surgery, 77% in the control arm underwent the procedure. Only 60% of the patients in both arms could complete the neoadjuvant and adjuvant processes. While the median EFS in the control arm was 18.4 months, the median EFS in the ICI arm was NR. HR: 0.58 (0.42-0.81) and p value: 0.00025. When the subgroups were examined, there was no significant difference among stage 2 patients, while there was a significant difference among stage 3 patients. Again, there was no difference in terms of EFS in the PD-L1 <1% group, while there was a significant difference in the PD-L1 ≥1% group. There was no difference EFS between the two arms in non-smokers. The ICI arm was seen to be superior in both single-station, and double-station N2 patients. pCR was detected in 25.3% of the patients in the ICI arm and 4.7% of the control arm. Again, the MPR rates were 35.4% and 12.1%. There was no difference regarding pCR in never smokers. The ICI arm was superior to the control arm in terms of pCR in all other subgroups. In terms of EFS, HR was 0.33 in patients with pCR and 0.79 in patients without pCR. Regarding EFS, patients with MPR had an HR of 0.40, whereas those without MPR had an HR of 0.85 [39].

Neotorch is a phase 3 study. Five hundred patients with stage 2-3 NSCLC were randomized 1:1 in a clinical trial. Patients with

EGFR and ALK mutations were excluded from the study. In the ICI arm, he received 3 cycles of toripalimab + chemotherapy as neoadjuvant and then another cycle of toripalimab + chemotherapy as adjuvant, and 13 cycles of toripalimab every 21 days. In the control arm, they received 3 cycles of placebo + chemotherapy as neoadjuvant, and then another cycle of placebo + chemotherapy as adjuvant and 13 cycles of placebo. pCR was 24.8% in the ICI arm and 1% in the control arm. MPR was 48.5% and 8.4%, indicating results for two different conditions or metrics. EFS at 24 months was 64.7% in the ICI arm and 38.7% in the control arm. In terms of EFS, HR: 0.59 in patients with PD-L1 <1%, HR: 0.31 in patients with PD-L1 ≥1-49%, and HR: 0.31 in patients with PD-L1 ≥50% were found. Squamous cell disease patients had a better outcome than non-squamous cell disease patients [40].

The AEGEAN study is a phase 3 perioperative ICI study. 802 patients with Stage 2A-3B were randomized 1:1. The ICI arm received 4 cycles of durvalumab + chemotherapy, then underwent surgery, and received 1 year of adjuvant durvalumab. The control arm received 4 cycles of placebo + chemotherapy, followed by surgery and received placebo for 1 year. While EFS did NR the median in the ICI arm, the median EFS in the control arm was 25.9 months. The HR (HR: 0.68). pCR was 17.2% in the ICI arm and 4.3% in the control arm. MPR was found to be 33.3% in the ICI arm and 12.3% in the opposite arm. OS data have not yet reached the median [41].

Although there are no studies comparing neoadjuvant or perioperative immunotherapy, which treatment strategy is superior is one of the most important problems we encounter in clinical practice. It is observed that very good EFS results were obtained in the CheckMate 816, CheckMate 77T, KEYNOTE-671, and Neotorch studies in patients with pCR. However, in patients without pCR, the HR in the CheckMate 816 study was 0.84, while the HR in the CheckMate 77T, KEYNOTE-671, and Neotorch studies was 0.73, 0.69, and 0.53, respectively. This situation indicates that perioperative immunotherapy is superior to neoadjuvant immunotherapy, especially in patients without pCR. Biomarkers such as ctDNA and baseline four-gene inflammatory score will be used to facilitate follow-up of patients and individualize treatment strategies in the future. Neoadjuvant and perioperative ICI studies are summarized in Table 2.

Immunoterapy Strategies in Inoperable Locally Advenced NSCLC

Among locally advanced NSCLC patients, some are considered inoperable. Patients with multiple N2 lymph node involvement, bulky lymph nodes, N3 involvement, or with vascular invasion are considered to have inoperable locally advanced disease. However, with the emergence of neoadjuvant and perioperative immunotherapy studies, some patient groups previously considered inoperable have begun to be evaluated

Table 2. Characteristics of neoadjuvant and perioperative immunotherapy trials

Trial	Phase	Stage	N	Trial design / Treatment	Primary endpoint	pCR rate	MPR rate	EFS	OS
CheckMate 816	3	1B-3A	358	Neoadjuvant Neoadjuvant CT + nivolumab	pCR, EFS	24% vs. 2.2%	36.9% vs. 8.9%	31.6 m vs. 20.8 m HR: 0.63	-
LungMate 002	2	2-3	50	Neoadjuvant Neoadjuvant CT + toripalimab	Safety, MPR	27.8%	55.6%	-	-
NADIM II	2	3A-3B	86	Perioperative Neoadjuvant CT + nivolumab, adjuvant nivolumab after surgery	PFS	36.8% vs. 6.9%	52.6% vs. 13.8%	PFS: NR vs. 18.3 m HR: 0.47	NR vs. NR HR: 0.43
KEYNOTE-671	3	2-3B	786	Perioperative Neoadjuvant CT + pembrolizumab, adjuvant pembrolizumab after surgery	EFS, OS	18.1% vs. 4%	30.2% vs. 11%	NR vs. 17 m HR: 0.58 p<0.00001	NR vs. 45.5 m HR: 0.73 p: 0.02124
CheckMate 77T	3	2A-3B	461	Perioperative Neoadjuvant CT + nivolumab, adjuvant nivolumab after surgery	EFS	25.3% vs. 4.7%	35.4% vs. 12.1%	NR vs. 18.4 m HR: 0.58	-
Neotorch	3	2A-3B	406	Perioperative Neoadjuvant CT + toripalimab, adjuvant durvalumab after surgery	EFS, MPR	24.8% vs. 1%	48.5% vs. 8.4%	NR vs. 15.1 m HR: 0.40	NR vs. 30.4 m HR: 0.62
AEGEAN	3	2A-3B	802	Perioperative Neoadjuvant CT + durvalumab, adjuvant durvalumab after surgery	EFS, pCR	17.2% vs. 4.3%	33.3% vs. 12.3%	NR vs. 25.9 m HR: 0.68	-

HR: Hazard ratio, EFS: Event free survival, OS: Overall survival, PFS: Progression free survival, CT: Chemotherapy, N: Sample size, pCR: Pathologic complete response, MPR: Major pathologic response, NR: Not reached, m: Month, vs: Versus

as potentially operable [42]. Operability for patients diagnosed with NSCLC is a frequently discussed topic soon. However, the results of adjuvant immunotherapy after definitive CRT inoperable patients are noteworthy.

The PACIFIC trial is a phase 3 randomized trial. In the study, 709 patients were randomized in a 2:1 ratio. All patients received ≥2 cycles of platinum-based doublet chemotherapy and definitive radiotherapy. The ICI arm then received durvalumab for up to 1 year, while the control arm received placebo. Median PFS was 16.8 months in the ICI arm and 5.6 months in the control arm (HR: 0.52). At the beginning of the study, participants were stratified into groups of <25% and ≥25% in terms of PD-L1. When the subgroups were examined, an EFS benefit was observed in both groups in the ICI arm in terms of PD-L1. No benefit was shown in the subgroups, only in EGFR-positive patients [43]. The 5-year follow-up data were then published in 2022. Median OS was 47.5 months in the ICI arm and 29.1 months in the control arm (HR: 0.72). The 5-year OS was 42.9% vs 33.4%. Five-year PFS was 33.1% in the ICI arm and 19% in the control arm. When subgroups were evaluated according to OS data, no OS contribution was shown in the PD-L1 <25% group. Subsequently, it was re-stratified as <1% and ≥1% according to PD-L1. While no OS contribution was shown in the PD-L1 <1% group, adjuvant durvalumab was shown to contribute to OS in patients with PD-L1 ≥1%. Grade ≥3 side effects were seen in 30% in the ICI arm and 26% in the opposite arm [13].

Conclusion

In adjuvant ICIs studies, a contribution to OS was observed in patients with PD-L1 ≥50% in IMpower-010. OS contribution was shown in patients with PD-L1 ≥1% in KEYNOTE-091/PEARLS, but not in patients with PD-L1 ≥50%. At the same time, the contribution of adjuvant durvalumab to EFS could not be shown in the Adjuvant BR-31 study. However, the contribution of pCR, MPR, EFS, and OS in favor of ICIs in all groups in neoadjuvant and perioperative studies is remarkable. We see that OS and EFS contribution cannot be assessed in the adjuvant ICIs studies in some cases. The superior results of neoadjuvant and perioperative studies compared to neoadjuvant and perioperative studies are better than adjuvant studies can be attributed to the continuation of the antigenic effect of the primary tumor in the neoadjuvant phase and the stronger immune response associated with this effect. At the same time, the immune system is not suppressed by surgery, and the structure of the lymphatic system is not disrupted, both of which are in favor of neoadjuvant ICIs. Today, perioperative ICIs have come to the forefront for patients with operable or potentially operable NSCLC diagnosis, especially stage 3. For inoperable locally advanced NSCLC, adjuvant durvalumab after definitive CRT is a valuable option.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: Y.D., Design: Y.D., Literature Search: A.K., S.K., Writing: A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Clinicopathological and Demographics Analysis of Testicular Tumors: A Single-center Experience

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ABSTRACT

Aim: Testicular cancers are among the most prevalent solid tumors in young males. The majority of these cases involve germ cell tumors, with seminomas emerging as the predominant histological subtype. This study aimed to investigate both the clinical and demographic characteristics of patients diagnosed with testicular tumors and the distribution of histopathological subtypes within this cohort.

Methods: Patients aged 18 years who were diagnosed with testicular tumors other than secondary malignancies and were followed up at our clinic between 2008 and 2022 were included in the study. Comprehensive clinical and pathological data were meticulously recorded for each patient. Survival outcomes were compared using the Kaplan-Meier method with the log-rank test.

Results: Germ cell tumors exhibited a median onset age of 29. Among the cases, non-seminomatous tumors accounted for 55.9% of the cases, whereas seminomas accounted for 44.1%. Within the non-seminomatous tumor category, mixed germ cell tumors were the most frequently encountered subtype, accounting for 45.4% of cases. Testicular involvement was noted predominantly in the right-side testis (56.7%), followed by the left-side testis (42.3%), and bilateral involvement was rare (1%). The percentage of patients diagnosed at stage 1 was 56.7%.

Conclusion: Germ cell tumors are primary testicular malignancies and remain a significant health problem in young men. Although seminomas have historically been predominant, there has been an increase in the rates of non-seminomatous tumors in recent years. Early and accurate diagnosis remains the most important step toward successful treatment of such tumors.

Keywords: Testicular cancer, epidemiology, germ cell neoplasms, seminoma, non-seminomatous germ cell tumor

Introduction

Testicular cancer is the most common solid tumor in young males [1]. The vast majority (>95%) of testicular cancers are testicular germ cell tumors. According to the current World Health Organization classification system, germ cell tumors are classified into two main subgroups: seminomas and non-seminomatous tumors. Approximately 50% of these cases are seminomas. Non-seminomatous tumors include embryonal carcinoma, choriocarcinoma, yolk-sac tumor, teratoma, and mixed germ cell tumors formed by various combinations of these elements [2]. Most cases occur in young men aged 15-40 years [3].

The etiopathogenesis and risk factors associated with testicular cancers remain not fully elucidated. However, undescended testes (cryptorchidism) represent a prominent risk factor, increasing the risk of testicular cancer development by fivefold [4]. Additionally, diet, environmental factors, infertility, and history of testicular cancer in the contralateral testis are risk factors for new testicular cancer development [3].

Approximately 70% of patients are diagnosed at an early stage (normal tumor marker levels, absence of lymph node involvement or distant metastases), whereas approximately 30% receive a diagnosis at an advanced stage [5]. In the metastatic stage, the International Germ Cell Cancer Collaborative Group's risk classification system stratifies

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patients into good, intermediate, and poor risk groups. Patients in the poor-risk group have a worse prognosis [6,7].

This study aimed to investigate epidemiological data, histopathological characteristics, and survival rates by screening patients diagnosed with testicular cancer at our hospital over the past 15 years.

Methods

Medical records of patients who were followed up at our medical oncology clinic between 2008 and 2022 were screened. Patients aged 18 years and above diagnosed with testicular cancer were included in the study. Patients with testis metastasis from another cancer were excluded. The total number of patients enrolled in the study was 95. Patient data were retrieved from the hospital database and follow-up records. Data such as age, pathological diagnoses, histopathological subgroups, tumor location, tumor stage, current status, and last follow-up date were recorded.

The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (code: AEŞH-BADEK-2024-150, date: 06.03.2024). This study was conducted in compliance with the principles outlined in the 1964 Declaration of Helsinki.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences (SPSS) Statistical Software (IBM SPSS statistics version 22.0, IBM SPSS, USA). Descriptive analysis was used to analyze the clinical and demographic characteristics of the patients. Categorical and numerical variables are presented as numbers and percentages (n, %). Continuous data were reported as means±standard deviation if they followed a normal distribution; otherwise, they were presented as medians and ranges. Survival outcomes were assessed using the Kaplan-Meier method with the log-rank test (univariate analysis) or Cox proportional hazard regression model (multivariate analysis). A p value of <0.05 was considered statistically significant for all analyses.

Results

A total of 95 patients were included in the study, with a median age of 29 (18-79) years. The number of patients with a history of smoking and alcohol consumption was 51 (53.7%) and 10 (10.5%), respectively. Most patients (93.7%) did not have comorbidities. Of the patients, 93 (97.9%) were diagnosed with germ cell tumors. The general characteristics of the patients are presented in Table 1.

Non-seminomatous tumors were the most common germ cell tumor subtype (55.9%). Only 2 patients had Leydig cell tumors classified as non-germ cell tumors. Histopathological subtypes of the tumors are presented in Table 2.

Among the patients, 54 (56.8%) had right testis tumors. At diagnosis, 55 patients (57.9%) were in stage 1 and 23 (24.2%) were in stage 2. Among the stage 1 patients, 12 (21.8%) received one cycle of carboplatin (area under the curve=7), 11 (20%) received one cycle of bleomycin/etoposide/cisplatin (BEP), and 5 (9.1%) received three cycles of BEP, whereas 27 (49.1%) did not receive any treatment. Among the stage 2 patients, 20 (87%) received three cycles of BEP, whereas 3 (13%) received four cycles of BEP. Among the stage 3 patients, 13 (76.5%) received three cycles of BEP, while 4 (23.5%) received four cycles of BEP.

The median overall survival has not yet been determined. The 5-year overall survival was 89% for the entire patient group, with rates of 98%, 94%, and 57% for stages 1, 2, and 3, respectively. Kaplan-Meier curves according to stage are presented in Figure 1.

Discussion

It is widely acknowledged that the incidence of cancer is progressively rising worldwide. In 2020, a total of 74,500

Table 1. General characteristics of the patients

	n	%
Age (median, range)	29 (18-79)	
Smoking history		
Yes	51	53.7
No	44	46.3
Alcohol consumption		
Yes	10	10.5
No	85	89.5
Comorbidity		
Yes	6	6.3
No	89	93.7
Germ cell tumors	93	97.9
Non-germ cell tumors	2	2.1
Laterality		
Right	54	56.8
Left	40	42.2
Bilateral	1	1
Stage at diagnosis		
Stage 1	55	57.9
Stage 2	23	24.2
Stage 3	17	17.9

Table 2. Histopathological distribution of testicular tumors

	n	%
Seminoma	41	43.2
Non-seminoma (54.7%)		
Embryonal carcinoma	7	7.4
Mixing germ cell tumors	44	46.3
Yolc sac tumor	1	1
Leydig cell tumors	2	2.1
Total	97	100

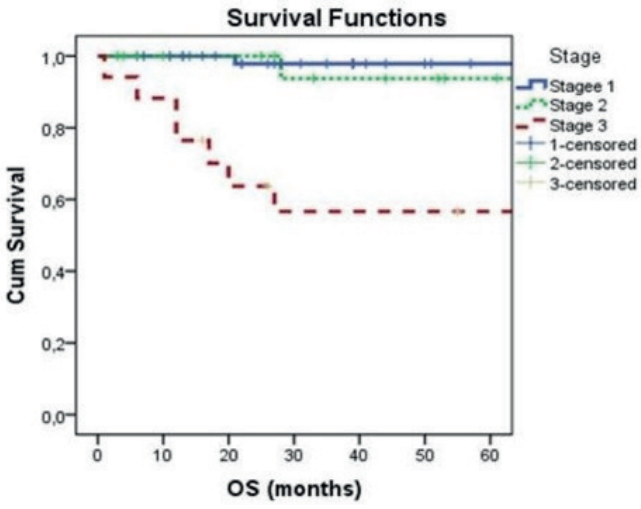

Figure 1. Kaplan-Meier plot according to tumor stage
OS: Overall survival

new cases of testicular cancer were reported globally, placing testicular cancer as the 20th most prevalent malignancy [8]. However, when focusing on younger age groups, the landscape shifts. Testicular tumors reaching their peak incidence within the 15-40 age range are recognized as the most frequent solid cancers in this demographic [3]. This trend is also evident in retrospective studies conducted in Türkiye. In the study of Çalışkan et al. [9], the mean age was 36.9, while Yalçınkaya et al. [10] reported a mean age of 32.9. Similarly, Gürsoy et al. [11] noted the most frequent occurrence within the 26-32 age bracket. Consistent with this trend, our study determined a median age of 29 years, which is the age range in which testicular tumors are most commonly observed. Despite slight variations across series, the consistency of the age group at the peak incidence is coherent.

Existing literature has suggested a lower prevalence of non-seminomatous tumors [12]. However, studies conducted in our country revealed a higher incidence of non-seminomatous tumors. Both Gürsoy et al. [11] and Çalışkan et al. [9] reported a higher incidence of non-seminomatous tumors compared to seminomas. Similarly, in our study, non-seminomatous tumors constituted 54.7% of all testicular tumors. While it is challenging to fully elucidate this discrepancy in the retrospective Turkish series compared with the literature, genetic, sociocultural differences, and specific environmental exposures may contribute to these variations.

Regarding subtypes within non-seminomatous tumors, mixed germ cell tumors are the most common. They are the second most common type of germ cell tumor in adults, the following seminomas. Embryonal carcinoma is the second most common non-seminomatous subtype. Teratomas and yolk sac tumors are less frequently encountered [11]. Our study similarly found the highest prevalence of mixed germ cell tumors within non-seminomatous tumors, with embryonal carcinoma being the second most frequent subtype.

Irrespective of histopathological subtype, germ cell tumors exhibit a greater predilection in the right testes. After analyzing laterality, the studies previously mentioned and conducted in our country consistently reported a higher prevalence of right testicular tumors compared with left testicular tumors. This phenomenon can be attributed to the higher frequency of undescended testes in the right testes. Additionally, although bilateral testicular tumors are reported to range between 1% and 7% in the literature, our study observed a bilateral occurrence rate of 1% [13].

Testicular cancers are recognized as chemosensitive tumors, thereby rendering survival outcomes generally favorable, whether in the adjuvant or metastatic setting. Gürsoy et al. [11] reported a 5-year overall survival rate of 88% across the entire patient group. In our study, the 5-year survival rate for the entire patient cohort was 89%, while stage 3 patients exhibited a rate of 57%. These data underscore the significance of administering adjuvant chemotherapy to patients at risk of recurrence or metastasis to enhance survival. Furthermore, the 5-year survival rate was 92% for seminomas and 89% for non-seminomatous tumors in our study. Despite the numerical distinctions, statistical significance was not observed.

Study Limitations

Several limitations are inherent to our study. Primarily, being a single-center, retrospective study, inherent biases are unavoidable. Second, the relatively small number of cases may impact the study's power to provide comprehensive epidemiological insights. Additionally, the lack of information on salvage treatments for patients who experience relapse is another limitation. Therefore, when interpreting the study's outcomes, it is advisable to consider these factors.

Conclusion

Germ cell tumors constitute the majority of testicular malignancies. Although the incidence of these tumors within the general population may be relatively low, they are the most prevalent solid organ tumors among young men. Historically, seminomas have been reported to dominate germ cell tumors; however, recent studies have indicated an increasing prevalence of non-seminomatous tumors. Treatment outcomes, particularly in the early stages, demonstrate near-optimal results. Hence, early and accurate diagnosis remains a pivotal step toward successful management of these tumors.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (code: AEŞH-BADEK-2024-150, date: 06.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: Y.D., Design: Y.D., Data Collection or Processing: S.G., A.K., Analysis or Interpretation: Y.D., Literature Search: B.Ö., Writing: B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Evaluation of the Effect of Radiotherapy Timing on Toxicity in HER2-Positive Breast Cancer Receiving Trastuzumab Emtansine During the Adjuvant Period

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ABSTRACT

Aim: Breast cancer is the second leading cause of cancer-related deaths in women. Approximately 20-25% of breast cancers express HER2 and are associated with poor prognosis. With the use of HER2-targeted therapies, there has been an increase in treatment success for breast cancer cells overexpressing HER2. Trastuzumab extensive (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent extensive (DM1), a maytansine derivative and microtubule inhibitor. The aim of our study was to evaluate the effect of continuing T-DM1 therapy on toxicity in patients receiving adjuvant radiotherapy using real-world data. There is no study in the literature that evaluates the toxicity of adjuvant T-DM1 in real life.

Methods: Patient files were examined retrospectively. The primary endpoint of the study was whether the timing of radiotherapy increased adjuvant T-DM1 toxicity. Patients were divided into two groups: those who continued T-DM1 during and after T-DM1 adjuvant radiotherapy.

Results: A total of 50 patients were included in the study. Twenty (40%) of the patients received sequential radiotherapy with T-DM1, thirty (60%) continued T-DM1 during radiotherapy. No significant difference was detected in terms of toxicity in both groups.

Conclusion: In our study, we observed that some physicians started T-DM1 after radiotherapy considering that toxicity might increase. However, we observed in the analysis that there was no significant increase in the toxicities with simultaneous use. We believe that as the use of antibody-drug conjugates in the clinic increases, more studies are needed to determine the timing of radiotherapy.

Keywords: Antibody-drug conjugates, adjuvant T-DM1, trastuzumab extensive, HER2-positive breast cancer

Introduction

Breast cancer is the second leading cause of cancer-related deaths among women [1]. Approximately 20-25% of breast cancers have HER2 overexpression and are associated with poor prognosis [2]. With the use of HER2-targeted therapies, there has been an increase in treatment success for breast cancer cells overexpressing HER2. In the phase II NeoSphere study, pertuzumab was added to trastuzumab and docetaxel in patients with localized or locally advanced HER2-overexpressing breast cancer, and a significant increase in pathological complete response rates was observed (29% vs. 46%). An increase in pathological response rates is associated with improved survival [3].

Trastuzumab extensive (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent extensive (DM1), a maytansine derivative and microtubule inhibitor. T-DM1 maintains trastuzumab activity while ensuring intracellular delivery of DM1 to cells overexpressing HER2 [4]. In the

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Katherine study, the use of T-DM1 and trastuzumab in the adjuvant period was compared among patients who received neoadjuvant treatment and had residual disease in the breast or axillary lymph node. A total of 1486 patients were included in the study and randomized 743 in the T-DM1 group and 743 in the trastuzumab group. Invasive disease or death occurred in 91 patients (12.2%) in the T-DM1 group and 165 patients (22.2%) patients in the trastuzumab group. Invasive disease-free survival was significantly higher in the T-DM1 group than in the trastuzumab group (HR, 0.50; 95% confidence interval, 0.39 to 0.64; p<0.001). T-DM1 was continued during the adjuvant period of adjuvant radiotherapy. No significant increase in toxicity was observed in this study [5].

In clinical practice, radiotherapy and chemotherapy in the adjuvant period are sequentially applied to breast cancer, as in most cancers. Concurrent application suggests that toxicity may increase. Some clinicians wait until the end of radiotherapy to start T-DM1 in the adjuvant period. The aim of our study was to evaluate the effect of continuing T-DM1 therapy on toxicity in patients receiving adjuvant radiotherapy using real world data. There are no studies in the literature that evaluate the toxicity of adjuvant T-DM1 in the real world.

Methods

Fifty breast cancer patients with HER2 overexpression, aged >18 years, who received adjuvant T-DM1 after receiving neoadjuvant treatment between 2021 and 2023 were included in the study. The study was conducted in a multicenter setting. Patients who had a pathological complete response to neoadjuvant therapy but did not receive T-DM1 during the adjuvant period were excluded from the study.

Approval was received from the Non-Invasive Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision number: 2023-11/91, date: 16.11.2023). The patient files were examined retrospectively. Demographic data, such as age, sex, menopausal status, family history of breast cancer, clinical stage at the time of diagnosis, treatment received during the neoadjuvant period, and pathological stage, were recorded. Toxicities that developed while receiving adjuvant T-DM1 were examined. Toxicities were evaluated and graded according to CTCAE version 5. All grade 1-4 toxicities were considered significant and noted. The primary endpoint of this study was to determine whether the timing of radiotherapy increased adjuvant T-DM1 toxicity. Patients were divided into two groups: those who continued T-DM1 during and those who started using T-DM1 after adjuvant radiotherapy.

Statistical Analysis

In the descriptive statistics of the research, continuous variables are presented as mean (standard deviation) or median (range); categorical variables are presented as frequency (percentage). Chi-square or Fisher's exact test was used to compare categorical variables between two independent groups. The independent sample t-test was used to compare parametric data, and Mann-Whitney U test was used to compare non-parametric data.

Results

A total of 50 patients were included in the study. Twenty (40%) of the patients received sequential radiotherapy with T-DM1, thirty (60%) continued T-DM1 during radiotherapy. Twenty-seven (54%) patients were premenopausal, while 23 (46%) were peri-postmenopausal. Forty-five patients (90%) were node-positive upon diagnosis (the demographic characteristics of the patients are shown in Table 1).

Of the patients who received sequential radiotherapy with T-DM1 in the adjuvant period, one (5%) had neutropenia, seven (35%) had thrombocytopenia, one (5%) had anemia, and two (10%) had hepatotoxicity. A decrease in ejection fraction was observed in one (5%) of them. All of these toxicities were at grade 1-2 level. Radiodermatitis was observed in five (25%) patients, with one (5%) having grade 3 and four (20%) was grade 1-2.

In patients who continued T-DM1 during adjuvant radiotherapy, two (6.6%) developed neutropenia, three (10%) developed thrombocytopenia, two (6.6%) developed anemia, and two (6.6%) developed hepatotoxicity. All of these toxicities were at grade 1-2 level. Neuropathy was observed in one patient, and because it was at grade 3, treatment was discontinued, and trastuzumab was continued. In one patient, treatment was discontinued because pneumonitis was observed at the radiotherapy site, and trastuzumab was continued. Radiodermatitis was observed in five (16%) patients, and three (10%) of them were at grade 3 level (shown in Table 2).

Discussion

In our study, we aimed to evaluate the effect of the timing of radiotherapy on toxicities in patients with HER2 positive breast cancer who received T-DM1 in the adjuvant period. In the Katherine study, patients who received T-DM1 in the adjuvant period also received radiotherapy simultaneously [5]. When we looked at the entire study, there was no significant increase in toxicities compared with the use of T-DM1 during the metastatic period. Of course, this result may be due to the better performance and better drug tolerance of patients in the early stages. In most cancers, chemotherapy and radiotherapy are not used simultaneously during the adjuvant period because of the potential increase in toxicity. For example, in lung cancer, postoperative radiotherapy is recommended in cases with positive surgical margins or N2 disease, but it is recommended that the timing of radiotherapy be planned after chemotherapy [6]. Antibody-drug conjugates have become widely used in clinical practice in recent years. These drugs, which are primarily used in the metastatic stage, were indicated for use in the early stage because the use of T-DM1 in the adjuvant period resulted in progression-free survival. We believe that in the future, as the use of antibody-drug conjugates increases and new indications develop, the

Table 1. Demographic characteristics of patients

	Sequenced radiotherapy (n=20)	Concurrent radiotherapy (n=30)	p value	All patients
Age (mean)	50.6	49.3		49.8
Menopause				
Premenopausal	10 (50)	17 (57)	0.643	27
Peri-postmenopausal	10 (50)	13 (43)		23
Familial breast cancer				
No	14 (70)	23 (76.7)	0.599	37
Yes	6 (30)	7 (23.3)		13
Clinical stage T				
T1	2 (10)	2 (6.7)	0.744	4
T2	14 (70)	23 (76.7)		37
T3-T4	4 (20)	5 (16.6)		9
Clinical nodal status				
Node positive	19 (5)	26 (86.6)	0.024	45
Node negative	1 (95)	4 (13.3)		5
ER status				
Positive	14 (70)	19 (63.3)	0.626	33
Negative	6 (30)	11 (367)		17
PR status				
Positive	13 (65)	17 (56.7)	0.556	30
Negative	7 (35)	13 (43.3)		20
Grade				
Grade 1-2	7 (35)	12 (41.3)	0.672	19
Grade 3	13 (65)	17 (58.6)		30
pT stage				
T0-1-2	18 (90)	26 (90)	0.406	44
T3-4	2 (10)	3 (10)		5
pN stage				
N0-1	16 (80)	24 (82.7)	0.616	40
N2-3	4 (20)	5 (17.2)		9

ER: Estrogen receptor, PR: Progesterone receptor

Table 2. Trastuzumab emtansine related toxicities

	Sequenced RT		Concurrent RT		p value
	Yes	No	Yes	No	
Neutropenia	1 (5)	19 (95)	2 (6.6)	28 (93.3)	0.657
Thrombocytopenia	7 (35)	13 (65)	3 (10)	27 (90)	0.027
Anemia	1 (5)	19 (95)	2 (6.6)	28 (93.3)	0.657
Hepatotoxicity	2 (10)	12 (90)	2 (6.6)	28 (93.3)	0.521
Decrease in ejection fraction	1 (5)	18 (95)	0 (0)	30 (100)	0.388
Neuropathy	0 (0)	20 (100)	1 (3.3)	29 (96.7)	0.600
Pneumonitis	0 (0)	20 (100)	1 (3.3)	29 (96.7)	0.600
Radiodermatitis	5 (25)	15 (75)	5 (16)	25 (84)	0.390
All toxicities	9 (45)	11 (55)	12 (40)	18 (60)	0.556

timing of radiotherapy in the adjuvant period should be more frequently discussed. In our study, we observed that some physicians started T-DM1 after radiotherapy considering that toxicity might increase. However, we observed in the analysis that there was no significant increase in toxicities with concurrent use. Although there was no statistically significant increase in toxicities, pneumonitis was observed in the radiotherapy field in one of the patients receiving concurrent therapy, leading to treatment discontinuation, and neuropathy was observed in one patient, which could lead to treatment discontinuation. This supports reservations about concurrent use.

Study Limitations

The main limitations of our study were its retrospective nature and small number of patients. The increase in concurrent use may reach statistically significant levels as the number of patients increases.

Conclusion

As a result, we believe that as the use of antibody-drug conjugates in the clinic increases, more studies are needed to determine the timing of radiotherapy.

Ethics

Ethics Committee Approval: Approval was received from the Non-Invasive Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision number: 2023-11/91, date: 16.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.D.O., Concept: İ.D.O., Design: İ.D.O., C.K., Ö.A., Data Collection or Processing: O.K., G.K., Ö.F.K., T.B., Analysis or Interpretation: İ.D.O., C.K., Literature Search: İ.D.O., Writing: İ.D.O., C.K.

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Original Article

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Does Wilms Tumour-1 Gene Mutation Affect Treatment Options and Response in Acute Myeloid Leukaemia?

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ABSTRACT

Aim: The prognostic impact of Wilms tumour-1 (WT-1) mutations is controversial for patients with acute myeloid leukaemia (AML). In this study, we aimed to determine the clinical effects of WT-1 mutations.

Methods: We retrospectively analysed the data of a total of 139 patients with AML, 50 negative and 89 positive, in whom WT-1 analysis was performed at the time of diagnosis.

Results: Among the patients, 47% were female and 53% were male; median age was 62 (18-88) years in the WT-1 negative group and 47 (18-90) years in the WT-1 positive group; median follow-up period was 5 (1-144) months in the WT-1 negative group and 28 (1-110) months in the WT-1 positive group. When the induction treatments were analysed, the regimen containing idarubicin and cytarabine was the most commonly used regimen in both groups (73% in the WT-1 positive group and 36% in the WT-1 negative group). When the response to treatment was evaluated in WT-1-negative and positive groups, complete response was 58% to 80% for WT-1-negative and positive groups respectively; partial response was 14% to 2%; refractoriness was 26% to 16%, respectively. Recurrence was 16% in the WT-1 negative group and 5.6% in the positive group. The survival rate was found to be 64% in the WT-1 negative group and 67.4% in the positive group.

Conclusion: It is uncertain whether the WT-1 test will be interpreted in diagnosis, treatment, and follow-up, or if its prognostic significance and future studies are much needed.

Keywords: Acute myeloid leukemia, prognosis, WT-1 mutations

Introduction

Acute myeloid leukaemia (AML) has a heterogeneous course due to many patient- and tumour-related factors [1-3]. Genetic characteristics are important prognostic factors [4]. *Wilms tumour-1* (WT-1) gene shows both tumor suppressor effects and oncogenic effects by controlling transcription, translation, and RNA metabolism at cellular levels [5,6]. WT-1 positivity is observed in 6-15% of newly diagnosed AML cases [7]. The European Leukaemia Network (ELN) 2022 update does not include WT-1 positivity in the genetic risk classification [4]. In the presence of WT-1, it has been reported that some mutations, including ten-eleven translocation methylcytosine dioxygenase 2, isocitrate dehydrogenase-1, isocitrate dehydrogenase-2 (IDH-2), and CCAAT/enhancer binding protein alpha (CEBPA), were not observed [8,9]. Detection of WT-1 levels is a marker of both residual disease and future relapse [10,11]. In addition, it is considered that WT-1 triggers malignant events through its interaction with Bcl-2, which is a protooncogene, and the *p53* gene, which is a tumor suppressor gene [12]. In one study, it was found that WT-1 positivity was more common under the age of 65 years, and affected relapse-free survival. Again in this study, it was reported that the frequency of WT-1 decreased in the presence of nucleophosmin (NPM1) and CEBPA [13]. In a phase-2 study evaluating the efficacy of azacitidine in myelodysplastic syndrome, no correlation was found between WT-1 level and treatment response. In other words, in this

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study, WT-1 was not a predictor of treatment response [14]. In another study, WT-1 was found to be associated with DEK oncogene and was reported to cause cytarabine, doxorubicin or azacitidine resistance [15]. Despite the partial understanding of this complex association and advances in the field of genetic mutation analyses, treatment remains elusive.

Our aim in this study was to retrospectively review the data of WT-1 positive AML patients, to determine the presence of concomitant mutations, to analyse the treatment response according to the type of treatment, to determine the prognostic effect, and, if possible, to make a treatment recommendation.

Methods

In our study, 139 patients diagnosed with AML who were followed up in the adult hematology clinic between 2011 and 2023 and who underwent *WT-1* gene mutation test analysis were included. Along with the demographic characteristics of the patients, complete blood count, genetic results, and treatment content at the time of AML diagnosis, treatment response and whether recurrence developed during follow-up were analysed, and overall survival rates were calculated. ELN 2022 categorises summarised: t(8;21)(q22;q22.1); RUNX1::RUNX1T1, inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB::MYH11, mutated *NPM1*, in-frame bZIP mutated are favorable; t(6;9)(p23;q34.1)/DEK::NUP214, (v;11q23.3)/KMT2A rearranged, t(9;22)(q34.1;q11.2)/BCR::ABL1, t(8;16)(p11;p13)/KAT6A::CREBBP, inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM (EVI1), t(3q26.2;v)/MECOM (EVI1)-rearranged, -5 or del(5q); -7; 17/abn(17p), monosomal karyotype or complex karyotype are adverse, t(9;11)(p21.3;q23.3)/MLLT3::KMT2A and cytogenetic and/or molecular abnormalities not classified as favorable or adverse are intermediate risk groups [4]. The genetic risks of the patients were determined.

The study was carried out with the permission of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (decision no: 2024-07/107, date: 05.09.2024).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) statistics (SPSS V26.0, Armonk, NY) was used for statistical analysis. Descriptive statistics were used to present the data. Categorical data were presented as numbers and ratios, and numerical data were presented as median, minimum, and maximum. Comparison of numerical data in two groups was performed using the Mann-Whitney U test. Comparison of categorical variables was performed using chi-square or Fisher's exact tests. Overall survival (OS) was defined as the duration from the first day of the treatment to the date of death or to the last follow-up date for survivors. Kaplan-Meier survival analysis was applied for OS. P values of ≤0.05 were considered statistically significant.

Results

A total of 139 patients, 50 WT-1 negatives and 89 positives, were included in our study. The female to male ratio was 0.78 in the WT-1 negative group and 0.49 in the WT-1 positive group. The median follow-up period was 5 (1-144) months in the WT-1 negative group and 28 (1-110) months in the positive group. When evaluated according to blood group, A, B, O and AB blood groups were found to be 40.8%, 28.5%, 26.5%, 4%, respectively, in the WT-1 positive group and 39%, 9%, 26.5%, 9%, respectively, in the WT-1 negative group (p=0.01). When analysed according to performance status, Eastern Cooperative Oncology Group (ECOG) 0-1 was found more frequently in the WT-1 positive group than in the WT-1 negative group, with proportions of 70% and 30%, respectively. ECOG ≥2 was found to be 11% more frequent in the WT-1 negative group compared to 34% in the WT-1 positive group, but this difference was not statistically significant (p=0.07). Extramedullary involvement rates were not significant between the groups (p>0.05). Patient characteristics were summarized according to the groups in Table 1.

The frequency of leukaemia with genetic abnormalities was 78% in the WT-1 negative group and 25.8% in the WT-1 positive group. In the WT-1 positive group, 21% were in the poor; 42% in the medium; 37% in the good risk group. In the WT-1 negative group, 20% were in the poor; 46% in the medium; 34% in the good risk group. No statistically significant difference was found between the two groups in terms of genetic risk class distribution (p=0.87). When the correlation between WT-1 and other molecular genetic mutations was analysed, WT-1 was positive in 12 of 14 patients with the positive NPM1 mutation, 2 of 3 patients with the positive CEBPA mutation, 4 of 6 patients with the positive FLT-3 mutation, and 4 of 4 patients with the positive PML-RAR-A mutation (p=0.15). The FISH negative detection rate was 75% higher in the WT-1 positive group (p=0.00). The most common translocations were t(15;17) and t(8;21), which were found more frequently in the WT-1 negative group (88% and 80%, respectively). There was no difference between the groups, in terms of the detection of anomalies in karyotyping (p>0.05).

When the induction treatments were analysed, the regimen containing idarabucine and cytarabine was the most commonly used regimen in both groups (73% in the WT-1 positive group and 36% in the WT-1 negative group). The second most frequently used regimen were hypomethylating agents, which were preferred by 20% and 24% in the WT-1 positive and negative groups, respectively (p=0.00). When the response after induction therapy was grouped as complete, partial response, and refractoriness, it was 58%, 14%, 26% in the WT-1-negative group and 80%, 2%, 16% in the WT-1-positive group, respectively (p=0.01). The rate of receiving reinduction therapy was 14% in the WT-1 negative group and 15% in the WT-1 positive group (p=0.87). Recurrence was 16% in the WT-1 negative group and 5.6% in the positive group (p=0.04). Allogeneic bone marrow transplantation (ABMT) was performed in a total of 36 patients; the rate of ABMT was 22% in the WT-1 negative group and 28% in the positive group (p=0.43).

The survival rate was found to be 64% in the WT-1-negative group and 67.4% in the positive group (p=0.18) (Figure 1).

Table 1. Characteristics of patients with or without WT-1 mutations

	WT-1 genetic status	No (n)	Median (min-max)	p
Gender (female/male)	Negative Positive	22/28 44/45		0.597
Age (years)	Negative		62 (18-88)	0.175
	Positive		47 (18-90)	
Follow-up period (month)	Negative		5 (1-144)	0.000
	Positive		28 (1-110)	
Performance status (ECOG ≥2)	Negative Positive	17 10		0.07
Blood type	Negative A/B/O/AB Positive A/B/O/AB	20/14/13/2 34/8/37/8		0.014
Leukocyte count (/µL)	Positive		2670 (90-160000)	0.001
	Positive		9755 (430-361000)	
Hemoglobin (g/dL)	Negative		8.6 (4.4-10.9)	0.060
	Positive		8.9 (5.5-15.2)	
Platelet (/µL)	Negative		42500 (6000-327000)	0.416
	Positive		64000 (8000-300000)	
Genetic risk	Negative Good Medium Poor Positive Good Medium Poor	 17 23 10 33 37 19		0.87

ECOG: Eastern Cooperative Oncology Group, min-max: Minimum-maximum, *WT-1: Wilms tumour-1*

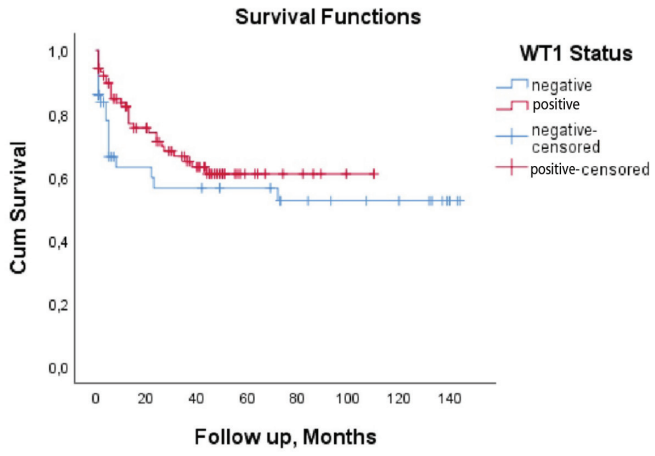

Figure 1. Survival data AML patients with and without WT-1 mutations
WT-1: Wilms tumour-1, AML: Acute myeloid leukaemia

Discussion

In our study, statistically significant differences were found between WT-1 negative and positive AML groups in terms of blood groups, frequency of defining genetic abnormalities, treatment regimens, treatment response, and relapse rates. Although AML-defining conditions such as t(8;21) and t(15;17), which are also associated with good genetic risk, are detected more frequently in the WT-1 negative group, the better performance status in the WT-1 positive group may contribute to better response and reduced relapse with the more frequent use of intensive induction therapy. Although WT-1 is not used in the genetic risk analysis of ELN, the correlation between genetic mutations and WT-1 mutation raises questions about its importance in the choice of treatment. Our study includes a long follow-up period in the WT-1 positive group, and different study kits were used for the detection of WT-1 mutation presence. Therefore, WT-1 expression levels at the time of diagnosis could not be evaluated. We believe that there is still a need to evaluate the prognostic role of WT-1 in AML.

The *WT-1* gene, located on chromosome 11p13, plays a role in the regulation of cell survival, proliferation, and differentiation and can function both as a tumor suppressor and oncogene [16,17]. According to the ELN 2022 risk stratification, the prognostic significance of WT-1 mutation in three risk groups is unclear. In one study, it was reported that WT-1 positivity was a negative factor in terms of both overall and disease-free survival and overall response rates in the absence of FLT-3 and NPM1. The expression level at the time of diagnosis was also important in terms of prognosis. However, in the presence of

FLT-3 and NPM1 mutations, WT-1 positivity was not a negative risk factor in terms of treatment efficacy and survival [18]. In another study, it was reported that WT-1 positivity has been managed with cytarabine and anthracycline-based treatment, and even increased expression was an independent positive factor for complete response [19]. In another study, in which 173 patients with normal cytogenetic analysis were evaluated, WT-1 status was found to be associated with event-free survival, while a high WT-1 expression level was found to be associated with a higher leukocyte count and a blunted FLT-3 ITD and NPM1 mutation [20]. It was found that high expression of WT-1 was associated with inv(16), NPM1, and 11q23 rearrangement, whereas low expression of WT-1 was associated with t(8; 21) [21,22]. In another study, no correlation was found between WT-1 positivity and age, gender, leukocyte, platelet, response, relapse, and transplantation rates at the time of diagnosis, while good genetic risk was higher in the WT-1 negative group and intermediate risk was higher in the WT-1 positive group. NPM1, FLT3, and IDH-2 mutations were correlated with expression levels. The most commonly used regimen is the treatment schedule containing cytarabine and idarubicin, and no difference was found between WT-1 negative and positive groups in terms of treatment response [23].

In our study, the frequency of fusion defined in AML was higher in the WT-1, negative group. There was no correlation between WT-1 positivity and other molecular genetic markers. However, we consider that this may be because the expression level could not be evaluated due to the difference in WT-1 study kit and the low number of positive results for other molecular mutations. The most commonly used treatment regimen was idarubicin and cytarabine. In terms of response, more complete responses were obtained and recurrence was less common in the WT-1 positive group. There was no difference between the two groups in terms of overall survival. This may be explained by the positive contribution of the idarubicin and cytarabine treatment regimen to complete response rates. However, WT-1 expression levels at the time of diagnosis and WT-1 mutation status after treatment could not be evaluated.

Study Limitations

There are some shortcomings in our study. Firstly, it is retrospective. Secondly, the expression levels could not be included in the study, due to variations in WT-1 study kits. Thirdly, WT-1 mutation evaluation could not be performed in each patient in response to treatment; therefore, a detailed evaluation could not be made regarding the type of treatment.

Conclusion

Our study includes long-term data from a good patient population and WT-1 may be associated with some genetic abnormalities. Although no association between WT-1 and prognosis was found in our study, there is a need to evaluate WT-1 mutation positivity or even burden in treatment response. We believe that large cohort studies with not only the presence of WT-1 mutation but also the WT-1 expression level are needed.

Ethics

Ethics Committee Approval: The study was carried out with the permission of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (decision no: 2024-07/107, date: 05.09.2024).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., Concept: S.Y., T.Z., S.C., E.H., A.D., N.O., A.B., Design: S.Y., T.Z., A.D., N.O., A.B., Data Collection or Processing: S.Y., T.Z., S.C., E.H., Analysis or Interpretation: S.Y., N.O., Literature Search: S.Y., Writing: S.Y.

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Artificial Intelligence Chatbot as a Companion for Cancer Patients About Most Common Questions: Analysis of Readability and Quality

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ABSTRACT

Aim: Advances on artificial intelligence (AI) have led to development of AI chatbots and more people are using AI chatbots to seek answers to their questions every day. We conducted this study to investigate the readability and quality of answers generated by large language model AI chatbots as companions in answering questions for cancer patients.

Methods: After surveying 508 patients admitted to the outpatient clinic of Ankara University Faculty of Medicine, Department of Medical Oncology, we selected the most frequently asked questions about the four most common cancer types and general cancer knowledge. We asked these questions of ChatGPT (an AI chatbot from OpenAI) and calculated readability and quality scores, and the statistical difference between suggested and calculated reading scores. Means and the t-tests (one-way and/or paired) were used for statistical analysis.

Results: A total of 57 questions, including those about colorectal, breast, lung, prostate cancer, and general cancer questions, were selected for analysis. The mean Flesch Reading Ease Score for all questions was 48.18 [standard deviation (SD) ±11.65], which was significantly lower than the suggested reading score of 60 points ($p<0.01$). The mean score for graded readability scores was 13.21 (SD ±2.49), which was consistent with college-level readability and significantly higher than a suggested value of 6th graders ($p<0.01$). The mean DISCERN score of all questions was 51.98 (SD ±7.27) and the Global Quality Score was 3.91 (SD ±0.69). Breast cancer responses were easier to read on graded scales ($p=0.02$) and had higher quality ($p=0.05$).

Conclusion: ChatGPT may be a good companion for cancer patients despite its limitations, but it should be used carefully.

Keywords: Artificial intelligence, chatbots, cancer education, ChatGPT

Introduction

Approximately 40% of individuals are expected to develop cancer during their lifetime, and nearly 1.9 million new cases of cancer are expected to be diagnosed in the United States in 2022 [1]. Most cancer patients have questions they want to ask their oncologist about their cancer; however, most oncologists spend less than 25 minutes per visit with each patient [2]. And the time they do spend with their patients is not enough to answer all the patients' questions. Consequently, most questions remain unanswered, and patients use search engines for their questions, and most of the answers they find may be misleading. Patients are concerned about cancer and strive to find reliable sources of online information such as blogs, videos, and news sites [3,4]. Most patients tend to use trustworthy websites; they need a reliable source of information. Given that many individuals have low health literacy, it is essential to provide adequate and reliable health information to meet patients' needs [5].

Advances in neural networks, deep learning, and artificial intelligence (AI) have led to the development of large language model (LLM) AI chatbots. While older chatbots could respond in simple sentences, newer chatbots such as ChatGPT (an AI chatbot from OpenAI) have advanced to the point of generating more sophisticated responses that can fool even experienced scientists [6,7]. Since its public opening in

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November 2022, ChatGPT has become a prominent source of information that is likely to outrank popular search engines. Nowadays, an increasing number of people are using ChatGPT to access online information, and more companies are starting to develop new AI chatbots.

As an increasing number of people use ChatGPT, it is likely that cancer patients and their relatives especially will utilize ChatGPT to access more medical information. Therefore, we should be concerned about the quality and readability of the information provided by AI chatbots such as ChatGPT.

This study aimed to evaluate the appropriateness and readability of the chatbot-generated responses to patients' questions.

Methods

Question Selection

Between February 1, 2023, and February 28, 2023, after obtaining verbal and written informed consent, we surveyed patients and their caregivers admitted to Ankara University Faculty of Medicine Outpatient Oncology Clinic, Department of Medical Oncology. Ankara University Faculty of Medicine Ethical Board of Human Research approved the study protocol (application number: AUTF-KAEK 2023/34, approval date: 1.2.2023). We asked about the most common questions they had asked online about the four most common cancers worldwide (colorectal cancer, breast cancer, lung cancer, and prostate cancer) in Turkish. The in-person survey collected only the patients' primary malignancy diagnosis, the 10 most common questions they asked online, and didn't include any demographic information. The patients' questions were answered in the outpatient clinics, but were not included in the analyses. The most frequently asked questions about colorectal cancer, breast cancer, lung cancer, prostate cancer, as well as general cancer information were extracted from the survey data, translated into English, and consolidated for analysis.

Asking Questions

The questions collected in the patient survey, in English, were asked to ChatGPT following a prefatory statement such as "Can you answer the following questions as I have... cancer?" We asked ChatGPT the questions sequentially, and after each set of questions about a particular type of cancer, we cleared the browser cache and opened a new chat session. All sessions were performed on the same computer, over virtual machines created from scratch, on custom user accounts. Apart from the pre-determined questions, no additional questions or potentially interfering sentences were posed to ChatGPT. The collected answers were copied into plain unformatted text files and prepared for further analysis.

Readability and Reliability Analyses of Responses

The readability analyses were performed using the TextStat package on Python 3.11 only with simple command line prompts using plain unformatted texts. We calculated the Flesch Reading Ease and the grade-equivalent reading scales Flesch-Kincaid (FK) Grade Level, SMOG Index, Gunning-Fog Score, Automated Readability Index (ARI), Coleman-Liau Index, and Linsear Write Formula. The mean readability score and standard deviation were calculated to obtain more accurate results.

To evaluate the readability and quality of the materials, we utilized several established scoring systems and scales. Readability was assessed using the FK Grade Level, which determines the US school grade level required to comprehend the text based on syllables per word and words per sentence. The SMOG Index estimated the years of education needed by focusing on the number of polysyllabic words, while the Gunning-Fog Scale assessed text complexity by considering average sentence length and the percentage of complex words. Additionally, the ARI and Coleman-Liau Scale provided grade level estimates based on characters per word and letters per 100 words, respectively. The Linsear Write Formula further evaluated readability by distinguishing between easy and hard words.

The DISCERN Score and Global Quality Score (GQS), although not originally developed for written AI responses, were calculated for reliability and quality analyses of all responses from each author. All authors have agreed on the DISCERN and GQS Scores. The DISCERN Score was used to measure the reliability and quality of the information, with higher scores indicating better quality. The GQS offered an overall subjective evaluation of the content's flow, ease of use, and reliability. These scoring systems collectively ensured a comprehensive analysis of both the complexity and quality of the materials, enhancing the study's overall rigor.

Statistical Analysis

Means were calculated for descriptive analysis, and Student's t-test was used for continuous variable analysis. One-sided one-sample t-tests were calculated for the analysis of the difference between the Flesch Reading Ease Score proposed value of 60 and graded readability of 6th-grade level [8]. Differences between scores of different cancer types were calculated with paired samples t-test. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and R 4.1 (the R Foundation, Vienna, Austria).

Results

Determining the Most Common Questions About the Four Most Common Cancer Types

A total of 508 patients participated in the study, including 226 with colorectal cancer, 115 with breast cancer, 91 with lung cancer, and 76 with prostate cancer. After reviewing the collected questions, we selected 57 questions, including 11 questions on colorectal cancer, breast cancer, lung cancer, and general cancer knowledge; and 13 questions on prostate cancer. The most common questions that patients ask online are listed in Table 1. Selected questions were mostly about survival depending on stages, how are treatments done,

benefits of treatments, and they were consistent with the National Health Institute's "Questions to Ask Your Doctor about Treatment" [9].

Ease of Reading

The mean Flesch Reading Ease Score for all questions was 48.18 [standard deviation (SD) ±11.65] meaning the answers were difficult to read. In topic-specific calculation, the mean Flesch Reading Ease Score was 46.27 (SD ±11.31) for colorectal cancer, 52.66 (SD ±13.49) for breast cancer, 48.36 (SD ±11.3) for lung cancer, 46.27 (SD ±12.52) for prostate cancer, and 47.12 (SD ±10.25) for general questions. All topics were difficult to read, except for breast cancer, with questions on breast cancer being fairly challenging in score interpretation. The Flesch Reading Ease Score ranged from 15.24 to 70.36. No significant differences were found for colorectal cancer (Student's t-test, p=0.66), breast cancer (Student's t-test, p=0.16), lung cancer (Student's t-test, p=0.96), prostate cancer (Student's t-test, p=0.51), and general questions (Student's t-test, p=0.74) when each was compared to the others. The mean score of Flesch Reading Ease was significantly lower than the suggested score of at least 60 points in all topics (one-way t-test, p<0.01).

The mean score of graded readabilities for all questions was 13.21 (SD ±2.49), corresponding to college-graded reading level requirements. In topic-specific calculations, the mean scores were 13.43 (SD ±2.46) for colorectal cancer, 11.93 (SD ±2.16) for breast cancer, 13.58 (SD ±2.87) for lung cancer, 13.32 (SD ±1.71) for prostate cancer, and 13.8 (SD ±2.82) for general cancer questions. Breast cancer responses had a lower readability score, equivalent to a high school grade level, while the other topics were at a college grade level. The graded readability scores ranged from 8.55 to 18.96. The mean score was lower (p=0.02) for breast cancer responses than for colorectal cancer (Student's t-test, p=0.69), lung cancer (p=0.56), prostate cancer (p=0.82), and general questions (p=0.28). The mean value of graded readability was significantly higher in all topics than the suggested value for sixth graders (one-way t-test, p<0.001). The one-way ANOVA test showed no significance among the graded readability scores (p=0.21). A summary of the reading ease and graded readability scores is shown in Table 2.

Table 1. Most frequently asked questions

Colorectal cancer (n=226)	Breast cancer (n=91)	Lung cancer (n=91)	Prostate cancer (n=76)	General questions (n=506)
How is colorectal cancer staged and what is the prognosis and survival depending on stage?	Where does breast cancer spread and metastasize?	How is lung cancer staged, categorized and what is the prognosis like depending on stage and type?	What are the stages of Prostate cancer and how are they treated depending on stage?	What is an adjuvant chemotherapy and what are the benefits?
How colorectal cancer treated if I had surgery?	Which chemotherapies are used in breast cancer and what are the side effects?	Which one is better for early-stage LC, surgery, radiotherapy, or chemotherapy? What are the benefits and potential harms of these treatment modalities?	How are prostatectomy or prostate irradiation done and which one is better?	Is adjuvant chemotherapy necessary when treating patients?
What is adjuvant treatment and which chemotherapies are used in adjuvant treatment?	How is mastectomy done and what are the problems that I will suffer afterward?	What is the probability of recurrence and survival of NSCLC depending on stages?	What is the hormone therapy for prostate cancer and how long does it take?	How is cancer staged and what is the importance of cancer stage?
How long should the treatment take?	How is breast cancer staged? What is the early or late stage of breast cancer?	What are the adjuvant treatments used on NSCLC and what are the benefits and side effects?	What is castration, and what does castration-sensitive or castration-resistant mean?	How is cancer treated and what modalities are being used?
When should the PET/CT done?	When should the breast reconstruction be done, same time as mastectomy or afterward?	Which chemotherapies are used on lung cancer and what are the side effects?	How does prostate cancer spread and metastasize?	What is cancer and there are how many cancer types?
Is radiotherapy necessary?	What is the probability of losing hair on breast cancer chemotherapy and will it be permanent?	What are the molecular profiles on pathology reports of lung cancer and what do they mean?	What is Gleason's Score and what does it mean?	Is there a chance that I will recover from late-stage cancer?

Table 1. Continued

Colorectal cancer (n=226)	Breast cancer (n=91)	Lung cancer (n=91)	Prostate cancer (n=76)	General questions (n=506)
What should I eat to prevent my cancer from recurring?	What are estrogen receptor, progesterone receptor, HER2, and Ki67 on my breast cancer pathology report and what do they mean?	How can I know if I'm a candidate for smart drugs?	Does prostate cancer curable in later stages?	What are the main side effects of chemotherapy and how can I overcome the side effects?
Are metastases operable? Is metastatic disease curable?	How long does adjuvant radiotherapy take?	Is SCLC curable? If it is not curable, which problems will I encounter if I don't take any chemotherapy?	When is a PET scan taken on prostate cancer?	How should my diet be included to prevent my cancer from recurring?
I have colon cancer. What is the probability of developing cancer in my family?	What are the hormonal therapies, how long do they take and what are the benefits and side effects?	When can I receive immunotherapy for lung cancer, and will it cure my cancer?	What targeted therapies are mostly used on prostate cancer, and what are the benefits and side effects?	When are the targeted therapies used in cancer treatment?
When is immunotherapy used for colon cancer?	What are the targeted therapies, when are they used, and what are the benefits and side effects?	Where does lung cancer spread and metastasize and how metastases are treated?	What will I encounter in my sexual life while on prostate cancer treatment?	Is surgery necessary when treating early-stage cancer?
Is FOLFOX or XELOX better?	What is the expected survival of breast cancer depending on stages?	Should I quit smoking?	When is chemotherapy used for prostate cancer?	Can tumor markers predict cancer recurrence or do they have any use in diagnosis?
-	-	-	Is only PSA monitorization sufficient in prostate cancer treatment?	-
-	-	-	What are the survival rates of prostate cancer depending on stages?	-

PET/CT: Positron emission tomography/computed tomography, SCLC: Small-cell lung cancer, NSCLC: Non-SCLC, PSA: Prostate-specific antigen, HER2: Human epidermal growth factor receptor 2, LC: Lung cancer

Table 2. Readability scales

Question topic	Flesch Reading Ease		Graded scales	
	Mean (±SD)	p*	Mean (±SD)	p*
Colorectal cancer	46.84 (±11.31)	0.66	13.43 (±2.46)	0.69
Breast cancer	52.66 (±13.49)	0.16	11.93 (±2.16)	**0.02**
Lung cancer	48.36 (±11.3)	0.96	13.53 (±2.87)	0.56
Prostate cancer	46.27 (±12.52)	0.51	13.32 (±1.71)	0.82
Common questions	47.12 (±10.25)	0.74	13.8 (±2.82)	0.28
Total	48.18 (±11.65)	-	13.21 (±2.49)	-

*Paired samples t-test, the analyses were used to determine the difference between one topic and all the others.
SD: Standard deviation

Mean scores for graded readability were 13.02 (SD ±2.19) on the FK Scale, 13.86 (SD ±1.90) on the SMOG Scale, 12.87 (SD ±2.01) on the Gunning-Fog Scale, 14.72 (SD ±2.45) in the ARI Scale, 12.65 (SD ±1.63) in the Coleman-Liau Scale, and 13.13 (SD ±3.47) in the Linsear Scale. The difference between Scales was significant ($p<0.05$) in the FK, SMOG, Gunning-Fog, ARI,

and Coleman-Liau Scales, whereas it wasn't significant in the Linsear Scale (paired-samples t-test, p=0.77).

Quality of Responses

The mean DISCERN score was 51.98 (SD ±7.27) for all questions, indicating responses of good quality. In topic-specific calculation, the mean DISCERN scores were 54.27 (SD ±8) for colorectal cancer, 52.91 (SD ±9.19) for breast cancer, 49.27 (SD ±6.75) for lung cancer, 53 (SD ±4.6) for prostate cancer, and 50.27 (SD ±7.59) for another cancer type. The DISCERN scores ranged between 33 and 65. Mean DISCERN values did not differ for any cancer type (p=0.17-0.57) and all topics had good-quality responses. For question 4 of DISCERN "Is it clear what sources of information were used to compile the publication (other than the author or producer)?" only one question received 2 points, the others 1 point, and for question 5 of DISCERN "Is it clear when the information used or reported in the publication was produced?" all questions received 1 point because ChatGPT didn't specify the sources it used to prepare the responses. The means and standard deviations of the DISCERN questions are shown in Table 3.

The mean GQS for all questions was 3.91 (SD ±0.69): indicating that the responses were of nearly good quality. In the topic-specific calculations, the mean GQS scores were 3.73 (SD ±0.65) for colorectal cancer, 4.27 (SD ±0.65) for breast cancer, 3.64 (SD ±0.81) for lung cancer, 3.85 (SD ±0.55) for prostate cancer, and 4.09 (SD ±0.7) for general questions. The breast cancer, and general questions were rated as good quality in GQS scoring; whereas colorectal cancer, prostate cancer, and lung cancer were rated as medium quality. The GQS scores ranged between 2 and 5 for all topics. The mean GQS score was significantly higher for breast cancer than for the other cancers, with a statistically significant difference indicated by $p<0.05$. Details of the GQS scores can be found in Table 4.

None of the responses included references, and most responses (7/57) included a disclaimer and sentences with the

Table 3. DISCERN questionnaire

Question number	DISCERN questions	Mean	SD
1	Are aims clear?	4.72	0.53
2	Does it achieve its aims?	4.32	0.81
3	Is it relevant?	4.30	0.80
4	Is it clear what sources of information were used to compile the publication (other than the author or producer)?	1.02	0.13
5	Is it clear when the information used or reported in the publication was produced?	1.00	0.00
6	Is it balanced and unbiased?	4.35	0.79
7	Does it provide details of additional sources of support and information?	1.58	0.53
8	Does it refer to areas of uncertainty?	2.21	0.98
9	Does it describe how each treatment works?	3.53	1.38
10	Does it describe the benefits of each treatment?	3.37	1.42
11	Does it describe the risks of each treatment?	3.04	1.36
12	Does it describe what would happen if no treatment is used?	2.28	1.22
13	Does it describe how the treatment choices affect the overall quality of life?	3.51	1.21
14	Is it clear that there may be more than one possible treatment choice?	4.44	1.10
15	Does it provide support for shared decision-making?	4.37	1.22
16	Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices	3.96	0.73
-	**Total DISCERN score**	**51.98**	**7.27**

SD: Standard deviation

Table 4. Statistics of GQS by topics

Question topic	Mean	SD	p*
Colorectal cancer	3.73	0.65	0.33
Breast cancer	4.27	0.65	**0.05**
Lung cancer	3.64	0.81	0.14
Prostate cancer	3.85	0.55	0.69
Common questions	4.09	0.7	0.34
Total	3.91	0.69	-

*Paired samples t-test, the analyses were used to determine the difference between one topic and all the others.
GQS: Global Quality Score, SD: Standard deviation

meaning that it is recommended to consult the health care provider.

Discussion

The quality and readability of online medical information have long been a subject of debate, and as technology continues to evolve, more issues will be added. LLM AI chatbots have been in use for several years, and concerns about their reliability have been growing since their public introduction. ChatGPT is one of the first commercially successful LLM AI chatbots, and more than 400 scientific articles or editorials have been written about it from its release in November 2022 to May 2023.

The information obtained by ChatGPT remains controversial. There is a possibility that it provides fabricated information (hallucinations) and gives non-existent references. Additionally, since it is not connected to the Internet and trained on Q4 2021 information, it may deliver outdated or wrong information about anything, and the fabricated abstracts can even fool experienced researchers [6,7,10].

Although literacy is increasing in the world, experts suggest that medical articles published online should be easy to read, and materials should ideally be written at a 6th-grade level [8]. While more patients are reading medical information about their disease online; older adults tend to prefer a direct doctor visit when they have questions, so the 6th-grade reading level may not fully reflect the actual information needs of patients. Even patients with college degrees may encounter misleading information or be unable to distinguish between fake or fabricated medical articles and real, trustworthy medical information. The Health on the Net recognition seal is an important tool for assessing the reliability of an online article. It is recommended to check reliability and quality using a higher score from DISCERN or JAMA [11]. However, due to the nature of LLM AI chatbots, their evaluation is challenging. Therefore, people should be cautious when using these tools for their health-related questions. Additionally, there is a gap in online cancer information, and individuals tend to seek answers to their questions not only in online articles or search engines but also in videos on platforms such as YouTube [4,12].

Most cancer patients spend about 5% of their remaining lifetime in the health care system. Since most oncologists spend less than 25 minutes per visit with their patients, their families are frustrated and try to find answers to their questions online [2,13]. Guy and Richardson's [13] study suggests that the pay-for-performance system leads to an increase in patient volume and a decrease in visit time, which in turn may lead to unanswered questions. AI chatbots, especially ChatGPT, are expected to provide great convenience for cancer patients to access online information [10].

Our results showed that readability on the Flesch Reading Ease score was lower than the recommended score of 60. College-level reading was required to understand the responses, which is well above the recommended educational level of a sixth grader. A study by Li et al. [14] showed that most online information about four common cancers had a grade-level readability score of 10.9, which is consistent with our findings. Stevens et al. [15] showed that even the online information on a narrow topic such as neoadjuvant treatment of pancreatic cancer had a readability of grade level 10.96; Ozduran and Büyükçoban [16] showed that the information about post-Coronavirus disease-2019 pain had a readability grade level 9.83-10.9. Because ChatGPT was trained to use online information up until Q4 2021, the lower readability could be a result of the training data collected online.

Although not designed for scoring LLM responses, the average DISCERN score for questions was 51, which can be considered a good score. ChatGPT only answers the question asked and does not provide further details. DISCERN scoring asks questions about alternative treatments, such as what happens if you apply them or do not apply them. If ChatGPT asked more questions about DISCERN, the average score of DISCERN would be higher. However, this might lead to a decrease in overall quality and an increase in the risk of hallucinations. The GQS assessment yielded a mean score of 3.91, which is close to good quality and could reflect higher quality if more comprehensive questions were included.

Study Limitations

The main limitations of our study are the survey didn't include demographic data such as age, or stage of the cancer patients, and ChatGPT can give a personalized answer and therefore cannot be easily evaluated. Additionally, since the survey did not include data on educational level, our analysis could not examine patients' educational status or assess whether it differed from the proposed 6th-grade reading level. The patients' questions were translated into English, and the responses were also retrieved in English, thus, the evaluation in Turkish is not available. The patients or their caregivers did not ask questions about the specific survival of the patient. This may be caused by Turkish cultural aspects because in Turkish culture it is considered inappropriate to talk about survival and death. Since the questions we asked were short and concise, lacking in detail, the quality of the response might have been affected. Other AI chatbots, besides ChatGPT, weren't included in our study, and the results cannot be generalized to all AI chatbots. Although the study used multiple graded scoring systems, it examined only the mean scores, limiting its generalizability and the manuscript's readability. Despite these limitations, ChatGPT appears to be a good information-gathering tool for cancer patients. There is also a need for better tools to evaluate the quality of information provided by AI chatbots, as well as newer AI chatbots that are specialized in medical topics. Further studies are needed to confirm our results.

Conclusion

ChatGPT, by answering unresolved questions, can be a useful source of information for people undergoing cancer treatment. However, the answers generated require a higher level of education than the recommended 6th-grade level, making

them more difficult to understand. Despite this limitation, the quality of the responses can be good when assessed against both the DISCERN and GQS Scales. As the responses produced depend largely on the questions asked, it is important to be cautious when relying on AI chatbots. In addition, further research is needed to develop updated scales for assessing the quality of responses generated by chatbots.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Ethical Board of Human Research approved the study protocol (application number: AUTF-KAEK 2023/34, approval date: 01.02.2023).

Informed Consent: Verbal and written informed consent was obtained.

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No artificial intelligence tools of any kind were used for preparation of manuscript, only the selected answer of selected questions was prompted into OpenAI's ChatGPT. None of the authors has any affiliation with artificial intelligence companies.

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Footnotes

Authorship Contributions

Concept: E.C.E., G.U., Design: E.C.E., G.U., Data Collection or Processing: E.C.E., E.B.K., G.U., Analysis or Interpretation: E.C.E., E.B.K., G.U., Literature Search: E.C.E., E.B.K., Writing: E.C.E.

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The Effect of Video Streaming with Virtual Reality on Anxiety and Physiological Parameters During Chemotherapy Treatment in Hematologic Malignancy Patients

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ABSTRACT

Aim: The aim of this study is to determine the effect of using virtual reality glasses (VRG) on anxiety and physiological parameters in patients diagnosed with hematologic malignancies who are receiving chemotherapy for the first time.

Methods: This randomized study was conducted with 100 patients receiving chemotherapy for the first time in the adult hematology clinic of a tertiary university hospital. The Patient Identification Form, State Anxiety Scale, and Physiological Parameters Monitoring Form were administered to patients in both groups before chemotherapy. After chemotherapy, only the State Anxiety Scale and Physiological Parameters Monitoring Form were reapplied. During chemotherapy treatment, the patients in the experimental group watched videos for 30 minutes using VRG.

Results: Intergroup analysis has shown that the post-chemotherapy state anxiety mean scores are higher in the control group than in the experimental group (p=0.026). The post-chemotherapy state anxiety mean scores were found to be significantly lower than the pre-chemotherapy state anxiety mean scores in the experimental group (p=0.029). There was no statistically significant difference between the groups in terms of the pre-chemotherapy state anxiety mean scores (p>0.05) or in physiological parameters before and after chemotherapy.

Conclusion: VRG were shown to be effective in reducing chemotherapy-related anxiety in our study; however, did not affect physiological parameters.

Keywords: Virtual reality glasses, chemotherapy, anxiety, physiological parameters, effect

Introduction

Cancer is an important health problem that negatively affects the quality of life of individuals all over the world [1]. Hematological malignancies are a heterogeneous group of neoplasms that affect the blood, bone marrow, and lymph nodes [2]. Chemotherapy, radiotherapy, immunotherapy, and stem cell transplantation are the most used methods in the treatment of hematological malignancies [3]. Chemotherapy treatment may cause many physical and psychological side effects such as nausea, vomiting, oral ulcers, fatigue, skin reactions, anxiety, depression, hopelessness, and anger [4]. Like other cancer patients, the great majority of hematological cancer patients experience anxiety undergoing chemotherapy treatment [5]. Anxiety is usually defined as a feeling of restlessness and tension caused by factors that are unknown and incomprehensible [5]. This anxiety can complicate adherence to treatment and prolong hospital stays [5]. It is well known that anxiety levels are generally high during chemotherapy. For example, a study conducted with patients undergoing treatment for hematological cancer found a high prevalence of anxiety and depression [6]. In another study conducted in Australia, anxiety was reported in 27% of 304 patients [7]. Additionally, anxiety was observed in 23% of 319

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patients with hematological cancer [8]. These data indicate that anxiety is a common issue during chemotherapy and that it affects patients' overall health both physiologically and psychologically.

Physiological parameters play a critical role in assessing treatment processes by providing an objective measure of patients' overall health and body functions [9]. During stressful and intensive treatments such as chemotherapy, changes in these parameters reveal both the direct effects of the treatment and the patient's psychological and physiological responses [10]. Variations in fundamental parameters like heart rate, blood pressure, and respiratory rate help determine the response to treatment, the severity of potential side effects, and possible complications [11]. It is important to develop interventions that help patients better tolerate chemotherapy, improve their quality of life, and increase their chances of survival [12,13].

Currently, pharmacological and/or non-pharmacological methods are used to control anxiety [14]. However, it is known that the pharmacological methods may cause various side effects such as agitation, amnesia, and hyperactivity [14]. Therefore, mostly in recent years, non-pharmacological methods are being used to control anxiety [15]. Virtual reality (VR) is one of the non-pharmacological methods known to be effective in reducing anxiety [14,16].

VR is an advanced form of human-computer interaction that allows people to hear the sounds and stimuli accompanying the visual scene through headphones, enabling them to experience an immersive environment outside the hospital setting [17]. The basis of VR are mainly computers, tablets, and VR glasses (VRG) [16]. VRG are a computer simulation technology consisting of a pair of video glasses and headphones connected to a video player via a connection cable, which, creates a three-dimensional environment [16]. As one of the methods of diverting attention, VRG offers the possibility of creating therapeutic environments for the treatment of medical conditions; it is widely used in clinical practice to relieve symptoms [18,19]. What makes VR a powerful distraction is its ability to engage different senses simultaneously with visual images, spatial sounds, and sometimes synthetic stimuli such as tactile and olfactory feedback [20,21]. It has shown effectiveness as a distraction instrument to relieve pain and anxiety, especially during medical procedures [20-26].

VR is emerging as a promising instrument for supporting cancer patients and monitoring neurophysiological and biological feedback during intervention [27]. Since we could not find any study in the literature examining the effect of VRG on anxiety during chemotherapy treatment in patients with hematological malignancies, the aim of this study was to determine the effect of VRG on anxiety and physiological parameters in patients with hematological malignancies receiving chemotherapy for the first time.

Methods

Study Design

It was conducted as a randomized controlled experimental study. Randomization was applied using the http://www.randomizer.org, a computer program, to determine the patient groups. The research was carried out between 15 November 2021 and 15 July 2022 at the hematology outpatient chemotherapy unit of a tertiary hospital, located in the city center of Kayseri. This unit has a capacity of 20 beds and provides diagnostic, treatment, and follow-up services for patients with hematological malignancies such as leukemia, lymphoma, and multiple myeloma. The hematology unit is equipped with the necessary infrastructure and healthcare personnel to administer chemotherapy and monitor patients regularly.

Study Participants

The sample comprised patients who were receiving their first cycle of chemotherapy, met the research criteria, and agreed to participate in the study. The population of the study consisted of patients diagnosed with hematological cancer and receiving their first cycle of chemotherapy at the outpatient chemotherapy unit between November 15, 2021, and July 15, 2022. To determine the sample size, a comparison of two groups (VR and control) was conducted using the G*Power 3.1 software. Based on the results of similar studies [21,28], it was decided to include 50 patients in the control group and 50 patients in the VR group, for a total of 100 patients. A post-hoc power analysis using the G*Power program revealed an effect size of 0.86, type 1 error (α)=0.05, and power (1-β) of 95%. These results indicated that the sample size was sufficient for the study.

Hypotheses

H0. VRG applied to patients with hematological malignancies during chemotherapy treatment have no effect on anxiety and physiological parameters.

H1. VRG applied to patients with hematological malignancies during chemotherapy treatment reduce state anxiety levels.

H2. VRG applied to patients with hematological malignancies during chemotherapy treatment have an effect on increasing or decreasing physiological parameters.

The inclusion criteria were as follows:

- Patients over 18 years old,
- Patients with a diagnosis of hematological cancer,
- Patients receiving chemotherapy treatment for the first time,
- Clinically stable and well communicated patients,
- Patients with no psychiatric, mental, vision and hearing problems.

The exclusion criteria were as follows:

- Patients who are clinically unstable during chemotherapy,
- Patients using anxiolytic and/or sedative drugs,
- Patients who did not agree to participate in the study.

Data Collection Instruments

Patient identification form, state anxiety inventory (SAI), physiological parameters follow-up form, and VRG were used to collect data.

Patient identification form: This form included 10 questions to determine the sociodemographic characteristics of the study participants such as age, gender, marital status, educational status, occupation, and residence.

State-Trait Anxiety Scale: This inventory was developed by Spielberger [29]. The scale consists of 40 items. The validity and reliability studies of the scale in Turkish were conducted by Öner and Le Compte [30]. The Cronbach's alpha value for the state anxiety scale ranges from 0.94 to 0.96. In our study, the SAI was used. The SAI consists of 20 items (items 1-20) that evaluate the respondent's feelings at that moment. Each item is graded on a 4-point Likert scale from 1 (none) to 4 (too much). The subscale scores range from 20 to 80, and higher scores indicate the presence of a high level of anxiety [30]. In this study, the Cronbach's alpha reliability coefficient of the State Anxiety Scale was found to be 0.74.

Physiological parameters follow-up form: It was created to evaluate and record blood pressure, heart rate, respiratory rate, and oxygen saturation.

VRG: In this study, the VRG (support V5 VR Headset for 4.7-6.8 inch iPhone and Android) was used in the experimental group to watch videos during the chemotherapy regimen. The device divides the image into two equal windows and easily provides the viewfinder display required for panoramic viewing. VRG consists of a smartphone application compatible with the VRG title. After the title is attached to the individual, it can be adjusted according to the person. By downloading a suitable program that allows viewing 360° VR images on a compatible mobile phone, users can monitor the relevant content through the program. VRG application was started just before the chemotherapy treatment and applied for 30 minutes during chemotherapy. When determining the duration of VR glasses usage, practices from the literature were taken into consideration. It is known that prolonged use of VR glasses can lead to side effects such as headaches, dizziness, and nausea. Therefore, a 30-minute period was established based on existing literature [28,31]. The patient's desired videos, which were a licensed product with an atmospheric musical background containing relaxing underwater, museum, park, nature images, and nature sounds, were played.

Data Collection

Control group: The patient information form and SAI were completed by the responsible researcher 15 minutes before the chemotherapy treatment by the face-to-face interview method. In addition, the physiological parameters of the patients were evaluated 5 minutes before the start of chemotherapy treatment, and recorded in the follow-up form. Finally, the SAI was applied and recorded 30 minutes after the start of chemotherapy treatment, and again the physiological parameters of the patients were evaluated and recorded in the follow-up form at this same time point.

Experimental group: The patient information form and SAI were completed by researchers 15 minutes before the chemotherapy treatment using the face-to-face interview method. In addition, the physiological parameters of the patients were evaluated 5 minutes before the start of chemotherapy treatment and recorded in the follow-up form. VRG was placed over their eyes and they watched videos from the beginning of the chemotherapy regimen for 30 minutes. One of the relaxing videos with nature sounds, including underwater, museum, park, and hiking images, was shown for 30 minutes, based on each participant's preference. VRG was removed immediately after 30 minutes had elapsed. At the 30th minute of chemotherapy treatment, the patient's physiological parameters were re-evaluated and recorded in the follow-up form. Then, the SAI was administered again. The research implementation flowchart is summarized in Figure 1.

Ethical Approval

The research was approved by the relevant Ethics Committee of the Kayseri City Hospital (decision number: 503, date: 04.11.2021), and the consent of the volunteers included in the study and institutional permissions were obtained.

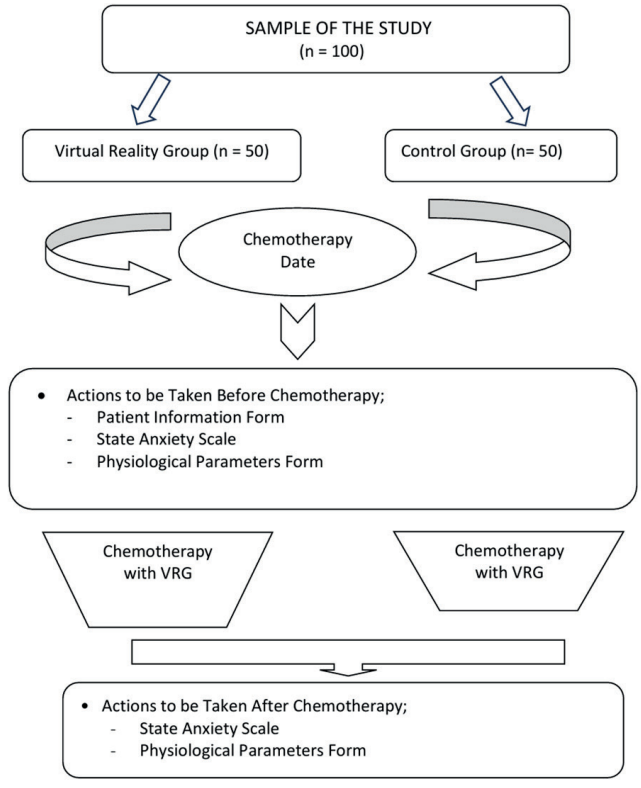

Figure 1. Research implementation flowchart
VRG: Virtual reality glasses

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) 25.0 statistical software (IBM SPSS statistics for Windows, version 25.0. Armonk, NY: IBM Corp., USA). The normality of the distribution of the variables was assessed using the Kolmogorov-Smirnov test. Since the data did not follow a normal distribution, non-parametric tests were used. The Mann-Whitney U test was employed for comparisons between two groups, and the Wilcoxon signed-rank test was used for within-group comparisons. The data were summarized using frequency, percentage, median, and interquartile range. Chi-square analysis was used for categorical variables. The differences in anxiety levels between the groups were examined by comparing the pre- and post-treatment anxiety scores. For physiological parameters (blood pressure, pulse, respiratory rate, and oxygen saturation), the changes between pre- and post-treatment measurements were analyzed using the Wilcoxon signed-rank test. P<0.05 was considered statistically significant.

Results

The descriptive characteristics of the patients are given in Table 1. It was determined that the individuals in the control and VR groups were similar in terms of demographic characteristics such as age, gender, marital status, educational background, place of residence, and preferred video styles. There was no statistically significant difference between the groups (p>0.05) (Table 1).

It was determined that the average age of the individuals in the control group was 50.18 years, (50.18±16.26), 48% were male, 88.0% were married, 78% had primary education level, 82% lived in a metropolitan area, and 36.0% liked to watch nature videos. It has been determined that the average age of the individuals in the VRG was 57 years (49.86±15.63), 50% were male, 90% were married, 80% had primary education level, 84% lived in metropolitan cities, and 40% liked to watch videos with park content.

Table 1. The descriptive characteristics of the patients

Parameters	Experimental group (n=50)		Control group (n=50)		Total (n=100)		Test statistics
Age, median (range)	57 (18-77)		56 (18-77)		56 (18-77)		p=0.76 z=0.3
	n	%	n	%	n	%	
Gender							
Male	25	50	24	48	49	49	p=1.00 X^2=0.00
Female	25	50	26	52	51	51	
Marital status							
Married	45	90	44	88	89	89	p=0.75 X^2=0.102
Single	5	10	6	12	11	11	
Educational status							
Elementary	40	80	39	78	79	79	p=0.64 X^2=1.679
High school	7	14	7	14	14	14	
University	2	4	4	8	6	6	
Graduate	1	2	0	0	1	1	
Location							
Village	5	10	1	2	6	6	p=0.41 X^2=2.858
Town	1	2	1	2	2	2	
City	6	12	7	14	13	13	
Metropolis	38	76	41	82	79	79	
Favorite video type							
Park	20	40	18	36	38	38	p=0.95 X^2=0.334
Hiking	17	34	18	36	35	35	
Underwater	11	22	11	22	22	22	
Museum trip	2	4	3	6	5	5	
Do you know your diagnosis?							
Yes	50	100	50	100	100	100	p=1 X^2=0
No	0	0	0	0	0	0	

Table 2 shows the comparison of the intra-group and inter-group SAI averages of individuals in the VRG group and control groups. In the intra-group comparison of patients in the control group, it was determined that the mean post-chemotherapy state anxiety score was 43 (34-50), increased from the mean pre-chemotherapy state anxiety score of 41.5 (33-58); and the difference was not statistically significant (p=0.14). In contrast, patients in the VRG exhibited a mean post-chemotherapy state anxiety score of 40 (33-50), which decreased compared to their mean pre-chemotherapy state anxiety score of 42 (33-49), and the difference was statistically significant (p=0.029). In our study, while there was no statistically significant difference in the pre-chemotherapy state anxiety scores between the control and VR groups, the post-chemotherapy state anxiety score of the control group was found to be significantly higher at 42 (33-49) compared to the post-chemotherapy state anxiety score of the VR group at 40 (33-50) (p=0.026).

The comparison of physiological parameters between groups is displayed in Table 3. No statistically significant difference was found between the groups in terms of blood pressure, heart rate, respiratory rate, and oxygen saturation variables before and after chemotherapy.

Discussion

The most striking finding of our study was that the post-chemotherapy average state anxiety score was found to be lower in the VR group, compared to the control group, and this difference was statistically significant (p=0.026) (Table 2). Another important finding of our study was that the post-chemotherapy state anxiety mean scores in the experimental group were significantly lower than the pre-chemotherapy state anxiety mean scores (p=0.029). The reason for this may be that VRG allows patients to focus their attention on another area both visually and auditorily. It reduces their negative emotions and anxiety, increases their positive emotions, and provides satisfaction and relaxation [31]. Therefore, the results of our study confirm hypothesis H1: "Watching videos with VR during chemotherapy has an effect on reducing state anxiety levels".

It has been reported that 35% of patients with hematological cancers develop anxiety and depression during treatment, and these conditions continue throughout the treatment period [5]. In our study, although the anxiety levels were higher in the VR group before chemotherapy, both groups had similar rates of moderate anxiety, and there was no statistically significant difference between the groups (p=0.52). This may be attributed to the fact that the patients were receiving their first cycle of chemotherapy the prognosis of the disease, and their recent diagnosis.

In the study of Dutucu et al. [32], it was reported that watching videos with VRG during mammography did not have a statistically significant effect on the anxiety levels of the patients in the experimental and control groups, but the average anxiety scores of the experimental group were lower than those of the control group. In another study, it was reported that VRG was effective in reducing anxiety and depression levels in patients with metastatic breast cancer, positively affecting their physical and mental well-being [33]. In a randomized controlled study conducted with 94 breast cancer patients receiving chemotherapy treatment in Italy, the experimental group watched nature- and sea-themed videos with VRG for 20 minutes during chemotherapy, and the anxiety levels of the patients after chemotherapy were found to be lower than the control group [21]. In another study, although there was no statistical difference between the pre-procedural state anxiety scores of the patients in both groups, the post-procedural state anxiety mean scores of the experimental group were found to be statistically significantly lower than those of the control group [28]. Therefore, our results show consistency with other studies in the literature.

Anxiety has physiological effects on the human body such as high blood pressure and high blood sugar, rapid breathing, rapid pulse, dizziness, dry mouth, nausea, and excessive sweating [34]. In particular, it has been reported that anxiety increases blood pressure, heart rate, respiratory rate, and body temperature [34]. There is only one study in the literature examining the effect of VRG application on the physiological parameters of anxiety in adult cancer patients [35]. Menekli et al. [36] reported that VR reduces pain, anxiety, systolic and diastolic blood pressures, heart and respiratory rates, and increases SpO_2 levels in oncology patients. In a study examining the effects of VR on anxiety and vital signs in patients undergoing colonoscopy, it was found that the use of VR headsets had a positive effect on respiratory rate and peripheral oxygen saturation during the procedure. Additionally, the average systolic blood pressure of patients in the experimental group was significantly lower than that of the control group post-procedure. In this study, an examination of the physiological parameters of patients

Table 2. The comparison of state anxiety scores between groups

Parameters	Control group (n=50)	Experimental group (n=50)	Intergroup test statistics
Pre-chemotherapy state anxiety (mean±SD)	41.5 (33-58)	42 (33-49)	Z=0.647 p=0.52
Post-chemotherapy state anxiety (mean±SD)	43 (34-50)	40 (33-50)	Z=-2.221 p=0.026*
Intragroup test statistics	Z=-1.473 p=0.14	Z=2.185 p=0.029*	

*Statistically significant.
SD: Standard deviation

Table 3. The comparison of physiological parameters between groups

Parameters	Experimental group (n=50)	Control group (n=50)	Intergroup test statistics
Systolic blood pressure	Median (min-max)	Median (min-max)	
1st measurement pre-chemotherapy	115.1 (100-150)	110.1 (100-150)	Z=0.214 p=0.83
2nd measurement post-chemotherapy	110.0 (100-140)	110.0 (100-136)	Z=0.575 p=0.57
Intragroup test statistics	Z=-1.151 p=0.25	Z=-1.525 p=0.12	
Diastolic blood pressure			
1st measurement pre-chemotherapy	70.3 (60-90)	70.0 (60-89)	Z=0.495 p=0.62
2nd measurement post-chemotherapy	70.1 (60-82)	69.5 (60-88)	Z=0.442 p=0.66
Intragroup test statistics	Z=-0.829 p=0.4	Z=-0.762 p=0.45	
Heart rate			
1st measurement pre-chemotherapy	92.0 (70-110)	91.0 (70-106)	Z=1.183 p=0.24
2nd measurement post-chemotherapy	92.0 (72-102)	92.0 (72-102)	Z=0.393 p=0.7
Intragroup test statistics	Z=-1.701 p=0.09	Z=-0.818 p=0.41	
Respiration rate			
1st measurement pre-chemotherapy	20.0 (18-22)	20.0 (18-22)	Z=0.946 p=0.34
2nd measurement post-chemotherapy	20.0 (18-22)	20.0 (18-22)	Z=-0.561 p=0.58
Intragroup test statistics	Z=-1.091 p=0.28	Z=-0.728 p=0.47	
Peripheral oxygen saturation			
1st measurement pre-chemotherapy	95.0 (92-99)	95.0 (92-99)	Z=-0.49 p=0.96
2nd measurement post-chemotherapy	95.1 (91-100)	95.1 (91-100)	Z=0.537 p=0.59
Intragroup test statistics	Z=0.666 p=0.51	Z=-0.1 p=0.92	

min-max: Minimum-maximum

revealed that the median difference in systolic blood pressure decreased in the VR group after chemotherapy compared to before chemotherapy; however, this difference was not statistically significant (p>0.05). In the inter-group evaluation, it was determined that the median differences in systolic blood pressure after chemotherapy were similar. Additionally, there was no statistically significant difference intra-group and inter-group evaluations based on the median differences in diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation before and after chemotherapy in both the VR, and control groups. In our study, we found that systolic blood pressure decreased post-chemotherapy in the VRG group, but the difference was not statistically significant. There was no statistically significant difference between the groups in terms of heart rate, respiratory rate, and oxygen saturation variables before and after chemotherapy. From the perspective of our study, the participants' experience of their first invasive procedure and the variability in individual responses to the procedure may have slightly influenced their physiological parameters.

Study Limitations

The study has some limitations. First, it was a study with a small sample size. A larger sample size in a general clinical setting might have elucidated the differences between groups. Second, wearing a standard size VRG in the study might have been uncomfortable for some participants and might have led to an inability to experience the full VR scene. Third, VRG was used only for 30 minutes in the study. Using it for a longer duration might have gotten significant differences in terms of physiological parameters.

Conclusion

VRG was shown to be successful in reducing chemotherapy-related anxiety in our study; however, it did not affect physiological parameters. Since VRG is a painless, safe, effective and easy-to-apply method, it can be considered to be included in nursing practices for aiming anxiety relief. Nonetheless, randomised controlled studies with a larger sample size are needed to externally validate our results.

Ethics

Ethics Committee Approval: The research was approved by the relevant Ethics Committee of the Kayseri City Hospital (decision number: 503, date: 04.11.2021).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: E.K., S.K., Design: E.K., Data Collection or Processing: E.K., Analysis or Interpretation: E.K., S.K., Literature Search: E.K., Writing: E.K., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Is Hemoglobin, Albumin, Lymphocyte, and Platelet Score a Prognostic Indicator in Metastatic Squamous Cell Lung Cancer?

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ABSTRACT

Aim: We aimed to determine the prognosis by using the HALP score as a prognostic marker in patients followed in our clinic due to metastatic lung squamous cell carcinoma (SCC).

Methods: The study retrospectively reviewed 35 patients diagnosed with metastatic lung SCC in our clinic between January 2015 and December 2022. Overall survival (OS) was calculated as the time from metastasis date to death or last follow-update. The HALP score was calculate dusing laboratory parameters at the time of metastasis, according to the formula [HALP = hemoglobin (g/L) × albumin (g/L) × lymphocyte count / thrombocyte count].

Results: Of the 35 patients included in the study, 28 were male (80%). There was no statistically significant association between the HALP score and gender (p=0.735), age groups (p=0.862), Eastern Cooperative Oncology Group performance status (p=0.915), receipt of palliative radiotherapy (p=0.238), and body mass index groups (p=0.615). In the overall cohort, the median OS was 18 months, while it was 14.4 months in the low HALP group and 20 months in the high HALP group.

Conclusion: Our study indicates that the HALP score could be a crucial prognostic marker for patients with squamous cell lung cancer. A lower HALP score is linked to a shorter OS.

Keywords: HALP score, lung cancer, squamous cell carcinoma

Introduction

Lung cancer stands as one of the most prevalent and fatal cancer types globally, with distinct categorizations into two main classes: small cell lung cancer (SCLC) and non-SCLC (NSCLC) [1,2]. Squamous cell carcinoma (SCC) is one of the most common subtypes of NSCLC and is characterized by its high potential for recurrence and metastasis, contributing significantly to its elevated mortality rates.

In lung cancer, the TNM classification system provides staging of the disease based on factors such as tumor size (T), lymph node involvement (N), and the presence of distant metastases (M). This classification system plays a significant role in determining the prognosis of lung cancer [3]. However, in some cases, different prognoses may be observed even among patients with the same TNM stage. Therefore, research continues to identify new prognostic factors to better determine and improve prognosis.

Neutrophils, lymphocytes, platelets, hemoglobin, albumin, and C-reactive protein are primary laboratory parameters used in clinical practice to assess inflammation and nutritional status. These parameters are commonly investigated because they are cost-effective and readily accessible. Recently, researchers have tested a composite score, known as the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, which combines several of these parameters, in various studies as a novel prognostic biomarker [4-10]. The HALP score is derived from the combination of indicators such as platelets and

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lymphocytes reflecting immune status, along with hemoglobin indicating anemia status, and albumin providing information about nutritional status.

In our study, our objective was to assess prognosis using the HALP score as a prognostic indicator in patients with metastatic lung SCC who are under follow-up at our clinic.

Methods

Study Design

From January 2015 to December 2022, we conducted a retrospective screening of patients diagnosed with lung cancer at our oncology clinic. Among these patients, individuals aged 18 and older who were initially diagnosed with early-stage lung SCC and subsequently developed metastasis were selected for inclusion in the study. Patients for whom medical records and hospital computer system data at the time of diagnosis were unavailable, as well as those with heart failure, inflammatory bowel disease, and those undergoing dialysis, were excluded from the study. A total of 35 patients were included in the analysis. Demographic and clinicopathological characteristics of the patients were retrieved and recorded from medical records and the hospital computer system. Overall survival (OS) was calculated as the time from metastasis date to death, or last follow-up date. The HALP score was calculated using laboratory parameters at the time of metastasis, prior to the initiation of chemotherapy, according to the formula [HALP = hemoglobin (g/L) × albumin (g/L) × lymphocyte count / thrombocyte count] [11]. The study was conducted in accordance with the principles of the Helsinki Declaration, and approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (decision no: 2024-321, date: 08.05.2024).

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) Statistical Software (IBM SPSS Statistics version 22.0, IBM SPSS, USA). Descriptive analysis was used to present clinical and demographic data. Categorical and numerical variables were reported as frequency and percentage (n, %). Continuous variables were presented as mean±standard deviation when they exhibited a normal distribution; otherwise, they were presented as median (interquartile range). Survival analyses were conducted using the Kaplan-Meier method and log-rank test (univariate analysis), or Cox regression model (multivariate analysis). A p value <0.05 was considered statistically significant for all analyses.

Results

Analysis was conducted on 35 patients who met the inclusion criteria. Among them, 28 patients (80%) were male. Every patient had a smoking history. Out of the total, 25 patients (71.4%) had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1, while 17 patients (48.6%) received palliative radiotherapy (RT). The average levels of hemoglobin, albumin, lymphocytes, and platelets were found to be 11.97±1.81 g/dL, 3.76±0.76 g/dL, 3.26±2.87x10^9/L, and 299.40±100.25x10^9/L, respectively. The clinicopathological and laboratory characteristics of the patients were presented in Table 1.

There was no statistically significant association between the HALP score and gender (p=0.735), age groups (p=0.862), ECOG performance status (p=0.915), receipt of palliative RT (p=0.238), and body mass index (BMI) groups (p=0.615). The relationship between the HALP score and patient characteristics is presented in Table 2.

In the entire cohort, the median OS was 18 months. However, in the low HALP group, it was 14.4 months, whereas in the high HALP group, it was 20 months. Subgroups were compared in terms of OS. In the univariate analysis, no statistically significant difference was observed in terms of OS among age groups (p=0.747), BMI groups (p=0.072), gender (p=0.104), and receiving palliative RT (p=0.146). However, there was a statistically significant difference among HALP groups (p=0.04) (Figure 1). In the multivariate analysis, where parameters with a p-value below 0.1 were included, the statistical significance of the difference between HALP groups persisted (p=0.032). The results of both univariate and multivariate analyses are summarized in Table 3.

Discussion

Lung cancer is the most common cause of cancer-related deaths [1]. NSCLC constitutes the majority of lung cancers, with SCC having a higher incidence of recurrence and metastasis with

Table 1. Clinicopathological and laboratory characteristics of 35 patients with metastatic squamous cell lung cancer

Characteristics	Values
Age [median (range)]	66 (45-81)
Gender (n, %)	
Female	7 (20%)
Male	28 (80%)
ECOG performance status (n, %)	
0-1	25 (71.4%)
2	10 (28.6%)
Palliative RT (n, %)	
Yes	17 (48.6%)
No	18 (51.4%)
Hemoglobin (mean±SD, g/dL)	11.97±1.81
Albumin (mean±SD, g/dL)	3.76±0.76
Lymphocyte (mean±SD, 10^9/L)	3.26±2.87
Platelet (mean±SD, 10^9/L)	299.40±100.25
BMI (mean±SD)	24.98±3.45
HALP score [median (range)]	34.1 (7.1-93.2)

ECOG: Eastern Cooperative Oncology Group, RT: Radiotherapy, SD: Standard deviation, BMI: Body mass index, HALP: hemoglobin, albumin, lymphocyte, and platelet

in this category. The poor prognosis and elevated treatment expenses linked to lung SCC patients have under scored the growing necessity for novel prognostic factors in this patient population.

The HALP score is a comprehensive score derived from factors reflecting immune status, such as platelets and lymphocytes, along with indicators providing information about nutrition, such as hemoglobin and albumin. Previous studies have indicated a relationship between immunity, nutrition, and cancer survival [12-15].

Anemia, characterized by low levels of hemoglobin, is often prevalent in cancer patients and has been linked to resistance to RT and chemotherapy, consequently indicating a poor prognosis [16]. Research has demonstrated that low serum albumin levels indicate the nutritional status of cancer patients and are associated with a poor prognosis [17,18].

Numerous studies have demonstrated the involvement of the inflammatory microenvironment in cancer development, where lymphocytes and platelets play crucial roles [19,20]. Lymphocytes play a crucial role in the anti-tumor immune response by impeding the proliferation of tumor cells. Lymphopenia, which is prevalent among patients with advanced cancer, acts as a prognostic indicator for both OS and disease-free survival [20]. Platelets contribute to this microenvironment by releasing factors that facilitate tumor invasion and angiogenesis [21]. Based on these studies, it has been established that high levels of serum albumin, hemoglobin, and lymphocytes confer an advantage to cancer patients, whereas elevated platelet levels are associated with a disadvantage. Consequently, the HALP score, integrating these parameters, has emerged as a novel prognostic index in cancer [4,22,23].

In our study, we employed the HALP score as a prognostic index for patients monitored due to metastatic lung SCC, examining its correlation with disease prognosis. Our findings revealed poorer survival in the low HALP score group (p=0.04). Similar to our study, Zhai et al. [5] (2021) conducted an analysis on patients with NSCLC who underwent radical lung resection. Their findings revealed that patients with a high HALP score exhibited better OS compared to those with a low HALP score

Table 2. Distribution of patients according to HALP score in subgroups

Features	HALP low n (%)	HALP high n (%)	p value
Gender			
Female	4 (22.2)	4 (22.2)	0.735
Male	14 (77.8)	14 (77.8)	
Age group			
<67	9 (50)	8 (47.1)	0.862
≥67	9 (50)	9 (52.1)	
ECOG performance status			
0-1	13 (72.2)	12 (70.6)	0.915
2	5 (27.8)	5 (29.4)	
Smoking			
No	0 (0)	0 (0)	
Yes	18 (100)	17 (100)	
Paliative RT			
No	11 (61.1)	7 (41.2)	0.238
Yes	7 (38.9)	10 (58.8)	
BMI group			
Low	10 (55.6)	8 (47.1)	0.615
High	8 (44.4)	9 (52.9)	

ECOG: Eastern Cooperative Oncology Group, RT: Radiotherapy, BMI: Body mass index, HALP: hemoglobin, albumin, lymphocyte, and platelet

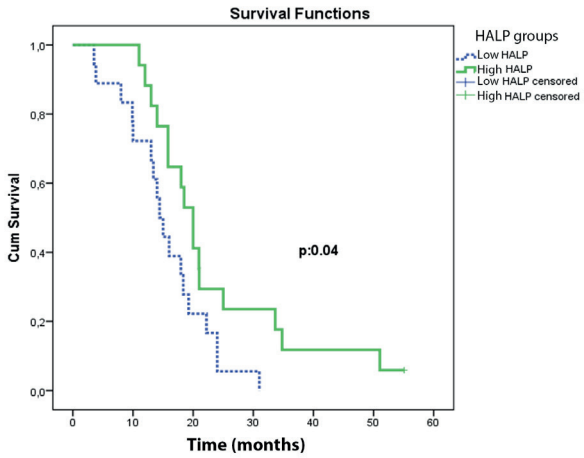

Figure 1. Comparison of HALP groups in terms of overall survival

Table 3. Analysis of prognostic factors in terms of overall survival

Features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
HALP groups				
HALP low	0.47 (0.23-0.97)	0.04	Ref	0.032
HALP high			0.45 (0.22-0.93)	
Age groups				
<67	0.89 (0.45-1.76)	0.747		
≥67				
BMI groups				
Low	0.52 (0.25-1.06)	0.072	Ref	0.057
High			0.50 (0.24-1.02)	
Gender				
Male	2.06 (0.86-4.93)	0.104		
Female				
Paliative RT				
No	0.60 (0.30-1.20)	0.146		
Yes				

CI: Confidence interval, HR: Hazard ratio, RT: Radiotherapy, BMI: Body mass index, HALP: hemoglobin, albumin, lymphocyte, and platelet

($p<0.001$). Wei et al. [7] (2022) obtained similar results in their study on NSCLC patients undergoing adjuvant chemotherapy. Our study stands out from the other two studies due to its exclusive inclusion of patients with squamous cell lung cancer and its specific focus on those in the metastatic stage.

Study Limitations

There are several limitations to our study. Firstly, it was conducted at a single center with a limited sample size, potentially limiting the generalizability of our findings and impacting thereliability of our results. Secondly, our study utilized a retrospective design, which may have resulted in missing data during the data collection process. Lastly, our study's findings are constrained in their ability to establish causal relationships and require validation by other studies. Nevertheless, despite these limitations, our study under scores the potential significance of the HALP score in predicting prognosis among lung cancer patients.

Conclusion

In summary, our study indicates that the HALP score could play a crucial role in predicting the prognosis of patients with squamous cell lung cancer. Lower HALP scores have been linked to decreased OS. Nonetheless, broader and prospective studies are required to validate and generalize these results. It's essential to acknowledge the limitations of this study and future research should thoroughly assess these prognostic factors.

Ethics

Ethics Committee Approval: The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (decision no: 2024-321, date: 08.05.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.D., Y.D., E.Ç., T.E., Concept: Ö.D., Design: Ö.D., Y.D., T.E., Data Collection or Processing: Ö.D., Y.D., E.Ç., Analysis or Interpretation: Ö.D., Y.D., Literature Search: Ö.D., Writing: Ö.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Impact of Metastasectomy on Survival Outcomes in Colorectal Cancer: A Single Center Retrospective Study

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ABSTRACT

Aim: Metastasectomy is a significant intervention in metastatic colorectal cancer (mCRC) management. This study uniquely evaluates metastasectomy outcomes by metastatic site and underscores the critical role of R0 resection, offering real-world insights into tailored treatment strategies for mCRC. Our findings align with existing literature, particularly regarding the survival benefits of lung metastasectomy and the importance of achieving complete tumor resection

Methods: This retrospective cohort study included 73 patients with colon cancer who underwent metastasectomy between January 2014 and June 2023. Demographic, clinical, and treatment data were analyzed. Survival outcomes were assessed using Kaplan-Meier analysis.

Results: The median overall survival (OS) for the entire cohort was 40.4 months. Patients undergoing lung metastasectomy demonstrated the longest median survival (53.6 months), followed by liver (41.7 months) and intraabdominal metastasectomy (35.5 months). R0 resections were associated with improved OS (median: 69.6 months), while non-R0 resections had poorer outcomes. Synchronous metastases were linked to shorter OS than metachronous metastases, although the difference was not statistically significant (p=0.09).

Conclusion: Metastasectomy significantly improves survival outcomes in mCRC, with lung metastasectomy showing the most favorable results. Achieving R0 resection is crucial for optimizing survival benefits. These findings underscore the importance of individualized treatment planning in patients undergoing metastasectomy.

Keywords: Colorectal cancer, metastasectomy, prognosis, survival outcomes, treatment planning

Introduction

Metastasectomy, the surgical removal of metastatic tumors, has emerged as a significant intervention for the management of metastatic colorectal cancer (mCRC). The potential benefits of this procedure have been demonstrated in various clinical settings, highlighting its role in improving progression-free survival (PFS) and overall survival (OS) in patients. However, the real-world efficacy of metastasectomy remains a critical area of investigation, as clinical trials may not fully capture the diverse patient populations encountered in everyday practice.

Metastasectomy practices have significantly increased across various cancer types over the past decade. This rise is largely attributed to reports of favorable long-term outcomes, which have sparked growing interest in the procedure despite the limited high-level evidence available [1-3]. Metastasectomy, particularly in the context of renal cell carcinoma and colorectal cancer, has been associated with improved survival outcomes. However, the evidence is primarily based on retrospective studies and registry data rather than randomized controlled trials [1,4,5].

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A comprehensive study involving 1064 patients with mCRC in Türkiye revealed that metastasectomy significantly improved median PFS and OS. Specifically, patients who underwent metastasectomy had a median PFS of 13.5 months compared to 9.9 months for those who did not and a median OS of 47.3 months versus 24.3 months, respectively [6]. This underscores the potential of metastasectomy to extend survival in real-life clinical settings.

Further supporting these findings, a population-based analysis of stage 4 colon cancer patients demonstrated that metastasectomy was associated with improved survival across various age groups and tumor grades. The study found that patients who underwent metastasectomy had a favorable survival outcome, with a hazard ratio (HR) for OS ranging from 0.68 to 0.72, except for those aged 85 years and older [7]. This suggests that metastasectomy can benefit a broad spectrum of patients, although its efficacy may diminish with advanced age.

In elderly patients, the feasibility and benefits of metastasectomy have also been explored. A single-center experience with patients aged 70 years and older indicated that metastasectomy and local ablative treatments could significantly enhance OS. The study reported a median OS of 25.6 months, with metastasectomy being an independent factor associated with improved survival (HR: 0.22, $p<0.001$) [8]. This highlights the potential for surgical interventions to offer substantial survival benefits even in older populations.

The role of metastasectomy in conjunction with primary tumor resection (PTR) has been a subject of debate. An analysis of data from the National Cancer Data Base revealed that while PTR alone significantly improved survival, the addition of metastasectomy did not confer a statistically significant survival advantage over PTR alone. The median OS for patients undergoing PTR with metastasectomy was 20.5 months compared to 21.8 months for those undergoing PTR alone [9]. This finding suggests that while PTR is crucial, the incremental benefit of metastasectomy may vary depending on individual patient factors.

Institutional factors also play a role in the outcomes of metastasectomy. A study examining the impact of the type of treating institution found that patients treated at academic or research hospitals had better survival outcomes. The median survival for patients undergoing metastasectomy at these institutions was 22.4 months, significantly longer than at other types of institutions. Factors such as higher income regions, chemotherapy (ChT), and treatment at academic/research hospitals were positively associated with undergoing metastasectomy and improved survival [10]. This indicates the importance of a multidisciplinary approach and possibly regionalizing care to optimize outcomes for patients with metastatic colon cancer.

In addition to liver and lung metastases, metastasectomy has also been explored for less common metastatic sites such as the spleen. Although data on splenic metastases are limited, studies suggest that metastasectomy for isolated splenic metastases can achieve long-term survival, particularly when performed laparoscopically [11].

Despite the promising outcomes of metastasectomy, its role remains controversial in certain contexts. For example, aggressive surgical resection of the primary tumor without metastasectomy in patients with unresectable liver-only metastases does not appear to provide a survival benefit compared to ChT alone [12]. This indicates that the decision to perform metastasectomy should be carefully considered based on individual patient factors and the extent of the disease.

In summary, metastasectomy has shown significant promise in improving survival outcomes for patients with mCRC. Its benefits are evident across various patient demographics and clinical settings. However, the extent of its efficacy can be influenced by factors such as age, the presence of PTR, and the type of treatment. These findings underscore the need for a tailored approach to the management of mCRC, incorporating metastasectomy as a key component of treatment strategies. In this context, our study provides a unique contribution to the existing literature by offering site-specific survival outcomes and emphasizing the importance of achieving R0 resection within a single-center cohort.

Methods

Study Design and Patient Selection

This retrospective single-center cohort study analyzed the impact of metastasectomy on survival outcomes in patients diagnosed with colon cancer. The study included 73 patients who underwent metastasectomy at our institution between January 2014 and June 2023. Inclusion criteria required patients to have a histopathologically confirmed diagnosis of colon cancer, documented metastasectomy, and available clinical and follow-up data for OS and disease-free survival (DFS). Patients with incomplete clinical data or concurrent malignancies were excluded.

Data Collection

Data were retrospectively extracted from patients' medical records. Demographic details such as age and gender were recorded alongside clinical data, including Eastern Cooperative Oncology Group performance status, primary tumor location, RAS and microsatellite instability status, and location of metastases. Treatment data encompassed pre- and post-metastasectomy systemic therapies, such as ChT and targeted therapies. Survival outcomes included OS, defined as the time from metastatic disease to death from any cause.

Statistical Analysis

Descriptive statistics summarized patient demographics, clinical characteristics, and laboratory findings. Categorical variables were compared using chi-square or Fisher's exact tests, while continuous variables were analyzed with independent t-tests or Mann-Whitney U tests based on data distribution. Kaplan-Meier survival analyses were conducted to evaluate OS and DFS, with comparisons between groups assessed using the log-rank test. Cox proportional hazards regression models were used for univariate and multivariate analyses to identify factors

independently associated with survival outcomes. A p value of <0.05 was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences statistics 26.0 (IBM Corporation, Armonk, NY, USA).

Ethical Considerations

This study was conducted in compliance with the principles of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (decision no: 3/11/010.99/2024, date: 25.12.2024). As this was a retrospective study, informed consent was waived; however, all patient data were anonymized to ensure confidentiality.

Results

A total of 73 patients were involved in the study. The median follow-up time was 24 months (range, 1-74), and the median age was 59 years (range, 36-84). Thirty-one (42.5%) patients were women. The proportion of patients with primary right colon cancer was determined to be 35.6%. Synchronous metastasis was detected in 50.7% of those who underwent metastasectomy. Isolated liver metastasectomy was performed in 68.5% of the patients, while 17.8% had lung metastasectomy, and the remaining 13.7% had intraabdominal metastasectomy. It has been shown that 2.3% of the patients have MSI-H, 47.4% have Ras mutation, and 6.9% have a mucinous component. Metastasectomy was performed after conversion therapy in 9.6% of patients (Table 1).

The median OS was 40.4 months [95% confidence interval (CI): 29.0-51.8] in the whole group (Figure 1).

The median survival time for patients with synchronous metastases was 35.5 months (95% CI: 22.3-48.7), compared to 47.5 months (95% CI: 33.2-61.8) for those without synchronous metastases. Although the median survival appeared longer in patients without synchronous metastases, the difference did not reach statistical significance (p=0.09) (Figure 2).

Table 1. Baseline characteristics of patients undergoing metastasectomy

Characteristic	n (%)
Total patients	73
Median follow-up time (months)	24 (1-74)
Median age (years)	59 (36-84)
Female patients	31 (42.5%)
Primary right colon tumors	26 (35.6%)
Synchronous metastasis	37 (50.7%)
Isolated liver metastasectomy	50 (68.5%)
Lung metastasectomy	13 (17.8%)
Intraabdominal metastasectomy	10 (13.7%)
MSI-H	2 (2.3%)
Ras mutation	35 (47.4%)
Conversion therapy before metastasectomy	7 (9.6%)
R0 resection	49 (67.1%)

MSI-H: Microsatellite instability-high

The analysis of survival outcomes across different metastasectomy sites revealed significant differences in median survival times. Patients who underwent lung metastasectomy had the longest median survival of 53.6 months (95% CI: 2.1-105.1), indicating a more favorable prognosis than metastasectomy at other sites. Liver metastasectomy was associated with a median survival of 41.7 months (95% CI: 24.5-58.9), while intraabdominal metastasectomy showed the shortest median survival of 35.5 months (95% CI: 0.7-70.3). Pairwise comparisons using the log-rank test did not reveal statistically significant differences between the metastasectomy sites, liver vs. lung (p=0.989), liver vs. intraabdominal (p=0.429), and lung vs. intraabdominal (p=0.278). These findings suggest that while there are observable differences in median survival across metastasectomy sites, the variations are not statistically significant (Figure 3).

Among 73 patients, R0 resection was achieved in 52 (71.2%), while 11 (15.1%) had R1, and 10 (13.7%) had R2 resections. Among R0 resections, 48.1% received no targeted therapy, 30.8% were treated with ChT and anti-vascular endothelial growth factors (VEGF), and 21.2% were treated with ChT and anti-epidermal growth factor receptor (EGFR) treatment. In R1-2 resections, ChT with anti-VEGF was most common (76.2%), followed by ChT with anti-EGFR (14.3%) and ChT with no targeted therapy (9.5%).

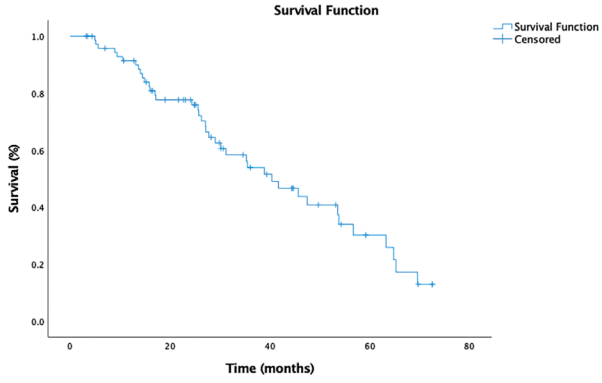

Figure 1. The Kaplan-Meier survival curve displays the overall survival function for the entire cohort

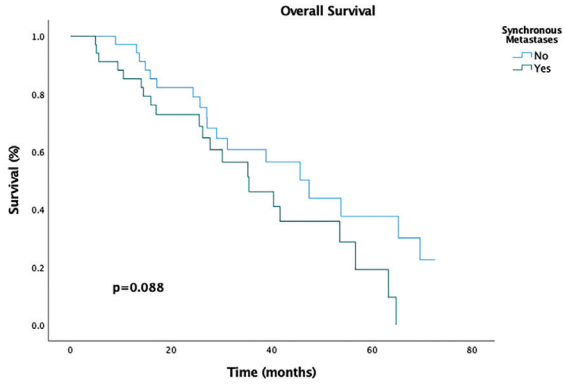

Figure 2. The Kaplan-Meier survival curve illustrates the overall survival of patients stratified by the presence of synchronous metastases

Patients who underwent R0 resection had a median survival of 45.7 months (95% CI: 25.4-66), compared to 35.3 months (95% CI: 19.9-50.7) for non-R0 resection patients. Survival outcomes showed that in R0 resections, non-targeted therapy with ChT had the highest median survival at 69.6 months (95% CI: NA), compared to 45.7 months (95% CI: 31.9-59.5) for anti-EGFR and 35.5 months for anti-VEGF (95% CI: 26.0-45.0) (Figure 4).

Pairwise comparisons using the log-rank test did not reveal statistically significant differences in survival distributions between the treatment groups: no targeted therapy versus anti-EGFR (p=0.66); no targeted therapy versus anti-VEGF (p=0.80); and anti-EGFR versus anti-VEGF (p=0.74). The overall comparison of survival distributions across all groups also yielded no statistically significant differences (p=0.889) (Figure 5).

For R1-2 resections, median survival was lowest with no targeted therapy (4.9 months, n=2), while ChT with either anti-VEGF or anti-EGFR showed 38.9 months (95% CI: 23.4-54.4) and 47.5 months (95% CI: 0-115.2), respectively. There were no significant survival differences between anti-VEGF and anti-EGFR treatments (p=0.08).

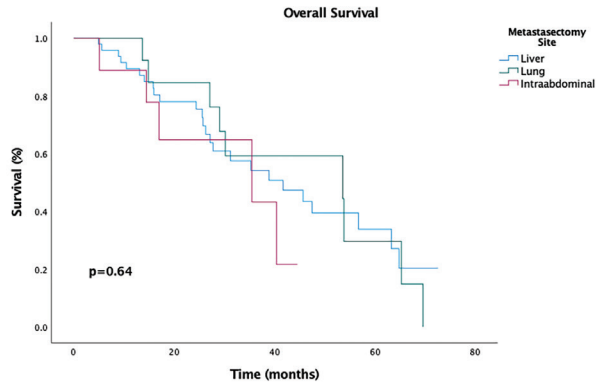

Figure 3. Kaplan-Meier survival curve demonstrates overall survival stratified by metastasectomy site

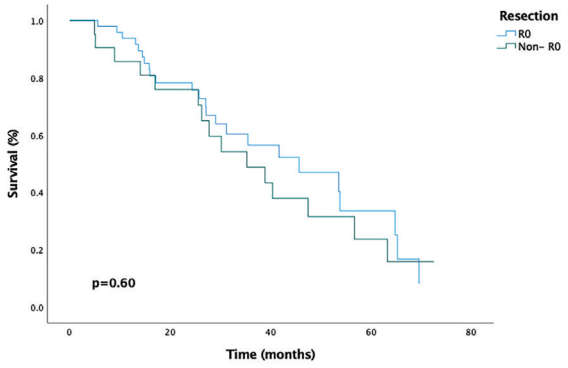

Figure 4. Kaplan-Meier survival curve illustrates OS in patients receiving adjuvant ChT after R0 metastasectomy, stratified by treatment type

OS: Overall survival, ChT: Chemotherapy

Discussion

The survival advantage of metastasectomy in mCRC is well-documented. Patients undergoing metastasectomy, have shown significantly improved OS compared to those who did not undergo the procedure [13,14]. For instance, a study reported that patients who received lung metastasectomy had a median OS that was not reached, compared to 41.4 months for those who did not undergo surgery, with an HR for death of 0.27 (95% CI: 0.14-0.53, p<0.001) [15]. Similarly, another study found that mCRC patients who underwent metastasectomy had a median OS of 54.9 months compared to 28.6 months for those who did not (p<0.001) [16].

The analysis of survival outcomes following metastasectomy in mCRC patients reveals significant benefits, particularly when considering the site of metastasis. Patients undergoing lung metastasectomy exhibit the longest median survival, with a median of 53.6 months (95% CI: 2.1-105.1), suggesting a more favorable prognosis than other metastatic sites. This aligns with findings that highlight the potential for long-term survival in patients with isolated pulmonary metastases, where a 5-year survival rate can exceed 50% in selected cases [17-19]. In a randomized controlled trial, the PulMiCC study, the 5-year survival rate for patients undergoing lung metastasectomy was estimated at 38%, compared to 29% in the control group, suggesting a modest survival benefit [20].

The potential mechanisms underlying the observed survival differences between metastasectomy sites may relate to both anatomical and biological factors. Rectal cancers, for instance, tend to metastasize more frequently to the lungs, while colonic cancers more commonly spread to the liver and peritoneum [21]. The unique microenvironments of these metastatic sites likely play a role in determining treatment outcomes. Lung metastases are often more amenable to complete surgical resection due to their isolated and localized nature than peritoneal metastases, which are often diffuse and associated with a worse prognosis. Furthermore, the liver's

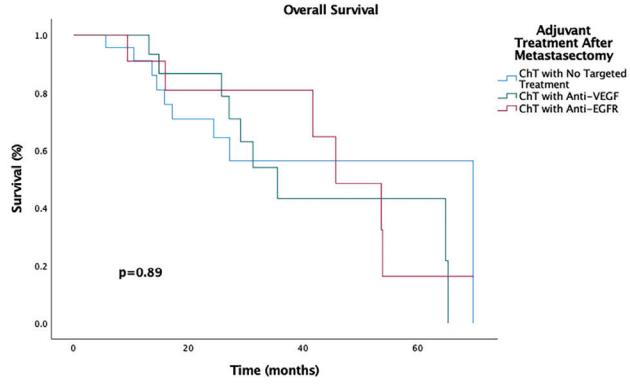

Figure 5. Kaplan-Meier survival curve illustrates OS in patients receiving adjuvant ChT after R0 metastasectomy, stratified by treatment type

OS: Overall survival, ChT: Chemotherapy, VEGF: Vascular endothelial growth factor, EGFR: Epidermal growth factor receptor

dual blood supply and susceptibility to hematogenous spread make it a common metastatic site, but a target for effective interventions like hepatic metastasectomy, which has shown significant survival benefits when feasible.

Another factor is the biology of the metastatic tumors themselves. Lung metastases from rectal cancer may exhibit distinct molecular profiles that make them more responsive to systemic therapies or surgical interventions. For instance, KRAS mutations are more common in liver and peritoneal metastases, correlating with poorer prognosis. In contrast, lung metastases may exhibit molecular features associated with better response to targeted therapies or immunotherapy [21]. Improved surveillance and surgical techniques for lung metastasectomy could also contribute to better outcomes [18,19].

Liver metastasectomy also demonstrates a substantial survival benefit, with a median survival of 41.7 months (95% CI: 24.5-58.9). This is consistent with historical data showing that resection of hepatic metastases can lead to improved outcomes, with 5-year survival rates ranging from 20% to 50% [22]. However, the survival benefit is less pronounced compared to lung metastasectomy, possibly due to the complexity and extent of liver involvement in mCRC [23].

Intraabdominal metastasectomy, however, is associated with the shortest median survival of 35.5 months (95% CI: 0.7-70.3). This may reflect the challenges in achieving complete resection and the aggressive nature of intraabdominal metastases [24]. Despite these challenges, surgical intervention in selected patients can still offer survival benefits, particularly when combined with systemic therapies [22].

The role of metastasectomy is further supported by studies indicating that patients who undergo the procedure have better OS and PFS than those who do not. For instance, patients receiving lung metastasectomy had a median OS benefit, with an HR for death of 0.27, indicating a significant reduction in mortality risk [15]. Similarly, patients undergoing metastasectomy during cetuximab-based therapy showed improved OS and PFS, highlighting the importance of integrating surgical and systemic treatments [16].

The median survival time for patients with synchronous metastases was 35.5 months (95% CI: 22.3-48.7), compared to 47.5 months (95% CI: 33.2-61.8) for those with metachronous metastases. Although a trend toward longer survival was observed in patients with metachronous metastases, the difference did not reach statistical significance (p=0.09). This finding aligns with prior studies reporting poorer outcomes in synchronous metastases than in metachronous cases [25]. However, advancements in surgical techniques and systemic therapies may have narrowed the survival gap between these groups [26].

The success of metastasectomy, particularly R0 resection, is influenced by several factors. Patients with a single metastatic location, metachronous metastatic disease, and no BRAF mutation were more likely to benefit from lung metastasectomy [15]. Additionally, a resected primary tumor and low carcinoembryonic antigen levels were associated with better outcomes [15].

Conversely, factors such as non-R0 resection, multiple metastatic sites, and synchronous metastasis were predictors of worse OS [27]. The importance of achieving R0 resection is underscored by its association with improved survival outcomes, as incomplete resection (non-R0) is linked to poorer prognoses [27].

Despite the promising outcomes, the decision to perform metastasectomy must be carefully considered. Factors such as the site of metastasis, the patient's performance status, and the potential for complete resection play crucial roles in determining the likelihood of success [24]. Moreover, while metastasectomy offers survival benefits, the risk of recurrence remains high, necessitating a comprehensive treatment approach that may include systemic therapies [28].

Study Limitations

This study has several limitations. First, its retrospective single-center design may limit the generalizability of the findings to broader patient populations and healthcare settings. The relatively small sample size of 73 patients reduces the statistical power to detect subtle differences, particularly in subgroup analyses, such as those stratified by metastasectomy site or synchronous versus metachronous metastases. Additionally, the lack of randomization introduces potential selection bias, as patients undergoing metastasectomy may inherently differ in baseline characteristics or disease biology compared to those not undergoing the procedure. To address selection bias, future studies should incorporate prospective designs with predefined inclusion and exclusion criteria, focusing on comprehensive patient stratification.

Moreover, detailed data on post-metastasectomy systemic therapies were not comprehensively analyzed, which could influence survival outcomes. The study also did not account for potential confounders such as comorbidities or socioeconomic factors that might impact treatment decisions and survival. Finally, while Kaplan-Meier and Cox regression analyses were employed to evaluate survival outcomes, the observational nature of the study precludes definitive conclusions about causality between metastasectomy and improved survival.

Conclusion

Metastasectomy significantly improves survival in metastatic colorectal cancer, particularly in patients undergoing lung metastasectomy and achieving R0 resection. Further multicenter, prospective studies are warranted to validate these findings and explore the potential mechanisms underlying the survival benefits associated with metastasectomy.

Ethics

Ethics Committee Approval: Approval was obtained from the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2024/010.99/11/3, date: 25.12.2024).

Informed Consent: Retrospective study.

Declaration Regarding the Use of AI and AI-Assisted Technologies: In the preparation of this manuscript, AI tools, including Translate GPT and Paperpal-AI, were utilized for translation and grammar checks. Their incorporation primarily impacted the language refinement process, ensuring accuracy, clarity, and consistency in the presentation of the text. After carefully reviewing and editing the content as necessary, the authors take full responsibility for the publication's content.

Footnotes

Authorship Contributions

Concept: O.K., Design: O.K., D.I., Data Collection or Processing: G.A., S.Y., H.Ş.Y., A.D., Analysis or Interpretation: Y.E.A., U.Ö., S.Ö., A.T., Literature Search: O.K., T.B., S.A., H.O., N.T., H.S., Writing: O.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Molecular and Hematological Characterization of α-Thalassemia in Denizli Province

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ABSTRACT

Aim: Alpha thalassemia, a common monogenic disorder, occurs with defective synthesis of the α-globin chain and has a very wide clinical spectrum depending on the disorders in the globin genes. This study aims to determine the frequency of α-globin gene mutations in patients suspected of having alpha thalassemia in Denizli province and to evaluate the phenotypic effects of detected mutations.

Methods: A total of 93 patients (55 female, 38 male) with suspected alpha thalassemia based on anemia, family history, premarital screening and high-performance liquid chromatography results were analyzed for α-thalassemia gene deletions. DNA was isolated from peripheral blood samples, and the results were evaluated using the "Seqline Alpha Thalassemia Diagnostic Kit" to detect common α-globin gene deletions: large deletions of 3.7 kb (-α3.7), 4.2 kb (-α4.2), and 20.5 kb (-(α)20.5) in *HBA1-2* genes, as well as MED1 (--MED) and SEA (--SEA).

Results: Among the 93 patients, mutations were detected in 38 patients, yielding a deletion detection rate of 40.9%. The most common mutation was -α3.7 (40.7%), followed by -(α)20.5 (17.1%), --MED (5.2%), and -α4.2 (2.6%). No - SEA deletions were identified.

Conclusion: This study represents the first molecular characterization of α-thalassemia in Denizli province, identifying four different α-thalassemia deletions and eight distinct genotypes. The findings provide valuable insights into the regional distribution and clinical implications of these mutations.

Keywords: Alpha thalassemia, alpha-globin gene, gene deletion, genotype-phenotype correlation

Introduction

Hemoglobinopathies are the most common autosomal recessive disorders in the world [1]. Alpha thalassemia (α-thalassemia), which is seen with high frequency in the population living in the Mediterranean, Southeast Asia, and the Middle East, is a common type of hemoglobinopathy characterized by deficiency or absence of alpha globin chain synthesis [2]. The α-globin gene cluster, located on chromosome 16p13.3, consists of two α-globin genes (α1 and α2) on each homologous chromosome, totaling four functional α-globin genes [3,4].

Alpha thalassemia syndromes result from mutations in one or more α-globin genes, and the molecular defects are usually gene deletions; however, point mutations might also be found [5]. α-Thalassemia is quite heterogeneous at the clinical and molecular levels. The form resulting from deletion/inactivation of one of the four α-globin genes is called a silent carrier state. It usually leads to insignificant hematological findings; in this form, patients' hemoglobin levels, erythrocyte parameters, and hemoglobin electrophoresis are normal. Deletion/inactivation of two α-globin genes in cis or trans leads to α-thalassemia trait, and patients show mild microcytic, hypochromic anemia. When three of the α-globin genes are deleted or inactivated,

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hemoglobin (Hb) H disease, characterized by severe anemia, is observed. Deletion/inactivation of four α-globin genes results in the most severe form, Hb Bart syndrome, which causes hydrops fetalis [6,7]. Although the phenotype of alpha thalassemia mutations is related to the number of affected alpha globin genes, its expression and genotype can be more complex and variable. Large deletions, non-deletion mutations, mutations in regulatory regions, mutations in epigenetic genes, and unstable mutations can all be effective in increasing the severity of the phenotype [8-10].

According to the World Health Organization (WHO) data, it is estimated that hemoglobin disorders have a frequency of 5% worldwide. More than 330,000 newborns are affected each year, 83% by sickle cell diseases and 17% by thalassemias [11]. Türkiye has a high prevalence of hemoglobinopathies, exacerbated by consanguineous marriages, making these disorders a significant public health concern. However, research on α-thalassemia in Türkiye remains limited, and no molecular studies on α-globin gene mutations have been conducted in Denizli province. Understanding the α-globin mutation spectrum in different regions is crucial for improving genetic counseling and establishing national health policies for α-thalassemia screening.

This study aims to investigate gene deletions in patients with suspected α-thalassemia referred to our center, analyze the molecular spectrum of deletions, and evaluate genotype-phenotype correlations.

Methods

This retrospective study included 93 patients (55 females, 38 males) who were referred to the Pamukkale University Genetic Diagnosis Center with a preliminary diagnosis of α-thalassemia between August 2020 and December 2024. Ethical approval was granted by the Pamukkale University Non-interventional Clinical Research Ethics Committee (decision no: E-60116787-020-657799, date: 19.02.2025).

DNA Isolation and Quantification

Genomic DNA was extracted from peripheral blood samples collected in K2EDTA tubes using the Qiacube automated DNA isolation system (Qiagen, Germany) based on the spin-column method. The concentration and purity of the extracted DNA were determined via spectrophotometric measurement using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). DNA samples with concentrations between 80 and 100 ng/µL were used for subsequent analyses.

α-thalassemia Deletion Analysis

Alpha-globin gene deletion analysis was performed using the "α-thalassemia Diagnostic Kit" (Seqline, Türkiye) which targets the detection of gross deletions in the *HBA1* and *HBA2* genes. The kit uses the Gap-polymerase chain reaction (PCR) method to detect deletions. This method detects deletions of 3.7 kb (-α3.7), which results in a deletion of part of the *HBA2* gene; 4.2 kb (-α4.2), which results in the deletion of the entire the *HBA2* gene; and deletions like (-(α)20.5), MED (--MED), and SEA (--SEA) that result in deletions both the *HBA2* and *HBA1* genes.

All procedures were performed according to the manufacturer's protocol. PCR amplification products were subjected to gel electrophoresis using a 1.4% agarose gel with a 50 bp-5000 bp DNA ladder. Electrophoresis was carried out at 110 V for 80 minutes, and bands were visualized under UV imaging.

The deletion regions examined and the expected band sizes in gel electrophoresis are given in Table 1.

This methodological approach ensured the accurate detection of common α-thalassemia deletions in the studied population.

Statistical Analysis

The overall group and subgroups (e.g., patients with and without mutations, male and female patients) were analyzed for mean and median age. Mutation distributions, allele frequencies, and hematological findings (with median values calculated) are presented as percentages.

Results

In this study, gross deletions in α-thalassemia genes were investigated in 93 patients, using the Gap-PCR method, and the distribution of the results was evaluated. While deletions were detected in 38 of the patients included in the study, no deletions were detected in 55 patients. This means that the deletion detection rate in alpha globulin genes in our study was 40.9% (Table 2).

The allelic frequencies of the determined α-thal gene deletions were as follows: -α3.7, 40.7% (n=31) -(α)20.5, 17.1% (n=13) --MED, 5.2% (n=4) -α4.2, 2.6% (n=2). -SEA deletion was not detected in the patients. Table 3 presents the allelic frequencies of the deletions found in the patients.

Table 1. Examined deletion regions and expected band sizes in gel electrophoresis

Deletion type	Band size (bp)
-α3.7	2020
α2 (wild-type)	1800
-α4.2	1630
--SEA	1350
-(α)20.5	1010
--MED	800

Table 2. Overview of our cohort (n=93)

	Patients (n)	Age at diagnosis Age (mean)	Frequency (%)
Male	38	30.8	40.9
Female	55	33	59.1
Deletion detected	38	28.6	40.9
No deletion detected	55	34.6	59.1
Total patient	93	32.2	100

Hematological parameters were analyzed by averaging according to the genotypes of the patients. It was observed that mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and MCH concentration (MCHC) values were related to the number of functional α-globin genes, and that a decrease in the number of genes caused these values to decrease. The mean values of Hb, MCV, MCH, and MCHC were higher in individuals with the -α3.7/αα genotype carrying a single gene deletion, while they were lowest in individuals with the -α3.7/-(α)20.5 genotype carrying three gene deletions. The results of all hematological parameters are given in Table 4.

Discussion

α-thalassemia is one of the most prevalent genetic disorders worldwide, with significant differences in prevalence and mutation spectrum influenced by ethnic and geographical factors. The WHO reported the global prevalence of α-thalassemia as 44.6% in 2008 [12]. However, regional prevalence varies considerably, with the highest carrier frequencies observed in the Middle East and the Mediterranean, reaching up to 40% in some populations [13,14]. In Türkiye, the carrier frequency of hemoglobinopathies also shows regional variation, with the highest rates found in the southern part of the country [15,16]. Studies conducted in Adana, a southern city of Türkiye, reported beta-thalassemia and alpha-thalassemia carrier frequencies as high as 13.5% and 7.5%, respectively [17,18].

Despite the high prevalence of α-thalassemia in Türkiye, very few studies have specifically focused on this disorder, and no prior study has investigated alpha-globin mutations in the Denizli region. Given the ethnic diversity of the Turkish population, it is crucial to determine the spectrum of alpha-globin mutations across different regions. Our study represents the first molecular characterization of alpha-thalassemia deletions in the Denizli region, providing valuable insights into the distribution and clinical implications of these mutations.

In our study, we identified four alpha-thalassemia deletions and eight genotypes among the study population. Notably, 59.1% of the patients referred to our clinic due to either anemia, family history, premarital screening, or abnormal high-performance liquid chromatography results did not have any alpha-globin gene deletions, while 40.9% carried a deletion. The most frequent deletion identified was -α3.7, with a prevalence rate of 40.7%. The other detected deletions were -(α)20.5 (17.1%), --MED (5.2%), and -α4.2 (2.6%). The --SEA deletion, which is commonly observed in Asian populations, was not present in our cohort. Our findings align with previous alpha-thalassemia studies conducted in Türkiye, in which the -α3.7 deletion was the most frequently observed mutation. Similar results were reported in a study conducted in Antalya by Keser et al. [19]. According to studies from different Turkish regions, the frequency of the -α3.7 deletion ranges between 35.2% and 52.28% [20-24].

Previous studies have reported regional variations in the prevalence of other deletions. Onay et al. [21] identified -(α)20.5 as the second most common mutation after -α3.7 in the Aegean region. Similarly, Keser et al. [19] found that the -(α)20.5 deletion was the second most common in their study in Antalya, which is consistent with our results. However, unlike our findings, Onay et al. [21] detected the --SEA deletion in one patient, while we did not observe this mutation in our study population. Additionally, we identified the -α4.2 deletion in two patients, whereas it was not reported in Onay et al.'s [21] study. Interestingly, studies conducted in other southern regions of Türkiye [9,16,19] reported a higher frequency of the --MED double gene deletion than the -(α)20.5 deletion, likely due to ethnic diversity in these regions. A comparative analysis of our mutation frequency data with those from other Turkish studies is presented in Table 5.

Table 3. Allele frequency of α-thalassemia deletions

Deletion	Allele	Frequency %
-α3.7	31	40.7
-(α)20.5	13	17.1
--MED	4	5.2
-α4.2	2	2.6
--SEA	-	-

Table 4. Distribution of α-thalassemia deletions and mean values of hematological findings of patients according to this distribution

	Patients (n)	Frequency (%)	Hb (g/dL) (12-18)[a]	Hct % (37-52)[a]	MCV Fl (80-100)[a]	MCH (pg) (27-31)[a]	MCHC (g/dL) (31-37)[a]	RDW (11.5-14.5)[a]	RBC M/uL (4.2-6.1)[a]
-α3.7/αα	13	14	13.18	40.53	73.79	23.95	32.44	15.47	5.50
-(α)20.5/αα	12	12.9	12.09	38.19	66.21	20.78	31.52	16.00	5.77
-α3.7/-α3.7	6	6.5	11.08	34.60	68.60	21.82	32.10	15.30	5.09
-α3.7/--MED	3	3.3	10.90	34	57.33	18.36	32	24.56	5.86
-α3.7/-α4.2	2	2.2	11.35	35.55	68.25	21.75	31.90	14.65	5.21
-α3.7/-(α)20.5	1	1	8.20	26.50	51.00	15.60	30.70	21.30	5.21
--MED/αα	1	1	12.60	39.60	65.10	20.60	31.70	16.40	6.09

[a]Normal values.
Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, RBC: Red blood cell

Table 5. Allel frequency of α-thallasemia mutation in Turkish population

Variant Method	This study % (AC: 76) Gap-PCR	Öztürk [26] 2024 İstanbul % (AC: 338) MLPA	Barış et al. [24] 2023 West Aegean % (AC: 206) MLPA	Keser et al. [19] 2021 Antalya % (AC: 224) StripAssay + MLPA	Demir et al. [23] 2021 Trakya % (AC: 156) MLPA	Onay et al. [21] 2015 Aegean % (AC: 285) StripAssay	Karakaş et al. [22] 2015 İstanbul % (AC: 190) StripAssay	Celik et al. [20] 2013 Hatay % (AC: 194) StripAssay	Guvenc et al. [17] 2010 Adana % (AC: 450) StripAssay
-α3.7	40.7 (31)	34 (115)	40.3 (83)	40.1 (90)	35.3 (55)	52.28 (149)	23.15 (44)	43.81 (85)	40.6 (183)
-α20.5	17.1 (13)	8.2 (28)	3.4 (7)	7.1 (16)	5.8 (9)	14.74 (42)	10.5 (20)	0.51 (1)	3.7 (17)
-αMED	5.2 (4)	17.8 (60)	6.8 (14)	3.5 (8)	2.6 (4)	10.53 (30)	8.9 (17)	5.67 (11)	9.5 (43)
-α4.2	2.6 (2)	1.2 (4)	1 (2)	-	0.6 (1)	-	1 (2)	0.51 (1)	0.6 (3)
-αSEA	-	0.6 (2)	1.4 (3)	-	1.9 (3)	0.35 (1)	-	-	-
ααααanti-3.7	ND	0.3 (1)	0.48 (1)	0.44 (1)	9.6 (15)	3.6 (9)	3.6 (7)	1.54 (3)	1.1 (5)
ααααanti-4.2	ND	0.3 (1)	-	-	-	-		-	-
-αHS40	ND	-	-	-	0.6 (1)	-	-	-	-
Whole gene deletion	ND	-	-	-	1.9 (3)	-	-	-	-
FIL/αα	ND	-	-	1.33 (3)	-	2.81 (8)	1 (2)	0.51 (1)	-
Point mutation			4.85 (10)						

AC: Allele count, ND: No data, PCR: Polymerase chain reaction, MLPA: Multiplex ligation-dependent probe amplification

The deletions examined in our study represent the most common mutations in α-thalassemia. For example, in the study by Keser et al. [19] (2021), 92.8% of the total mutations consisted of the three deletions included in our analysis: -α3.7 (73.3%), -(α)20.5 (13.0%), and --MED (6.5%). This may also indicate the importance of selecting molecular techniques based on the common mutations present in the target population to ensure cost-effectiveness and diagnostic accuracy.

The clinical impact of alpha-thalassemia is closely associated with hematological parameters. El-Kalla and Baysal [25] demonstrated that a reduction in the number of functional α-globin genes significantly decreases MCV values. Similarly, Guvenc et al. [17] emphasized that MCV, MCH, and MCHC values consistently correlate with the number of functional α-globin genes. In our study, we analyzed hematological parameters according to genotype and observed that the mean MCV was highest in individuals with the -α3.7/αα genotype (single gene deletion) and lowest in those with the -α3.7/-(α)20.5 genotype (three gene deletions). MCHC and MCH values also followed a similar pattern. This correlation between hematological indices and functional gene count further supports the clinical significance of molecular analysis in alpha-thalassemia diagnosis. However, hematological parameters alone are insufficient to determine the genotype of α-thalassemia, and definitive diagnosis requires molecular analysis. The correlation between genotype and hematological parameters in our study population is illustrated in Table 4.

Study Limitations

We used Gap-PCR analysis to detect common deletions in alpha-globin genes. While this technique effectively identifies the most prevalent mutations, it cannot detect rarer deletions or point mutations. Advanced molecular techniques such as next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA) could provide a more comprehensive understanding of the molecular spectrum of α-thalassemia by detecting less common mutations.

Conclusion

Our study provides critical insights into the molecular spectrum and distribution of alpha-thalassemia mutations in the Denizli region. The identification of four different deletions and eight genotypes highlights the genetic diversity of alpha-thalassemia in this region. Our findings are consistent with previous studies conducted in other parts of Türkiye, with the -α3.7 deletion being the most prevalent mutation. The correlation between genotype and hematological indices emphasizes the importance of molecular analysis in the accurate diagnosis and clinical management of α-thalassemia.

This study serves as a foundation for future research on α-thalassemia in Türkiye, particularly in regions where data is scarce. Expanding molecular analysis with more advanced techniques, such as NGS and MLPA, and increasing the study population size will provide a more comprehensive understanding of the alpha-thalassemia mutation spectrum.

Additionally, the integration of genetic screening programs and improved genetic counseling strategies based on regional mutation profiles can contribute to better disease management and prevention efforts. Future studies should focus on identifying rarer mutations and exploring their clinical implications to enhance our understanding of alpha-thalassemia in Türkiye and beyond.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval for this study was received from Pamukkale University Non-invasive Clinical Research Ethics Committee (decision no: E-60116787-020-657799, date: 19.02.2025).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.A., T.D., Concept: D.K., T.U.E., N.A.A., T.D., Design: D.K., Data Collection or Processing: D.K., T.U.E., Analysis or Interpretation: D.K., T.U.E., T.D., Literature Search: D.K., T.D., Writing: D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Two Rare Clinical Spectrums in a Hodgkin Lymphoma Patient: Super-acute Tumor Lysis Syndrome and Syndrome of Inappropriate Antidiuretic Hormone

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ABSTRACT

Tumor lysis syndrome (TLS) can be seen in hematological malignancies before and during treatment. Rapid tumor cell lysis by chemotherapy causes electrolyte abnormalities in patients, which can lead to organ failure and death. We aimed to present a case of a patient with super-acute TLS, which is not an expected finding in Hodgkin lymphoma patients. A 44-year-old male patient was admitted to the infectious diseases ward due to a fever of unknown origin. He had complaints of periodically recurring fevers, night sweats, fatigue, and weight loss for the last year. Excisional lymph node biopsy was performed because of the patient's B symptoms and multiple lymphadenopathy. The patient's excisional lymph node biopsy was reported as Classical Hodgkin lymphoma, mixed cellular type. Standard Hodgkin lymphoma chemotherapy: adriamycin-bleomycin-vinblastine-dacarbazine was planned after staging. However, the patient developed clinical and laboratory superacute TLS after bleomycin and vinblastine treatment. The patient could not receive adriamycin and dacarbazine treatment. The patient experienced a deterioration in general condition and seizures. During the follow-up, vinblastine-associated syndrome of inappropriate antidiuretic hormone was also observed while waiting for the general condition to improve before starting chemotherapy again. Both clinical conditions, which are rarely seen in patients with Hodgkin lymphoma, are potentially fatal. Treating physicians should be alert to the many manifestations of this potential Hodgkin lymphoma sequela.

Keywords: Hodgkin lymphoma, super-acute tumor lysis syndrome, inappropriate antidiuretic hormone syndrome

Introduction

One metabolic problem that might occur after starting cancer treatment is tumor lysis syndrome (TLS). Rapid tumor cell lysis causes metabolic abnormalities such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which can result in severe renal impairment, cardiac arrhythmia, seizures, and death [1,2]. In patients with hematological and other malignancies, oncologic emergency encounters are among the situations that result in mortality [3]. Chemotherapy or spontaneous cytolysis of malignant cells is two possible causes [4,5]. Hematological malignancies such as lymphoma and leukemia are most commonly linked to TLS [4,6,7]. On the other hand, hyponatremia, a common electrolyte disease, is frequently caused by the syndrome of inappropriate antidiuretic hormone (SIADH) in oncologic patients. Chemotherapy drugs are among the causes of SIADH. A few documented examples currently link vinorelbine to SIADH [8,9]. In this study, we aim to present a case of a Hodgkin lymphoma patient who developed TLS immediately after vinblastine and bleomycin treatment. Additionally, our patient developed SIADH after vinblastine treatment. Only 1-2 cases of TLS have been reported in the literature in Hodgkin lymphoma patients. We aimed to present this case because Hodgkin lymphoma patients rarely experience super-acute TLS findings.

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Case Report

A 44-year-old male patient was admitted to the department of infectious disease with an unknown fever. He had fevers recurring periodically over the last year, accompanied by night sweats, fatigue, and weight loss. The painless swelling on his neck had been gradually growing for a year. Its size gradually grew throughout the few weeks before the presentation. In his past medical history, he had a history of hypertension only. When asked about his family history, it was learned that his mother had Hodgkin lymphoma. On physical examination, fixed painful lymphadenopathy (LAP) was detected, measuring approximately 2 cm in the left cervical chains and extending to the supraclavicular region. Laboratory tests revealed C-reactive protein 171 mg/L, ferritin 2000 ng/mL, hemoglobin 10.7 g/dL, leukocyte $11x10^3/mm^3$, neutrophil $8x10^3/mm^3$, platelet $173x10^3/mm^3$, and lactate dehydrogenase level 335 U/L. Contrast-enhanced neck magnetic resonance imaging revealed multiple lymph nodes in the left cervical chain, the largest of which was at level 4, (13x10 mm in size), some round in appearance, and with increased cortical thickness. Due to the patient's B symptoms and multiple pathological LAP, an excisional lymph node biopsy was performed with the preliminary diagnosis of lymphoma. The patient's excisional LAP biopsy revealed the following histomorphological and histochemical findings: high Ki-67 index, Epstein-Barr virus positive, CD30, CD15, PAX 5 (faint), BCL6 (weak) positive, compatible with 'Classical Hodgkin lymphoma, mixed cellular type'. The patient underwent bone marrow aspiration and biopsy for staging purposes, and positron emission tomography/computed tomography (PET/CT) was performed. On PET/CT, lymph nodes measuring 13x10 mm in size and showing fluorodeoxyglucose (FDG) uptake [maximum standardized uptake value (SUV_{max}) 6.60] were observed in the left upper, middle, and lower cervical regions. Lymph nodes measuring 11×10 mm with FDG uptake (SUV_{max} 5.08) were observed in the left supraclavicular region adjacent to the left thyroid lobe. Lymph nodes measuring 27×16 mm in size and showing FDG uptake (SUV_{max} 11.64) were observed in the abdomen adjacent to the liver hilum and the paraaortic and paracaval regions. Focally increased FDG uptake was observed in the spleen (SUV_{max} 12.09). The patient was evaluated as stage IIIBS as depicted in Figure 1. After echocardiography, adriamycin, bleomycin, vinblastine, and dacarbazine treatment was planned for the patient. The patient had a seizure immediately after receiving vinblastine and bleomycin treatment, and developed TLS. Although the patient was started on allopurinol for TLS prophylaxis a few days before the start of chemotherapy, acute TLS was observed. Adriamycin and dacarbazine treatments could not be given. In biochemical findings, uric acid reached 17 mg/dL, creatinine 3.5 mg/dL, potassium 6 mmol/L, calcium 6 mg/dL, and phosphorus 12 mg/dL (Table 1). The patient was given rasburicase and supportive treatment. The patient's renal function tests and electrolytes returned to normal during follow-up. Hemodialysis treatment was not required. However, the patient was admitted to the intensive care unit with a sodium level of 105 mEq/L and a potassium level of 2 mmol/L as depicted in Figure 2. At the same time, the patient developed high creatinine levels again. The patient was initially considered to have SIADH due to vinblastine treatment. The patient was treated with isotonic saline and hypertonic saline. Close monitoring of fluid intake and output was performed. Fluid intake was restricted, and tolvaptan treatment was applied. The patient's serum sodium value reached 131 mEq/L after 4-5 days. We present this case because TLS is rarely seen in Hodgkin lymphoma.

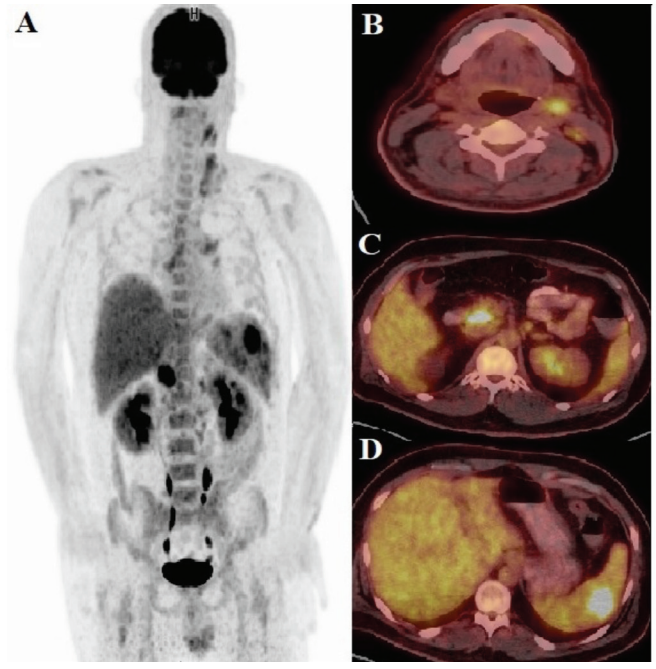

Figure 1. ^{18}F-FDG PET/CT maximum intense projection images (A) and transaxial fusion PET/CT images showed intense uptake of supra-diaphragmatic (B), infra-diaphragmatic (C) lymph nodes, and splenic nodal lesions (D) with increased ^{18}F-FDG uptake
^{18}F-FDG PET/CT: Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography

Table 1. Biochemical findings after vinblastine and bleomycin treatment

Parameters	The patient's baseline values	Laboratory values within minutes after vinblastine and bleomycin treatment	Reference value
Creatinine (mg/dL)	0.82	3.5	0.7-1.2
Urea (mg/dL)	34	112	16.6-48.5
Calcium (mg/dL)	8.1	6	8.6-10.5
Phosphorus (mg/dL)	2.3	12	2.5-4.5
Uric acid (mg/dL)	4.1	17	3.4-7

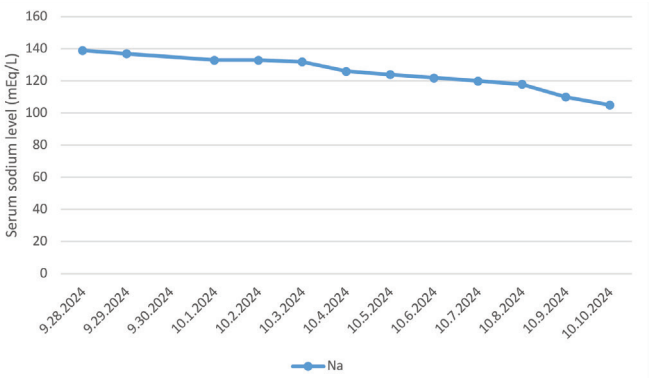

Figure 2. Serum sodium levels in the patient's follow-up after vinblastine and bleomycin treatment

Discussion

There are no universally validated diagnostic criteria or categorization system for TLS, even though it is generally agreed that a broad range of metabolic problems can arise in fast-growing neoplasms following the commencement of anticancer therapy. One kind of TLS that is characterized by biochemical alterations without clinical symptoms is laboratory-defined TLS. Severe metabolic disturbances might occur in patients without any symptoms. These need to be treated. Clinical TLS is characterized by manifestations of metabolic alterations requiring immediate treatment [1]. Some chemotherapy agents also have a higher risk of causing TLS. A recent study by Li et al. [10] reported that 164 antineoplastic agents precipitated TLS. Overall, rituximab was the most commonly reported antineoplastic agent in TLS reports, followed by cyclophosphamide, venetoclax, doxorubicin, and etoposide. TLS is more common in high-grade non-Hodgkin lymphoma (NHL) and acute leukemia. The following results from studies on children and adults in various facilities lend credence to this. To ascertain the frequency of TLS, Wasim et al. [11] examined 50 patients with hematologic malignancies. They found that acute leukemia, NHL, and chronic leukemia incidences were 14%, 4%, and 2%, respectively. Previous research has indicated that both elevated cytokine levels and heat cause tumor cell death. Patients with greater tumor sizes are at a higher risk [12]. Suzuki et al. [13] reported a case of super-acute onset of TLS accompanied by hypercytokinemia during treatment of Hodgkin's lymphoma with ABVD chemotherapy. It was reported that the patient developed a seizure within minutes of chemotherapy. Hypercytokinemia occurred with TLS, which led to pyrexia, convulsion, and loss of consciousness [13]. Similarly, in the case we presented, biochemical changes and clinical deterioration of the patient were observed within minutes after vinblastine and bleomycin treatment. Our patient also developed a seizure while neurological findings were observed. TLS is a rare clinical entity in Hodgkin lymphoma cases. According to reports, hypercytokinemia can occasionally accompany TLS [14]. Cancer chemotherapy (particularly in the treatment of hematologic malignancies) and several severe conditions (such as sepsis and trauma) can cause hypercytokinemia, which causes an overactive inflammatory response [15,16]. Recently, Hassan et al. [17] reported spontaneous TLS in a 7-year-old girl with Hodgkin lymphoma. The patient's condition deteriorated suddenly during his hospital stay for further work-up and treatment. Laboratory reports showed biochemical abnormalities confirming spontaneous TLS. He recovered completely with prompt stabilization and correction of electrolyte abnormalities. Spontaneous TLS is reported to be a life-threatening condition rarely seen in Hodgkin lymphoma patients [17]. The risk of developing spontaneous TLS is higher in patients with large tumors, high pretreatment uric acid levels, prior renal disorders, exposure to nephrotoxins, oliguria, acidic urine, and dehydration [18]. No risk factor increased the risk of developing TLS in our patient. Moreover, highly acute TLS was observed to have developed following the administration of only 2 of the 4 drugs included in the chemotherapy protocol.

The patient was observed to have SIADH related to vinblastine. Hyponatremia, a common electrolyte disorder, is frequently caused by SIADH in oncologic patients. Chemotherapy drugs are among the several causes of SIADH. Three examples linking vinorelbine to the SIADH have been described, according to Hoang et al. [8]. Garrett and Simpson [9] reported that vinorelbine was being administered to a 50-year-old Caucasian woman who had a history of advanced breast cancer and had not responded to various forms of treatment. Within seven days, blood chemistries showed significantly reduced potassium and salt concentrations compared to a normal baseline. Hyponatremia was verified by a follow-up blood chemistry analysis. After being brought to the hospital, the patient received treatment for SIADH. Non-steroidal anti-inflammatory drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, alkylating agents, platinum compounds, and vinca alkaloids are among the pharmacological types that can cause SIADH. Vinorelbine, a semisynthetic vinca alkaloid, is a member of the same class as vincristine and vinblastine. These compounds function by preventing the development of microtubules, which are essential for cell division. Within this class, SIADH is known to be induced by vincristine and, to a lesser extent, vinblastine [9,19]. We propose that this case will contribute to the literature. There are only a few cases in the literature that have reported TLS in Hodgkin lymphoma. Treatment with adriamycin, bleomycin, vinblastine, and dacarbazine was planned for this patient. However, since the patient developed TLS only after vinblastine and bleomycin treatment, adriamycin and dacarbazine treatment could not be applied. The patient also has SIADH after vinblastine treatment, which is a rare finding.

Conclusion

In conclusion, super-acute TLS in the case of Hodgkin's disease is a rare phenomenon. TLS is rare, but if it develops, it carries a high risk of poor clinical outcomes. Hypercytokinemia occurs in TLS, which can lead to symptoms such as fever, convulsions, and loss of consciousness, as observed in our patient. Often, the vague and non-alarming nature of the complaints makes it difficult to diagnose this easily treatable condition,

potentially leading to a series of fatal outcomes. This case report aims to draw the attention of general physicians to the rare but important occurrence of super-acute TLS in cases of Hodgkin's lymphoma. Hypercytokinemia occurs in TLS, which can lead to symptoms such as fever, convulsions, and loss of consciousness, as observed in our patient. Regular monitoring of sodium levels during vinorelbine treatment allows clinicians to improve the quality of life for patients, and take action before serious neurological problems of SIADH appear.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.Ç., Z.H., Concept: R.Ç., H.Ö., Design: R.Ç., Data Collection or Processing: R.Ç., Z.H., Analysis or Interpretation: R.Ç., H.Ö., Literature Search: R.Ç., Writing: R.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Malar Fat Pad Flap for the Reconstruction of the Orbit: Case Report

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ABSTRACT

Sebaceous carcinomas are rare malignant tumors of the eyelid. For defects of the orbit, the temporal muscle/fascia and peri-cranial flaps are the preferred options. However, these flaps require extensive dissection, leave obvious scars, and pose a risk of injury to the peripheral nerves. Malar fat flap (MFP) has not been previously described for the reconstruction of the orbital defects. In this paper, we aimed to present a case with an orbital defect after sebaceous carcinoma resection. The MFP was dissected laterally and inferiorly and then rotated superolaterally to fill the defect. The upper and lower eyelids were fixed to the lateral orbital rim to mimic the lateral canthus. No additional scar was created. The magnetic resonance imaging revealed good flap viability after 2 years. The flap was oncologically safe; no recurrence was reported during the 2-year follow-up period. Pedicled MFP offers a reliable and safe option for minor defects of the orbit.

Keywords: Fat pad, orbit, reconstruction, sebaceous gland neoplasms, pedicled flap

Introduction

Reconstruction of orbital soft tissue includes several options. The temporalis muscle flap is one of the most preferred flaps for this purpose [1]. Other popular flaps include the pericranial flaps in which the galea and periosteum are delivered into the orbit [2]. Although these flaps are useful, they require extensive dissection and pose a risk of injury to the peripheral nerves [3].

The malar fat pad (MFP) has a triangular shape with its base at the nasolabial fold and its apex at the malar eminence. It is situated between the skin and the superficial musculoaponeurotic system (SMAS). It is loosely attached to the SMAS and firmly attached to the skin [4]. Like other fat pads of the face, the MFP has its own blood supply that comes from perforator vessels [5]. To our knowledge, the MFP flap has not been used as a pedicled flap to reconstruct lateral defects of the orbit. In this article, we aimed to present a case of orbital reconstruction with a pedicled MFP flap after the resection of sebaceous gland carcinoma.

Case Report

An 83-year-old female patient was admitted to our clinic with the complaint of a mass around the right eye (Figure 1A). At physical examination, a 4x2 cm mass with ulceration and small bleeding foci was located at the lateral border of the orbit. Magnetic resonance imaging (MRI) revealed a solid mass lesion of heterogeneous character, filling the anterolateral side of the globe. The mass extends towards the extraconal fatty tissue lateral to the right globe. At this level, no distinction could be made between the right lateral rectus muscle and the mass (Figure 2A). The upper and lower eyelids were incised next to the mass and retracted superiorly and inferiorly, respectively. By performing subperiosteal dissection, the mass was resected. The involved lateral margins of the eyelids, the lacrimal gland, and the lateral rectus muscle were also resected (Figure 1B). The lateral and lower orbital borders were revealed. The dissection was continued to the posterior border of the globe. The resulting defect had dimensions of approximately 4 by 1.5 cm, exposing the medial wall of

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the zygomatic bone, the superior border of the maxillary bone, the inferior border of the frontal bone, and the lateral border of the globe. Mohs frozen sections revealed negative surgical borders. The resulting defect was planned to be reconstructed with the pedicled MFP flap. In order to reach the MFP, the lower eyelid was retracted. Dissection beneath the subcutaneous tissues started from the superior edge of the flap. By elevating the skin, dissection continued laterally and inferiorly with the medial connection of the fat pad being preserved (Figure 1C). The flap had approximate dimensions of 6×2 cm. The infraorbital foramen formed the medial border of the dissection. Then, the flap was rotated superolaterally and inserted into the orbit (Figure 1, panel D). It was ensured that the flap rotated easily to avoid pressure on the pedicle. A few dissolving stitches were enough to stabilize the flap by fixing it to the remaining periosteum of the superior orbital rim (Figure 1D). To reconstruct the lateral canthus, the upper and lower eyelids were approximated and sutured to each other and to the bone of the lateral orbital rim. During early postoperative management, the patient received artificial tear drops 24 times daily for the first three days, then 12 times daily for a week, and antibiotic ointment 1 once daily for a week. Unfortunately, the patient did not attend her plastic surgery follow-up appointments; thus, we were unable to evaluate the functional outcomes. However, by accessing her oncological follow-up records, we found that in the second postoperative year, MRI revealed normal fatty tissue on the lateral side of the globe without any signs of pressure (Figure 2B). Her records revealed no recurrence during the two-year follow-up period.

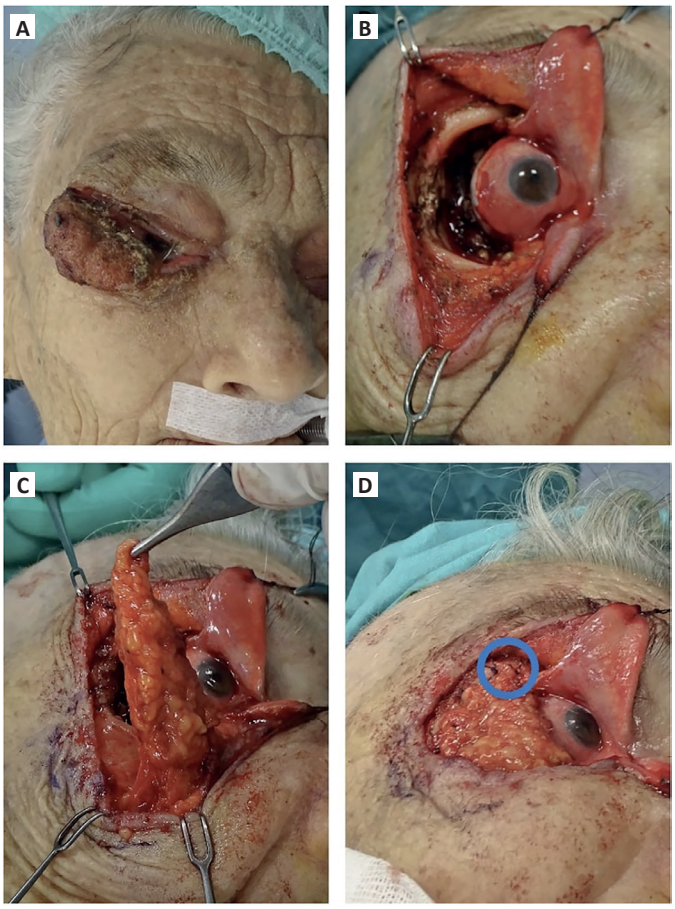

Figure 1. A) The preoperative view of the mass, B) The resulting defect after the excision of the mass, C) The pedicled MFP flap after being dissected. Note the rotation arc of the flap, D) Fitting the MFP flap into the defect. Red cycle indicates the stitches that were used to stabilize the flap by fixing it to the periost of the superior orbital rim
MFP: Malar fat flap

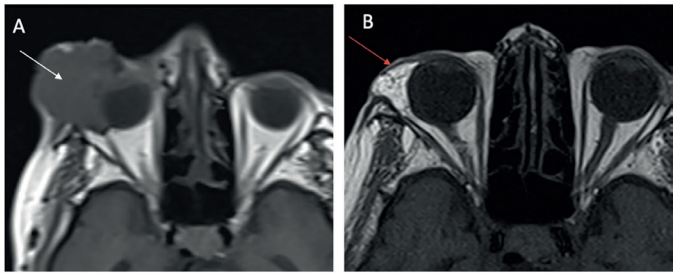

Figure 2. A) MRI revealing a mass at the anterolateral aspect of the right globe. White arrow indicates the mass, red arrow indicates the flap, B) Postoperative 2nd year MRI revealing a healthy fatty tissue (MFP flap) without any sign of pressure or fibrosis
MRI: Magnetic resonance imaging, MFP: Malar fat flap

Discussion

Facial fat pads are generally used for aesthetic procedures. They can be resected, transferred, or modified to obtain the desired shape and volume. MFP is often modified during lower blepharoplasty or midface lift procedures to enhance the aesthetic appearance [6]. Another example is Bichat's fat pad, which is generally resected in aesthetic operations to provide the cheeks with a thinner shape [7]. However, Bichat's fat pad is also the most preferred facial fat pad for reconstructive procedures. This is because Bichat's fat pad has a stable anatomy, a dominant vascularization, and can be transferred easily to cover intraoral defects [8].

With age, the MFP tends to move downward due to gravity. In the aesthetic procedures, this fat pad is dissected and elevated in the upward direction without any morbidity in the donor area [9]. In the technique we used, the fat pad was also dissected and elevated upward with a minimal donor area morbidity. Larger flaps may be preserved for large defects such as those resulting from enucleation procedures. In the case we present, the eyeball was not involved in the carcinoma invasion. Thus, the resulting defect was not large enough to require a larger flap. As observed from the MRI scan, the utilized flap provides an optimal volume that fits the defect very well. Moreover, the globe is originally surrounded by fatty tissues. Thus, reconstructing defects that are in close proximity to the globe using fatty tissues will provide more natural results.

Based on the localization, dimensions, and rotation arc of the flap, we can conclude that this flap is suitable for mild (2-5 cm) soft tissue defects that are located at the lower or lateral borders of the orbit. The flap is also suitable for covering exposed bone of the lower orbital rim, as reported in a case of SOOF flap [10]. Muscle flaps tend to develop fibrosis, which is not suitable for mobile parts of the body, such as the globe [11]. Fat flaps provide a more flexible bed for the mobile globe.

In our case, MRI findings revealed healthy fatty tissue without any signs of pressure or fibrosis. On the other hand, since the flap was dissected from the same incision, no additional scar was created. In contrast to other fat pads, such as Bichat's fat pad, the vascularization of MFP, is not well documented. Circulation in the relevant area is thought to be supplied by the branches of the transverse facial artery, internal maxillary artery, and angular vessels without a defined predominance [5].

In our case, the MFP flap was designed to be medially based. The MRI revealed good flap viability after two years. This may indicate that the MFP flap has a vascular supply through the angular artery. The simplicity of this flap makes it a good choice for defects that don't involve the globe. In our case, the remaining skin was used to cover the top of the flap. However, in cases where large skin excision is required, split-thickness skin grafts may be considered. The flap was oncologically safe. During the two-year follow-up period, no recurrence was reported.

Conclusion

Pedicled MFP flap is reliable and safe for use in small and minor defects of the orbit. In this technique, the flap can be delivered from the lower eyelid without any additional incisions. The flap has a wide rotation arc, which makes it suitable for both lower and lateral orbital regions.

Ethics

Informed Consent: The consent form was filled out by the participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.D., Concept: M.D., Design: M.Z., M.D., S.K., Data Collection or Processing: M.Z., Literature Search: M.Z., S.K., Writing: M.Z., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

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Acquired Hemophilia Developing After Whipple Operation

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ABSTRACT

Acquired hemophilia A (AHA) is a rare bleeding disorder. It is caused by autoantibodies produced against endogenous coagulation factors, without a family history of hemophilia. The incidence has been reported as 1.4 per million. The patients we see in the clinic are similar to those with hemophilia A and have a serious risk of bleeding, especially soft tissue, gastrointestinal, or mucocutaneous bleeding. The most important complication in hemophilia A cases is inhibitor development. Bypassing agents are the first choice in the treatment of AHA. In this case report, we present a patient who developed AHA after periampullary surgery.

Keywords: Acquired hemophilia, postoperative period, pancreaticoduodenectomy

Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder. It is caused by autoantibodies produced against endogenous coagulation factors [most commonly against factor VIII (FVIII)] without a family history of hemophilia [1]. The incidence has been reported as 1.4 per million. Typically, autoantibodies show a biphasic distribution, with peaks at 20-30 years of age, due to the effect of postpartum inhibitors, and at 68-80 years of age. Eighty-five percent of the patients are over 60 years of age, and age is associated with poor prognosis. It is observed equally in both sexes, except for a higher prevalence in females due to the effect of pregnancy between the ages of 20-40 [2]. The patients we see in the clinic are similar to hemophilia A and have a serious risk of bleeding, especially soft tissue, gastrointestinal or mucocutaneous bleeding. Hemarthrosis-type hemorrhages seen in hemophilia are not common [3]. Mortality in AHA varies between 9.7% and 33%. It causes varying levels of prolonged activated partial thromboplastin time (aPTT), which does not improve with normal plasma addition. In this study, we presented a rare case of AHA diagnosed in a patient who developed soft tissue bleeding two weeks after undergoing the Whipple procedure for a periampullary tumor.

Case Report

A 72-year-old male patient presented to our clinic with the complaints of loss of appetite and jaundice. The patient underwent distal subtotal gastrectomy due to gastric ulcer 42 years ago, and total gastrectomy (remnant gastric Ca) due to gastric cancer 13 years ago. There was no bleeding disorder in his history. There was jaundice throughout the body. Laboratory findings revealed obstructive jaundice, and imaging revealed dilated intrahepatic bile ducts in both lobes. The common bile duct was wider than normal, and a mass was observed at its distal end. Pre-operative coagulation tests were normal. In addition, admission hemoglobin was 7.5 g/dL. The patient who underwent the Whipple procedure developed an unexplained bleeding halfway through the surgery, which lasted 4 hours. After his bleeding was controlled, erythrocyte replacement and fresh frozen plasma replacement were performed in the perioperative period. Moreover, vitamin K and tranexamic acid were administered. No bleeding findings were observed in the patient followed up in the postoperative intensive care unit. A hematoma that started in the inguinal region on postoperative day 14 and gradually spread to the scrotum was observed (Figure 1). Despite replacing two units of packed red blood cells and fresh frozen plasma daily for three days, hemoglobin levels continued to decline, and hematoma persisted. After consulting

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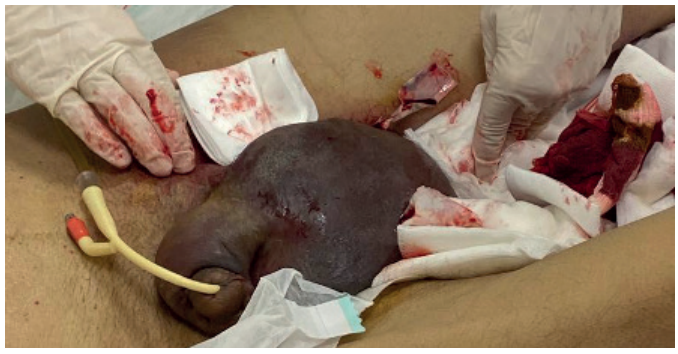

Figure 1. A hematoma that started in the inguinal region on postoperative day 14 and gradually spread to the scrotum

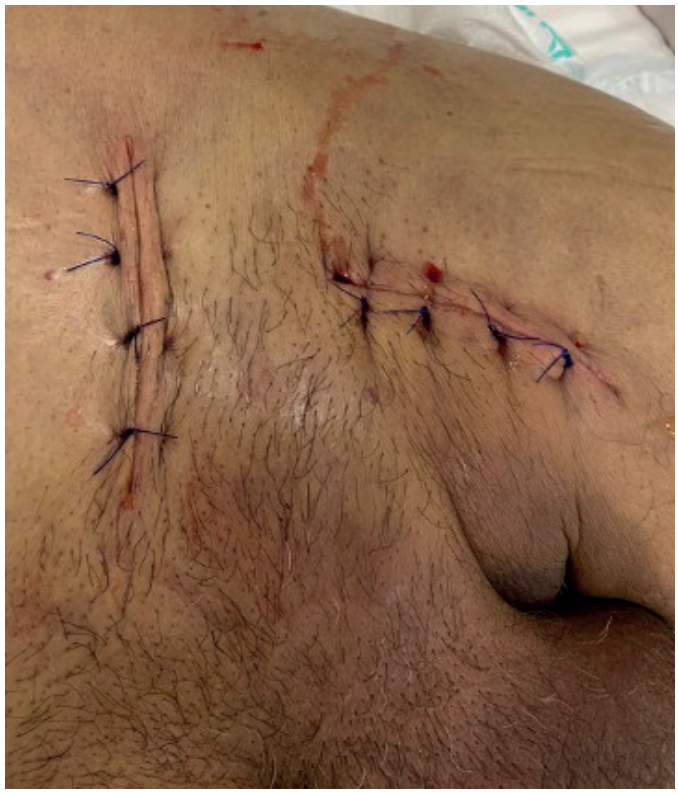

Figure 2. Drained image of a hematoma in the inguinal region

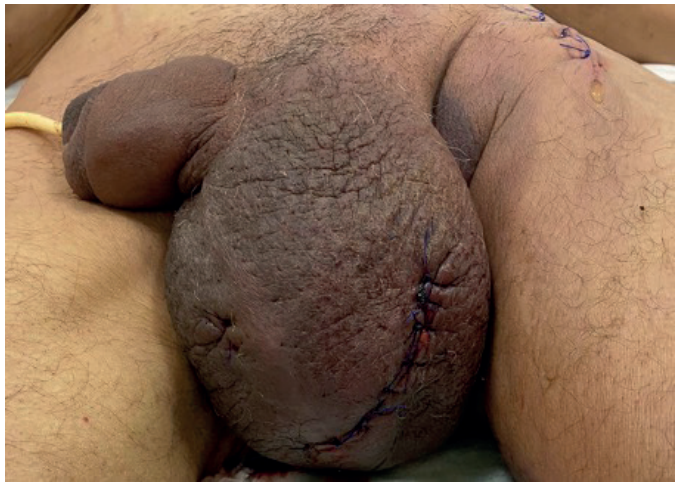

Figure 3. Drained hematoma in the scrotum

a cardiovascular surgeon, the medical team linked a blood gas sample taken from the femoral vein or artery to hematoma. The patient was taken to surgery in collaboration with the cardiovascular surgery department. The femoral vein and the artery were dissected. However, no active bleeding focus was detected. In the same session, the hematoma in the inguinal region and the scrotum was drained. The wound lips were left open, and a perineal drain was placed (Figure 2). During our follow-up, bleeding and a decrease in hemoglobin levels continued. In the patient, who was referred to hematology, the bleeding profile was evaluated. In the coagulation tests, aPTT was found to be prolonged. No improvement was detected in aPTT with the mixing test. Acquired hemophilia was thought to be a rare condition. Recombinant VIIa (activated eptacog alfa) at a dose of 90 mcg/kg was initiated and continued until hemostasis control was achieved. No active bleeding was observed 6 hours following the treatment. No decrease was observed in hemoglobin during the hemogram follow-up. Methylprednisolone was initiated at a dose of 1 mg/kg/day. The patient was discharged with steroid treatment (Figure 2, 3).

Discussion

AHA is a rare bleeding disorder. It is caused by autoantibodies produced against endogenous coagulation factors, most commonly against FVIII, in the absence of a family history of hemophilia. Isolated and long-term aPTT is often the first clue, and recognition of this feature is the key to the diagnosis of AHA [4]. Mixing normal pooled plasma with the patient's plasma by a 1:1 ratio and finding no improvement in aPTT values suggests the presence of an inhibitor. The patients we see in the clinic are similar to hemophilia A and have a serious risk of bleeding, especially soft tissue, gastrointestinal or mucocutaneous bleeding. Most of the cases are idiopathic (50%), while the remainder is associated with malignancy, autoimmune disorders, or seen in the postpartum period [5]. The mortality rate is approximately 7.9-22%, and these patients die within one week after the first symptoms develop [6-8]. The definitive treatment of AHA involves the destruction of the autoantibody through immunosuppression; however, since patients are at risk of severe and fatal bleeding (mortality rate 9-22% in case series), hemostatic treatment is required to treat the bleeding until eradication therapy is successful. The most commonly used treatment strategy achieves complete remission in approximately 70-80% of the patients, consists of steroids and cyclophosphamide [9]. For hemostatic treatment, rFVIIa or plasma derivatives (APCC) from bypassing agents should be used as the first-line therapy [10]. In case 1, bleeding was limited to the soft tissue. In our case, there was coexistence with malignancy.

Conclusion

AHA is a rare disease, but it should be considered in cases of any sudden, unexpected bleeding of any location or severity following surgery, especially, if aPTT is elevated and does not improve with the mixing test.

Ethics

Informed Consent: The consent form was filled out by the participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A., İ.H., Concept: İ.H., Design: İ.H., Data Collection or Processing: N.A., Analysis or Interpretation: N.A., Literature Search: N.A., Writing: N.A., İ.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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