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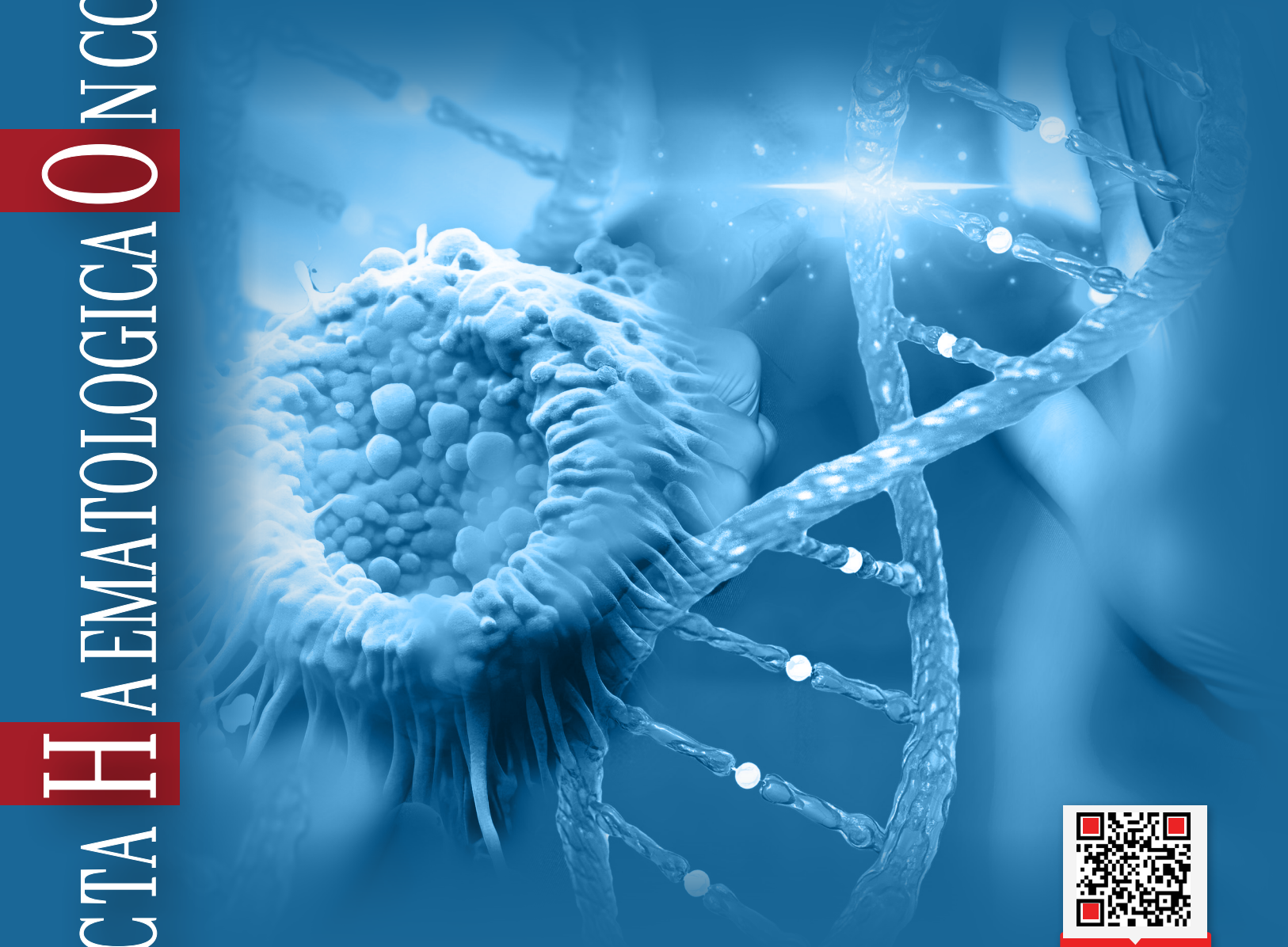

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Review

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Current Status and Future Perspectives of Immunotherapies in Bladder Cancer

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ABSTRACT

Bladder cancer exhibits a broad spectrum of progression, ranging from early stage to metastatic disease. Approximately 75% of newly diagnosed patients present with non-muscle-invasive bladder cancer, while the remaining 25% have muscle-invasive bladder cancer or metastatic disease. The prognosis of advanced urothelial carcinoma is poor, with more than 90% of patients succumbing to metastatic disease within five years of diagnosis. In recent years, the role of immunotherapies, particularly immune checkpoint inhibitors, in the treatment of bladder cancer has become increasingly recognized. This review aims to evaluate the current status of immunotherapies in bladder cancer and their future potential.

Keywords: Bladder cancer, checkpoint inhibitors, immunotherapy

Introduction

According to global data, bladder cancer is one of the most common urological malignancies worldwide [1]. Although most patients are diagnosed with the superficial or non-muscle-invasive form, it can also present as muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer (MBC). Unfortunately, MIBC and metastatic stages are associated with a high risk of mortality. Spanning a broad spectrum from non-invasive bladder cancer to the metastatic stage, this disease necessitates different treatment approaches. While surgical intervention, intravesical therapy, radiotherapy (RT), and chemotherapy (CT) are among the treatment options for bladder cancer, a growing understanding of immunological mechanisms in recent years has positioned immunotherapy as an important treatment alternative. Immunotherapies are utilized both to prevent tumor recurrence in early-stage disease and to control tumor progression in more advanced stages. The primary objective of immunotherapies is to enhance the natural response of the immune system against cancer cells. In particular, immune checkpoint inhibitors (ICIs) offer potential benefits not only in metastatic disease but also in early-stage bladder cancer. Notably, Bacillus Calmette-Guérin (BCG), which has been used in bladder cancer treatment for decades, is considered the gold standard for non-invasive bladder cancer therapy, highlighting the efficacy of immunotherapies. Immunotherapy is employed either as monotherapy or in combination with CT, and its role in intravesical therapies is being investigated, with promising results. This review comprehensively examines the current status of immunotherapies for bladder cancer and their potential future applications based on relevant clinical studies.

Bladder Cancer Staging

The staging of bladder cancer is crucial for assessing prognosis and determining appropriate treatment strategies. The tumor, node, metastasis classification, recommended by the World Health Organization and the American Joint Committee on Cancer, is considered the gold standard for bladder cancer staging. The T classification of bladder cancer is divided into two main categories: non-invasive and invasive. Non-invasive bladder cancer is typically confined to the superficial

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epithelium and includes a papillary tumor (Ta) and carcinoma *in situ* lesions. Invasive bladder cancer, on the other hand, encompasses stages in which the tumor infiltrates the muscle layer of the bladder wall (T2) and beyond, including perivesical invasion (T3) and spread to adjacent organs (T4). In addition, regional lymph node involvement (N1-3) and distant metastasis (M1) were evaluated. Tumors with muscle invasion exhibit a more aggressive course and generally require multimodal treatment.

Non-muscle Invasive Bladder Cancer Treatment

Bacillus Calmette-Guérin

BCG therapy is the standard treatment for non-muscle-invasive bladder cancer (NMIBC). BCG is a live-attenuated strain of *Mycobacterium bovis* and is used to reduce the risk of bladder cancer recurrence and its progression to a more invasive disease [2]. BCG is administered following transurethral resection of the tumor and is generally recommended for patients with high-risk NMIBC [2,3]. BCG therapy is rarely associated with significant side effects, such as sepsis and allergic reactions [4]. In the NIMBUS trial, reducing the standard dose and frequency of BCG administration was evaluated and found to be less effective than the standard regimen [4].

BCG resistance poses a significant challenge for the treatment of NMIBC. In BCG resistant cases, radical cystectomy is generally the recommended treatment approach. However, considering the high morbidity associated with this surgical procedure and its impact on patients' quality of life, there is a growing need for alternative treatment strategies. Alternative therapeutic options include intravesical CT, immunotherapy, antibody-drug conjugates, device-assisted therapies, gene therapy, RT [5]. Emerging treatment modalities offer promising outcomes for BCG-resistant patients and enable the development of bladder-sparing strategies. Ongoing research in this field aims to expand the treatment options and improve disease outcomes.

Immunotherapy Treatment Options in Bacillus Calmette-Guérin-resistant Bladder Cancer Immune Checkpoint Inhibitors

Various immunotherapy options are available for the treatment of NMIBC in BCG-resistant patients. ICIs play a significant role in the management of bladder cancer [3]. In the KEYNOTE-057 trial, intravenous pembrolizumab demonstrated efficacy with a complete response (CR) rate of 40.6% and a median response duration of 16.2 months, leading to Food and Drug Administration approval [3,6,7]. Common adverse events include pruritus, fatigue, and diarrhea, whereas high-grade adverse effects are rare (12.7%) [8]. In a SWOG S1605 trial, intravenous atezolizumab demonstrated a 6-month response rate of 27%. While its safety profile was similar to that of pembrolizumab, treatment-related serious adverse events were observed in 16% of patients [9]. In a study conducted by Sekino et al. [10], the combination of intravenous atezolizumab and RT was evaluated. Initial results suggest that RT may have a synergistic effect with immunotherapy. In a study conducted by Fragkoulis et al. [11], intravesical durvalumab reduced recurrence rates, and adverse effects generally did not disrupt the treatment process. In the CheckMate 9UT trial, the investigation of nivolumab as monotherapy and in combination with an indoleamine 2,3-dioxygenase (IDO-1) inhibitor is ongoing [12]. Table 1 provides a detailed overview of immunotherapy studies in NMIBC patients.

Gene Therapies and Oncolytic Viruses

Gene therapies and oncolytic viruses are being explored as novel approaches in the treatment of NMIBC. Oncolytic viruses such as nadofaragene firadenovec and CG0070 have demonstrated favorable efficacy with no significant adverse effects reported [3]. These therapies offer organ-preserving strategies, potentially improving patients' quality of life [13].

Interleukins and Other Immune Modulators

Interleukin-based therapies, particularly interleukin-15 and ALT-803, are currently being investigated for the treatment of NMIBC. These therapies aim to enhance the immune system, promoting a more effective response against tumor cells [3,6].

Non-metastatic Muscle Invasive Bladder Cancer Neoadjuvant Treatment

MIBC is an aggressive malignancy often characterized by early and distant recurrences. Cisplatin-based combination regimens are commonly used as neoadjuvant CT before radical cystectomy, providing overall survival (OS) and disease-free survival (DFS) benefits [14]. However, ICIs have revolutionized the treatment of metastatic urothelial carcinoma (mUC) and are now being investigated in the neoadjuvant setting [14,15].

In the ABACUS phase 2 trial, atezolizumab was administered as neoadjuvant therapy in cisplatin-ineligible patients with MIBC. A pathological CR (pCR), was observed in 31% of the patients, and the analysis of 2-year survival revealed a DFS of 68% and an OS of 77% [16]. In another study, atezolizumab combined with CT was tested in cT2-4aN0M0 patients who received neoadjuvant gemcitabine, cisplatin, and atezolizumab. With the combination treatment, 69% of patients achieved NMIBC (<pT2N0) and 41% achieved pCR. In the same study, the low rate of PD-L1 positive tumors limited the use of PD-L1 as a predictive marker [17].

The PURE-01 phase 2 trial is an open-label study evaluating the efficacy of neoadjuvant pembrolizumab in MIBC. The study included clinical stage T2-4aN0M0 patients and investigated the administration of three cycles of 200 mg pembrolizumab before radical cystectomy. A pCR rate of 42% was achieved, and PD-L1 expression and high tumor mutation burden were found to be strongly associated with treatment response [18,19]. Three-year OS rate was 83.8%, while the event-free survival (EFS) rate was 74.4% [20]. The results of the KEYNOTE-905/EV-303 phase 3 trial, which is investigating the efficacy and safety of perioperative pembrolizumab alone or in combination with enfortumab vedotin (EV) in MIBC patients who are ineligible for or decline cisplatin-based therapy, have not yet been reported [21].

Table 1. NMIBC studies and patient characteristics

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
NIMBUS	2013-2019	Randomized phase 3 clinical trial	Ta/T1	Arm A: Standard BCG schedule (15 instillations) Arm B: Reduced frequency BCG schedule (9 instillations)	The reduced frequency schedule was found to be inferior to the standard schedule for recurrence prevention. - Hazard ratio: 0.40 (with an upper 97.5% confidence interval of 0.68) Due to these findings, further recruitment into the reduced frequency group was stopped early to prevent harm.
KEYNOTE-057 (NCT02625961)	2015-2018	Open-label, single-arm, multicenter, phase 2 study	CIS	Pembrolizumab	Primary result: - cCR ratio (40.6%; 95% CI: 30.7-51.1) - Thirty-nine (41%) of 96 BCG-resistant CIS patients showed onse at 3 months of treatment. Secondary results: - Rate of serious treatment-related side effects: 8% - Grade 3 or 4 side effects: 12.7% (most common: arthralgia 2%, hyponatremia 3%)
SWOG S1605 (NCT02844816)	2016-2023	Single-arm, phase 2 clinical trial	CIS/Ta/T1	Atezolizumab	Primary result: - pCR rate at 6 months in CIS patients: 27% (20/74 patients) Secondary results: - Median response time: 17 month - In 56% of responding patients (95% CI: 34-77), the response was sustained through 12 months - 18-month event-free survival rate in Ta/T1 patients: 49% (95% CI: 38-60) - Twelve of 129 patients progressed to intramuscular invasive or metastatic disease - TRAEs, grade 3-5: 16% (26 patients) - Treatment-related deaths: 3 patients
BPT-ART (RCT2031180060)	2019-Ongoing	Open-label, phase 2, multicenter clinical study	T1-3	Atezolizumab+radiotherapy	Initial results suggest that radiotherapy may have a synergistic effect with immunotherapy. The study is ongoing.
NCT03759496	2018-2024	Single-arm, phase 2 clinical trial	High-risk NMIBC patients who fail BCG therapy	Intravesical durvalumab	Primary result: - 1-year HGR-free survival rate: 39% (95% CI: 18-59) Secondary results: - 1st, 3rd, and 6th month HGR-free survival rate: - 70% (95% CI: 45-85) - 1. months - 55% (95% CI: 31-74) - 3. months - 39% (95% CI: 18-59) - 6. months - 1-year bladder integrity preservation rate: 78% (95% CI, 57-89) - Treatment-related adverse events: Only grade 1 hematuria (in 5 patients-17%)
CheckMate 9UT	2019-ongoing	Multi-arm, phase 2 clinical trial	High-risk NMIBC unresponsive to BCG	Arm A: nivolumab monotherapy Arm B: nivolumab+intravesical BCG combination Arm C: nivolumab in combination with other mesylate-based agents	Initial results show that nivolumab is well tolerated and safe. The study is ongoing.

cTNM: Clinical tumor, node, metastasis, BCG: Bacillus Calmette-Guérin, CIS: Carcinoma *in situ*, cCR: Clinical complete response, CI: Confidence interval, HGR: High-grade relapse, BPT-ART: Bladder preservation therapy-accelerated radiotherapy, SWOG: Southwest Oncology Group, NCT: National clinical trial (number), NMIBC: Non-muscle-invasive bladder cancer

The Oncodistinct 004-AURA phase 2 trial (NCT03674424) investigated the impact of neoadjuvant perioperative avelumab, in cisplatin-eligible and ineligible bladder cancer patients. In the cisplatin-eligible cohort, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) and CG (cisplatin+gemcitabine), regimens combined with avelumab demonstrated high DFS and OS rates at 12 and 36 months, with the ddMVAC-A combination showing particularly strong efficacy (36-month DFS and OS rates of 77% and 87%, respectively). Patients who achieved a pCR maintained high DFS rates up to 36 months. In the cisplatin-ineligible cohort, avelumab monotherapy yielded promising results, while the PG (paclitaxel+gemcitabine) combination did not provide additional benefit. Overall, neoadjuvant avelumab combinations significantly improved survival outcomes in cisplatin-eligible patients, whereas lower efficacy was observed in cisplatin-ineligible patients [22].

The NABUCCO trial is a phase 1b, single-arm clinical study evaluating the efficacy and feasibility of preoperative ipilimumab and nivolumab combination therapy in patients with locally advanced urinary tract cancer (stage 3). The study included 24 patients who were ineligible for or declined cisplatin-based treatment, and received ipilimumab plus nivolumab over 12 weeks before surgery. The pCR rate was 46%, reaching 50% in lymph node-negative patients. The treatment was found to be effective regardless of preoperative CD8+ T-cell density, with higher response rates observed in patients with high PD-L1 expression [23]. In a phase 2 study conducted by Kim et al. [24] in 2023, the efficacy and safety of neoadjuvant nivolumab combined with gemcitabine/cisplatin (N+GC) were evaluated in patients with MIBC. A total of 51 patients received 3-4 cycles of nivolumab (3 mg/kg) along with gemcitabine/cisplatin. The clinical CR rate was 59%, while the pCR rate was 24% in the overall cohort and 35% in patients who underwent radical cystectomy. Median DFS was not reached, with 12- and 24-month DFS rates of 90% and 73%, respectively. The treatment was generally well tolerated, and subgroup analyses showed that PD-L1 positivity (CPS >1%) was not associated with pCR. The results of the ENERGIZE trial (NCT03661320), which investigates the use of nivolumab and linrodostat mesylate, have not yet been reported [25].

The phase 3 NIAGARA trial, which evaluates the efficacy and safety of perioperative durvalumab, enrolled 1.063 patients who were randomized in a 1:1 ratio [26]. One group received durvalumab combined with gemcitabine and cisplatin, while the control group received standard gemcitabine-cisplatin CT. OS was 82.2% in the durvalumab arm compared to 75.2% in the standard CT arm [hazard ratio (HR): 0.68, p<0.001]. The addition of perioperative durvalumab to standard CT resulted in a statistically significant improvement in EFS and OS. Treatment-related serious adverse events were observed at similar rates in both groups (~40%) [26]. Additionally, the NEMIO trial (NCT03549715), which is evaluating the neoadjuvant effects of durvalumab and tremelimumab in MIBC, is ongoing and its results await publication [27]. Table 2 provides a detailed overview of the study characteristics and outcomes.

Adjuvant Treatment

Adjuvant therapy in MIBC is recommended by guidelines for patients with high pathological risk [28]. The use of adjuvant ICIs is being considered as an alternative approach to standard CT regimens due to their tolerability advantages. This treatment modality has the potential to provide an additional therapeutic option, particularly for cisplatin-ineligible patients. Moreover, adjuvant immunotherapy may be beneficial for patient groups with poor prognosis following neoadjuvant CT and radical cystectomy, where standard treatment protocols have not yet been clearly established [29].

The phase 3 IMvigor010 trial compared adjuvant atezolizumab monotherapy with observation in patients with muscle-invasive urothelial carcinoma (MIUC) who were at high risk after radical surgery. This included patients with ypT2-4a or ypN+ disease following neoadjuvant CT, as well as those who had not received neoadjuvant CT but had pT3-4a or pN+ disease [30]. In the IMvigor010 trial, circulating tumor DNA (ctDNA) status was assessed in 581 enrolled patients. In ctDNA-positive patients, atezolizumab provided a significant OS benefit compared to observation [HR: 0.59, 95% confidence interval (CI): 0.42-0.83; median OS: 29.8 months vs. 14.1 months]. However, in ctDNA-negative patients, atezolizumab did not demonstrate an improvement in OS (HR: 1.38, 95% CI: 0.93-2.05). These findings highlight ctDNA status as a critical biomarker for identifying patients who may benefit from adjuvant immunotherapy. Although atezolizumab was associated with increased adverse event rates, its efficacy in ctDNA-positive patients is clinically significant.

The phase 3 AMBASSADOR trial evaluated adjuvant pembrolizumab in high-risk MIUC patients, similar in intent to the IMvigor010 study [31]. A total of 702 patients were randomized to receive pembrolizumab (200 mg every three weeks for one year) or observation after radical surgery. Median DFS was significantly improved with pembrolizumab (29.6 months) compared to observation (14.2 months) (HR=0.73, p=0.003). while no significant difference was observed in OS (HR=0.98). Although grade 3 adverse events were more frequent in the pembrolizumab arm (50.6% vs. 31.6%), disease recurrence was significantly reduced.

Similar to other immunotherapy studies, the phase 3 CheckMate 274 trial evaluated the efficacy and safety of adjuvant nivolumab in high-risk MIUC patients following radical surgery [32]. Nivolumab significantly prolonged DFS compared with placebo (20.8 months vs. 10.8 months; HR: 0.70; p<0.001), and this effect was more pronounced in patients with PD-L1 expression ≥1% (HR: 0.55; p<0.001). The safety profile was tolerable, similar to previous studies, and no significant deterioration in quality of life was observed.

Table 2. Non-metastatic MIBC neoadjuvant therapy studies and patient characteristics

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
ABACUS (NCT02662309)	2016-2022	Multicenter, single-arm, phase 2 clinical trial	T2-4aN0M0	Atezolizumab	Primary result: - pCR: 31% (in 27 of 88 patients) Secondary results: - 2 year DFS: 68% - 2 year OS: 77% - ctDNA positivity is associated with worse prognosis - Side effects were generally mild and manageable (grade 3-4 side effects: 12%)
NCT02989584	2016-Ongoing	Multicenter, single-arm, phase 2 clinical trial	cT2-4aN0MO	Atezolizumab+gemcitabine+cisplatin	Primary result: - pCR (<pT2N0): 69% (27/39 patients) - pCR rate: 41% (16/39 patients) Secondary results: - Patients with PD-L1 positive tumors: 100% showed <pT2N0 response. - In patients with low or negative PD-L1: 68% <pT2N0, 32% ≥pT2N0
PURE-01 (NCT02736266)	2017-2021	Open-label, single-arm, phase 2 clinical study	cT2-T4aN0M0	Pembrolizumab	Primary result: - 3 years EFS: 74.4% (95% CI: 67.8-81.7) - 3 years OS: 83.8% (95% CI: 77.8-90.2)
KEYNOTE-905/ EV-303 (NCT03924895)	2023-Ongoing	Open-label, multicenter, randomized phase 2 clinical trial	T2-4aN0M0 Veya T1-4aN1M0	Arm A: pembrolizumab Arm B: standard surgery Arm C: enfortumab vedotin+pembrolizumab	The study is still ongoing.
AURA (Oncodistinct 004) (NCT03674424)	2018-2024	Multicenter, randomized, phase 2 clinical trial	T2-4aN0M0 Veya T1-4aN1M0	<u>Cohort 1: (*cisplatin eligible*)</u> Arm A: ddMVAC+avelumab Arm B: cisplatin-gemcitabine+avelumab <u>Cohort 2: *sisplatin inegible*</u> Arm C: paclitaxel-gemcitabine+avelumab Arm D: avelumab monotherapy	ddMVAC + avelumab (ddMVAC-A): - 12 months DFS: 97% (95% CI: 83-100) - 36 months DFS: 77% (95% CI: 55-89) - 12 months OS: 95% (95% CI: 81-99) - 36 months OS: 87% (95% CI: 68-95) Cisplatin-gemcitabine+avelumab (CG-A): - 12 months DFS: 86% (95% CI: 70-94) - 36 months DFS: 68% (95% CI: 46-82) - 12 months OS: 84% (95% CI: 67-92) - 36 months OS: 61% (95% CI: 40-76) Paclitaxel-gemcitabin+avelumab (PG-A) (<u>*sisplatin inegible*</u>): - 12 months DFS: 52% (95% CI: 32-69) - 36 months DFS: data is not yet mature - 12 months OS: 67% (95% CI: 46-81) - 36 months OS: data is not yet mature Avelumab monotherapy (A) (<u>*sisplatin inegible*</u>): - 12 months DFS: 68% (95% CI: 47-82) - 36 months DFS: data is not yet mature - 12 months OS: 75% (95% CI: 55-87) - 36 months OS: data is not yet mature

Table 2. Continued

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
ENERGIZE (NCT03661320)	2018-ongoing	Multicenter, randomized, phase 3 clinical trial	T2-4aN0M0	Arm A: standard neoadjuvant chemotherapy (NAC) Arm B: NAC+nivolumab Arm C: NAC+nivolumab+BMS-986205	The study is still ongoing.
NABUCCO (NCT03387761)	2018-2023	Open-label, single-arm, phase Ib clinical study	T3-T4aN0M0 veya T1-4a, N1-2, M0	Nivolumab+Ipilimumab	Primary result: - pCR rate: 46% (11/24 patients) Secondary results: - pCR rate in PD-L1 positive patients: 67% - pCR rate in PD-L1 negative patients: 17% - After treatment, CD8+ T cell infiltration increased in the tumor microenvironment in 88% of patients. - irAE's: 30% grade 3-4 side effect - Rate of patients who could not complete treatment due to side effects: 21% (5/24 patients)
ONO-4538-X41 (KCT0003804)	2019-2020	Single-arm, phase 2 clinical trial	cT2-4aN0M0	Nivolumab+gemcitabine+cisplatin	Primary result: - pCR rate: - ITT population: 24% (12/49 patients) - In patients undergoing radical cystectomy: 35% (12/34 patients) Secondary results: - cCR rate: 59% (clinical response was seen in 29 of 49 patients) - PD-L1 expression did not appear to be a factor determining pathological response rates.
NIAGARA (NCT03732677)	2018-2024	Multicenter, randomized, phase 3 clinical trial	cT2-4a, N0-1, M0	Arm A: gemcitabine+cisplatin+durvalumab Arm B: gemcitabine+cisplatin	Primary result: - pCR rate: 34% (Arm A) vs. 20% (Arm B) - EFS (36 months): EFS 68% (Arm A) vs. 54% (Arm B) Secondary results: - OS: 72% (Arm A) vs. 60% (Arm B) - TRAEs: grade 3-4 side effect rate 28% - In the durvalumab group, treatment was discontinued in 10 patients due to immune-mediated side effects. - No strong correlation was found between PD-L1 expression and treatment response.
NEMIO (NCT03549715)	2018-2021	Open-label, randomized, phase 2 clinical trial	T2-4, N0-1, M0	Arm A: ddMVAC Arm B: ddMVAC+durvalumab Arm C: ddMVAC+durvalumab+tremelimumab	Primary result: - pCR rate: - ddMVAC (control groups): 30% - ddMVAC+durvalumab (ddMVAC+D): 45% - ddMVAC+durvalumab+tremelimumab (ddMVAC+D+T): 50% Secondary results: - DFS and OS results are monitored. - TRAEs (grade 3-4 side effect rate): - ddMVAC group: 22% - ddMVAC+Durvalumab group: 30% - ddMVAC+Durvalumab+tremelimumab group: 36%

MIBC: Muscle-invasive bladder cancer, pCR: Pathological complete response, DFS: Disease-free survival, OS: Overall survival, PD-L1: Programmed death-ligand 1, EFS: Event-free survival, NAC: Neoadjuvant chemotherapy, TRAEs: Treatment-related adverse events, ddMVAC: Dose-dense methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin, ITT: Intention-to-treat, cTNM: Clinical tumor, node, metastasis

The extended follow-up analysis of the CheckMate 274 study (median follow-up of 36.1 months) demonstrated a stronger DFS advantage with nivolumab in both the intention-to-treat (ITT) (HR: 0.71; 95% CI: 0.58-0.86) and PD-L1 ≥1% (HR: 0.52; 95% CI: 0.37-0.72) populations and presented OS data for the first time [33]. Nivolumab reduced the risk of death by 24% (HR: 0.76; 95% CI: 0.61-0.96) in the ITT population and by 44% (HR: 0.56; 95% CI: 0.36-0.86) in the PD-L1 ≥1% population. Efficacy was also confirmed in the MIBC subgroup, regardless of PD-L1 status.

The use of adjuvant immunotherapy may be an effective option for preventing relapse, especially in high-risk MIUC patients. The characteristics and results of the studies are presented in detail in Table 3.

Table 3. Non-metastatic MIBC adjuvant therapy studies and patient characteristics

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
IMvigor010 (NCT02450331)	2015-2024	Open-label, randomized, double-arm phase 3 clinical trial	T2-4, N0-1, M0	Arm A: atezolizumab Arm B: placebo	ctDNA positive patients OS: - Atezolizumab vs. observation group: HR: 0.59 (95% CI: 0.42-0.83) ctDNA negative patients OS: HR: 1.05 (95% CI: 0.78-1.40)
AMBASSADOR (NCT03244384)	2017-2024	Open-label, randomized, phase 3 clinical trial	T2-4a, N0-1, M0	Arm A: pembrolizumab Arm B: placebo	DFS: pembrolizumab vs. observation group: - HR: 0.73 (95% CI: 0.59-0.90), p=0.003 - Median DFS: pembrolizumab 29.6 months (95% CI: 20.0-40.7) vs. observation 14.2 months (95% CI: 11.0-20.2) - OS: - Pembrolizumab vs. observation group: - HR: 0.98 (95% CI: 0.76-1.26) 3 years OS rate: pembrolizumab 60.8% (95% CI: 55.3-66.9) vs. observation 61.9% (95% CI: 56.5-67.9) DFS results according to PD-L1 expression: - PD-L1 positive patients: median DFS: 36.9 months vs. 21.0 months (HR: 0.81, 95% CI: 0.61-1.08) - PD-L1 negative patients: median DFS: 17.3 months vs. 9.0 months (HR: 0.71, 95% CI: 0.53-0.95)
CheckMate 274 (NCT02632409)	2016-2021	Multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial	T2-4a, N0-1, M0	Arm A: nivolumab Arm B: placebo	DFS - Median DFS in the nivolumab arm: 20.8 months - Median DFS in placebo arm: 10.8 months - (HR: 0.70, p<0.001) DFS in PD-L1 positive patients: - Median DFS in the nivolumab arm: 22.0 months - Median DFS in placebo arm: 10.7 months - (HR: 0.55, p<0.001). Adverse effects: - Grade 3-4 adverse event rate in the nivolumab arm was 17.9% - The rate of grade 3-4 adverse events in the placebo arm was 7.2% - Treatment-related deaths: 3 patients in the nivolumab arm (pneumonitis and bowel perforation).

MIBC: Muscle-invasive bladder cancer, cTNM: Clinical tumor, node, metastasis, DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, PD-L1: Programmed death-ligand 1, CI: Confidence interval, ctDNA: circulating tumor deoxyribonucleic acid

Metastatic Bladder Cancer

MBC is associated with limited systemic treatment options and generally poor prognosis. Recently, immunotherapy, targeted therapies, and antibody-drug conjugates have emerged as promising treatment options in this setting [7].

The IMvigor130 trial is a randomized, controlled phase 3 study comparing first-line atezolizumab monotherapy with platinum-based CT in locally advanced or mUC [34]. In the overall population, atezolizumab did not significantly improve median OS (15.2 months vs. 13.3 months; HR: 0.98, 95% CI: 0.82-1.16). However, in patients with high PD-L1 expression, particularly those ineligible for cisplatin, potential survival benefits were observed (median OS: 18.6 months vs. 10.0 months; HR: 0.56, 95% CI: 0.34-0.91). Atezolizumab demonstrated a better safety profile with fewer severe adverse events (16% vs. 80% in the control group). These findings support atezolizumab as a treatment alternative in patients with PD-L1-positive tumors or those ineligible for cisplatin.

Similarly, the phase 3 IMvigor211 trial investigated the efficacy of atezolizumab in mUC patients who had progressed after platinum-based CT. Patients received either atezolizumab (1200 mg) or investigator's choice of CT (vinflunine, paclitaxel, or docetaxel). In the atezolizumab group, the 24-month survival rate was 23% compared to 13% in the CT group, while the 30-month survival rates were 18% and 10%, respectively (HR: 0.82; 95% CI: 0.71-0.94). Atezolizumab was associated with a lower incidence of severe adverse events (22% vs. 43%) [35]. These results demonstrate that atezolizumab is an effective and safe treatment option for patients with advanced urothelial carcinoma following platinum-based therapy, regardless of PD-L1 status.

In 2023, Balar et al. [36] evaluated the efficacy and safety profile of pembrolizumab in mUC patients with up to five years of follow-up data from the KEYNOTE-045 and KEYNOTE-052 trials. In the KEYNOTE-045 trial, pembrolizumab demonstrated a significant OS benefit compared to CT in platinum-resistant mUC patients (48-month OS: 16.7% vs. 10.1%) and a longer median duration of response (29.7 months vs. 4.4 months). In the KEYNOTE-052 trial, pembrolizumab emerged as a strong first-line option for cisplatin-ineligible patients, with an objective response rate (ORR) of 28.9% and a median duration of response of 33.4 months. Pembrolizumab was found to be effective and had a manageable safety profile, making it a reliable treatment option for both second-line therapy and cisplatin-ineligible patients. The KEYNOTE-361 trial evaluated the efficacy of pembrolizumab monotherapy or its combination with CT in advanced urothelial carcinoma. The findings indicated that pembrolizumab, whether as monotherapy or in combination with CT, did not provide a significant benefit as a first-line treatment. Instead, the results suggest that immunotherapy may be more effective when used as maintenance therapy [37]. The EV-302 trial is a randomized clinical study comparing the efficacy and safety of the EV-pembrolizumab combination with platinum-based CT as a first-line treatment for locally advanced or mUC. The combination therapy significantly improved progression-free survival (PFS) (12.5 months vs. 6.3 months; HR: 0.45, p<0.001) and OS (31.5 months vs. 16.1 months; HR: 0.47, p<0.001). Additionally, the combination demonstrated superiority in ORR (67.7% vs. 44.4%) and CR rate (29.1% vs. 12.5%). Treatment-related adverse events were less frequent in the combination group (55.9% vs. 69.5%), with the most common adverse effects being peripheral neuropathy and pruritus [38]. With this study, the EV and pembrolizumab combination has become the treatment option providing the longest survival benefit in metastatic urothelial cancer to date and has been integrated into routine clinical practice. In a study comparing erdafitinib and pembrolizumab in patients with fibroblast growth factor receptor mutations who progressed after platinum-based CT, erdafitinib demonstrated a higher ORR and PFS advantage. However, OS was similar between the two treatments (10.9 months vs. 11.1 months) [39].

The multicenter ARIES phase 2 trial evaluated the efficacy and safety of avelumab as a first-line treatment in PD-L1-positive patients with metastatic or locally advanced urothelial cancer who were ineligible for cisplatin-based therapy. The study reported a median OS of 10 months and a one-year survival rate of 43%, with an ORR of 24% [40]. The phase 3 JAVELIN Bladder 100 trial investigated the efficacy of avelumab maintenance in patients with advanced urothelial cancer who did not experience progression following platinum-based CT. Maintenance with avelumab significantly improved OS (23.8 months vs. 15.0 months; HR: 0.76, p=0.0036) and PFS (5.5 months vs. 2.1 months; HR: 0.54, p<0.0001) compared to best supportive care. Long-term follow-up (>2 years) confirmed the treatment's efficacy and manageable safety profile. Avelumab has now been established as a standard maintenance therapy option for advanced urothelial cancer following first-line treatment [41].

The CheckMate 901 trial demonstrated that the combination of nivolumab with gemcitabine-cisplatin significantly improved OS (21.7 months vs. 18.9 months; HR: 0.78, p=0.02) and PFS (7.9 months vs. 7.6 months; HR: 0.72, p=0.001) compared to gemcitabine-cisplatin alone in advanced urothelial carcinoma. Additionally, the CR rate was doubled in the combination group (21.7% vs. 11.8%), while the rate of treatment-related adverse events was reported as 61.8%. These findings suggest that concurrent nivolumab and CT could be an effective treatment strategy [42].

The multicenter randomized DANUBE trial compared durvalumab monotherapy and durvalumab plus tremelimumab combination therapy with standard platinum-based CT in patients with locally advanced or mUC. The study did not meet its primary endpoint of OS [43]. Table 4 provides a detailed overview of the study characteristics and outcomes.

Table 4. Metastatic MIBC treatment studies and patient characteristics

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
IMvigor130 (NCT02807636)	2016-2018	Randomized, controlled, phase 2 clinical trial	Locally advanced or mUC	Arm A: atezolizumab+platinum-based chemotherapy Arm B: atezolizumab monotherapy Arm C: platinum-based chemotherapy	mOS: - Atezolizumab+chemotherapy group: 16.0 months (95% CI: 13.9-18.0) - Chemotherapy alone group: 13.4 months (95% CI: 12.0-15.3) - HR=0.85 (95% CI: 0.72-1.02, p=0.04) - Atezolizumab monotherapy: 15.7 months - HR=1.02 (95% CI: 0.83-1.24, p=0.82)
IMvigor211 (NCT02302807)	2015-2016	Randomized, open-label, phase 3 clinical trial	Locally advanced or mUC	Arm A: atezolizumab Arm B: chemotherapy (vinflunine or paclitaxel or docetaxel)	mOS: - Atezolizumab group: 11.1 months (95% CI: 9.1-13.1) - Chemotherapy group: 10.6 months (95% CI: 8.4-11.8) - HR=0.87 (95% CI: 0.73-1.02, p=0.07) In patients with high PD-L1 expression (IC2/3): - Atezolizumab: 11.1 months - Chemotherapy: 10.6 months - HR=0.95 (95% CI: 0.74-1.24) Treatment-related adverse events (TRAEs): - Any grade adverse event rate: - Atezolizumab: 60.9% - Chemotherapy: 90.2% Grade 3-4 adverse event rate: - Atezolizumab: 20.9% - Chemotherapy: 43.2%
SAUL (NCT02928406)	2016-2018	Single-arm, phase 3b, clinical trial	Locally advanced or mUC	Atezolizumab	- In patients with high PD-L1 (IC2/3), OS was longer (11.6 months vs. 7.75 months, p=0.002). - Patients who received treatment 6 months before the last chemotherapy (TFLC >6 months) had a better advantage in terms of OS (11.63 months vs. 6.97 months, p<0.001). - Bellmunt risk factors (0, 1, 2-3) have a strong prognostic impact on survival. - The type of prior chemotherapy regimen (cisplatin/carboplatin) and the number of prior lines of therapy were not associated with survival outcomes.
KEYNOTE-045 (NCT02256436)	2015-2020	Phase 3, randomized controlled trial	mUC	Arm A: pembrolizumab Arm B: chemotherapy	- 48th month OS rate: Pembrolizumab 16.7%, Chemotherapy 10.1% - 48th months PFS rate: Pembrolizumab 9.5%, Chemotherapy 2.7% -DOR: Pembrolizumab 29.7 months, Chemotherapy 4.4 months - 36th months DOR rate: Pembrolizumab 44.4%, Chemotherapy 28.3%
KEYNOTE-052 (NCT02335424)	2015-2020	Phase 2, single-arm study	Cisplatin inegible mUC	Pembrolizumab	- ORR: 28.9% (95% CI: 24.3-33.8) - DOR: 33.4 months - 36th month DOR rate: 44.8%

Table 4. Continued

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
KEYNOTE-361 (NCT02853305)	2016-2021	Phase 3, open label, randomized controlled trial	mUC	Arm A: pembrolizumab Arm B: pembrolizumab+chemotherapy Arm C: chemotherapy	OS: - No statistically significant difference was observed between the pembrolizumab+chemotherapy arm and the chemotherapy alone arm (HR: 0.86; 95% CI: 0.72-1.02; p=0.0407; statistical significance threshold was set at p<0.0242). - No significant difference was detected between pembrolizumab monotherapy and chemotherapy arms (HR: 0.91; 95% CI: 0.77-1.08). PFS: - The pembrolizumab+chemotherapy arm did not provide a statistically significant improvement compared to chemotherapy alone (HR: 0.78; 95% CI: 0.65-0.93; p=0.0033; statistical significance threshold set at p<0.0019). - Pembrolizumab monotherapy has shown inferior PFS results compared to chemotherapy
EV-302/ KEYNOTE-A39 (NCT04223856)	2020-2024	Phase 3, open label, randomized controlled trial	mUC	Arm A: enfortumab vedotin+pembrolizumab Arm B: platinum based chemotherapy	OS: - EV+P group: 31.5 months (95% CI: 25.3-not reached) - Chemotherapy group: 16.1 months (95% CI: 13.9-18.8) - HR=0.47 (95% CI: 0.38-0.58, p<0.0001) PFS - EV+P group: 12.5 months (95% CI: 10.4-15.0) - Chemotherapy group: 6.3 months (95% CI: 6.2-6.4) - HR=0.51 (95% CI: 0.41-0.62, p<0.0001) ORR - EV+P group: 67.9% (complete response: 29.1%, partial response: 38.8%) - Chemotherapy group: 44.9% (complete response: 12.4%, partial response: 32.5%) - p<0.0001
THOR (NCT03390504)	2018-2024	Phase 3, open-label, randomized controlled trial	mUC	Arm A: erdafitinib Arm B: pembrolizumab	OS: - Erdafitinib: 10.9 months (95% CI: 9.2-13.4) - Pembrolizumab: 11.1 months (95% CI: 8.9-14.3) - HR=1.18 (95% CI: 0.92-1.51, p=0.18) PFS - Erdafitinib: 4.4 months (95% CI: 3.6-5.3) - Pembrolizumab: 2.7 months (95% CI: 2.0-3.4) - HR=0.88 (95% CI: 0.70-1.10) ORR: - Erdafitinib: 40.0% (complete response: 7.5%, partial response: 32.5%) - Pembrolizumab: 21.6% (complete response: 5.7%, partial response: 15.9%) - Relative risk =1.85 (95% CI: 1.32-2.59)

Table 4. Continued

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
ARIES (NCT03869190)	2020-2022	Phase 2, open-label, single-arm study	mUC	Avelumab	mOS: 10.0 months (95% CI: 5.5-14.5 months) - 1-year survival rate: 43% ORR - Complete response: 8.5% - Partial response: 15.5% - Overal response rate (ORR): 24.0
JAVELIN Bladder 100 (NCT02603432)	2016-2024	Phase 3, open label, randomized controlled trial	mUC	Arm A: avelumab maintenance Arm B: BSC	OS: - Avelumab group: 23.8 months (95% CI: 19.9-27.7) - BSC group: 15.0 months (95% CI: 13.0-17.4) - HR=0.69 (95% CI: 0.56-0.85, p<0.001) - 2 years OS: - Avelumab group: 54.3% - BSC group: 39.8% mPFS: - Avelumab group: 5.5 months (95% CI: 4.6-6.2) - BSC group: 2.2 months (95% CI: 2.1-3.2) - HR=0.62 (95% CI: 0.52-0.75, p<0.0001) ORR: - Avelumab group: 25.6% - BSC group: 10.3% - p<0.001 DOR: - Avelumab group: 20.2 months - BSC group: 8.5 months TRAEs: - 47.4% of patients receiving avelumab experienced adverse events of any grade. Grade 3-4 adverse event rate: 12.9% - Grade 3-4 adverse event rate in the BSC group: 6.3%
CheckMate 901 (NCT03036098)	2017-2024	Phase 3, open label, randomized controlled trial	mUC	Arm A: nivolumab+gemcitabine-cisplatin Arm B: gemcitabine-cisplatin	OS: - Nivolumab+gemcitabine-cisplatin arm: 21.7 months (95% CI: 18.6-26.4) - Gemcitabine-cisplatin arm: 18.9 months (95% CI: 14.7-22.4) - HR=0.78 (95% CI: 0.63-0.96, p=0.02) PFS: - Nivolumab+gemcitabin-sisplatin arm: 7.9 months (95% CI: 7.6-9.5) - Gemcitabin-sisplatin arm: 7.6 months (95% CI: 6.1-7.8) - HR=0.72 (95% CI: 0.59-0.88, p=0.001) ORR: - Nivolumab+gemcitabine-cisplatin arm: 57.6% (complete response: 21.7%, partial response: 35.9%) - Gemcitabine-cisplatin arm: 43.1% (complete response: 11.8%, partial response: 31.2%) - p<0.001 Grade 3-4 adverse event rate: - Nivolumab+gemcitabine-cisplatin: 61.8% - Gemcitabine-cisplatin: 51.7%

Table 4. Continued

Trial ID/name	Study period	Study design	cTNM	Study arm	Oncological outcomes
DANUBE (NCT02516241	2015-2020	Phase 3, open label, randomized controlled trial	Unresectable, locally advanced or muc	Arm A: durvalumab monotherapy Arm B: durvalumab+tremelimumab arm c: standard chemotherapy	OS: - Durvalumab monotherapy (patients with high PD-L1 expression): 14.4 months (95% CI: 10.4-17.3) - Chemotherapy arm: 12.1 months (95% CI: 10.4-15.0) - HR 0.89 (95% CI: 0.71-1.11, p=0.30) - Durvalumab+tremelimumab arm: 15.1 months (95% CI: 13.1-18.0) - Chemotherapy arm (all patients): 12.1 months (95% CI: 10.9-14.0) - HR=0.85 (95% CI: 0.72-1.02, p=0.075) PFS: - Durvalumab monotherapy: 2.1 months - Durvalumab+tremelimumab: 3.6 months - Chemotherapy: 6.1months ORR: - Durvalumab monotherapy: 23.5% - Durvalumab+tremelimumab: 31.5% - Chemotherapy: 40.2% Grade 3-4 adverse events rate: - Durvalumab monotherapy: 14% - Durvalumab+tremelimumab: 27% - Chemotherapy: 60%

MIBC: Muscle-invasive bladder cancer, mOS: Median overall survival, HR: Hazard ratio, TRAEs: Treatment-related adverse events, PD-L1: Programmed death-ligand 1, OS: Overall survival, TFLC: Total free light chains, DOR: Duration of response, ORR: Objective response rate, PFS: Progression-free survival, EV: enfortumab vedotin, BSC: Best supportive care

Conclusion

Immunotherapy has become a key treatment option across the entire spectrum of bladder cancer, from non-invasive disease to metastatic stages. In particular, ICIs have demonstrated significant efficacy in both neoadjuvant and adjuvant settings, as well as in metastatic disease, either as monotherapy or in combination with CT and targeted therapies. However, critical challenges remain, including patient selection, biomarker-driven treatment strategies, resistance mechanisms, and immune-related adverse events. The integration of novel agents such as antibody-drug conjugates and oncolytic viruses into treatment protocols offers promising advancements in cancer therapy.

The integration of personalized immunotherapies into treatment algorithms will further refine therapeutic approaches. Future studies should focus on optimizing combination therapies, improving the identification of predictive biomarkers, and clarifying treatment sequencing. As the role of immunotherapy in bladder cancer continues to expand, a multidisciplinary approach is crucial for enhancing long-term patient outcomes.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ç., B.D., Concept: B.D., Design: G.Ç., Data Collection or Processing: G.Ç., Analysis or Interpretation: B.D., Literature Search: G.Ç., Writing: G.Ç., B.D.

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Readability and Quality Analysis of ChatGPT o1's Responses on Colorectal Cancer: A Study of an AI Language Model

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ABSTRACT

Aim: This study aimed to evaluate the readability and quality of the responses provided by the ChatGPT model to the most frequently searched questions by patients about colorectal cancer on the internet.

Methods: The 20 most frequently searched topics related to colorectal cancer were identified from Google and Yandex search engine statistics. These topics were posed to the ChatGPT o1 model, and the obtained responses were analyzed for readability using the Ateşman and Çetinkaya-Uzun readability formulas. Quality assessment was performed using the DISCERN instrument and the Global Quality Score (GQS). Statistical analyses included Pearson correlation and one-way ANOVA tests.

Results: The average word count of the responses was 654.9 [standard deviation (SD)=221.62]. According to the Ateşman readability score, the mean score was 55.45 (SD=6.06, medium difficulty readability), and according to the Çetinkaya-Uzun score, it was 85.53 (SD=4.0, 5th-7th grade level, independently readable). The mean total DISCERN score was 54.55 (SD=5.75, which indicates good quality), and the mean GQS was 4.35 (SD=0.75, which suggests between good and excellent). No significant correlation was found between DISCERN and GQS scores (p=0.831).

Conclusion: The responses provided by the ChatGPT o1 model to patients' most frequently asked questions about colorectal cancer have medium-level readability and good-quality content. Therefore, it can be considered a helpful resource for patients seeking information.

Keywords: Artificial intelligence in oncology, cancer education, colorectal cancer

Introduction

Artificial intelligence (AI) language models such as ChatGPT (OpenAI Inc., California, United States) have become one of the most frequently used information sources by patients and their relatives since their introduction into daily use [1]. Numerous studies in the literature demonstrate that these models have sufficient medical knowledge, comparable to the level required to successfully pass medical licensing exams in various countries [2,3]. Based on these studies, it is believed that these models can provide appropriate answers to patients' questions. Studies prepared with this assumption have shown that healthcare providers indeed respond appropriately to patient inquiries [4].

The readability and quality of medical information obtained from the internet are among the biggest sources of concern. Therefore, many different analysis techniques have been developed for readability assessment. Methods such as DISCERN and the Global Quality Score (GQS) have been devised for evaluating content quality [5,6]. For Turkish publications, readability scores like Ateşman and Çetinkaya-Uzun are available for readability assessment and are frequently used in research [5]. Information can be obtained from various online sources such as videos, blogs, news sites, and forums. The comprehensibility and readability of this information, especially for elderly individuals and those with low literacy levels, raise serious concerns [7].

With the increasing daily use of artificial intelligence (AI) language models and the advantages provided by newly developed ones, it is likely that patients will use AI language models like ChatGPT more frequently to access information. On 12/09/2024, OpenAI introduced the ChatGPT o1 model,

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which was designed to offer higher education, especially doctoral-level information. However, information regarding the responses of this model to patient questions is rarely found in the medical literature [8].

Methods

Data Collection

Our study was planned as a bibliographic study aimed at performing readability and quality analyses. The questions that patients searched for on the internet regarding colorectal cancer were obtained from the Google statistics (Google LLC, California, United States) and Yandex statistics (Yandex LLC, Moscow, Russia) search engines. Since there was no time limitation in Google statistics, information from 19/07/2019 to 18/07/2024 was collected. In Yandex statistics, due to a one-month limit on statistical data, information from 18/06/2024 to 18/07/2024 was obtained. After obtaining the statistics, the top 20 most searched topics were identified.

Once the topics were determined, questions were sequentially posed to the ChatGPT o1 model, and the obtained responses were saved as plain text files. To complete the readability analyses in the plain text files, punctuation and spelling errors were manually corrected. ChatGPT was not informed about the purpose of asking the questions, as the study aimed to evaluate the quality and readability of patients' questions.

Readability Analyses

Two different readability analysis methods specifically developed for the Turkish language were used.

The first analysis was conducted using the readability analysis developed by Ateşman [9] and published in 1997. The readability analysis developed by Ateşman [9] is an adaptation of the Flesch formula to Turkish which was originally developed for English. The formula is as follows: Readability score=198.825-40.175 (x_1, average syllables per word) -2.610 (x_2, average words per sentence). According to the formula developed by Ateşman [9], readability levels are determined as follows: 1-29: very difficult; 30-49: difficult; 50-69: moderately difficult; 70-89: easy; and 90-100: very easy.

The second analysis was conducted using the readability analysis developed by Çetinkaya and Uzun [10] and published in 2010. The readability analysis developed by Çetinkaya-Uzun is based on whitespace identification, and the formula is as follows: Readability score = 118.823 – (25.987 × average word length) – (0.971 × average sentence length). According to the formula developed by Çetinkaya-Uzun, readability levels are determined as follows: 0-34: insufficient reading level, corresponding to 10^{th}-12^{th} grade; 35-50: educational reading level, corresponding to 8^{th}-9^{th} grade; ≥51: independent reading level, corresponding to 5^{th}-7^{th} grade.

Simple code was written using Python 3.12 for readability analysis, and the analysis was performed on plain text files.

Quality Analyses

For quality analyses of the obtained materials, the DISCERN score and the GQS were used.

The DISCERN score was developed in English in 1998 and consists of 16 questions. Among these questions, 1-8 are about reliability, 9-15 are about treatment options, and question 16 is about overall quality. Each question is scored between 1 (poor) and 5 (good), and the total score is used for analysis. The recommended evaluation for the DISCERN score is as follows: 16-29: very poor; 30-40: poor; 41-51: fair; 52-63: good; 64-80: excellent.

The GQS is a simple scoring system ranging from 1 to 5. According to this score: 1: very poor; 2: poor; 3: fair; 4: good and 5: excellent.

Quality analyses were conducted by two different observers. Since there was complete agreement between them, the scores were assigned identically.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 10 (GraphPad Inc., New Jersey, United States). For descriptive statistics, the mean and standard deviation (SD) were used. Pearson correlation analysis was employed to evaluate the relationships between scores; and one-way analysis of variance (ANOVA) was used to analyze different scores according to topics. A p value of less than 0.05 was considered statistically significant.

The observers' comments and the obtained texts were subjected to qualitative analysis techniques, with general thematic analyses also conducted. Qualitative data analysis was performed manually, identifying recurring words and themes. Graphs for the qualitative analysis were created using Python 3.12 and the "matplotlib" package.

Ethics Statement

Since the study was bibliographic in nature, ethical committee approval was not deemed necessary. The ChatGPT AI system was only used during the data collection phase, and it was not utilized in any analyses. The study was conducted in accordance with current and universal ethical standards.

Results

Readability Analysis

Twenty of the most frequently searched topics were obtained from the Google and Yandex search engines. When these topics were provided to the ChatGPT o1 model, the average number of words in the generated responses was calculated to be 654.9 (SD=221.62). According to Ateşman's [9] readability formula, the average readability score was 55.45 (SD=6.06), which was evaluated as moderately difficult to read. According to the Çetinkaya-Uzun readability formula, the average readability score was 85.53 (SD=4.0), and it was assessed as independently readable at the 5^{th}-7^{th} grade level. In the Pearson correlation analysis, R^2=0.395 was calculated and deemed statistically significant (p=0.003). The ranking of the obtained topics by frequency, word counts, Ateşman [9] readability scores, and Çetinkaya-Uzun readability scores is presented in Table 1 and Figure 1.

Quality Analysis

According to the DISCERN quality analysis, which consists of sixteen questions, Question 1, ("Is it relevant?") and Question 15 ("Does it provide support for shared decision-making?") received a score of 5 in all topics. Question 4 ("Are the sources of information used in compiling the publication clearly stated?") and Question 5 ("Is it clear when the published information is being used or reported?") received a score of 1 across all topics because no information was provided. The average score for the responses to the questions was 3.41 (SD=1.68). When all questions were evaluated together, significant score differences were observed with the use of the ANOVA test (p<0.001, F=79.82). The results of the scoring of DISCERN quality analysis questions are detailed in Figure 2.

Table 1. Determined topic headings, word count, and readability analysis

Topic heading	Word count	Ateşman readability	Çetinkaya-Uzun readability
Rectal cancer symptoms	161	91.03	56
Colon cancer	251	89.34	48
Colon cancer symptoms	387	87.12	62
Rectal cancer surgery	613	81.12	56
Rectal cancer treatment	805	76.85	42
What is rectal cancer?	621	85.03	58
Intestinal cancer symptoms	536	88.76	62
What causes rectal cancer?	559	90.45	57
What is colon cancer?	753	84.70	60
Blood from the anus	692	86.08	58
Colon and rectal cancer	1001	83.96	52
Experiences of those with rectal cancer	712	79.43	47
Stage 1 rectal cancer symptoms	544	88.86	65
Experiences of those with colon cancer	855	78.16	47
What causes colon cancer?	712	87.72	51
Colon cancer life expectancy	584	88.76	61
Stage 4 colon cancer	944	84.94	60
Rectal cancer life expectancy	976	84.52	58
Stage 3 colon cancer survival chance	798	86.30	52
What is a colon?	594	87.50	57
Average (SD)	**654.9 (SD=221.62)**	**85.53 (SD=4.00)**	**55.45 (SD=6.06)**

SD: Standard deviation

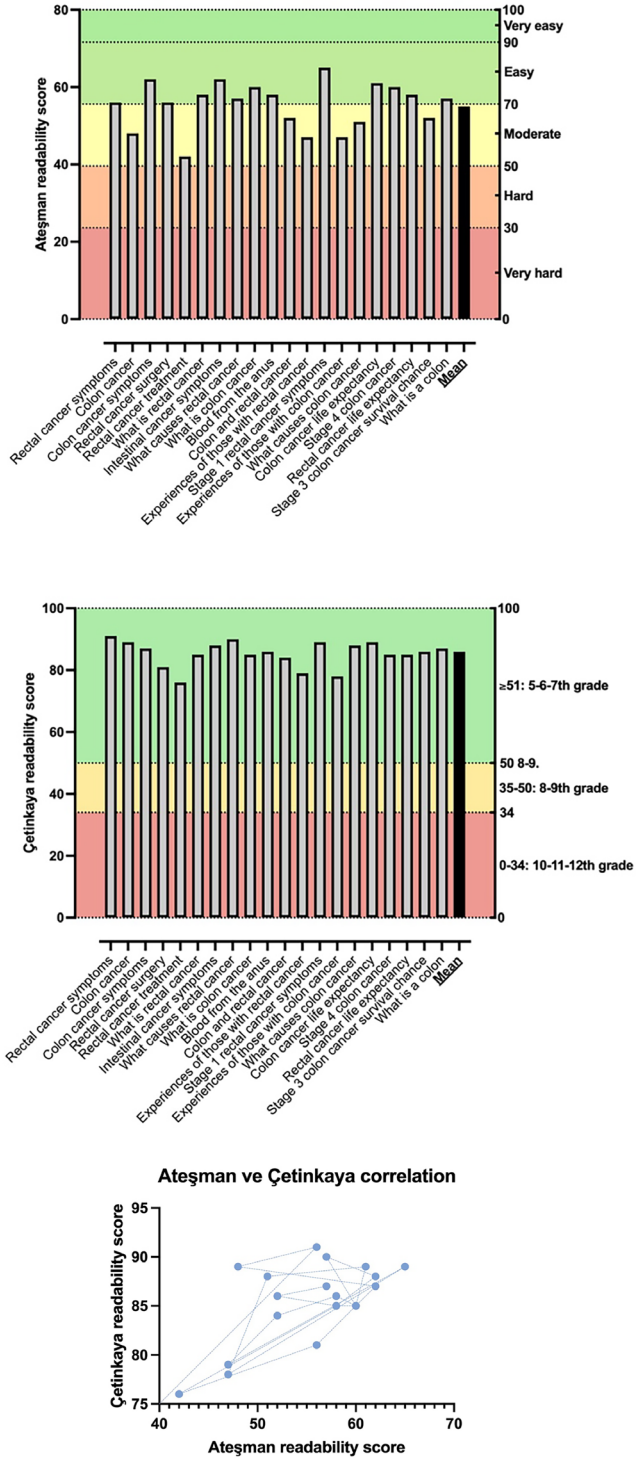

Figure 1. Ateşman and Çetinkaya-Uzun readability scores and their correlation

The total DISCERN score was calculated to have an average of 54.55 (SD=5.75), with the lowest score being 43 for the "colon cancer" topic and the highest score being 66 for the "blood from the anus" topic. The average total DISCERN score was classified as good. It was observed that 13 topics (65%) could be described as good, 6 topics (30%) as fair, and 1 topic (5%) as excellent. It was noted that none of the topics could be evaluated as poor or very poor according to the DISCERN analysis of the ChatGPT o1 model. The GQS score had an average of 4.35 (SD=0.75), indicating a rating between good and excellent. It was observed that 10 topics (50%) received a score of 5 and could be evaluated as excellent, 7 topics (35%) received a score of 4, evaluated as good, and 3 topics received a score of 3, evaluated as fair. In the correlation analysis, no significant correlation was observed between the DISCERN scores and GQS scores (R^2=0.002, p=0.831). The total DISCERN and GQS scores are presented in Table 2 and Figure 3.

A comparative analysis was not performed because the evaluators' scores were consistent.

Qualitative Analyses

In the qualitative analyses conducted, independent of the topic headings, the themes of the content were identified as cancer definitions, symptoms, risk factors, diagnostic methods, treatment options, life expectancy and prognosis, prevention and early diagnosis, and quality of life. Particularly, recurring content included definitions of colon and rectal cancer, risk factors, explanations of treatment methods, and recommendations for early diagnosis and screening.

Table 2. Total DISCERN and GQS scores for determined topic headings

Topic heading	Total DISCERN score	GQS score
Rectal cancer symptoms	44	5
Colon cancer	43	5
Colon cancer symptoms	45	4
Rectal cancer surgery	57	5
Rectal cancer treatment	61	5
What is rectal cancer?	54	4
Intestinal cancer symptoms	51	4
What causes rectal cancer?	53	4
What is colon cancer?	58	4
Blood from the anus	66	5
Colon and rectal cancer	57	4
Experiences of those with rectal cancer	56	5
Stage 1 rectal cancer symptoms	51	5
Experiences of those with colon cancer	56	5
What causes colon cancer?	51	3
Colon cancer life expectancy	57	4
Stage 4 colon cancer	59	5
Rectal cancer life expectancy	58	3
Stage 3 colon cancer survival chance	56	3
What is a colon?	58	5
Average (SD)	**54.55 (SD=5.75)**	**4.35 (SD=0.75)**

SD: Standard deviation, GQS: Global Quality Score

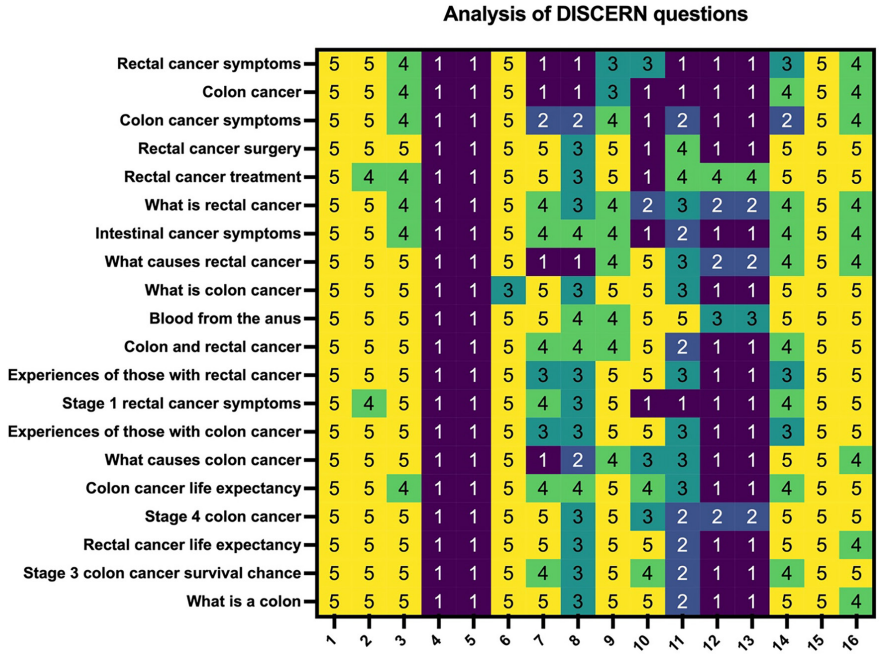

Figure 2. Analysis of DISCERN questions according to topic headings

The nine most frequently used words across all texts were observed to be “cancer” (215 occurrences), “colon” (189), “treatment” (142), “symptoms” (98), “stage” (87), “surgery” (76), “chemotherapy” (64), “life” (61), and “risk” (59). The frequency and cross-connections of the words used in the text are presented in Figure 4.

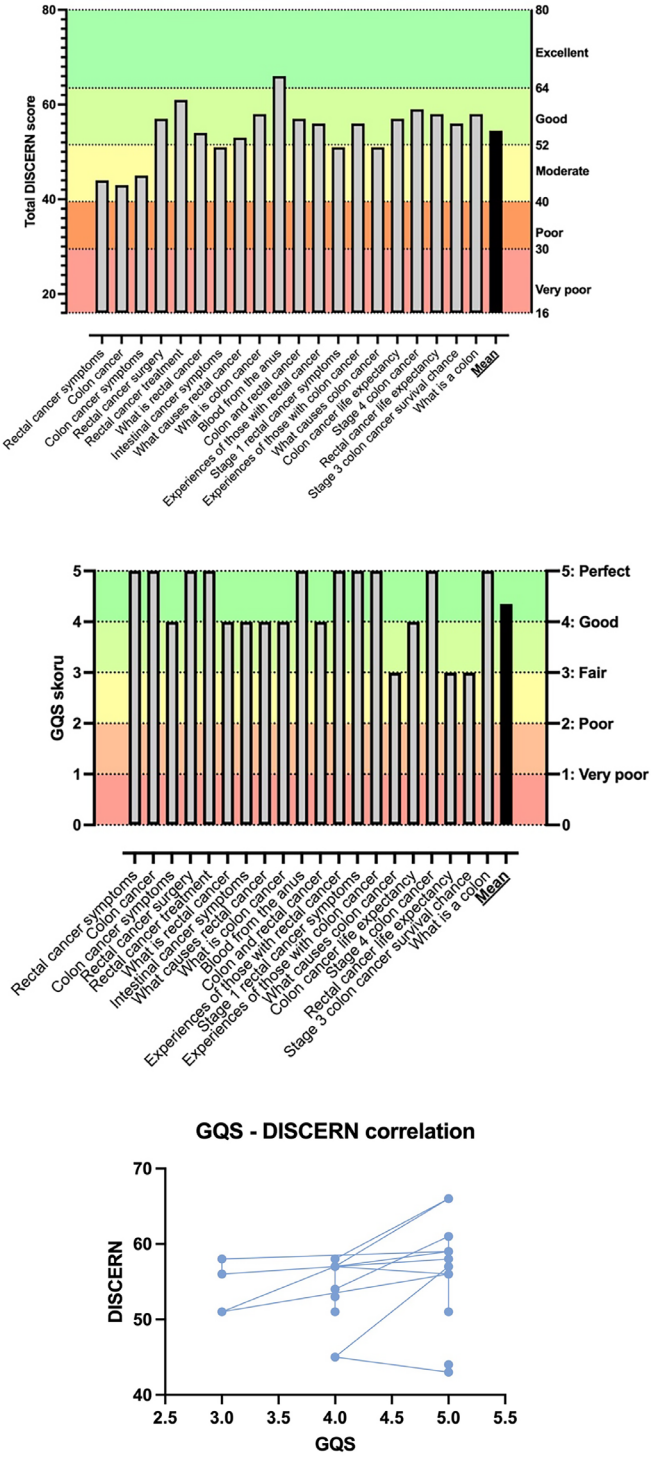

Figure 3. DISCERN and Global Quality Score (GQS) quality analysis and correlation

Discussion

In our study, the readability and quality levels of the responses provided by the ChatGPT o1 model to the most frequently searched patient questions related to colorectal cancer were examined. The results indicate that the responses from the ChatGPT o1 model possess a moderate level of readability and good quality.

Readability is critically important for patients to understand and apply health-related information. The Ateşman [9] and Çetinkaya and Uzun [10] readability formulas are reliable tools for determining the readability levels of Turkish texts. The readability scores obtained in our study demonstrate that the responses from the ChatGPT o1 model are generally understandable to the public. Specifically, according to the Çetinkaya-Uzun score, the texts are at a 5th-7th grade reading level, indicating that even individuals with low education levels can comprehend this information. This readability level is consistent with the internationally accepted 6th-grade readability standard for medical articles aimed at the public [11]. Additionally, it was observed that English terms that may slightly reduce comprehensibility were included in the responses generated by the ChatGPT o1 model. A limitation of the readability formulas is that they are solely based on words, syllables, and sentences. Therefore, the readability scores do not account for words originating from other languages.

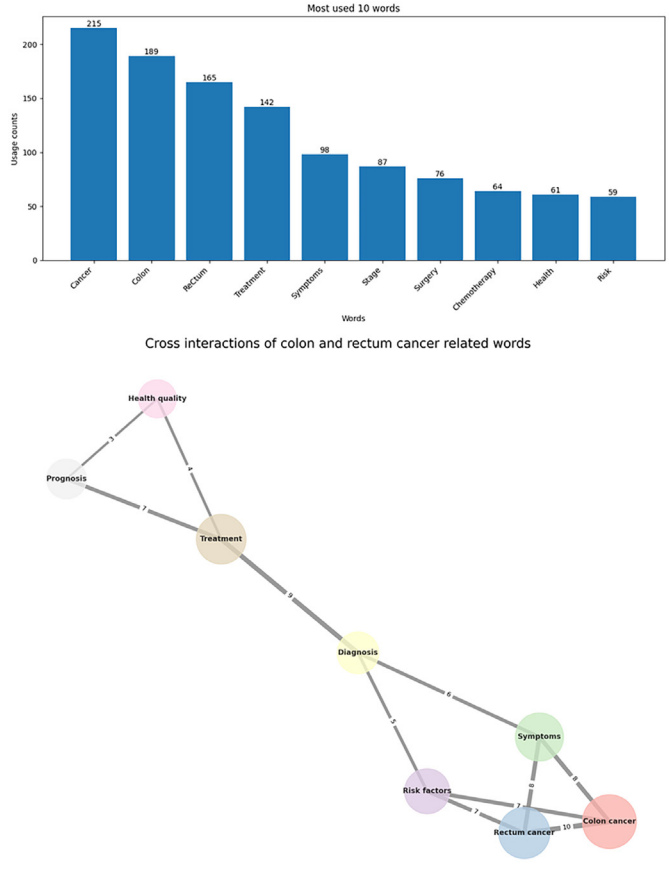

Figure 4. Word frequency and cross-connections graph in qualitative analysis

The DISCERN and GQS scores used in the quality assessment provide important information about the reliability and usability of health information materials. The average total DISCERN score is in the good quality range, and the GQS scores range between good and excellent. This suggest that the ChatGPT o1 model is capable of generating responses that meet patients' informational needs. However, the requirement for references in the DISCERN score and the inclusion of questions regarding the benefits and harms of all types of treatments, pose challenges. As these aspects cannot be adequately addressed within the generated texts based on the topic headings, the DISCERN score is insufficient for evaluating AI language models. Customized scoring systems appear to be necessary for the medical evaluation of texts generated by AI language models.

When the obtained scores are compared with other online sources, they can be considered to be of higher quality. It has been observed that approximately one-third of internet videos related to colorectal cancer and cancer screening are of poor quality in terms of information [12]. Additionally, publications report the inadequacy of online information sources concerning potential adverse events following rectal surgery [13]. Furthermore, information obtained from commercially operating websites carries a significant risk of bias [14].

Moreover, there is a risk of generating incorrect information, referred to as "hallucinations" in AI terminology [15]. These findings support the notion that AI language models could be a resource for accessing information in the health sector. However, due to the risk of hallucinations, caution is necessary.

Study Limitations

Our study has several limitations. Firstly, the research focused solely on the top 20 frequently searched topics related to colorectal cancer; therefore, the results may not be generalizable to all types of cancer or medical subjects. Additionally, readability and quality assessments were conducted using specific formulas and scales; the subjective nature of these methods may influence the results. Furthermore, the evaluations are based only on the performance of the ChatGPT o1 model within a specific time frame; future updates to the model and the emergence of more advanced models could alter these findings.

Conclusion

This study demonstrated that the responses provided by the ChatGPT o1 model to the most frequently asked patient questions regarding colorectal cancer have a moderate level of readability and good quality. The findings suggest that the model is a helpful resource for patients in accessing information.

Looking ahead, the implementation of AI in patient knowledge is poised to become even more transformative. Future advancements will likely enhance the accuracy and personalization of the information provided. AI models could integrate real-time updates from the latest medical research, ensuring that patients receive the most current and relevant information.

Moreover, the potential for AI to support patient education is immense. With the development of more sophisticated language models, AI could offer tailored educational content based on individual patient needs and learning styles. As AI continues to evolve, it holds the promise of empowering patients with the knowledge they need to make informed decisions about their health.

Ethics

Ethics Committee Approval-Informed Consent: Since the study was bibliographic in nature, ethical committee approval was not deemed necessary. The ChatGPT AI system was only used during the data collection phase, and it was not utilized in any analyses. The study was conducted in accordance with current and universal ethical standards.

Footnotes

Authorship Contributions

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

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

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Original Article

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Sexuality in Cancer Treatment: Knowledge, Attitudes, and Practices Among Oncology Physicians

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ABSTRACT

Aim: This study aimed to evaluate the knowledge, attitudes, and practices of oncology clinicians regarding sexual health in cancer patients, an often overlooked yet essential component of patient care.

Methods: A cross-sectional survey was conducted among 145 oncology specialists in Türkiye, including medical oncology, radiation oncology, surgical oncology, gynecologic oncology, and hematology professionals. A 31-item questionnaire assessed clinicians' knowledge, attitudes, and practices related to sexual health during cancer treatment. Statistical analyses were performed using Statistical Package for the Social Sciences v25.

Results: A very small proportion of clinicians (3.4%) had received specific training on sexual health in cancer care, while 86.9% expressed a desire for further education. Discussions on sexual health were infrequent, with 15.2% of clinicians never addressing it at treatment initiation and 33.1% never addressing it during follow-up. A lack of time and insufficient knowledge were the most cited barriers. Although 57.9% believed they provided adequate information, 42.1% felt underprepared.

Conclusion: Sexual health remains under-discussed in oncology practice due to limited training and systemic barriers. Enhancing clinician education-especially regarding newer therapies such as immunotherapy-through continuous medical programs is essential. Addressing sexual health proactively may significantly improve the overall quality of life for cancer patients.

Keywords: Cancer treatment, oncology clinicians, quality of life, sexual health

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, affecting both men and women. According to GLOBOCAN 2020 data, it is estimated that nearly 2 million new cancer cases will be diagnosed in the United States [1]. Early-onset cancers, which are diagnosed in patients aged 18 to 49, are increasing in prevalence, especially in developed countries. Although cancer continues to be a significant cause of mortality, survival rates have significantly improved for certain cancer types, such as breast cancer in women and prostate cancer in men. As a result, it is crucial to prioritize the quality of life during treatment and follow-up for cancer patients [2]. As the life expectancy of cancer survivors increases, greater attention must be paid to the side effects of cancer treatments. Among young cancer patients, sexual health should be considered an increasingly important aspect of quality of life [3].

Although sexuality is often overlooked or downplayed for various reasons, it is fundamentally one of the most basic human needs. In this context, discussing sexual health with patients and providing recommendations when necessary becomes crucial. Regardless of the cancer type, it is expected that clinicians transparently explain the potential side effects of treatments and interventions on sexual health, as well as the preventive measures that can be taken, throughout the course of cancer treatment [3]. Chemotherapy, radiotherapy, surgery, and hormonal treatments can negatively affect sexual health in both men and women with cancer due to multifactorial physical, psychological, and sociocultural factors [4]. For example, a survey conducted among women with breast cancer observed that sexual activity, reported at 71.9% before chemotherapy, decreased to 47% by the end of chemotherapy [5]. In general, the most common sexual problems reported in men are erectile dysfunction and decreased libido, while

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in women, the most common sexual issues include vaginal dryness, other genital changes causing pain during sexual activity, and loss of sexual desire [6]. In a study conducted by Özbek and Kılıç Uçar [7], sexually active women with cancer were evaluated. It was found that 55% of the patients experienced sexual problems after their diagnosis, with only 29.2% of those experiencing issues shared this with healthcare providers. In another study by Flynn et al. [8], 74% of cancer patients reported that discussing sexual issues with oncology specialists was important. However, the percentage of patients who received information about sexual function varied by cancer type (23% for lung cancer, 29% for breast cancer, 39% for colorectal cancer, and 79% for prostate cancer). Clearly, despite the high prevalence of sexual problems in both men and women, these issues are seldom discussed with patients and healthcare providers.

Based on the current literature and the existing gap in communication between cancer patients and healthcare providers regarding sexual issues, our study aimed to investigate the knowledge and attitudes of oncology professionals towards sexual health in cancer patients. We designed a cross-sectional survey to assess their general knowledge of sexual health and their approach to discussing sexual concerns during the diagnosis and treatment phases. Through this study, we sought to highlight the importance of addressing sexual health issues in oncology care identify areas for improvement in communication between oncologists and patients and ultimately enhance the quality of life for cancer patients.

Methods

Our study is designed as a cross-sectional survey. Based on current information and literature, a questionnaire named the “oncology physicians” knowledge and attitudes regarding sexuality in cancer treatment’ was prepared by the researchers. The survey was distributed online to specialists in medical oncology, radiation oncology, surgical oncology, gynecological oncology, and hematology, who were asked to voluntarily complete the questionnaire. This approach aimed to investigate the specialists’ general knowledge of sexuality and their attitudes towards patients during routine clinical practice. After obtaining ethical approval, the participants were requested to complete the online survey forms between March 1, 2025 and March 31, 2025.

The questionnaire, consisting of a total of 31 questions, ensured the confidentiality of the participants’ personal information. Basic data such as gender, age, area of specialization, professional experience, and the institution at which they work, were recorded. In addition to questions assessing the participants’ basic knowledge on sexual health in cancer patients, questions were specifically included to evaluate their knowledge and attitudes towards patients, particularly at the time of initial diagnosis, and during various stages of treatment. Participants’ responses to these questions were recorded.

Ethical approval for the study was obtained from the Non-invasive Clinical Research Ethics Committee of Uşak University and was conducted in accordance with the Declaration of Helsinki (decision no: 578-578-09, date: 20.02.2025).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences statistics for Windows, version 25 (IBM Corp., Armonk, NY, U.S.A.). Descriptive statistics were presented as frequency distributions and percentages. The chi-square test or Fisher’s exact test was used to compare independent categorical variables. Two-way statistical analyses were conducted in this study, and a p of <0.05 was considered statistically significant.

Our study was planned and conducted in accordance with good clinical practice guidelines. As this was a cross-sectional survey study conducted exclusively among physicians, no patient participation or patient data were involved. All participants were oncology specialists who voluntarily completed the anonymous online questionnaire. Therefore, a signed patient consent form is not applicable in this context.

Results

A total of 145 participants were included in our study. Of the participants, 79 (54.5%) were male and 66 (45.5%) were female. Overall, 126 physicians (86.9%) were aged 45 or younger. Among the participating physicians, 67.6% were medical oncology specialists, 16.6% were radiation oncology specialists, and the remaining 15.9% consisted of hematology, gynecologic oncology, and surgical oncology specialists. The basic demographic characteristics of the participants in our survey are detailed in Table 1.

The majority of participants (n=140, 96.6%) answered “No” to the question posed to the physicians, “Do you ask patients about their sexual preferences during their first treatment?” Various questions were directed at the participants regarding the communication, attitudes, and approaches of physicians when starting treatment, as well as during the follow-up and treatment processes for oncological patients. One of the most important questions in this field, crucial for quality of life in clinical practice, is: “How frequently do you have an informative discussion about sexual health with your patients when starting oncological treatment?” Twenty-two participants (15.2%) answered “I never have such discussions.” Eighty participants (55.1%) stated that they rarely have such discussions, while 28 participants (19.3%) said they sometimes do. Only 13 participants (9.0%) reported that they frequently have discussions on this matter with their patients. In general, it was striking that discussions on sexual health topics remained infrequent. Similarly, when asked “How frequently do you assess or discuss your patients’ sexual health during the follow-up and treatment process?”, 48 participants (33.1%) answered “I never discuss it”. Seventy one participants (49.0%) said “I rarely discuss it. Twenty participants (13.8%) stated that they sometimes have such discussions, while just 5 physicians (3.4%) reported that they frequently

Table 1. Basic demographic characteristics of the participants

Total number of participants: 145		Number (%)
Gender	Male Female	79 (54.5%) 66 (45.5%)
Age	25-35 36-45 46-55 56-65 >65	50 (34.5%) 76 (52.4%) 13 (9.0%) 4 (2.8%) 2 (1.4%)
Medical specialty	Medical oncology Radiation oncology Hematology Surgical oncology Gynecological oncology	98 (67.6%) 24 (16.6%) 10 (6.9%) 12 (8.3%) 1 (0.7%)
Years of experience in the specialty	0-3 year 4-6 year 7-10 year 11-15 year >15 year	56 (38.6%) 44 (30.3%) 21 (14.5%) 11 (7.6%) 13 (9.0%)
Institution type	State hospital Training and research hospital City hospital University hospital Private hospital	12 (8.3%) 51 (35.2%) 3 (2.1%) 62 (42.8%) 17 (11.7%)

have these discussions. In a follow-up question, which aimed to explore the reasons why physicians do not discuss sexual health with their patients and allowed multiple answers, the majority of physicians (n=79, 54.5%) cited, "I don't have enough time" as the reason. The second most common reason was that patients did not wish to discuss this matter (n=73, 50.4%). Similarly, 45 physicians (31.0%) reported that patients were not concerned with this issue. Notably, 28 participants (19.3%) stated that they lacked sufficient knowledge about cancer and sexuality to discuss it with their patients.

Various questions were directed at the participants to assess their practical approaches to discussing sexual health with patients during cancer treatment, aiming to evaluate their general behavior and attitudes in clinical practice. The majority of physicians (n=95, 65.5%) stated that they felt comfortable or very comfortable when discussing these matters with their patients. Notably, most participants (n=120, 82.8%) emphasized that they felt it was essential to discuss sexual health with patients, particularly in cases where the goal is to achieve remission. The questions evaluating the physicians' general behavior and attitudes towards sexuality, along with their responses, are detailed in Table 2.

Following the questions assessing clinicians' general approach and attitudes towards patients, additional questions were posed to examine their general knowledge on sexuality, and their practical approaches during specific treatments. When asked, "Do you think you provide accurate and sufficient information when your patients ask you questions about sexuality?", 84 participants (57.9%) answered "Yes," while 61 participants (42.1%) answered "No." The questions regarding clinicians' knowledge and practical approaches during treatment, along with their responses, are detailed in Table 3.

Among the clinicians involved in the care of cancer patients, a very small proportion (5 participants, 3.4%) had received specific training on sexual health in cancer patients, while 140 participants (96.6%) had not received such training. Finally, when asked, "Would you like to receive training to enhance your knowledge on sexual health during cancer treatment?" 126 participants (86.9%) answered "Yes."

When asked, "Do you think you can provide accurate and sufficient information when patients ask you questions about sexual health?" it was observed that both male and female clinicians responded similarly, with "Yes" responses noted (57.6% for females and 59.0% for males, p=0.86). Similarly, when asked, "Would you like to receive training to enhance your knowledge on sexual health during cancer treatment?", female and male clinicians answered "Yes" at rates of 90.6% and 83.5%, respectively (p=0.19). When comparing based on professional experience, the proportion of participants who answered "Yes" to the first question was as follows: 42.9% for clinicians with 0-3 years of experience, 65.9% for those with 4-6 years, 71.4% for those with 7-10 years, 72.7% for those with 11-15 years, and 66.7% for those with more than 15 years of experience. Although it was observed that the level of knowledge increased with experience, this difference between groups did not reach statistical significance (p=0.05). Similarly, the proportion of participants wishing to receive training was 91.1% for those with 0-3 years of experience and 76.9% for those with more than 15 years of experience (p=0.59). Similar comparisons based on age groups, specialties, and institutions revealed no statistically

Table 2. Evaluation of physicians' general attitudes and behaviors regarding sexuality

Total number of participants: 145		Number (%)
Question	**Response options**	
How do you feel when discussing sexual health with your patients?	Comfortable Fairly comfortable Not very comfortable Uncomfortable	71 (49.0%) 24 (16.6%) 48 (33.1%) 2 (1.4%)
Do you refer your patients to a relevant specialist (psychiatry, urology, gynecology) when you deem it necessary to address sexual health concerns?	Yes No	130 (93.1%) 15 (10.0%)
Which patient group do you particularly feel the need to inform about sexual health?*	Early-stage patients Urogenital/gynecological cancers Advanced/metastatic patients	120 (82.8%) 87 (60.0%) 40 (27.6%)
Which age group of patients do you inform about sexual health?*	18-35 years old 35-50 years old 51-65 years old 66-75 years old >75 years old	131 (90.0%) 131 (90.0%) 73 (50.4%) 29 (20.0%) 17 (11.7%)
Do you think an active sexual life should be maintained during cancer treatment?	Yes No	132 (91.0%) 13 (9.0%)
When discussing sexual health with your patients, which topic(s) do you address?*	Reproductive health Sexual functioning Sexual side effects of treatment	91 (62.8%) 103 (71.0%) 98 (67.6%)
Is there a designated staff member or unit available to support patients with sexual health concerns during cancer treatment?	Yes No	13 (9.0%) 132 (91.0%)

*Multiple selections were allowed for this items

significant differences in knowledge levels and the desire to receive training among the groups.

Discussion

This study highlights that sexual health is often an overlooked area in oncology practice during the cancer treatment process. The findings reveal that clinicians working with cancer patients engage in infrequent discussions and provide minimal information on sexual health, indicating a significant lack of education in this regard. Our study emphasizes the importance of developing a more comprehensive and effective approach to sexual health during the cancer treatment process.

This survey, in which the majority of participants were medical oncologists, provided an opportunity to evaluate the approach of other disciplines, such as hematology and radiation oncology, and offered additional insights. Additionally, it demonstrates the fundamental attitudes and approaches of various populations regarding both professional experience and the institutions at which they work. One of the most notable observations during patient follow-up and treatment was that 15.2% of clinicians had never discussed sexual health with their patients prior to treatment, and 33.1% during treatment, respectively, while 55.1% and 49.0% reported having infrequent discussions. More than half of the participants indicated that the most common reason for these gaps was a lack of time. Receiving a cancer diagnosis can bring about many physical and psychosocial issues. In a study by Özbek and Kılıç Uçar [7]. It was observed that, before cancer diagnosis, 22.5% of female patients reported issues with sexual health, while this rate increased to 55.0% after diagnosis. Furthermore, only one-third of patients shared their sexual problems with healthcare professionals. Similarly, a study by Demirtas and Pinar [9]. on patients with gynecological cancers also showed a statistically significant increase in sexual problems after the cancer diagnosis. Many studies exist in the literature on this topic across various cancers, with sexual health problems during treatment reported in up to 68% of breast cancer patients and 98% of prostate cancer patients [10,11]. As clearly demonstrated by the studies mentioned above, sexual health, a significant cornerstone of quality of life for cancer patients, requires more time and attention. It is crucial that comprehensive and detailed information on sexual health be provided by oncologists and the healthcare team involved in cancer treatment. In addition to routine outpatient services, it may be valuable to have trained personnel create an environment where patients feel comfortable expressing themselves and allow extended time for patient education on this topic.

Although more than half of the clinicians believe they can provide sufficient answers to questions about sexual health, 42.1% of the remaining clinicians reported not feeling adequately knowledgeable on the subject. In response to the question, "Do you recommend active sexual activity during specific treatments?" the number of clinicians who answered "I have no information" for patients undergoing chemotherapy, immunotherapy, targeted therapies, and hormonal treatments was recorded as 12.4%, 18.6%, 17.2%, and 8.3%, respectively. Although this may be attributed to

Table 3. Clinicians' knowledge and practical approaches regarding sexual health in cancer care		
Total number of participants: 145		**Number (%)**
Question	**Response options**	
Do you think you provide accurate and sufficient information when your patients ask questions about sexual health?	Yes No	84 (57.9%) 61 (42.1%)
How knowledgeable do you consider yourself regarding sexual life during oncological treatment?	None Very little/insufficient Moderate Good Excellent	0 (0.0%) 57 (39.3%) 64 (44.1%) 23 (15.9) 1 (0.7%)
In which topic(s) do you feel most inadequate when responding to patients' questions?*	Reproductive health Sexual functioning Sexual side effects of treatment	26 (17.9%) 81 (55.9%) 41 (28.3%)
What source(s) do you use when providing information to your patients about sexual health?*	Current international guidelines Multidisciplinary approach Own clinical knowledge	63 (43.4%) 89 (61.4%) 87 (60.0%)
Do you recommend that your patients receiving chemotherapy maintain an active sexual life during treatment?	Yes, if there are no contraindications It depends on the individual case Yes, with contraception I do not recommend it I have no idea	71 (49.0%) 48 (33.1%) 1 (0.7%) 7 (4.8%) 18 (12.4%)
Do you recommend that your patients receiving immunotherapy maintain an active sexual life during treatment?	Yes, if there are no contraindications It depends on the individual case Yes, with contraception No, I do not recommend it I have no idea	89 (61.4%) 24 (16.6%) 1 (0.7%) 4 (2.8%) 27 (18.6%)
Do you recommend that your patients receiving targeted therapy maintain an active sexual life during treatment?	Yes, if there are no contraindications It depends on the individual case Yes, with contraception No, I do not recommend it I have no idea	89 (61.4%) 26 (17.9%) 1 (0.7%) 4 (2.8%) 25 (17.2%)
Do you recommend that your patients receiving hormonal therapy maintain an active sexual life during treatment?	Yes, if there are no contraindications It depends on the individual case Yes, with contraception No, I do not recommend it I have no idea	107 (79.3%) 20 (13.8%) 0 (0.0%) 6 (4.1%) 12 (8.3%)
Do you recommend that your patients receiving radiotherapy maintain an active sexual life during treatment?	Yes, if there are no contraindications It depends on the individual case Yes, with contraception No, I do not recommend it I have no idea	72 (49.7%) 42 (29.0%) 0 (0.0%) 9 (6.2%) 22 (15.2%)
*Multiple selections were allowed for this items		

the multidisciplinary nature of the groups participating in the study, it is important to enhance knowledge and training in this area. A recent cross-sectional survey conducted with 2,530 oncology nurses highlighted that they have a moderate level of knowledge and a positive attitude regarding sexual health, supporting the need for broader training initiatives in this field [12]. In our current study, among clinicians specifically involved in the care of cancer patients, only 5 participants (3.4%) had received specific training on sexual health in cancer patients. Additionally, when asked, "Would you like to receive training to enhance your knowledge on sexual health during cancer treatment?," 126 participants (86.9%) responded affirmatively. Interestingly, although the increase in knowledge level was not statistically significant, there was a noticeable trend, whereby clinicians' knowledge improved with increasing professional experience. Taken together, these findings suggest the need to develop continuous medical education programs that include sexual health, especially regarding emerging treatment approaches such as immunotherapy and targeted therapies.

Study Limitations

This study has some limitations. First, the study included not only medical oncologists but also clinical specialists from various oncology disciplines such as hematology, radiation oncology, gynecological oncology, and surgical oncology. This broad range of participants allows for a more generalized perspective in evaluating the results, however, the heterogeneous sample may still limit the ability to clearly

delineate the differences in attitudes and practices related to sexual health within each discipline. Furthermore, since the knowledge gaps and attitudes regarding sexual health are based on self-assessment, the accuracy of responses may be limited by personal perceptions and how openly the survey participants were able to express themselves. The study was also conducted solely in oncology clinics in Türkiye, and cultural and geographical factors may affect the applicability of the results in other countries. Moreover, as the responses were based on self-assessment, they may reflect subjective perceptions. Furthermore, cultural norms might have influenced participants' openness and frequency in addressing sexual health issues. Additionally, the cross-sectional nature of the data limits the ability to establish causal relationships. Long-term follow-up studies will provide an opportunity to more thoroughly examine the effects of education and changes in attitudes within this field.

Conclusion

This study has highlighted that sexual health during cancer treatment is often overlooked and emphasized a significant knowledge gap in this area. Addressing the sexual health issues encountered by patients undergoing cancer treatment and improving their quality of life is an essential part of oncology practice. The study's findings indicate the importance of dedicating more time to sexual health in clinical settings and the inclusion of trained healthcare personnel in this regard. In addition to clinical settings, it is crucial for oncology specialists to receive continuous education on sexual health in order to provide more effective counseling during the treatment process. In this context, awareness of sexual health should be increased, and educational programs in this area should be strengthened. Patients experiencing sexual health issues during cancer treatment should be addressed not only with treatment but also with psychosocial support. This study, by drawing attention to this important issue, has provided a solid foundation for future research.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Non-invasive Clinical Research Ethics Committee of Uşak University and was conducted in accordance with the Declaration of Helsinki (decision no: 578-578-09, date: 20.02.2025).

Informed Consent: Our study was planned and conducted in accordance with good clinical practice guidelines. As this was a cross-sectional survey study conducted exclusively among physicians, no patient participation or patient data were involved. All participants were oncology specialists who voluntarily completed the anonymous online questionnaire. Therefore, a signed patient consent form is not applicable in this context.

Footnotes

Authorship Contributions

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

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The Effect of Intraoperative Boost Dose Radiotherapy on Wound Complications in Breast Cancer Patients Operated with Upper Outer Quadrantectomy by Using Intraglandular Flap Mobilization Technique

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ABSTRACT

Aim: In this study, the technical aspects of intraoperative radiotherapy (IORT) application and its effect on early wound complications were evaluated.

Methods: Fifty consecutive patients operated with upper outer quadrantectomy and intraglandular flap mobilisation and given IORT between 2013 and 2014 were included. Radiotherapy at a boost dose of 10 Gy was given to 21 patients. The control group consisted of 29 patients who were operated with the same surgical technique but were not given IORT.

Results: The median age of the patients was 51.5±10.9 years. The average specimen weight was 266±83 g. The surgical resection margin evaluation with frozen section was negative in all patients. Four patients were reported to have involved margins at permanent sections. When both groups were compared in terms of early postoperative complications, there were 6 (28.5%) patients with seroma in the IORT group and 2 patients (6.8%) in the control group. While 5 (23.8%) patients were seen to have surgical site infection (SSI) in the IORT group, there was no SSI in the control group. There were 7 (33.3%) patients with delayed wound healing in the IORT group and 2 patients (6.8%) in the control group. While 2 (6.8%) patients had hematoma in the control group, there was no hematoma in the IORT group. While one (4.7%) patient was seen to have minor wound dehiscence in the IORT group, there was no wound dehiscence in the control group.

Conclusion: In this study, we concluded that IORT may negatively impact wound healing by increasing the incidence of seroma, SSI, and delayed wound healing in patients undergoing oncoplastic breast surgery. Increased awareness and preventive measures are necessary, especially in centers newly implementing IORT.

Keywords: Breast cancer, breast conserving surgery, complication, intraoperative radiotherapy

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Introduction

Loco-regional treatment of breast cancer aims to resect cancer with safe surgical margins and decrease local recurrences to the greatest extent possible. Nowadays, given the increased survival times, maintaining the body integrity of patients with an emphasis on aesthetic outcomes has become a target. With traditional breast conserving surgery (BCS) techniques, the preservation of the natural shape of the breast or the correction of deformities of previous biopsy sites is not always possible. Oncoplastic breast surgery (OBS) is one of the most intriguing areas of surgical oncology in recent years, with increasing applications to obtain better cosmetic results. OBS offers advantages such as wider surgical margins, fewer reoperation rates, and better cosmetic results [1]. The upper outer quadrant is the area where breast tumors are most frequently located. Therefore, the most common surgical procedures are performed in this quadrant. Volume displacement techniques are effective methods that are frequently used in OBS for upper external quadrant tumors, and the best-defined intraglandular flap technique is used with a racket incision [2].

Adjuvant whole breast irradiation and boost dose of radiotherapy to the tumor bed after OBS are a standard approach. Intraoperative radiotherapy (IORT), which is a type of partial breast irradiation (PBI), is increasingly used today because it shortens the duration of treatment and protects surrounding tissues such as the heart, lungs, and normal breast tissue [3]. In IORT implementation, intervening with external equipment occurs when a surgical open wound is present. The effects of the intervention on wound complications should be known, as these complications are the most important factors that negatively affect cosmetic results.

This study was planned to investigate the effect of IORT on early wound complications in patients operated on using OBS with a racket incision for the tumors located in the upper external quadrant of the breast.

Methods

Study Design

Fifty consecutive patients operated with the same surgical technique (upper outer quadrantectomy with intraglandular flap mobilisation) were included. Among these patients, the group of patients with IORT as a boost to the tumor bed with mobile Mobetron (Intraop Medical Incorporated, SantaClara, CA), constituted the study group. Patients who did not receive IORT constituted the control group.

The incisions defined for upper external quadrantectomy were radial and fusiform, in shape, through the tumor bed, including the removal of the skin over the tumor. The incision was extended from the axillary hair area to the areola. The sentinel lymph node was found with the help of a gamma probe and guided to the frozen section using this incision. Subsequently, skin flaps were prepared medially to the upper border of the mammary gland and laterally to the breast sulcus using the subcutaneous plan employed in mastectomy. A fusiform-shaped excision centered on tumor tissue was made with inclusion of subcutaneous tissue and pectoral fascia. After removal of specimen, a frozen section evaluation was performed for 4 sides and the base. Metallic clips were placed for the pectoral muscle, and lateral surgical margins. Later, the breast tissue was mobilized from the pectoral fascia to the limits prepared by the flaps. In the control group, the cavity was closed with glandular flaps sewn together with absorbable sutures (Figure 1). In patients with IORT, the flaps were temporarily approximated by placing an acrylic disc underneath. Subsequently, IORT was administered by placing the appropriate applicator with a 10 Gy boost dose (Figure 2). After completion of radiotherapy, temporary sutures of the flaps were opened, acrylic disc removed, and mobilized glandular flaps were sutured to each other and to the muscle. The crescent-shaped skin was de-epithelialized at the areola opposite the incision. The Nipple areola complex, is sewn to the de-epithelialized area in the center of the re-shaped breast. Skin was closed at subcutaneous plane. Level 1-2 axillary dissection was performed using the same incision for sentinel lymph node biopsy (SLNB) positive disease. There was no drain in the lumpectomy field. A negative pressure aspiration drain was placed in patients undergoing axillary dissection. Adjuvant external radiotherapy was applied in all patients in the study and control groups.

The age, radiological, and pathological tumor size, the distance of tumor to areola, skin and pectoralis muscle, flap thickness, hormone receptors and CERB-B2 status, and co-morbid diseases of the patients were recorded. Wound complications were evaluated in two groups: minor complications and major complications. Seroma, hematoma, surgical site infection (SSI), delayed wound healing, and minor incisional dehiscence were studied in the minor group. Major wound dehiscence was studied in the other group.

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, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2014/356, date: 15.05.2014). Written informed consent was obtained from all individual participants included in the study.

Statistical Analysis

The Statistical Package for the Social Sciences software, version 17, (Inc, Chicago, USA) was used for statistical analysis. The Kolmogorov-Smirnov and Levene tests were used to assess the homogeneity and normality of the scaled data. Pearson's chi-square and Fisher's tests were used to evaluate each group's nominal data; $p<0.05$ was deemed statistically significant.

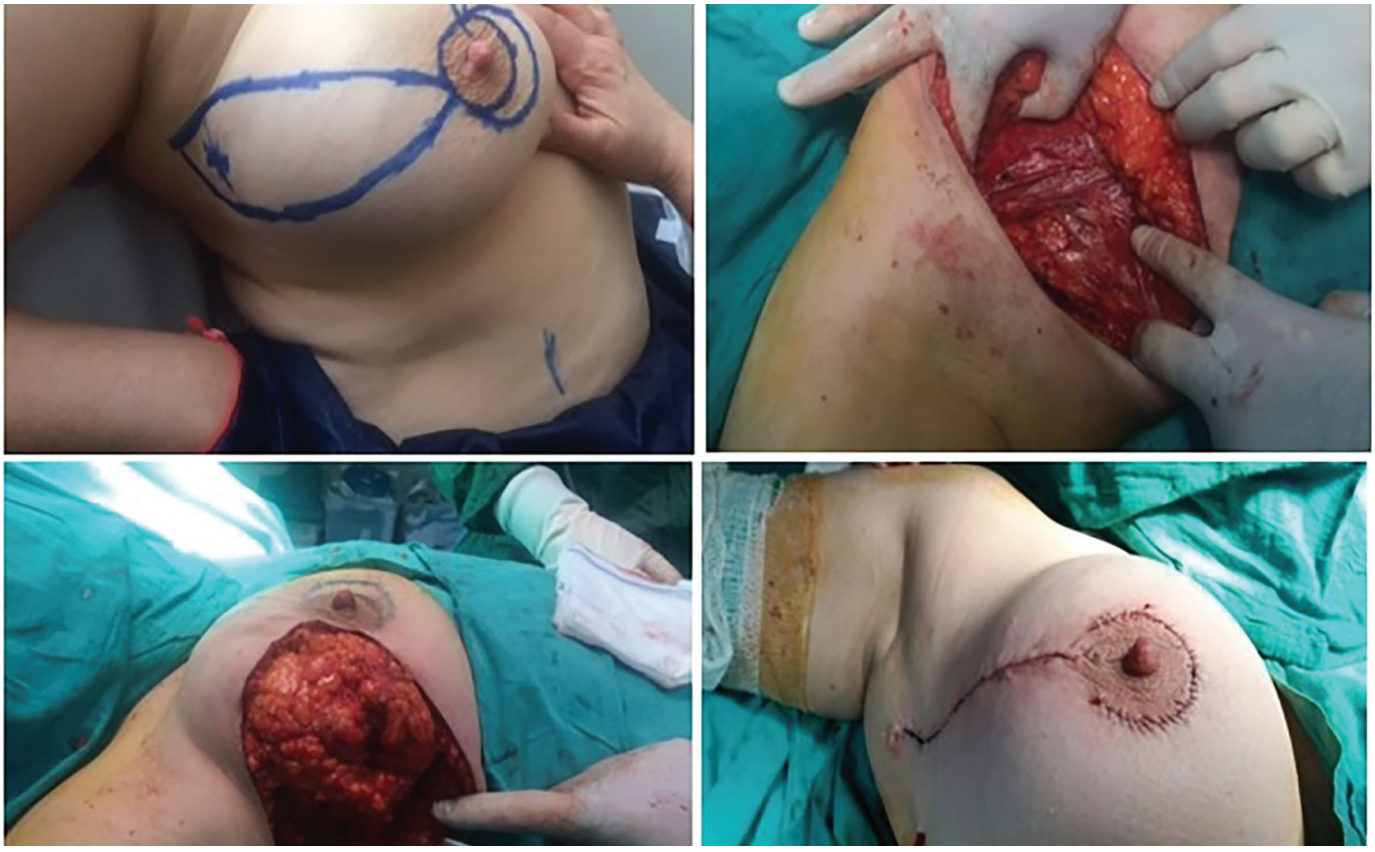

Figure 1. Incision, resection site, reconstruction with intraglandular flaps and postoperative view

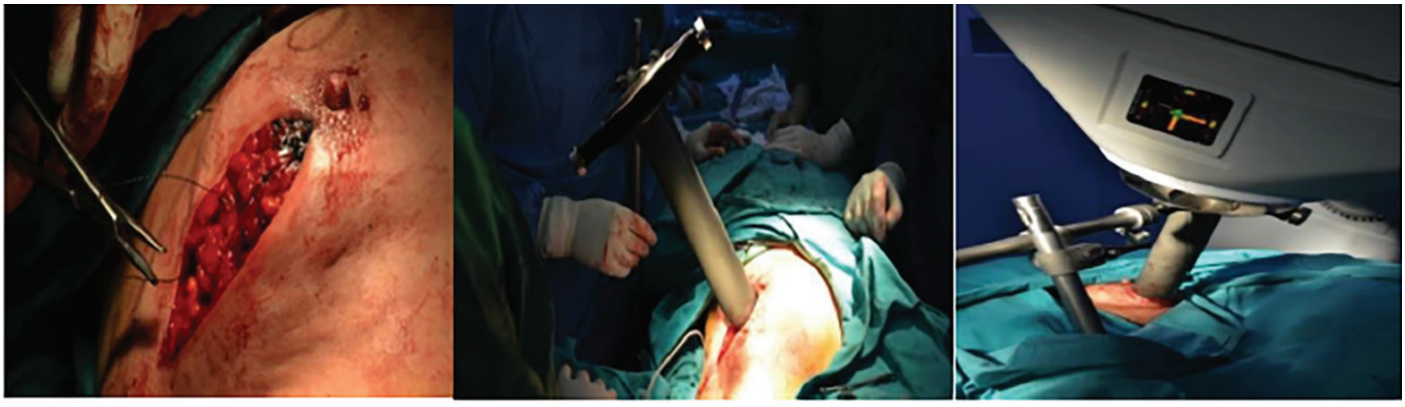

Figure 2. Temporary fixation of the flaps after placement of the acrylic disc, placement of the applicator and application of IORT
IORT: Intraoperative radiotherapy

Results

Fifty consecutive patients operated with the same surgical technique (upper outer quadrantectomy with intraglandular flap mobilisation) and who received IORT (n=21) or did not receive IORT (n=29) were included. The median age of the patients included in the study was 51.5±10.9 years. While the median size of the tumors at radiological examination was 16±5.9 mm, it was 19.5±8 mm at pathological examination. The average distances of the tumors to the skin, areola and pectoralis major muscle were measured as 2 cm, 4 cm and 2 cm, respectively. While the average skin flap thickness was 1.6 cm, the average specimen weight was 266±83 g. The incision sizes in the IORT group and the control group were 11.9±2.3 and 12.1±1.9, respectively. Estrogen receptor, and progesterone receptor were positive in 41 and 27 patients, respectively, and CERB-B2 was negative in 33 patients. The grade distribution of the patients from 1 to 3 was 5, 32, and 13 patients, respectively. The surgical resection margin evaluation with frozen section was negative in all patients. The general characteristics of the patients in both groups are summarized in Table 1.

The preparation time for IORT after resection in patients in the IORT group was 25 minutes. The average RT duration was 2 minutes. SLNB was performed in 46 of 50 patients. Four patients with clinically present axillary metastases were

treated with dissection. Axillary dissection was applied in 11 of the SLNB treated patients, as the frozen result proved to be carcinoma metastasis. There was no statistically significant difference between IORT and control group, with respect to age, radiological and pathological tumor size, the distance of tumor to areola, skin and pectoralis muscle, flap thickness, weight of the specimen and tumor characteristics (hormone receptors, grade and CERB-B2 status) (Table 1).

When both groups were compared in terms of early postoperative complications, there were 6 (28.5%) patients with seroma in the IORT group and 2 patients (6.8%) in the control group ($p<0.05$). While 5 (23.8%) patients were seen to have SSI in the IORT group, there was no SSI in the control group ($p<0.05$). There were 7 (33.3%) patients with delayed wound healing in the IORT group, and 2 patients (6.8%) in the control group ($p<0.05$). While 2 (6.8%), patients had hematoma in the control group, there was no hematoma in the IORT group. While one (4.7%) patient was seen to have minor wound dehiscence in IORT group, there was no wound dehiscence in control group. There was no statistically significant difference between the groups, with respect to hematoma and minor wound dehiscence incidence ($p>0.05$). There was no major wound dehiscence in either group (Table 2).

While 8 patients in the IORT group experienced early wound complications, complications were observed in 4 patients in the control group. While 9 (42.8%) patients underwent axillary dissection in the IORT group, 6 (20.6%) patients had axillary dissection in the control group. Axillary dissection application ($p>0.05$) and comorbidities ($p>0.05$) had no effect on early wound complications.

Discussion

Application of 45-50 Gy to whole breast after BCS, followed by 10-16 Gy boost to tumor bed, is accepted as standard in early breast cancer. The role of boost application on local control has been shown in several studies [4]. In a randomized trial by EORTC comparing patients with BCS who received and did not receive boost radiotherapy, it was found that 50 Gy of whole breast radiotherapy followed by 16 Gy of boost application to the tumor bed showed a significant improvement in local control [5]. While the target volume for boost dose is being determined, the resection borders of the tumor bed are very important [6]. There may be shifts in the tumor bed during the mobilization of glandular flaps, prepared to fill the cavity required for reconstruction. The clips placed in the tumor bed can also be displaced. When boost area is determined by external radiotherapy techniques, there are some concerns about the location and the larger volume of the tumor bed. With IORT, the entire dose of therapeutic radiotherapy can be given in a single fraction, to the surgical bed directly in the operating room. As the patient selection criteria are still not clear, only the boost dose is given as IORT in our center, while whole breast irradiation is given in the form of external radiotherapy. Immediately after the tumor has been surgically removed, the necessary boost dose can be applied directly as

Table 1. Distribution of demographic and clinical factors according to IORT and control groups

Demographic and clinical factors	No. of patients (%) IORT control (21 patient 42%) (29 patient 58%)		p
Age, year, median, range	51	49	$p=0.4^{U}$
Radiological dimension, mm, median	17	15	$p=0.2^{U}$
Pathological dimension, mm, median	20	19	$p= 0.1^{U}$
Distance to pectoral muscle, mm, median	25	28	$p=0.4^{U}$
Distance to areola, mm, median	35	40	$p=0.3^{U}$
Distance to skin, mm, median	20	27	$p=0.2^{U}$
Flap thickness, mm, median	15	15	$p=0.1^{U}$
Incision size, mm, median	11	12	**$p=0.09^{U}$**
Weight, gr, median	260	240	$p=0.4^{U}$
ER status: n (%) Absent Present	 3 (14.2%) 18 (85.8%)	 6 (20.6%) 23 (79.4%)	p=0.42
PR status: n (%) Absent Present	 9 (42.8%) 12 (57.2%)	 14 (48.2%) 15 (51.8%)	p=0.42
Her 2 status: n (%) Absent Present	 15 (71.4%) 6 (28.6%)	 19 (65.5%) 10 (34.5%)	p=0.42
Grade: n (%) Grade 1 Grade 2 Grade 3	 4 (19.1%) 11 (52.3%) 6 (28.6%)	 1 (3.4%) 21 (72.4%) 7 (24.1%)	p=0.12

SD: Standard deviation, X^2: Chi-square test, ^{U}: Mann-Whitney U test, IORT: Intraoperative radiotherapy, ER: Estrogen receptor, PR: Progesterone receptor

Table 2. Distribution of general complications

Complications	No. of patients (%) IORT control (21 patient 42%) (29 patient 58%)		p
Seroma status: n (%) Absent Present	 15 (71.4%) 6 (28.6%)	 27 (93.1%) 2 (6.9%)	**p=0.042**
Surgical site infection: n (%) Absent Present	 16 (76.1%) 5 (23.9%)	 29 (100%) 0 (0%)	**p=0.0052**
Hematoma: n (%) Absent Present	 21 (100%) 0 (0%)	 27 (93.1%) 2 (6.9%)	p=0.22
Minor wound dehiscence: n (%) Absent Present	 20 (95.2%) 1 (4.8%)	 29 (100%) 0 (0%)	p=0.12
Delayed wound healing: n (%) Absent Present	 14 (66.6%) 7 (33.4%)	 27 (93.1%) 2 (6.9%)	**p=0.0062**

χ^2: Chi-square test, IORT: Intraoperative radiotherapy

IORT without any further intervention on the tumor bed. In this way, tissue displacement problems seen during OBS can be avoided and and an effective and homogeneous dose was applied with high accuracy to a smaller volume compared to external radiotherapy with complete protection of surrounding tissues (heart and lung). As a result, the skin can be moved away from the irradiated area, skin reactions are reduced, and better cosmetic results can be obtained [7]. Tumor proliferation and invasion can be prevented by the destruction of tumor cells in the microenvironment, through instantaneous high-dose administration to the tumor bed with IORT. Moreover, as the interval between surgery and radiotherapy disappeared, repopulation of microscopic residual cells was blocked. Because the rich vascular structure and aerobic metabolism are not distorted yet, compared to externally administered boost treatment, IORT boost treatment is considered more effective in terms of radiobiology [8]. However, during IORT, while an open wound is present, manipulations are performed and radiation is given. This situation raises increased concern about the early postoperative infective and non-infective complications that pose a risk of deterioration of cosmetic results.

In the TARGIT study comparing external radiotherapy with IORT, the rates of hematoma, seroma, wound dehiscence, and SSI in the IORT group were 1%, 2.1%, 2.8% and 1.8%, respectively. These rates were reported as 0.6%; 0.8%; 1.9%; and 1.3% in the external radiotherapy group. Statistically, only seroma formation was found to be significantly higher in the IORT group [9]. In this study, hemorrhages requiring surgical exploration were considered a hematoma, while SSI was defined as that requiring antibiotherapy and surgical drainage. The low rates of wound complications in this study may be related to the descriptions of complications. Ruano-Ravina et al. [10] reviewed 15 reports and investigated the safety of IORT in comparison with external radiotherapy. In this review, seroma was the most common wound complication following fibrosis and skin reactions in patients receiving IORT. These complications are significantly higher than in patients receiving external radiotherapy, and the rates vary between 3-25%. In a study of 55 patients reported from Australia investigating early IORT complications, seroma was encountered in 28 patients (51%) [11]. In a study reported from China and including 72 patients who underwent IORT, the mean time for complete healing of the BCS incision was 13-22 days in the IORT group and 9-14 days in the EBRT group [12].

The effects of administering high doses of radiation to a radiobiologically limited area have been studied *in vitro* and may account for increased infective and non-infective complications. This suggests that in the new microenvironment created after radiotherapy, tissue composition is altered and signaling pathways to initiate wound healing are not activated. In addition, a decrease in blood circulation due to vascular damage after radiotherapy is a mediator of this process [13,14].

In our study, the rates of seroma, SSI, and delayed wound healing were significantly higher in the group receiving IORT compared to the group not receiving IORT among patients who underwent OBS for an upper outer quadrant tumor. In addition to the effects of high-dose radiotherapy applied to a limited area, possible factors should also be questioned in this procedure where manipulative procedures are performed. After resection, the protective disk and the appropriate applicator are placed in the surgical field, and then the operating table is shifted towards the IORT device and adjustments are made. In addition to the surgical team, radiotherapy specialists, technicians, and physical engineers are also involved in the operating room. After resection, the IORT procedure takes approximately half an hour to perform. Prolonged operation time, loss of sterility during procedures, and the presence of excess personnel beyond the surgical team in the room may be other factors that increase the complication rates.

Study Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small (n=50), which may limit the statistical power and generalizability of the findings. Second, the analysis focused only on early postoperative wound complications, without long-term follow-up data on late complications, cosmetic outcomes, or oncological efficacy. Third, as this was a single-center study, the results may reflect the specific surgical and radiation techniques, patient selection criteria, and institutional protocols used in our center, limiting broader applicability. Additionally, this study represents the early experience with IORT in our institution, and procedural learning curves or increased operating room traffic during IORT delivery may have influenced complication rates. Finally, potential confounding factors such as surgeon variability, perioperative antibiotic protocols, and wound care practices were not analyzed in detail and could have impacted outcomes.

Conclusion

The effect of IORT on complications in patients who underwent OBS may indirectly and negatively affect treatment outcomes and cosmetic results. In this study, which represents our first experience with IORT, we concluded that IORT has negative effects on seroma, SSI, and wound healing. Consider that wound complications may increase in centers where IORT is newly applied. Necessary precautions should be taken to prevent compromise of sterile conditions in the operating room, and wound healing of the patients should be carefully followed. With increasing experience in this field, better outcomes can be achieved. Reporting the results of studies with higher patient volumes from centers where IORT has been applied for a long time will contribute to the understanding of this treatment approach.

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, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2014/356, date: 15.05.2014).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

Footnotes

Authorship Contributions

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

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Original Article

Clinical Outcomes of Endocrine Therapy Plus CDK4/6 Inhibitors in Elderly Patients with HR+/HER2-Low Metastatic Breast Cancer

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ABSTRACT

Aim: The combination of endocrine therapy (ET) and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is the current standard treatment approach for patients with hormone receptor-positive (HR+) / human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). However, studies specifically evaluating the efficacy of this standard treatment in elderly patients within the HER2-low subgroup, which is considered a new entity, are limited. The aim of our study was to investigate the treatment efficacy and survival data for this specific group.

Methods: Patients with HR+/HER2- MBC defined as HER2-low (+1 or +2 by immunohistochemistry and negative by *in situ* hybridization) who were followed up between 2019 and 2023 were included in the study. The results of 92 patients over the age of 65 who received a CDK4/6 inhibitor and ET for at least 3 months were evaluated.

Results: Our study evaluated 92 patients ≥65 years and older. Survival analyses were conducted for the HER2-low and HER2-zero groups. The median overall survival (OS) for all patients was 108 months [95% confidence interval (CI): 64-152]. In the HER2-low group, the median OS was 88 months (95% CI: 22-154), whereas the median OS was not reached in the HER2-zero group (p=0.054). Although not statistically significant, the difference between the two groups is clearly observed in the Kaplan-Meier graph. Median progression-free survival (PFS) for the overall population was 27 months (95% CI: 15.9-38.1). Similarly, when mPFS was compared between the two groups, outcomes were better in the HER2-zero group, with a median of 34 months (95% CI: 28.8-39.1) versus 17 months (95% CI: 9.2-24.8), which was statistically significant (p=0.026).

Conclusion: The behavior and prognosis of the HER2-low subgroup are still being investigated in recent studies. Our study indicated that the HER2-low group might be associated with poorer survival outcomes and treatment resistance to CDK4/6 inhibitors and endocrine therapy in elderly MBC patients.

Keywords: Cyclin-dependent kinase 4/6 inhibitors, hormone therapy, aged

Introduction

Despite therapeutic advancements, breast cancer remains the most prevalent cancer in women and ranks second in cancer-related mortality [1]. Despite new treatment developments, metastatic breast cancer (MBC) is not yet considered a curable disease. Breast cancer includes different intrinsic subtypes, each with different treatment approaches and prognoses [2,3]. The majority of MBC cases are hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-). The combination of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors and endocrine therapy (ET) has shown efficacy and safety, and has is proven as standard treatment in first-line and subsequent treatment lines [4,5]. Approximately 20% of all breast cancer cases exhibit HER2 overexpression. Before HER2-targeted therapies, this subtype was associated

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with poor prognostic outcomes [6]. Recently, patients exhibiting 1+ and 2+ results via immunohistochemistry (IHC) and testing negative for HER2 using *in situ* hybridization (ISH) were defined as the *HER2-low expression* group.

The HER2-low group represents approximately half of the HER2-non-amplified population. Although the HER2+ group was effectively treated with anti-HER2 monoclonal antibodies for an extended period, the efficacy in the HER2-low group was insufficient [7,8]. Until the results of the latest clinical trials, the prognostic impact of this subgroup was not fully understood, and there was no consensus on the approach to these patients. However, the efficacy of trastuzumab deruxtecan, an antibody-drug conjugate, has been demonstrated in this subgroup, establishing its significance among subsequent-line treatment options [9].

HER2-low breast cancer, similar to HER2+ breast cancer in clinical practice, can be either HR+ or HR-. It may achieve improvements in progression-free survival (PFS) and overall survival (OS) in the metastatic setting through a combination of targeted therapies and hormone therapy [10,11].

Aberrant signaling within growth factor receptor pathways has been recognized as a major contributor to ET resistance in HR+ cancer cells. Clinical and experimental findings indicate that the bidirectional interaction between estrogen receptor and HER2 signaling pathways significantly influences this resistance, potentially leading to treatment failures [12]. Therefore, this situation led researchers to evaluated the treatment efficacies of the HR+/HER2-low group.

Elderly patients are an important population for breast cancer, and considering the increasing incidence of cancer and the different biological behavior of tumors, it is necessary to further investigate the effectiveness of treatment in this subgroup [13].

Age-related changes in pharmacokinetics, pharmacodynamics, and the tumor microenvironment may alter treatment responses and survival outcomes. Which can significantly affect the efficacy and tolerability of cancer treatments [14]. Geriatric patients, particularly those over 65, are frequently underrepresented in clinical trials, leading to a gap in evidence regarding the safety and efficacy of treatments in this group [15]. By focusing on this group, we aim to address this important gap in research and provide insights into how CDK inhibitors may offer tailored treatment strategies, particularly in HER2-low and HER2-zero populations. Several multicenter studies have evaluated the efficacy of CDK4/6 inhibitors and ET for HR+/HER2- MBC in elderly patient groups and have shown that it is generally an effective and tolerable treatment option [16,17]. Another important point is that while there are studies demonstrating the efficacy of CDK 4/6 inhibitors and ET in both the HER2-low and HER2-zero groups, research in the elderly patient population is limited.

The primary aim of the study was to compare the PFS of HER2-low and HER2-zero groups in elderly HR+/HER2- patients receiving CDK4/6 inhibitors and ET. Secondarily, it aimed to evaluate the effects of certain prognostic parameters on PFS, and compare the OS outcomes between the HER2-low and HER2-zero groups.

Methods

Patient Population and Data Collection

The study includes patients aged 65 years and older, with histologically confirmed metastatic HR+/HER2- breast cancer who were monitored between 2019 and 2023, and tolerated treatment with a CDK4/6 inhibitor for at least 3 months.

Patients with a HER2 status of 0 or +1 by IHC or those with a HER2 status of +2 by IHC, but determined to be HER2-negative by ISH, were included in the study. Patients were categorized into two groups: HER2-low (patients with a HER2 status of +1 or +2 by IHC) and HER2-zero (patients with a HER2 status of 0 by IHC). Patients with a second malignancy, those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1, and males were excluded from the study. Systemic treatments and outcomes of 92 eligible patients were recorded.

Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/69, date: 17.04.2025). Since the data were collected from medical records without revealing the identities of the participants and the study was retrospective, consent was not obtained from the patients.

Statistical Analysis

Survival outcomes were analyzed using the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Categorical data were presented as counts and proportions (n, %). For continuous variables, depending on the data distribution, either the mean with standard deviation or the median with range was reported. Variables found to be statistically significant ($p \leq 0.05$) in univariate analyses were included in the multivariate regression model to determine the independent determinants of the outcome. A p of <0.05 was accepted as the threshold for statistical significance. We used Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) to perform all statistical analyses.

Results

Of the patients included in the study, 33.7% (n=31) were classified as HER2-low, while 66.3% (n=61) were categorized as HER2-zero. Among the HER2-low group, 21.7% (n=20) had a HER2 status of 1+ by IHC and 12% (n=11) had a HER2 status of 2+ but were determined to be HER2-negative by ISH. The groups were similar in clinical and demographic characteristics, including comorbidity status, visceral and non-visceral metastasis, metachronous and *de novo* metastasis rates, line of therapy, endocrine treatment, and choice of CDK 4/6 inhibitor (Table 1).

The mean age at treatment initiation was 72.9±5.8 years. A total of 68 patients were treated with a CDK4/6 inhibitor and ET in the first line, whereas 24 patients received these treatments in the second line. In the subgroups, 71% (n=22) of the HER2-low group received combination therapy as first-line treatment, while 29% (n=9) received it as second-line treatment. In the HER2-zero group, 75.4% (n=46) were treated with combination therapy in the first line, and 24.6% (n=15) in the second line.

The impact of comorbidities, metastatic status, site of metastasis, type of CDK 4/6 inhibitor, and HER2 status on mPFS was evaluated using univariate analysis. Among these factors, only HER2 status was found to have a significant effect on mPFS (p=0.03).

The median PFS for the overall population was 27 months [95% confidence interval (CI): 15.9-38.1]. When comparing mPFS between the two groups, the HER2-zero group demonstrated better outcomes, with a median of 34 months (95% CI: 28.8-39.1) compared to 17 months (95% CI: 9.2-24.8) in the HER2-low group, a difference that was statistically significant (p=0.026) (Figure 1). Among patients who received CDK4/6 inhibitor and ET in the first line setting, the mPFS was 43 months (95% CI: 31-55) in the HER2-zero group, compared to 24 months (95% CI: 14.7-33.2) in the HER2-low group. This difference was statistically significant (p=0.049).

The median OS for the entire study population was 108 months (95% CI: 64-152). In the HER2-low group, the median OS was 88 months (95% CI: 22-154), whereas it was not reached in the HER2-zero group. Although statistical significance was not achieved, a notable trend was observed (Figure 2). At a median follow-up of 40 months (95% CI: 30-50), mOS was not reached in either of the HER2-low or the HER2-zero groups.

Discussion

Among breast cancer subtypes, HR-positive/HER2-negative disease is the most frequently observed, comprising roughly 66% of MBC diagnoses [18].

As a result of recent studies, the combination of CDK4/6 inhibitors and ET has become the new standard treatment for HR+/HER2- MBC and has been included in guideline recommendations [19].

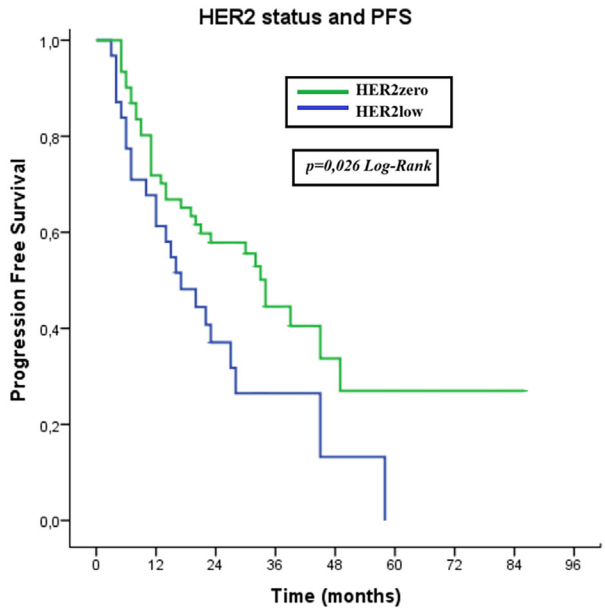

Figure 1. Kaplan-Meier curve for PFS according to HER2-low and HER2-Zero
PFS: Progression-free survival, HER2: Human epidermal growth factor receptor 2-negative

Table 1. Clinical characteristics of the patients

HER2 status	HER2-low n (%)	HER2-zero n (%)	p
Comorbidity Available Not-available	 22 (71) 9 (29)	 46 (75.4) 15 (24.6)	0.646*
Metastatic status Recurrent (secondary resistance) *De novo*	 16 (51.6) 15 (48.4)	 34 (55.7) 27 (44.3)	0.707*
Metastatic sites Non-visceral Visceral	 16 (51.6) 15 (48.4)	 27 (44.3) 34 (55.7)	0.504*
Treatment line 1 2	 22 (71) 9 (29)	 46 (75.4) 15 (24.6)	0.646*
Treatment option Ribociclib Palbociclib	 14 (45.2) 17 (54.8)	 33 (54.1) 28 (45.9)	0.418*
Endocrine therapy AI SERD	 16 (51.6) 15 (48.4)	 38 (62.3) 23 (37.7)	0.325*

*p<0.05
AI: Aromatase inhibitor, SERD: Selective estrogen receptor degrader, HER2: Human epidermal growth factor receptor 2-negative

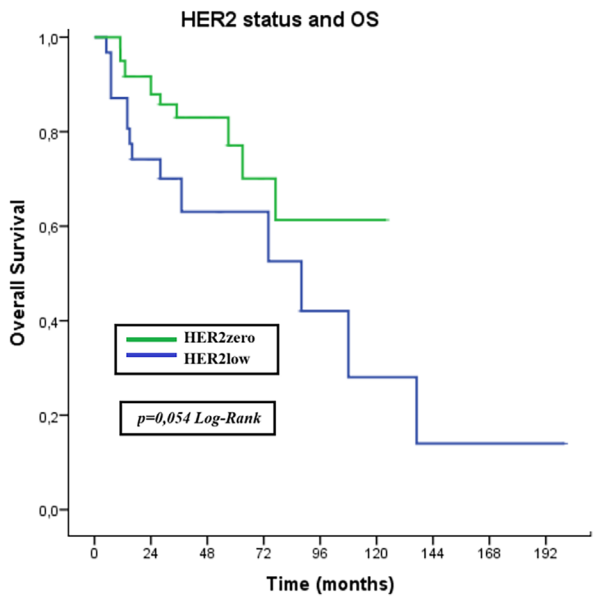

Figure 2. Kaplan Meier curve for OS according to HER2-Low and HER2-Zero
OS: Overall survival, HER2: Human epidermal growth factor receptor 2-negative

HER2-negative disease was historically regarded as a single entity, prior to the recognition and characterization of HER2-low as a distinct subgroup in contemporary research. We know that the differential efficacy of CDK4/6 inhibitors between HER2-low and HER2-zero tumors is not fully established. This study provides compelling evidence supporting the efficacy of CDK4/6 inhibitors in both HER2-low and HER2-zero subgroups, particularly in the elderly population (age 65 years and older), and highlights the importance of addressing the unique characteristics and treatment challenges faced by this underrepresented group in oncology. By limiting our cohort to patients aged 65 years and older, we aimed to reduce heterogeneity and provide more clinically relevant insights for this growing patient group. Although our results focus on treatment efficacy, they are very important as a source of inspiration for translational and clinical research.

Previous studies, such as the study by Schettini et al. [20], have emphasized clinicopathological differences between HER2-low and HER2-zero subtypes, including higher frequency of nodal involvement and larger tumor size in HER2-low tumors. Although our study did not focus on such baseline characteristics, our findings provide additional insight by demonstrating that these biological differences might also translate into differential treatment responses to CDK4/6 inhibitors in the elderly population.

Zattarin et al. [21] found that HER2-low status was associated with significantly worse PFS and OS in patients with HR+/HER2- advanced breast cancer receiving CDK 4/6 inhibitors and ET. Median PFS was 23.6 months in the HER2-low group vs. 32.3 months in the HER2-zero group (p=0.014); OS was 48.7 vs. 58.3 months, respectively (p=0.029). Similar to our study, HER2 status may constitute an independent and significant risk factor for both PFS and OS in this patient group.

In a similarly designed study evaluating 258 metastatic patients, a substantial numerical difference in PFS was observed between the groups (HER2-low and zero), although it did not reach statistical significance. This difference was nearly twofold. mPFS in the HER2-low group was 27.6 months compared with 44.3 months in the HER2-zero group (p=0.341). Furthermore, in patients treated with ribociclib, a more pronounced difference was observed, with the HER2-low group showing a MmPFS of 24.2 months compared to 53.1 months in the HER2-zero group [22]. Two key differences of this study are that it included only patients receiving first-line therapy and that the number of patients treated with ribociclib as the CDK4/6 inhibitor was higher. In our study, when we specifically analyzed the subgroup of patients who received first-line treatment, similar PFS outcomes were observed compared to those reported in a previous study. This finding suggests that, even when focusing on the geriatric patient population, survival outcomes comparable to those reported in the literature can be achieved in older age groups as well.

However, some studies have shown no significant difference. Guliyev et al. [23] reported similar PFS and OS outcomes between HER2-low and HER2-zero groups (mPFS: 25.2 vs. 22.6 months, mOS: NR vs. 37.5 months; p=0.972, p=0.707, respectively). The discrepancy between our study and the current one may be explained by the differing distributions of *de novo* and recurrent metastatic patients, a parameter that inherently includes prognostic factors such as endocrine resistance, which can significantly impact survival outcomes. Similarly, Ralser et al. [24] found no difference in mPFS (17 vs. 18 months) and also observed no significant impact of HER2 status conversion between primary and metastatic tissues.

There are also studies evaluating the efficacy of CDK4/6 inhibitors and ET in elderly patients, which are the patient group assessed in our study. In a study conducted by Pla et al. [16], it was demonstrated that patients in the geriatric age group (>70 years) achieved similar outcomes in terms of PFS and OS compared to younger patient groups, both in first-line and second-line treatment settings. This study demonstrates that it is an effective and safe treatment option for the geriatric population. Although this study includes a similar number of geriatric patients to our own, it does not provide an additional analysis regarding the relationship between HER2-low or HER2-zero status and survival outcomes.

While HER2 status is a potential risk factor, current evidence is conflicting, especially for elderly patients, a population typically underrepresented in clinical trials. Moreover, treatment development in this group progresses more slowly. Studies often evaluate HER2-low and elderly patients separately, and to our knowledge, no prior study has focused specifically on elderly patients with HER2-low disease. Our single-center study addresses this gap and, by including a relatively large elderly cohort with uniform follow-up, offers insights which may assist in guiding future research and treatment approaches.

Study Limitations

The study has several limitations. First, while the single-center design helps eliminate follow-up heterogeneity, it also limits the generalizability of the findings to a broader population. Secondly, to ensure an adequate sample size in our single center cohort, patients receiving first and second line treatments were analyzed together; although the characteristics were similar across HER2 status, this approach may introduce bias. Larger, multicenter studies with sufficient patient numbers and stratified analyses by treatment line are needed to draw more definitive conclusions and strengthen the evidence base. One of our limitations is that more than 50% of the patients used palbociclib. Until recent developments, we believed there was no difference in survival in patients treated with CDK 4/6 inhibitors. Therefore, there are many studies in which palbociclib is used frequently, as in our study. Therefore, this distribution reflects real life rather than treatment selection bias. Another factor was the patients' PS, evaluated using the ECOG performance scale; only patients with ECOG scores of 0-1 were included. In the elderly patient group, incorporating frailty assessments into the evaluation process may contribute to the selection of patient populations with better treatment tolerance, thus improving the relevance and applicability of treatment outcomes.

Conclusion

Our study specifically investigated the efficacy of CDK4/6 inhibitors in the HR+/HER2-low subgroup of elderly patients with MBC, an area that is largely under-researched in the current literature. Despite ongoing debate regarding the prognostic implications of the HER2-low phenotype, our findings suggest that this subgroup may have reduced sensitivity to CDK4/6 inhibitors, with outcomes in the geriatric population similar to those in other age groups. By addressing this knowledge gap, our study not only adds meaningful data to the limited available evidence, but also highlights the need for further research to optimize treatment strategies and improve clinical outcomes in this patient group.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/69, date: 17.04.2025).

Informed Consent: Since the data were collected from medical records without revealing the identities of the participants and the study was retrospective, consent was not obtained from the patients.

Footnotes

Authorship Contributions

Concept: S.Y., B.K.İ., Design: S.Y., B.K.İ., B.K., F.Y., Data Collection or Processing: P.K.T., E.A., A.T., N.D., Analysis or Interpretation: S.Y.,B.K.İ. Literature Search: Ş.U., Ö.A., Writing: S.Y., F.Y.

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

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Original Article

Elranatamab in Heavily Pretreated Triple-class Refractory Multiple Myeloma: A Single-center Experience

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ABSTRACT

Aim: This study aimed to assess the real-world performance of elranatamab in terms of its effectiveness, safety, and tolerability among patients diagnosed with triple-class refractory-multiple myeloma (TCR-MM) who have undergone extensive prior treatment.

Methods: A retrospective review was conducted at a single medical center, involving 12 TCR-MM patients who received elranatamab. Data were analyzed on demographics, cytogenetics, disease burden, prior therapies, infectious complications, and survival outcomes. Responses were assessed according to International Myeloma Working Group criteria, and adverse events were graded per common terminology criteria for adverse events version 5.0.

Results: The overall response rate was 83.3%, with a median progression-free survival of 8.0 months and a median overall survival of 11.0 months. Common adverse events included grade ≥3 infections (75%) and cytokine release syndrome (CRS), which occurred in 41.7% of the participants, with only grade 1-2 CRS observed. No immune effector cell-associated neurotoxicity syndrome was reported.

Conclusion: Elranatamab demonstrated promising clinical efficacy and an acceptable safety profile in a heavily pretreated TCR-MM population. The elevated risk of infections necessitates close clinical surveillance.

Keywords: Multiple myeloma, antibodies, bispecific, cytokine release syndrome, immunotherapy, B-cell maturation antigen

Introduction

Multiple myeloma (MM) is a malignancy of plasma cells characterized by cycles of remission and relapse, eventually resistance to therapy. The advent of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies, particularly anti-cluster of differentiation (CD) 38 agents, has significantly extended survival in MM [1]. A subset of patients eventually becomes triple-class refractory (resistant to a PI, an IMiD, and an anti-CD38 monoclonal antibody), facing poor prognoses with a median overall survival (OS) frequently falling below one year [1]. Elranatamab, a humanised bispecific antibody designed to engage B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T-cells, enables T-cell-mediated cytotoxicity in a manner independent of major histocompatibility complex presentation [2]. Initial data from the MagnetisMM trials have shown encouraging clinical activity, with the MagnetisMM-3 study reporting an overall response rate (ORR) of 61% in the heavily pretreated subgroup [2]. Notably, elranatamab is administered subcutaneously, which reduces the severity of cytokine release syndrome (CRS) compared to intravenous BCMA therapies. Real-world data regarding the effectiveness, tolerability, and logistical considerations of elranatamab remain scarce. These insights are particularly important for institutions managing patients with multiple comorbidities, cumulative toxicities, and treatment fatigue-features common in the triple-refractory population. This paper presents a single-center experience evaluating elranatamab, in such a cohort, aiming to contextualize its clinical utility and safety profile outside of a controlled trial setting.

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Methods

Study Objective

The primary endpoint of this single-center retrospective study is to evaluate the ORR, progression-free survival (PFS), and OS in patients with heavily pretreated, triple-class refractory MM, treated with elranatamab. These outcomes are benchmarked against results from prospective clinical trials and published real-world evidence. The secondary end point is to assess the safety and tolerability of elranatamab in this population, with a specific focus on infectious complications and immune-related adverse events, including CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).

Informed consent was obtained from all the patients for the use of medical data. Patient confidentiality was maintained throughout the study, in accordance with the Declaration of Helsinki. Approval was obtained from the Acıbadem University Ethics Committee for the study (decision no: 2025-08/64, date: 22.05.2025).

Study Design and Patient Selection

The study reviewed clinical records of 12 patients with confirmed TCR-MM who received elranatamab between 2023 and 2024. Inclusion required patients to be 18 years or older, have been documented as refractory to a PI, an IMiD, and an anti-CD38 monoclonal antibody, and to have received elranatamab via compassionate use, early access, or routine post-approval care.

Data Collection

Demographic, clinical, and laboratory data were extracted from electronic health records using a structured data abstraction form. Collected variables included age, gender, eastern cooperative oncology group performance status, number of prior lines of therapy, disease burden, presence of extramedullary disease, infection history, and baseline immune status defined by immunoglobulin G levels and cytomegalovirus (CMV) reactivation on follow-up. Cytogenetic risk profile was determined using the fluorescence *in situ* hybridization method by assessment of IGH/FGFR3, IGH/CCND1, IGH/CCND3, IGH/MAF, IGH/MAFB, IGH, 13q14 RB1, del D104S319, trisomy 12, 17p13.1 p53, CKS1B/CDKN2C, and MYC mutations. Elranatamab was administered subcutaneously at 12 mg on day 1.32 mg on day 4, and 72 mg on day 8, followed by weekly doses of 72 mg for six weeks, and then administration of 72 mg every two weeks until progression or adverse effects occurred. Premedication with 20 mg dexamethasone, paracetamol, diphenhydramine, and montelukast was given before every dose of elranatamab. All patients were admitted to the hospital for the first 5 days of elranatamab treatment to facilitate close monitoring of potential CRS.

The response evaluations at each clinical follow-up were done according to the International Myeloma Working Group (IMWG) criteria. Adverse events were graded per CTCAE v5.0 guidelines. The dates of disease progression or death for each patient were recorded and used for the survival analyses. A summary of baseline demographics and disease characteristics is presented in Table 1.

Outcome Measures

Responses were classified using IMWG guidelines. Adverse events were documented per CTCAE v5.0 criteria**.** CRS is a condition that occurs when the immune system reacts excessively, releasing cytokines. According to the American Society of Transplantation and Cellular Therapy consensus, CRS severity ranges from fever (grade 1) to life-threatening consequences (grade 4) [3].

Statistical Analysis

Kaplan-Meier analysis was employed for survival estimates. Statistical computations were performed using Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, Ill., USA) and R version 4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

This retrospective analysis included 12 patients with triple-class refractory MM. All patients were refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. The median number of prior lines of therapy was 6, reflecting a heavily pretreated population. At a median follow-up of 13 months, the ORR-defined as the proportion of patients achieving a very good partial response (VGPR), partial response (PR), or complete response (CR)-was 83.3%. This included 5 CR, (41.6%), 1 PR, (8.3%), and 4 VGPR (33.3%). Only two patients (16.6%) had stable or progressive disease as best response. The median PFS was 8.0 months, and the median OS was 11.0 months (Figures 1, 2). At the time of analysis, 9 of the 12 patients (75%) were still alive. The median number of elranatamab treatment cycles administered was 7. Most patients continued treatment beyond initial responses, with a few receiving more than 15 cycles.

Grade 3 or higher infections occurred in 75% of patients. CMV reactivation was documented in 25% of cases, indicating a need for routine virological surveillance. CRS occurred in 5 patients, 41.6% (grade 1 in 4 patients, 33.3%, and grade 2 in 1 patient, 8.3%). Only one patient needed tocilizumab treatment for CRS. ICANS was not reported in any patient. Grade 3 cytopenia was observed in 66.7% of the cohort, with 72.3% of patients requiring granulocyte colony-stimulating factor administration and 42.6% requiring platelet transfusions. Infections, CMV reactivation, and severe cytopenias were predominant causes for dose interruptions and reductions which were required in 75% of the patients.

Discussion

The introduction of BCMA-targeted bispecific antibodies has significantly expanded the therapeutic armamentarium for patients with TCR-MM. Elranatamab, a subcutaneously administered bispecific antibody engaging CD3+ T-cells and BCMA+ myeloma cells, has emerged as a promising agent. This study represents a single-center real-world analysis that reinforces the clinical benefit observed in pivotal trials while offering insights into treatment logistics, adverse event profiles, and infection risks in a real-world population.

In our cohort of 12 heavily pretreated patients, the ORR reached 83.3%, including a significant proportion achieving complete or VGPR. These outcomes align favorably with the MagnetisMM-3 trial, where an ORR of 61% was reported, increasing to over 70% in patients without prior BCMA therapy [2]. Similarly, in the MagnetisMM-1 phase 1 trial, elranatamab demonstrated an ORR of 73%, establishing early signals of robust efficacy [4]. Our study's median PFS of 8 months and median OS of 11 months, are comparable to those reported in published trial data. However, our analysis is limited by a small sample size and limited follow-up. Importantly, this reflects outcomes in a real-world population; many of whom would not

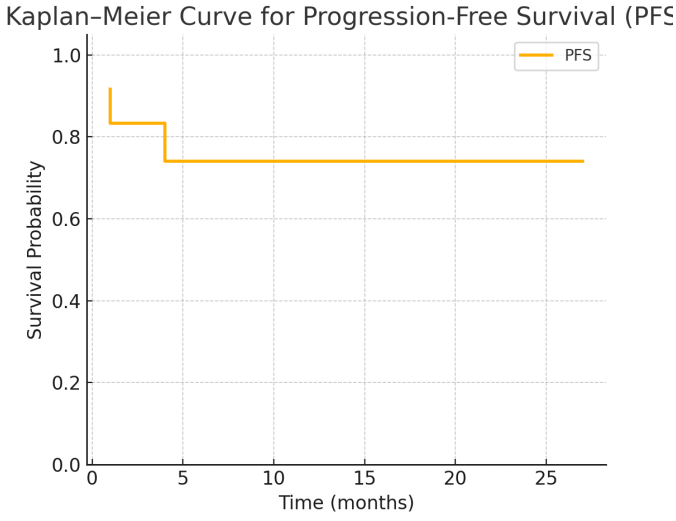

Figure 1. Kaplan-Meier estimate of progression-free survival

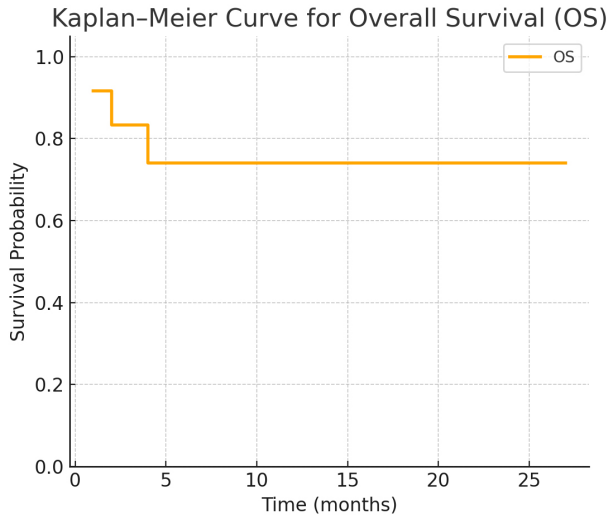

Figure 2. Kaplan-Meier estimate of overall survival

Table 1. Baseline characteristics of heavily pretreated myeloma patients treated with elranatamab

Characteristic	Value
Median age, years (range)	59.5 (39-73)
Gender, n (%)	Male: 7 (58.3%), female: 5 (41.7%)
MM type	IgG-kappa 5 (42%) IgA-kappa 4 (34%) IgG-lambda 1 (8%) IgA-lambda 1 (8%) Kappa monoclonal 1 (8%)
R-ISS-2 R-ISS-3	9 (75%) 3 (25%)
ECOG 1, n (%)	5 (42%)
ECOG 2, n (%)	2 (16%)
ECOG 3, n (%)	4 (34%)
ECOG 4, n (%)	1 (8%)
Standard risk cytogenetics, n (%)	9 (75%)
High risk cytogenetics, n (%)	3 (25%)
Median number of prior lines of therapy (range)	6.0 (4-8)
Presence of extramedullary disease, n (%)	Yes: 5 (41.7%), no: 7 (58.3%)
IgG level at treatment initiation (median, range) (mg/dL)	1261.5 (110-2900)
Received IVIG treatment, n (%)	Yes: 7 (58.3%), no: 5 (41.7%)

MM: Multiple myeloma, R-ISS: Revised international staging system, ECOG: Eastern Cooperative Oncology Group, IgG: Immunoglobulin G, IVIG: Intravenous immunoglobulin

qualify for trial enrollment due to comorbidities or frailty. Our findings also align with the results of the French Compassionate Use Program, highlighting similarly encouraging responses and underscoring the high rate of infectious complications, including CMV reactivation [5]. In our cohort, CMV reactivation occurred in 25% of patients, and grade 3 or higher infections were observed in 75%; necessitating stringent infection monitoring protocols. While CRS was common, it remained grade 1-2 and manageable in all cases. No ICANS events were observed. The administration of elranatamab in our center was logistically feasible, and treatment duration extended up to 27 cycles in some patients. This extended exposure suggests durable tolerability, in line with observations from the MagnetisMM-9 trial, which continues to evaluate long-term use and fixed-duration strategies [6].

Seval et al. [7] presented results from a single-center study comparing the efficacy of salvage autologous stem cell transplantation (ASCT), selinexor, and elranatamab in heavily pretreated myeloma patients. In this study, the patients who received elranatamab had significantly higher ORRs compared to salvage ASCT and selinexor (73% vs. 54% vs. 64.7%), and a longer 1-year PFS was reported (71.3% vs. 55.5% vs. 68.3%). Notably, patients receiving elranatamab had a higher rate of serious infections, compared to the other groups, and low-grade CRS, was reported in 69% of the patients. This data, along with the results from the MagnetisMM-17 trial [8], which included 20 relapsed and refractory MM patients, are both parallel to our study's results and reflect the efficacy of elranatamab, while highlighting the critical side effects associated with elranatamab treatment.

Study Limitations

This study has inherent limitations due to its retrospective design, small sample size, and brief follow-up period. However, its strengths lie in reflecting real-world practice, capturing toxicity profiles, and adding to the growing post-marketing evidence.

Conclusion

In this single-center retrospective analysis, elranatamab demonstrated high response rates and encouraging survival outcomes in a cohort of heavily pretreated, triple-class refractory MM patients. The treatment was generally well tolerated, though infectious complications, particularly CMV reactivation, were notable and underscore the need for proactive monitoring strategies. Our findings support the real-world effectiveness of elranatamab and provide additional clinical insight into its safety and feasibility outside of controlled trial settings. Larger prospective studies and extended follow-up are warranted to validate these outcomes and optimize supportive care strategies.

Ethic

Ethics Committee Approval: Approval was obtained from the Acıbadem University Ethics Committee for the study (decision no: 2025-08/64, date: 22.05.2025).

Informed Consent: Informed consent was obtained from all the patients for the use of medical data.

Footnotes

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

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Original Article

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Assessing Pathological Complete Response in Locally Advanced Breast Cancer: The Role of Inflammatory and Nutritional Biomarkers

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ABSTRACT

Aim: Neoadjuvant chemotherapy (NAC) aims to achieve pathological complete response (pCR), which is linked to improved outcomes in locally advanced breast cancer (LABC). Identifying reliable predictors of pCR remains a clinical priority.

Methods: This retrospective study included 44 women, with a median age of 50 years, with stage 2B-3C breast cancer who underwent NAC followed by surgery. Inflammatory markers [systemic inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), erythrocyte-to-lymphocyte ratio (ELR), lymphocyte-to-C (LCR)] and nutritional indices [glucose-to-albumin ratio (GAR), hemoglobin-to-albumin ratio (HAR), prognostic nutritional index (PNI)] were analyzed. Receiver operating characteristic analysis determined optimal cut-off values, and binary logistic regression evaluated independent predictors of pCR.

Results: The overall pCR rate was 38.6%. Among histological subtypes, luminal B tumors were more frequent in both groups, with 40.7% in the non-pCR group and 29.4% in the pCR group. Triple-positive and HER2-positive tumors were more common in the pCR group. GAR ≤2.04 emerged as the only independent predictor of pCR (odds ratio=0.09, 95% confidence interval: 0.01-0.70, p=0.02). ELR >2.69 and LCR >0.64 showed significant associations with pCR (p=0.03 and p=0.04, respectively), though they lacked independent predictive value. SII, NLR, PLR, HAR, and PNI demonstrated no significant correlation with pCR.

Conclusion: This study assessed significant cut-off values, ELR >2.69 and LCR >0.64, that might predict the pCR in LABC. GAR, with a cut-off value of 2.04, was found to be an independent predictive marker for pCR.

Keywords: Breast cancer, inflammatory marker, neoadjuvant chemotherapy, nutritional marker, pathological complete response

Introduction

Breast cancer is the most frequently diagnosed cancer in women and the leading cause of death in women [1]. Breast cancer is divided into various subtypes according to the receptor status [2]. These subtypes play a crucial role in treatment decisions, as several studies have shown that achieving pathological complete response (pCR) after neoadjuvant treatment significantly improves breast cancer prognosis [3,4].

A meta-analysis demonstrated that pCR was associated with prolonged survival [5]. Recently, Huang et al. [6] confirmed the strong association between pCR and long-term survival outcomes, especially in triple-negative breast cancer (TNBC) patients.

Since achieving pCR has become a target in patients receiving neoadjuvant treatment, recent studies have focused on predicting the neoadjuvant chemotherapy (NAC) response [7]. Tools are inflammatory markers such as systemic inflammation index (SII), tumor-infiltrating lymphocytes, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR). They effectively predicted treatment response in TNBC, with NLR standing out as an independent predictor [8]. Another

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study showed that while markers such as NLR, white cell count, and lymphocyte count could help predict pCR, their use in specific breast cancer subtypes remains uncertain due to the lack of standardized cut-off values, highlighting the need for further research [9]. In a meta-analysis, high PLR was associated with poor prognosis, lymph node metastasis, advanced tumor node metastasis (TNM) stage, and distant metastasis in breast cancer patients [10]. High NLR has been consistently associated with poorer survival outcomes in breast cancer patients. Its prognostic significance remains robust across various clinicopathological parameters, including disease stage and molecular subtypes [11].

Other markers have also been studied in various studies. Hu et al. [12] demonstrated that a low preoperative hemoglobin-to-albumin ratio (HAR) is an independent risk factor for poor short-term survival in gastric cancer patients. Low values of the lymphocyte to C-reactive protein (CRP) ratio (LCR) indicated poor prognosis in early-stage breast cancer [13]. Additionally, nutritional indexes, such as the prognostic nutritional index (PNI), might predict the treatment response in cancer patients. The PNI has been reported to have a stronger prognostic value than inflammatory markers [14].

The pCR is a well-known endpoint for neoadjuvant treatment in breast cancer. Additionally, predicting responses has become popular with usable tools in daily applications. Hence, we aimed to evaluate the predictive role of inflammatory markers and nutritional indexes in predicting the response to NAC to better understand which patients will achieve the best outcome from chemotherapy.

Methods

From 2023 to 2024, a total of 44 women evaluated by a multidisciplinary tumor board opted to undergo NAC treatment prior to curative surgery and were subsequently included in the study. Pathological diagnosis was established through needle biopsy, and surgical specimens. The study used the eighth edition of the American Joint Committee on Cancer's TNM staging system. It included patients with locally advanced breast cancer (LABC), specifically those with stage 2B disease (T3N0) and those with stage 3A to 3C disease, AJCC [15]. After the completion of NAC, all patients underwent breast-conserving surgery (BCS) or modified radical mastectomy (MRM) and axillary lymph node dissection (ALND) or sentinel lymph node biopsy.

Patients' data regarding age, laboratory parameters, pathological reports, and chemotherapy regimens were retrospectively obtained from their charts. Patients did not sign the informed consent form, were under 18 years old, had oligometastatic disease, could not complete the NAC, and had eastern cooperative oncology group performance status 2, 3, and 4 were excluded from the data analysis.

A written informed consent form was obtained from each patient at the time of admission to our clinic. The Local Ethics Committee of University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital approved the study (decision no: KAEK/2024.01.5, date: 05.01.2024).

The markers evaluated in this study were defined as follows:

1. SII: This was calculated by multiplying the platelet count by the neutrophil count and then dividing by the lymphocyte count.

2. NLR: This was determined by dividing the neutrophil count by the lymphocyte count.

3. PLR: This was determined by dividing the platelet count by the lymphocyte count.

4. Glucose-to-albumin ratio (GAR): This was calculated by dividing serum glucose levels by serum albumin levels.

5. Erythrocyte-to-lymphocyte ratio (ELR): This was obtained by dividing the erythrocyte count by the lymphocyte count.

6. HAR: This was calculated by dividing hemoglobin levels by albumin levels.

7. LCR: This was calculated by dividing the lymphocyte count by the CRP level.

8. PNI: This was derived using the formula: 10×serum albumin (in g/dL)+0.005×total lymphocyte count (per mm^3).

Pathological Assessment

Histopathological classification was carried out using immunohistochemistry (IHC). The luminal subtype was identified as human epidermal growth factor receptor (HER)2-negative and estrogen receptor (ER)-positive. This group was further divided into luminal A, characterized by low Ki-67 (<20%), and luminal B, characterized by high Ki-67 (≥20%). HER2 positivity was indicated by IHC 3+or silver in situ hybridization positivity. The triple-negative (TN) subtype was defined by the absence of ER, progesterone receptor (PR), and HER2 expression. The pCR was defined as a complete absence of residual invasive cancer in the breast tissue.

Neoadjuvant Chemotherapy Regimens

Patients in the luminal group were administered four cycles of either epirubicin (75 mg/m^2) or adriamycin (60 mg/m^2) combined with cyclophosphamide (600 mg/m^2) [adriamycin (doxorubicin)+cyclophosphamide/epirubicin+cyclophosphamide (AC/EC)] every three weeks. This was followed by 12 weekly cycles of paclitaxel (80 mg/m^2). For those with HER2-positive tumors, the treatment included AC/EC followed by paclitaxel in conjunction with dual HER2 blockade: trastuzumab (initial dose of 8 mg/kg, then 6 mg/kg, administered every three weeks) and pertuzumab (initial dose of 840 mg, then 420 mg, administered every three weeks). TNBC patients received a dose-dense regimen consisting of four cycles of AC/EC followed by 12 weekly cycles of paclitaxel, with those having BRCA mutations also undergoing 12 cycles of carboplatin [2 area under the curve (AUC)].

Statistical Analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Data evaluation incorporated descriptive statistics, such as mean, standard deviation, median, frequency, ratio, minimum, and maximum values, and the Shapiro-Wilk test to

assess the normality of data distribution. Pearson correlation coefficients were used for variables with normal distribution, whereas Spearman rank correlation was applied for non-normally distributed variables. The Student's t-test was employed to compare quantitative data between two groups with normal distribution, while the Mann-Whitney U test was used for non-normally distributed groups. A receiver operating characteristic (ROC) analysis was conducted to determine the optimal cutoff values of inflammatory markers for predicting a pCR. The relationship between survival time and each independent variable was quantified using 95% confidence intervals (CI). All statistical tests were two-tailed, with p≤0.05 deemed statistically significant.

Results

Forty-four women, with a median age of 50 (range: 30-72), were included in this study. Twenty-six were premenopausal, while 18 were postmenopausal. At baseline, radiological assessment showed T1 disease in 14 women, T2 in 26, T3 in 3, and T4 in 1. Meanwhile, ten, seven, twenty-four, and 3 women had radiologically assessed N0, N1, N2, and N3 disease, respectively.

All tumors exhibited invasive ductal carcinoma histology. The molecular subtypes of the patients were categorized as follows: nine patients were classified in the luminal A group, 16 patients were in the luminal B HER2-negative group, 10 patients in the luminal B HER2-positive group, three patients in the HER2-positive ER-negative group, and six patients were classified in the TN group.

Thirty-three had undergone BCS (i.e., lumpectomy or partial mastectomy), and the remaining patients had undergone modified or subcutaneous mastectomy. Despite 27 women having N2 or N3 disease at the baseline, only 9 of them underwent ALND. Histopathological analysis of surgical specimens after NAC revealed pCR in 17 cases (38.6%).

Table 1 summarizes the patient's characteristics.

The Mann-Whitney U test demonstrated a significant association between pCR and LCR (p=0.04), GAR (p=0.006), and ELR (p=0.03) (Table 2). However, there was no association between pCR and SII, NLR, PLR, HAR and PNI (all >0.05).

ROC analysis was performed to determine cut-off values, which identified thresholds of 2.69 for ELR (p=0.02, AUC: 0.70, 95% CI: 0.56-0.91), 0.64 for LCR (p=0.04, AUC: 0.71, 95% CI: 0.51-0.91), 102.8 for prognostic index (PI) (p=0.03, AUC: 0.26, 95% CI: 0.08-0.45), and 2.04 for GAR (p=0.006, AUC: 0.20, 95% CI: 0.04-0.37), respectively (Figure 1). The sensitivity and specificity were 53.8% and 62.1% for LCR, 61.5% and 12.1% for PI, 53.8% and 72.2% for ELR, 61.5% and 12.1% for GAR, respectively (Figure 1).

Table 1. The patients and tumor characteristics according to the pCR status

Characteristics	pCR n (%)	Non-pCR n (%)	p
Total patients	17 (38.6%)	27 (61.4%)	-
Menopausal status			
Premenopause	11 (64.7%)	15 (55.6%)	0.6
Postmenopause	6 (35.3%)	12 (44.4%)	
Initial T status			
T1	7 (41.2%)	7 (25.9%)	0.6
T2	9 (52.9%)	17 (63%)	
T3	1 (5.9%)	2 (7.4%)	
T4	0	1 (3.7%)	
Initial nodal status			
N0	6 (35.3%)	4 (14.8%)	0.03
N1	0	7 (25.9%)	
N2	11 (64.7%)	13 (48.1%)	
N3	0	3 (11.1%)	
Histologic type			
Luminal A	2 (11.8%)	7 (25.9%)	0.5
Luminal B	5 (29.4%)	11 (40.7%)	
HR positive HER-2 positive	5 (29.4%)	5 (18.5%)	
HR negative HER-2 positive	2 (17.6%)	1 (3.7%)	
TNBC	3 (17.6%)	3 (11.1%)	
ELR			
≤2.69	3 (21.43%)	11 (78.57%)	0.03
>2.69	10 (58.82%)	7 (41.18%)	
LCR			
≤0.64	4 (26.67%)	11 (73.33%)	0.09
>0.64	9 (56.25%)	7 (43.75%)	
GAR			
≤2.04	7 (77.78%)	2 (22.22%)	0.01
>2.04	6 (27.27%)	16 (72.73%)	

HR: Hormone receptor, TNBC: Triple negative breast cancer, ELR: Erythrocyte lymphocyte ratio, LCR: Lymphocyte C-reactive protein ratio, GAR: Glucose-to-albumin ratio, pCR: Pathological complete response

Table 2. The mean values of systemic inflammatory markers

Marker	pCR mean±SD	Non-pCR mean±SD	Mann-Whitney U test p
ELR	2.9±1.0	2.9±0.8	<0.05
NLR	2.8±1.2	2.8±1.0	≥0.05
PLR	158.2±59.7	158.2±61.5	≥0.05
LCR	1.8±1.7	1.8±6.4	<0.05
HAR	0.3±0.03	0.3±0.02	≥0.05
PNI	485.6±32.0	485.6±30.8	≥0.05
SII	712.5±310.4	758.1±347.7	>0.05
GAR	2.0±0.3	2.6±1.0	<0.05

ELR: Erythrocyte lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LCR: Lymphocyte C-reactive protein ratio, HAR: Hemoglobin albumin ratio, PNI: Prognostic nutritional index, SII: Sytemic immune inflammation index, GAR: Glucose-to-albumin ratio, pCR: Pathological complete response, SD: Standard deviation

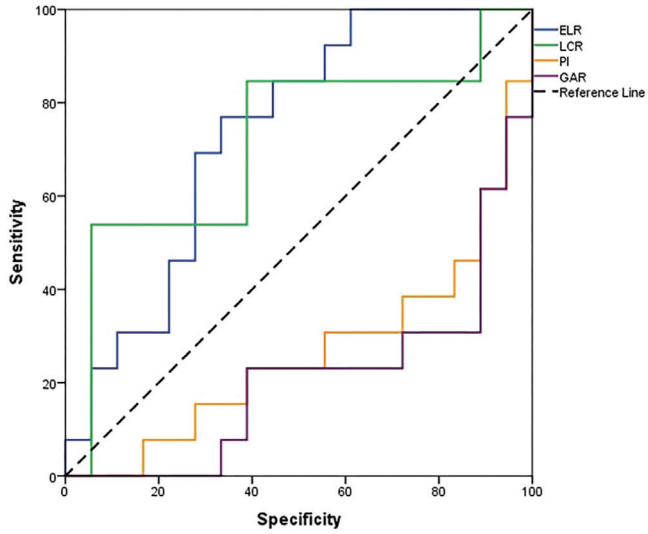

Figure 1. The ROC curve for inflammatory and nutritional markers predicting pCR
ROC: Receiver operating characteristic, pCR: Pathological complete response, ELR: erythrocyte-to-lymphocyte ratio, LCR: Lymphocyte-to-C-reactive protein ratio, GAR: Glasgow albumin ratio, PI: Prognostic index

In comparing the pCR and non-pCR groups, no significant differences were observed across histological subtypes and menopausal status. Among histological subtypes, luminal B tumors were more frequent in both groups, with 40.7% in the non-pCR group and 29.4% in the pCR group. Triple-positive and only HER2+tumors were more prevalent in the pCR group. For inflammatory markers, patients with a low GAR (≤2.04) showed a significantly higher proportion of pCR (53.8%) compared to the non-pCR group (p=0.01) (Figure 2). Similarly, patients with an ELR >2.6 had a significantly higher rate of pCR (76.9%) compared to those below this threshold (p=0.03) (Figure 3). Although a trend toward higher pCR rates was observed among patients with an LCR above 0.64, this did not reach statistical significance (Table 2).

The binary logistic regression analysis indicated that GAR was the only significant predictor of pCR, with a coefficient (β) of -2.3 and an odds ratio (OR) of 0.09 (p=0.02, 95% CI: 0.01-0.70). Lower GAR values were associated with a significantly higher likelihood of achieving pCR, with a 91% increase in the odds of pCR for each unit decrease in GAR. The other markers, including ELR, LCR, and PI, did not reach statistical significance, with ORs of 2.3 (95% CI: 0.38-14.76), 1.5 (95% CI: 0.26-9.31), and 0.3 (95% CI: 0.03-2.83), respectively (Table 3).

Discussion

Predicting the response to NAC in breast cancer reduces exposure to ineffective treatments, protects against side effects, and improves patients' quality of life [16]. Accurate prediction of response improves overall survival (OS) by enabling the creation of personalized treatment plans [17]. Furthermore, achieving pCR is directly related to long-term survival and allows us to determine appropriate treatment strategies [18].

A meta-analysis by Haque et al. [5] reported that 19% of 13,939 women achieved pCR after neoadjuvant treatment. According to subgroups, the pCR rate was lowest in the luminal A subtype at 0.3% and highest in the HER2-positive subtype at 38.7%.

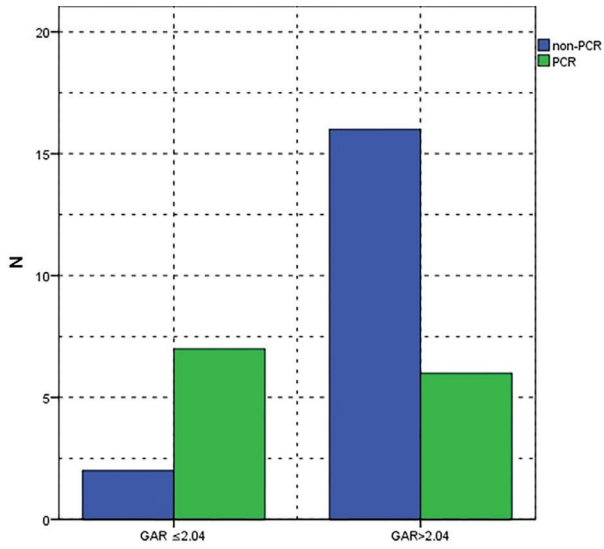

Figure 2. The number of patients in the pCR and non-pCR groups in terms of GAR value
pCR: Pathological complete response, GAR: Glasgow albumin ratio

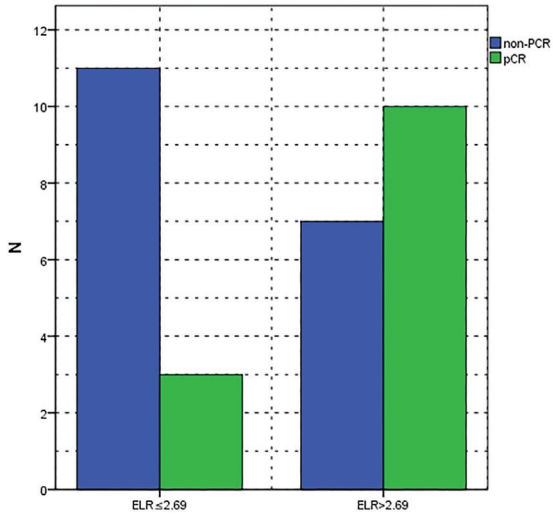

Figure 3. The number of patients in the pCR and non-pCR groups in terms of ELR value
pCR: Pathological complete response, ELR: Eosinophil-to-lymphocyte ratio

Table 3. The binary logistic regression analysis for the pCR predictivity of inflammatory and nutritional markers

Factors < vs ≥	Coefficient β	Wald x^2	p	OR	95% CI
ELR	0.86	0.86	0.3	2.3	0.38-14.76
LCR	0.45	0.24	0.6	1.5	0.26-9.31
GAR	-2.3	5.29	0.02	0.09	0.01-0.70

ELR: Erythrocyte lymphocyte ratio, LCR: Lymphocyte C-reactive protein ratio, GAR: Glucose-to-albumin ratio, pCR: Pathological complete response, OR: Odds ratio, CI: Confidence interval

Antonini et al. [19] showed that the overall pCR rate was 22.7%, and higher pCR rates were reported in TN and luminal B subtypes. In addition, HR status was predictive of pCR rates, and ER-/PR +phenotype showed increased pCR rates due to its sensitivity to chemotherapy [20]. Our study's overall PCR rate was 38.6%, which was higher than the rate reported in the literature. The reason might be the inclusion of a higher rate (36%) of HER2-positive or TNBC patients. On the other hand, the small sample size might also cause bias.

Another aim of neoadjuvant treatment is to omit the ALND and to reduce the mastectomy rates [21]. Goktas Aydin et al. [22] reported that 51.6% and 43.1% of patients underwent BCS and SNLB, respectively. In our study, we demonstrated the efficacy of neoadjuvant treatment on surgical outcomes by showing that only five patients (11.3%) underwent MRM and six patients (13.6%) underwent ALND.

In terms of inflammatorymarkers; ELR hasn't been studied well in breast cancer however Wang et al. [23] found it was a significant predictor for axillary lymph node metastasis which was also linked with the survival. We evaluated the predictive significance of the ELR and identified a significant cutoff value of 2.69 (p=0.02, AUC: 0.70, 95% CI: 0.56-0.91). Among patients who achieved pCR, 3 (21.4%) had an ELR ≤2.69, compared to 11 (78.6%) in the non-pCR group. These findings suggest that a lower ELR (≤2.69) may be associated with a reduced likelihood of achieving pCR, highlighting its potential role as a predictive marker in this setting.

A study, examining 299 breast cancer patients undergoing NAC suggested that patients with a higher baseline LCR (cut-off: 1.9) tended to respond better to treatment. Those who achieved a pCR had slightly lower LCR levels at diagnosis (p=0.049) [24]. In contrast, our findings demonstrated a lower LCR cut-off value of 0.64 (p=0.04, AUC: 0.71, 95% CI: 0.51-0.91) associated with pCR, though logistic regression analysis did not confirm it as an independent predictor for neoadjuvant treatment response. A few studies have examined LCR that might explain the discrepancy, with most focusing on CRP for prediction and prognosis. These retrospective studies included diverse breast cancer subtypes, limiting generalizability.

The predictive and prognostic role of SII, NLR, and PLR has been extensively researched. Yang et al. [25] revealed that SII, NLR, and PLR with a cut-off value of 0.827, 0.827, and 0.810, respectively, indicated a higher predictive value for response to NAC. A meta-analysis confirmed these results by showing a significant association between high SII and poor OS in breast cancer patients [26]. A recent study also reported lower SII (OR=0.596; 95% CI: 0.429-0.827; p=0.002) and higher NLR (OR=1.320; 95% CI: 1.016-1.716; p=0.038), and PLR (OR=1.474; 95% CI: 1.058-2.052; p=0.022) were significantly associated with a higher likelihood of achieving pCR [27]. In contrast to these positive findings, Garcia-Torralba et al. [28], concluded that NLR lacked prognostic utility in early breast cancer, showing no significant association with survival across different tumor subtypes. Also, Ji and Wang [26] reported limited prognostic utility for NLR and PLR in breast cancer patients.

However, our results did not show a significant association between SII, NLR, or PLR and pCR rates, which challenges their predictive value in this cohort. This lack of correlation may be attributed to several factors, including the relatively small sample size, heterogeneity of molecular subtypes, or baseline disease burden variations.

Pan et al. [29] reported that GAR may be a clinically significant risk factor in breast cancer. A meta-analysis showed that low GAR was significantly associated with shorter OS and higher lymph node metastasis rates in cancer patients [30]. Similarly, our study identified GAR as the only independent predictor of pCR in binary logistic regression analysis, with a cut-off value of 2.04. Patients with GAR ≤2.04 had a significantly higher pCR rate (53.8%), and each unit decrease in GAR increased the odds of achieving pCR by 91%. Clinically, GAR could function as an early stratification tool: patients with high GAR values may benefit from more intensive monitoring, alternative therapeutic strategies, or additional nutritional and metabolic interventions to enhance chemosensitivity. Incorporating GAR into pre-treatment evaluation may thus enable more tailored neoadjuvant approaches, reducing overtreatment and improving therapeutic outcomes.

Higher PNI values have been associated with increased pCR rates and survival in trials [31,32]. Although Qu et al. [31] demonstrated that patients with a high PNI (≥53) had a significantly increased pCR rate (OR=2.217, 95% CI: 1.215-4.043, p=0.009), our study couldn't determine any correlation with the pCR.

HAR, another nutritional marker, is an orphan marker that hasn't been studied in cancer patients. Lower HAR values were significantly linked with poor survival in gastric cancer patients [12]. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score was studied in early-stage breast cancer patients, showing that higher HALP scores independently predicted prognosis in both OS and progression-free survival [33]. Contrary to this, we could not demonstrate any significance between treatment responses and HAR. The discrepancy might be explained by the absence of survival outcomes in our study. We only assessed the PCR rates, which are believed to be closely linked to survival.

Study Limitations

This study's primary limitation is the small sample size, which may restrict the statistical power needed to establish significant associations. The absence of long-term survival data further limits the ability to evaluate the prognostic value of the studied markers. Additionally, heterogeneity in molecular subtypes may introduce variability in response rates. However, our study contributes to the evolving understanding of inflammatory and nutritional markers in predicting NAC response in LABC. By identifying GAR as an independent predictor and proposing novel cut-off values for ELR, LCR, and PI, this research offers potential clinical guidance for stratifying patients likely to achieve pCR. These insights and existing literature may support personalized treatment planning and improve outcomes.

Conclusion

Our findings highlight GAR's capability as a robust, standalone predictor of pCR in LABC. Additionally, ELR and LCR may offer valuable insights for creating personalized treatment strategies and improving predictions for NAC response. However, due to this study's limited sample size and retrospective nature, these results should be viewed carefully. Future research involving larger, multicenter cohorts or prospective designs is highly recommended to confirm the predictive value of GAR and other identified biomarkers.

Ethics

Ethics Committee Approval: The Local Ethics Committee of University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital approved the study (decision no: KAEK/2024.01.5, date: 05.01.2024).

Informed Consent: A written informed consent form was obtained from each patient at the time of admission to our clinic.

Footnotes

Authorship Contributions

Concept: S.G.A., S.D., Design: S.G.A., Data Collection or Processing: E.N.D., E.K.Y., T.E., S.D., Z.B.Y.İ., M.U., F.B.A., O.T., Analysis or Interpretation: S.G.A., T.E., S.D., Literature Search: E.N.D., E.K.Y., S.G.A., Writing: E.N.D., E.K.Y., S.G.A.

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

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Original Article

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Prognostic Role of Sarcopenia in High-grade Lymphoma: A Retrospective PET/CT-Based Study

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ABSTRACT

Aim: This study aimed to evaluate the impact of sarcopenia and myosteatosis on progression-free survival (PFS) in patients with aggressive non-Hodgkin lymphoma (NHL).

Methods: A retrospective analysis was conducted on 33 high-grade NHL patients diagnosed between 01.01.2018 and 31.12.2019, who had pre- and post-treatment ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (CT) imaging. Body composition was semiautomatically measured using axial CT slices at the lumbar L3 vertebral level, focusing on the psoas muscle (PM). The right and left average hounsfield unit (HU) values [right psoas HU corrected (RPHUc) and left psoas HU corrected (LPHUc)] were recorded as myosteatosis parameters. The cross-sectional area of the PM was adjusted for body size by dividing it by the square of the patient's height in meters, resulting in the PM index, expressed in cm²/m².

Results: The average age of the patients was 57±16.2 years, and sarcopenia was identified in 39.4% of the cohort. During follow-up, relapse occurred in 9 patients (27.3%). A significant association was found between relapse and age (p=0.002), Eastern Cooperative Oncology Group (ECOG) performance status (p=0.003), and RPHUc (p=0.015). Receiver operating characteristic analysis for RPHUc (cut-off >33.550) in predicting PFS showed an area under the curve of 0.778 (p=0.015), with 66.7% sensitivity and 33% specificity. Univariate analysis identified age (p=0.001), ECOG score (p=0.000), and RPHUc (p=0.017) as significant prognostic factors for PFS. In multivariate analysis, only age remained an independent prognostic factor (p=0.04).

Conclusion: Our study demonstrated that age and RPHUc values have prognostic significance for PFS in aggressive lymphoma patients. These parameters, easily obtainable from routine imaging, may aid in guiding clinical management strategies.

Keywords: Lymphoma, sarcopenia, progression free survival, psoas muscle, myosteatosis

Introduction

Aggressive lymphomas are fast-growing subtypes of non-Hodgkin lymphoma (NHL) characterized by high proliferation rates. The most common type is diffuse large B-cell lymphoma (DLBCL). Others include mantle cell lymphoma (MCL), Burkitt lymphoma, high-grade B-cell lymphomas, primary mediastinal large B-cell lymphoma, and peripheral T-cell lymphomas [1]. Treatment typically involves intensive chemotherapy, targeted therapies, immunotherapy, and, in some cases, stem cell transplantation [2]. The heterogeneity in DLBCL's immunophenotype, genetic profile, and histology influences treatment response and long-term prognosis [3,4]. Although the MCL International Prognostic Index (IPI) has been introduced as a tool for risk stratification, its prognostic utility continues to be a subject of discussion [5,6]. Identifying new prognostic factors is crucial for disease management and survival. Established indices like the IPI, revised IPI, and National Comprehensive Cancer Network (NCCN)-IPI underscore the need for novel biomarkers to predict aggressive disease courses.

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Sarcopenia, defined as reduced skeletal muscle mass, quality, and function, is often age-related but may also result from an underlying disease or treatment side effects [7]. Studies in various malignancies suggest sarcopenia adversely impacts survival [8]. Current evidence supports low skeletal muscle mass as a prognostic biomarker in cancer patients [9], including hematologic malignancies [10]. Sarcopenia has been associated with an increased risk of adverse outcomes, including falls, bone fractures, functional impairment, and overall mortality [7,11]. Cancer patients may lose 15-50% of skeletal muscle mass, reducing chemotherapy tolerance and quality of life [12-14]. In recent years, it has also garnered attention as a potential prognostic marker in NHL [11,15].

This study aimed to expand the current literature by evaluating the prognostic significance of both sarcopenia and myosteatosis in patients with high-grade lymphoma.

Methods

This study was designed as a retrospective analysis of patients diagnosed with high-grade lymphoma between January 1, 2018, and December 31, 2022. Patients who had pre-treatment, post-treatment, and relapse, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging available were included in the study. Patients with missing data, incomplete treatment records, or insufficient follow-up information were excluded from the analysis. Patient data, including age, sex, disease stage, ECOG performance score, lactate dehydrogenase levels, sedimentation rate, treatment regimens, relapse dates, last follow-up dates, and other relevant clinical findings, were recorded. Body composition parameters were obtained from the CT component of each patient's ^{18}F-FDG PET/CT scans. The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital (decision no: 345, date: 07.02.2025).

Body Composition Assessment

All ^{18}F-FDG PET/CT images were evaluated using the AW 4.7 workstation (Advantage Workstation software version 4.7; GE Healthcare, Milwaukee, WI, USA). The body composition of the psoas muscle (PM) was semiautomatically measured on axial CT slices at the level of the L3 lumbar vertebra from pre-treatment, post-treatment, and relapse ^{18}F-FDG PET/CT scans. The hounsfield unit (HU) thresholds for PM were set between -29 and +150 HU [16]. Separate regions of interest were manually drawn around the right and left PM, avoiding bone and adipose tissue, and the average HU values [right psoas hounsfield unit corrected (RPHUc) and left psoas hounsfield unit corrected (LPHUc)] were recorded as myosteatosis parameters. To calculate the PM index (PMI), the PM area was normalized by dividing it by the square of the patient's height in meters (m^2) (Figure 1) [17,18]. Sarcopenia was defined as PMI ≤5.1 cm^2/m^2 in men and ≤43 cm^2/m^2 in women [19].

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 25.0 (IBM Corporation, Armonk, New York, United States). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare quantitative variables between two independent groups. The Kaplan-Meier (product-limit method) and log-rank (Mantel-Cox) tests were used to evaluate the impact of factors on progression-free survival (PFS). Cox regression analysis was applied to assess the prognostic effects of variables on PFS, with significant independent variables entered into the model both as single (individually) and multiple (collectively) variables. The relationship between predicted classification based on calculated cut-off values and actual classification was evaluated using sensitivity and specificity rates derived from receiver operating characteristic curve analysis. Variables were analyzed at a 95% confidence level, with a $p<0.05$ considered statistically significant.

Results

The study included 13 female and 20 male patients, with a mean age of 57±16.2 years (range: 20-85). Disease staging revealed one patient with stage 1, 5 with stage 2, 10 with stage 3, and 17 with stage 4 disease. ECOG performance status was 1 in 22 patients, 2 in 10 patients, and 3 in 1 patient. The median right psoas average HU (RPHUc) was 36.5±10.9. During follow-up, relapse occurred in 9 patients (27.3%), and one patient (3.03%) died. The median lactate dehydrogenase level prior to treatment initiation was 296.0 U/L, with values ranging from 139 to 4900 U/L. A statistically significant association was found

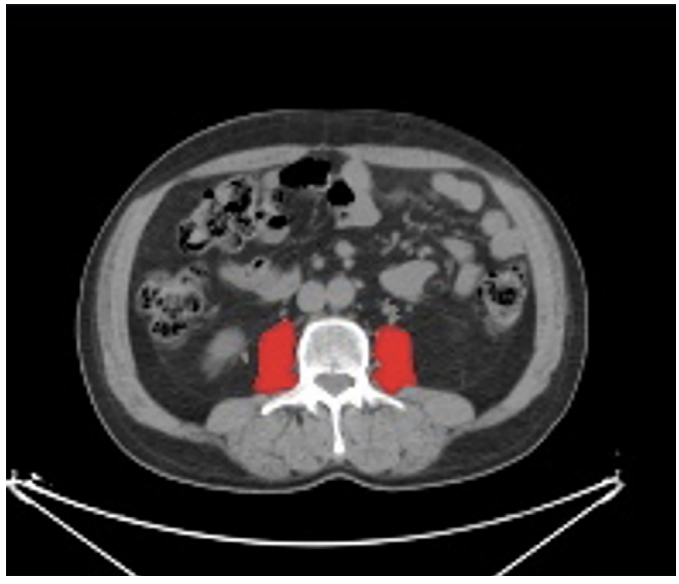

Figure 1. Axial PET/CT image demonstrating psoas muscle assessment
An axial PET/CT image from one of the cases included in our study, showing delineation of the right and left psoas muscles for radiodensity measurement. These measurements were used in the calculation of the psoas muscle index
PET: Positron emission tomography, CT: Computed tomography

between relapse and age (p=0.002), ECOG performance status (p=0.003), and RPHUc (p=0.015). Relapse was more frequently observed in patients of advanced age, with compromised ECOG performance status and reduced RPHUc levels. Among the 9 relapsed patients, 5 had sarcopenia in the PM, but no statistically significant relationship was found between relapse and sarcopenia. Other descriptive parameters are presented in Table 1. An RPHUc cut-off value of >33.55 predicted better PFS (area under the curve: 0.778, p=0.015) with 66.7% sensitivity, and 33.0% specificity (Figure 2). For RPHUc <33.550, the median PFS was 76.9 months at 1 year, while it was 27.4 months at 4 years. For RPHUc >33.550, the median 1-year and 4-year PFS were both 88 months. The median PFS was 10.03 months (range: 5-48) in relapsed patients and 22.72 months (range: 5-63) in non-relapsed patients (Figure 3). Univariate Cox regression analysis identified age (p=0.001), ECOG performance score (p=0.000), and RPHUc (p=0.017) as significant prognostic factors for PFS (Table 2). In multivariate Cox regression analysis, only age remained an independent prognostic factor for PFS (p=0.04).

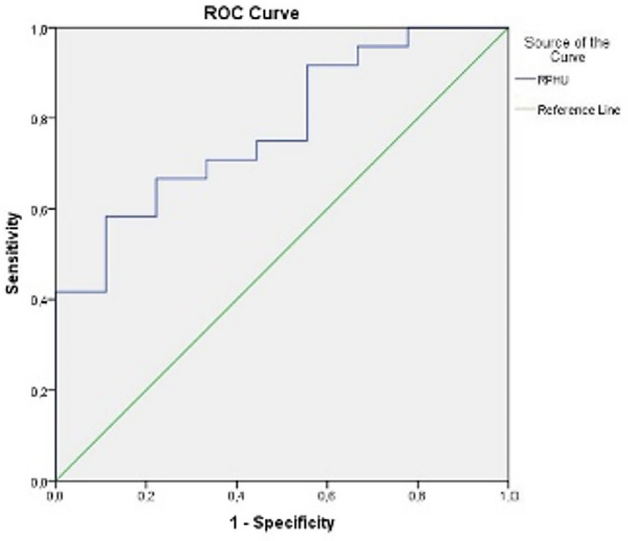

Figure 2. ROC curve of right psoas hounsfield unit cut-off value in predicting progression-free survival
ROC: Receiver operating characteristic

Table 1. Comparison of demographic and radiological sarcopenia-related parameters according to relapse status

Variable	Relaps	Median (min-max)
Age (years)	No	54 (20-80)
	Yes	72 (49-85)
Right psoas mean (HU)	No	38.1 (16.6-57.4)
	Yes	31.2 (14.6-43.1)
Left psoas mean (HU)	No	38.7 (22.3-56.8)
	Yes	32.7 (26.1-45.7)
PMI (cm^2/m^2)	No	5.34 (2.67-14.18)
	Yes	5.27 (3.43-7.08)

HU: Hounsfield unit, PMI: Psoas muscle index, min-max: Minimum-maximum

Discussion

Studies have demonstrated that NHL patients may lose up to 31% of their total body weight [20]. In advanced-stage cancers, including both solid tumors and hematologic malignancies, cancer cachexia affects approximately 60-80% of patients [7,10]. This condition can lead to adverse clinical outcomes such as reduced tolerance to chemotherapy and diminished quality of life [12,13].

Aging represents one of the most significant risk factors for sarcopenia development, contributing to progressive muscle mass loss. Additionally, various pro-inflammatory cytokines released by tumors, including interleukin-1, interleukin-6, tumor necrosis factor, and interferon gamma, accelerate muscle tissue catabolism [21]. Tumor-induced abnormalities in protein and amino acid metabolism, combined with malnutrition and reduced physical activity during treatment, result in more pronounced muscle mass reduction [22].

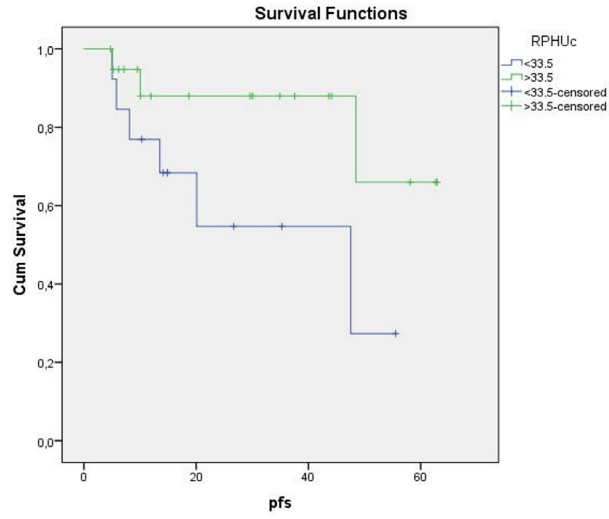

Figure 3. Kaplan-Meier curve for progression-free survival based on right psoas muscle HU cut-off value
RPHUc: Right psoas hounsfield unit corrected, HU: Hounsfield unit

Table 2. Cox regression analysis of clinical and radiological parameters for progression-free survival

Parameter	B	OR	95% CI	p
Age	0.127	1.135	1.051-1.226	**0.001**
Gender	0.779	2.179	0.451-10.538	0.333
Stage	0.143	1.154	0.506-2.634	0.734
ECOG	2.180	8.843	2.747-28.464	**0.000**
LDH	0.000	1.000	0.999-1.001	0.692
Sedimentation rate	0.005	1.005	0.980-1.030	0.717
PMI	1.029	2.799	0.742-10.552	0.128
Right psoas average	-0.085	0.919	0.857-0.985	**0.017**
Left psoas average	-0.022	0.978	0.909-1.052	0.548

B: Regression coefficient, OR: Odds ratio, CI: Confidence interval, PMI: Psoas muscle index, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase

Cancer treatments may also induce loss of fat and bone mass alongside muscle depletion [23]. The age-dependent increase in sarcopenia prevalence has been well-documented [24,25]. In our study of aggressive lymphomas, univariate analysis identified age as a prognostic factor for PFS (p=0.001), with multivariate analysis confirming its independent prognostic value (p=0.04). This finding contrasts with Albano et al. [26] study of older MCL patients (mean age 72.7±5.6 years), which found no significant association between age and PFS. Our study's inclusion of relatively younger patients provides valuable insights into the independent effect of age on PFS in sarcopenic patients.

While one MCL study in elderly patients reported significantly higher sarcopenia prevalence in women (93% vs. 47%, p=0.001) [25], Xu et al. [27] DLBCL study found no gender-specific association regarding gender differences between sarcopenia and prognosis. The lack of significant gender-PFS correlation in our study may reflect our inclusion of various high-grade lymphoma subtypes and relatively younger patients.

Saglam et al. [28] study of 112 patients identified ECOG performance status as a prognostic factor for PFS in both univariate and multivariate analyses. While our univariate Cox regression confirmed this association (p=0.000), multivariate analysis did not. This discrepancy may result from our limited sample size, cohort differences, or potential confounding effects of other variables in the model.

In our study, sarcopenia was identified in 36% of patients, aligning with the findings of Xiao et al. [29], who reported a prevalence exceeding 30% based on pretreatment CT evaluations in individuals with DLBCL. However, we found no significant association between PMI and PFS (p=0.128).

Myosteatosis, defined as muscle weakening due to fat infiltration and measured by HU [30,31], has been associated with worse OS in various malignancies including lymphoma [32]. In our cohort, PFS differed significantly based on RPHUc cut-off values: median PFS was 10.03 months in relapsed patients, versus 22.72 months in non-relapsed patients. These findings suggest that muscle quality rather than quantity may influence PFS. Univariate analysis confirmed RPHUc as a prognostic factor (p=0.017), aligning with reports of significantly worse PFS in patients with low skeletal muscle density (hazard ratio: 2.28, p=0.002) [33].

Sarcopenia assessment may prove particularly valuable when deciding between standard R-CHOP chemoimmunotherapy and dose-reduced regimens for elderly patients or those with poor performance status, comorbidities.

Study Limitations

One of the key strengths of this study is the use of an objective radiological parameter (RPHUc) to assess muscle quality and the investigation of its prognostic significance in a relatively younger and clinically heterogeneous high-grade lymphoma cohort. The limited number of prior publications exploring RPHUc in this setting enhances the novelty and potential clinical relevance of our results. Study limitations include the small sample size, retrospective design, lack of gender-specific analysis, and absence of DLBCL subtype and treatment toxicity data. Nevertheless, the study by Lanic et al. [34] reported no significant association between sarcopenia and the GCB or non-GCB subtypes.

Conclusion

Our findings suggest that both age and RPHUc are valuable prognostic indicators in high-grade lymphoma. This simple, routinely accessible imaging parameter may enhance risk stratification and guide individualized treatment approaches.

Ethics

Ethics Committee Approval: The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital (decision no: 345, date: 07.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Original Article

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Prognostic Value of Inflammatory Markers, CA 19-9, MELD Score, and ECOG in Stage 4 Gastric Cancer with Liver Metastases

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ABSTRACT

Aim: This study aimed to investigate the prognostic significance of the Model for End-Stage Liver Disease (MELD) score in patients with stage 4 liver metastatic gastric cancer and to investigate whether other clinical pathological data are prognostic indicators.

Methods: Stage 4 liver metastatic gastric cancer patients who were followed up retrospectively between January 2014 and November 2024 were included in the study. Demographic and clinical data of the patients were entered into the database. Survival analyses were performed using the Kaplan-Meier method and the log-rank test. Independent effects of prognostic factors were evaluated using the Cox proportional hazards regression model (Cox). Statistical significance was accepted as $p<0.05$.

Results: One hundred and fifty patients were included in the study. The median age of the patients was 64 years, and 26.3% were female. The estimated median overall survival (mOS) was 7.9 months. The mOS was 10.5 months in the Eastern Cooperative Oncology Group (ECOG) 0-1 group compared to 3.6 months in the ECOG 2-3 group ($p<0.001$). According to the ideal cut-off value of carbohydrate antigen (CA) 19-9, survival was 9.7 months in the ≤37.1 U/mL group and 6.7 months in the >37.1 U/mL group ($p=0.017$). There was no difference in survival according to the determined categories of age ($p=0.395$), gender ($p=0.670$), smoking status ($p=0.764$), body mass index (BMI) ($p=0.563$), carcinoembryonic antigen (CEA) ($p=0.057$), neutrophil-to-lymphocyte ratio (NLR) ($p=0.359$), platelet-to-lymphocyte ratio (PLR) ($p=0.158$), monocyte-to-lymphocyte ratio (MLR) ($p=0.811$), and MELD score ($p=0.561$). In univariate Cox regression analysis, an ECOG score of 2 and above [hazard ratio (HR) 4.03; $p<0.001$] and a CA 19-9>37.1 U/mL (HR 1.54; $p=0.018$) were determined as poor prognostic factors, and BMI, NLR, PLR, MLR, MELD score, and CEA did not show prognostic significance.

Conclusion: We found that CA 19-9 level and ECOG performance status are markers that can be used in determining prognosis in liver metastatic gastric cancer, and the analyzed blood values (NLR, PLR, MLR) and MELD score did not demonstrate any prognostic significance in this patient group.

Keywords: CA-19-9 antigen, clinical oncology, gastrointestinal cancer, MELD score, metastasis, oncology, stomach neoplasms

Introduction

Gastric cancer is the fifth most frequently diagnosed cancer worldwide, and it holds the fourth position among cancers causing mortality [1]. In recent years, its prevalence has been increasing, especially among young people, due to changing consumption habits [1]. With early-stage diagnosis and curative treatments, 5-year survival rates can reach 70% [2]. However, despite early diagnosis and screening programs, the emergence of cancer-related symptoms often leads to diagnosis in locally advanced or metastatic stages. Despite the development of the health system and innovative treatments,

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one-year survival rates are still below 25%, and the median overall survival (OS) in the metastatic stage is less than one year [3,4].

Cancer is a disease that affects not only the specific organ, but also all systems. Systemic inflammation occurs with the development of cancer, leading to decreased performance, cachexia, and later failure of systems and death. Some prognostic markers have been proposed for stomach cancer and many other types of cancer, with parameters beginning with inflammation and affecting other systems [5]. Although the tumor, node, metastasis staging system is also used as a prognostic factor in stomach cancer, it defines stage 4 stomach cancer in a single category [6]. Patients with similar stages can show a heterogeneous prognosis. Therefore, in recent years, prognostic indicators based on simple hematological indicators reflecting systemic inflammation and nutritional status have become increasingly important [7]. Inflammatory parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) obtained from complete blood count provide indirect information about the immune response, tumor microenvironment, and systemic inflammation level [8,9]. However, low body mass index (BMI) values, in particular, can also predict a negative prognosis as an indicator of malnutrition and poor immunity [2].

The Model for End-Stage Liver Disease (MELD) score, which is a similar blood parameter and reflects liver dysfunction, has also been associated with morbidity and mortality, especially after surgery, in gastric cancer patients in some studies [10,11]. Although the MELD score does not directly indicate tumor burden in patients with metastatic gastric cancer, it can provide prognostic information by indicating the severity of liver function impairment due to cancer [12]. However, there is insufficient information on whether these markers are prognostic in the group with liver metastatic gastric cancer that will progress to liver failure.

In this study, we aimed to investigate prognostic markers, especially the MELD score, in patients with liver metastatic gastric cancer.

Methods

This retrospective study included stage 4 gastric cancer patients with liver metastases who had complete follow-ups between January 2014 and November 2024. This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ministry of Health of the Republic of Türkiye (decision no: 118/05, date: 23.08.2023).

Inclusion criteria were being have pathologically confirmed gastric cancer, 18 years of age and older, patients with radiological or pathological liver metastases, and complete follow-ups, no concurrent chronic kidney disease, no current or past history of malignancy, and patients with gastric adenocarcinoma who were not receiving active infectious disease, immunosuppressive drugs or nutritional support. Patients with multiple cancers, patients without liver metastases, patients with esophageal junction tumors, and patients with known human epidermal growth factor receptor 2 gastric cancers were excluded in the study.

Demographic information, patient clinicopathological parameters, and serum blood parameters measured before chemotherapy were obtained from the hospital automation system.

Calculating Indexes

- BMI=Weight (kg) / [height (m)]^2
- NLR=Absolute neutrophil count / absolute lymphocyte count
- PLR=Platelet count / lymphocyte count
- MLR=Monocyte count / lymphocyte count
- MELD=3.78×ln(bilirubin)+11.2×ln[international normalized ratio (INR)]+9.57×ln(creatinine)+6.43

Statistical Analysis

Statistical analyses in this study were carried out using Statistical Package for the Social Sciences (SPSS) statistics software version 24 (SPSS Inc., Chicago, IL). In the study, variables were categorized, and the ratio of each to the total patient group was written as a percentage. In the study, the receiver operating characteristic (ROC) curves and the area under the curve (AUC) analyses were performed to determine the ideal cut-off points to be used in the analyses. In the parameters for which a specific cut-off could not be determined by the ROC-AUC method, the median value was used as the cut-off. Survival analyses were performed using the Kaplan-Meier technique. Group comparisons were statistically analyzed using the log-rank test. Factors affecting survival were evaluated using univariate Cox proportional hazards (Cox) regression analysis. OS was calculated as the time from the date of diagnosis of metastasis to the date of death or last follow-up. A p of <0.05 was used as the criterion for statistical significance.

Results

The research encompassed 150 patients in its entirety. The median age of the patients was 64 (minimum: 32, maximum: 89). Forty-one of the patients were female (26.3%) and 84 of the patients (56.0%) had a smoking history of 10 packs/year or more. Other clinical data are shown in Table 1. The ideal cut-off values of carcinoembryonic antigen (CEA), CA199, NLR, PLR, MLR, and MELD score for gastric cancer were investigated using ROC-curve analysis. The ideal cut-off values were determined as 10.7 for CEA (cut-off sensitivity: 54.7%, specificity: 62.7%) and 37.1 for carbohydrate antigen (CA) 19-9 (cut-off sensitivity: 54.7%, specificity: 61.3%). The ideal cut-off value for NLR, PLR, MLR, and MELD score could not be determined, and median values were used in the analyses (3.6, 192.5, 0.40, 7.2, respectively) (Figure 1, Table 2).

Median OS was determined as 7.9 months [95% confidence interval (CI): 6.4-9.4 months]. In the group with Eastern Cooperative Oncology Group (ECOG) performance status 0-1,

Table 1. Clinical and laboratory data of the patients and estimated median overall survival analyses

Parameter	Category	N	%	Median OS (months) (95% CI)	p*
Age	<60	47	31.3	8.10 (3.86-12.34)	0.395
	≥60	103	68.7	7.70 (6.19-9.21)	
Gender	Female	41	27.3	7.00 (4.96-9.04)	0.670
	Male	109	72.7	8.50 (6.38-10.62)	
ECOG	0-1	113	75.3	10.50 (7.71-13.29)	**<0.001**
	≥2	37	24.7	3.60 (2.17-5.03)	
Smoking status	No	66	44.0	8.10 (5.96-10.24)	0.764
	Yes	84	56.0	7.20 (5.26-9.14)	
BMI	<20	15	10.0	12.40 (9.39-15.41)	0.563
	≥20	135	90.0	7.70 (6.40-8.99)	
CEA	<10.7	81	54.0	10.20 (7.15-13.25)	0.057
	>10.7	69	46.0	7.00 (6.02-7.98)	
CA 19-9	≤37.1	81	54.0	9.70 (7.30-12.10)	**0.017**
	>37.1	69	46.0	6.70 (5.33-8.07)	
NLR	≤3.6 (median)	77	51.3	9.50 (7.59-11.41)	0.359
	>3.6	73	48.7	6.50 (4.87-8.13)	
PLR	<192.5 (median)	75	50.0	9.70 (7.98-11.42)	0.158
	≥192.5	75	50.0	7.00 (5.26-8.75)	
MLR	≤0.40 (median)	77	51.3	8.40 (6.28-10.52)	0.811
	>0.40	73	48.7	7.70 (5.66-9.74)	
MELD	≤7.19 (median)	79	52.7	8.80 (6.42-11.02)	0.561
	>7.19	71	47.3	7.20 (6.03-8.37)	

*p values were obtained by Kaplan-Meier analysis.
OS: Overall survival, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for end-stage liver disease

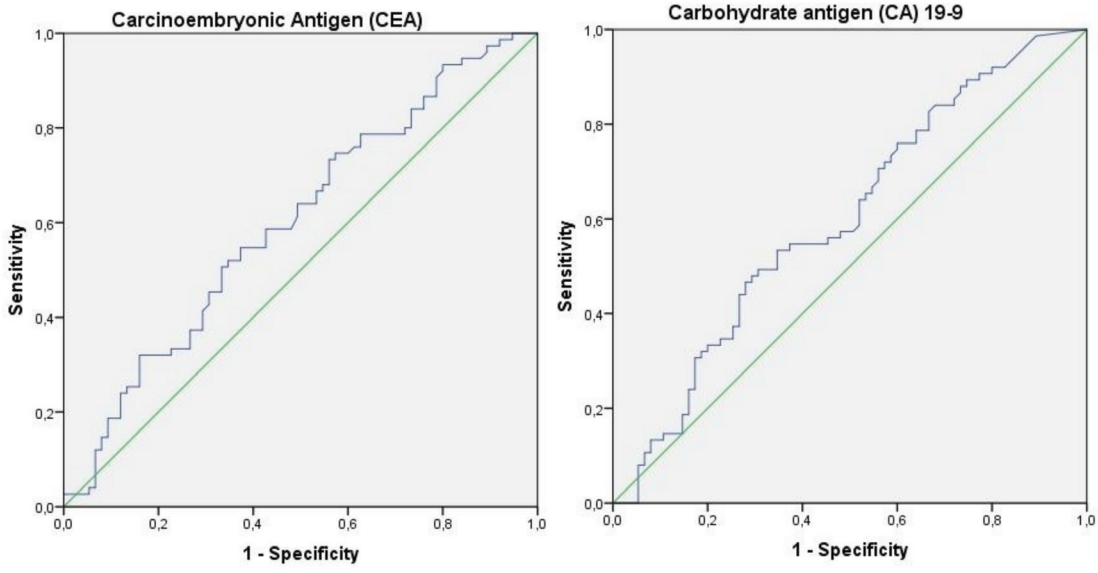

Figure 1. ROC-curve analysis to determine the ideal cut-off for variables
ROC: Receiver operating characteristic

median OS was 10.50 months (95% CI: 7.71-13.29) and in the group with ECOG 2-3, median OS was 3.60 months (95% CI: 2.17-5.03) (log-rank p<0.001). In the CA 19-9 ≤37.1 U/mL group, OS was 9.70 months (7.30-12.10), and in the >37.1 U/mL group, OS was 6.70 months (95% CI: 5.33-8.07) (log-rank p=0.017). For CEA <10.7 ng/mL, the median OS was 10.20 months (95% CI: 7.15-13.25), while for CEA >10.7 ng/mL, it was 7.00 months (log-rank p=0.001). Smoking status (log-rank p=0.764), BMI (<20 vs. ≥20 kg/m²; log-rank p=0.563), NLR (≤3.6 vs >3.6; log-rank p=0.359), PLR (<192.5 vs. ≥192.5; log-rank p=0.158), MLR (≤0.40 vs. >0.40; log-rank p=0.811), and MELD (≤7.19 vs. >7.19; log-rank p=0.563) were not found to be statistically significant for OS (Table 1).

ECOG performance status was found to be predictive of survival in the 0-1 vs 2-3 comparison [hazard ratio (HR) 4.03; 2.625-6.194; p<0.001]. CA 19-9>37.1 was associated with decreased OS compared to CA 19-9 levels of 37.1, U/mL and below (HR 1.54; 1.077-2.201; p=0.018). Other factors such as age (<60 vs ≥60 years; HR 1.18; 0.806-1.720; p=0.398), gender (female vs male; HR 0.92; 0.617-1.364; p=0.671), smoking status, BMI (0.566), CEA (0.059), NLR (0.361), PLR (0.161), MLR (0.812), and MELD (0.563) scores were not significantly associated with OS (Figure 2, Table 3).

Discussion

In this study, data of 150 metastatic gastric cancer patients with liver metastases were analyzed. Patients with ECOG performance score 0-1 had an estimated median OS of 10.5 months, while patients with ECOG 2-3 had only an mOS of 3.6 months (p<0.0001). Patients with high CA 19-9 had worse survival rates than those with low CA 19-9 (p=0.017). When evaluated with Cox regression analysis, CA 19-9 and ECOG were prognostic markers, while NLR, PLR, MLR, and MELD score were found to be not prognostic markers in liver metastatic gastric cancer.

In stage 4 gastric cancer, many guidelines recommend chemotherapy to prolong survival and achieve a longer life span [13]. However, in some patients, survival is shorter than expected, and palliative care is offered as an option [14]. In metastatic gastric cancer, ECOG performance score plays a major role as a determinant in predicting prognosis and chemotherapy toxicity [15,16] In their study, ECOG was determined as a prognostic indicator. Similar results were presented in the study by Demirelli et al [17]. In our study, ECOG performance score served as a prognostic indicator, which is consistent with the literature.

Table 2. Determination of ideal cut-off values of variables using ROC-curve analysis

Variables	AUC (95% confidence interval)	Ideal cut-off	Sensitivity for cut-off	Specificity for cut-off	p
CEA	0.601 (0.510-0.691)	10.7	54.7%	62.7%	0.034
CA 19-9	0.600 (0.509-0.690)	37.1	54.7%	61.3%	0.035
NLR	0.529 (0.436-0.621)	3.6 (median)			0.545
PLR	0.554 (0.462-0.646)	192.5 (median)			0.256
MLR	0.516 (0.423-0.609)	0.40 (median)			0.735
MELD	0.549 (0.456-0.641)	7.2 (median)			0.303

CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for End-Stage Liver Disease, ROC: Receiver operating characteristic, AUC: Area under the curve

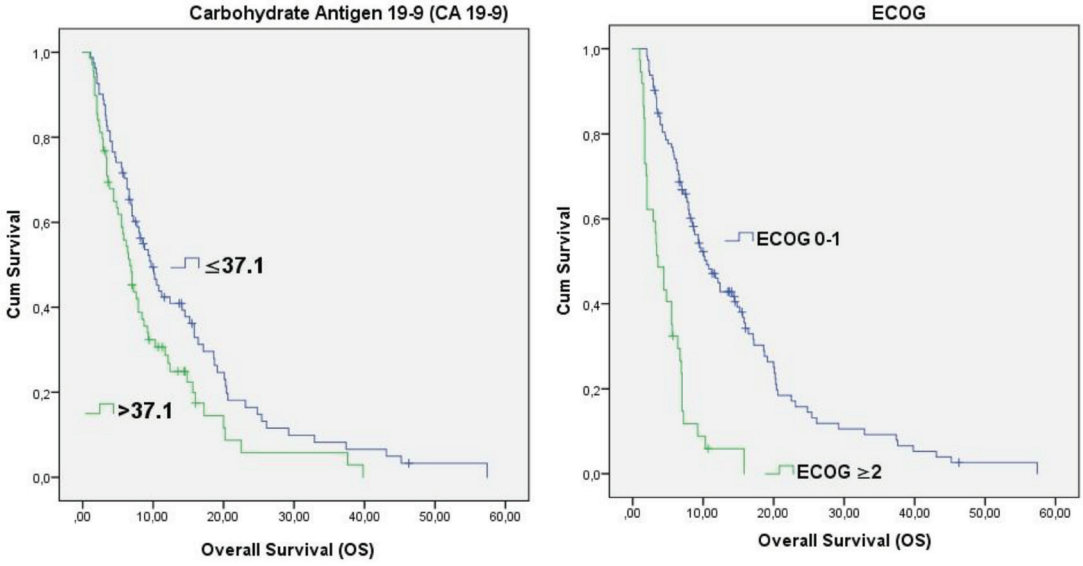

Figure 2. Survival graph of ECOG and CA 19-9
ECOG: Eastern Cooperative Oncology Group, CA: Carbohydrate antigen

Table 3. Univariate COX-regression analysis of variables for overall survival

Variable	Category	HR (95% CI)	p
Age	<60 years vs. ≥60 years	1.18 (0.806-1.720)	0.398
Gender	Male vs. female	0.92 (0.617-1.364)	0.671
ECOG performance status	0-1 vs. 2-3	4.03 (2.625-6.194)	**<0.001**
Smoking status	<10 pack-years vs. ≥10 pack-years	1.06 (0.739-1.508)	0.765
BMI	<20 kg/m² vs. ≥20 kg/m²	1.19 (0.655-2.167)	0.566
CEA	≤10.7 ng/mL vs. >10.7 ng/mL	1.42 (0.987-2.032)	0.059
CA 19-9	≤37.1 U/mL vs. >37.1 U/mL	1.54 (1.077-2.201)	**0.018**
NLR	≤3.6 vs. >3.6	1.18 (0.827-1.683)	0.361
PLR	<192.5 vs. ≥192.5	1.29 (0.905-1.827)	0.161
MLR	≤0.40 vs. >0.40	0.96 (0.675-1.360)	0.812
MELD	≤7.19 vs. >7.19	1.11 (0.781-1.574)	0.563

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for End-Stage Liver Disease, Cox: Cox proportional hazards regression model, CI: Confidence interval, HR: Hazard ratio

CA 19-9, also known as sialyl-Lewis^a, is a glycoprotein complex with a tetrasaccharide structure located on the cell surface [18]. This antigen is naturally found in pancreatic ductal cells, bile duct epithelium, stomach, colon, endometrium, and salivary gland epithelium. Blood serum concentrations above 30-40 U/mL are usually pathological. CA 19-9 can be elevated in many types of cancer, especially in pancreatic and biliary tract cancers. In the study by Yu et al. [19], high levels of CA 19-9 were shown to be a prognostic marker in gastric cancers. In their study, Roşu et al. [20] showed that CA 19-9 was also a prognostic marker for gastric cancers. In our study, similar results were obtained as reported in the literature, and CA 19-9 was shown to be a prognostic marker.

The MELD score is a prognostic index based on laboratory data developed to estimate the 90-day mortality risk in patients with advanced liver disease who underwent a transjugular intrahepatic portosystemic shunt procedure [21]. The MELD score can evaluate the severity of liver failure, especially cirrhosis, using serum bilirubin, creatinine, and international normalized ratio values [22]. In their study on patients with liver metastatic colon cancer, Karadağ and Karakaya [23] showed that high MELD scores were an indicator of poor prognosis. It has been shown that it can be a marker of mortality in patients with gastric cancer who underwent surgery [11,24]. Although the MELD score is not a marker that directly reflects tumor biology in terms of metastatic gastric cancer, it can provide information about liver reserve, especially in patients with liver metastases, and this can predict prognosis. However, in our study, it was shown that the MELD score would not be a prognostic marker in patients with gastric cancer with liver metastasis. Although the MELD score indicates liver functions, mortality occurs following liver function deterioration in metastatic gastric cancer, which may explain why this score is not found to be prognostic.

Study Limitations

The most important limitation of our study is its retrospective design. Due to its retrospective nature, data were obtained from past records and may contain potential biases. In addition, since some data, such as ECOG performance scores, are based on subjective assessments, individual evaluation differences may have occurred in the results.

Conclusion

As a result, we demonstrated that CA 19-9 and ECOG performance score can be markers for prognosis in liver metastatic gastric cancer, and that NLR, PLR, MLR scores together with MELD score do not possess predictive properties. These results should be validated in future studies.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ministry of Health of the Republic of Türkiye (decision no: 118/05, date: 23.08.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.Z., T.E., G.İ.İ., S.G., Y.D., A.K., Design: E.Z., T.E., G.İ.İ., Y.D., A.K., Data Collection or Processing: S.G., Analysis or Interpretation: E.Z., S.G., Literature Search: E.Z., T.E., G.İ.İ., Y.D., Writing: E.Z., A.K.

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Original Article

Adjuvant Gemcitabine-cisplatin Combination for Biliary Tract Cancer: A Real Life Experience

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ABSTRACT

Aim: Biliary tract cancers (BTCs), including gallbladder and cholangiocarcinomas, are aggressive malignancies with poor long-term survival despite surgical resection. The efficacy of adjuvant therapy in BTCs remains controversial, particularly in the absence of consistent phase 3 data supporting its survival benefit.

Methods: We conducted a retrospective, single-center study including 49 patients who underwent surgery for BTC and received adjuvant chemotherapy between 2013 and 2022. Patients with stage 1 disease, neoadjuvant treatment, unresectable/metastatic disease, or missing pathology were excluded. Survival outcomes were analyzed using Kaplan-Meier and Cox regression methods.

Results: The median overall survival (mOS) for the entire cohort was 44.8 months. The gemcitabine-cisplatin (GemCis) group had significantly longer mOS (71.5 months) than patients receiving other regimens (41.8 months; p=0.033). Advanced T stage, lymph node involvement, and tumor, node, metastasis stage 3 were associated with poorer survival. In multivariate analysis, treatment other than GemCis [hazard ratio (HR): 2.38; p=0.040] and stage 3 disease (HR: 3.32; p<0.01) were independent risk factors for decreased mOS.

Conclusion: Our findings suggest that the gemcitabine-cisplatin combination may confer a survival advantage in selected patients with BTCs, especially younger individuals with good performance status. These results support further investigation in randomized controlled trials to clarify the role of gemcitabine-cisplatin in the adjuvant setting.

Keywords: Biliary tract cancer, adjuvant chemotherapy, gemcitabine-cisplatin combination, capecitabine, cholangiocarcinoma

Introduction

Biliary tract cancers (BTCs) refers to cancers that develop in the gallbladder or the biliary epithelium of the intra-and extrahepatic bile ducts [1]. The incidence of gallbladder cancer in women is declining, while the incidence of intrahepatic cholangiocarcinoma is increasing, and extrahepatic cholangiocarcinoma remains stable [2,3]. The 5-year survival rate for patients with cholangiocarcinoma is approximately 20% [4]. Despite an increase in the early-stage diagnosis of gallbladder cancer, the 5-year survival rate for patients with advanced-stage gallbladder cancer and cholangiocarcinoma is less than 5% [5].

Surgery represents the only curative treatment option for BTCs; however, even after achieving R0 resection, the recurrence rates remain relatively high. In a study where patients were followed up after resection, 48.8% died from malignancy and 11.3% died from non-malignant causes within 28 months [6].

The effectiveness of adjuvant therapy in treating BTCs is still a subject of ongoing debate, especially with the emergence of immune checkpoint inhibitors as adjuvant treatment options

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in various cancer types [7-9]. Apart from the BTC cancer capecitabine trial (BILCAP) study, no phase 3 study has provided evidence demonstrating that adjuvant therapy is superior to a placebo [10]. Additionally, two phase 3 studies have shown that treatments containing gemcitabine did not significantly improve outcomes compared to a placebo [11,12]. The occurrence of distant recurrences, particularly in gallbladder cancers, emphasizes the need for effective adjuvant treatments [13]. In contrast to phase 3 studies, several retrospective studies have indicated that adjuvant chemotherapy agents and adjuvant chemoradiotherapy can enhance survival outcomes [14,15]. One meta-analysis of gallbladder cancers and two separate meta-analyses of cholangiocarcinomas have demonstrated that adjuvant chemotherapy improves overall survival (OS) [16-18]. However, there is a lack of phase 3 studies directly comparing different chemotherapy regimens.

The phase 2 STAMP trial compared gemcitabine-cisplatin (GemCis) and capecitabine in patients with resected, lymph node-positive extrahepatic cholangiocarcinoma and found similar median OS (mOS) in both arms (around 35.7 months), with no significant difference [hazard ratio (HR) ≈ 1.08, p=0.40] [19]. A phase 3 study (ACTICCA-1), comparing 8 cycles of GemCis with 6 months of capecitabine in resected BTCs, has been conducted, and the final results are currently awaited. This trial is expected to clarify whether GemCis offers any advantage over capecitabine in the adjuvant setting [20]. Despite its proven benefit in advanced disease, GemCis does not appear to be clearly superior to fluoropyrimidine monotherapy in the adjuvant setting. The ongoing challenge of distant recurrence, particularly in gallbladder cancer, underscores the urgent need for more effective systemic adjuvant treatments.

The objective of our study was to analyze the mOS and assess the efficacy of various chemotherapy regimens in patients with BTCs who received adjuvant chemotherapy.

Methods

Our study is a retrospective, single-center investigation that included patients aged 18 and above who underwent surgery for gallbladder cancer or cholangiocarcinoma, and received adjuvant treatment at a university cancer institute between 2013 and 2022. Patients who received neoadjuvant therapy, were at stage 1, had metastatic-unresectable tumors, or for whom pathology data could not be obtained were excluded from the study.

We collected baseline patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, tumor pathology information, details of the treatment agents used, as well as baseline hemoglobin and albumin levels. Additionally, survival data were collected. Anemia was defined as a hemoglobin level below 12 g/dL, and hypoalbuminemia was defined as an albumin level below 3.5 g/dL.

The selection of adjuvant chemotherapy regimens was based on the treating physician's clinical judgment, taking into account factors such as patient age, performance status, and comorbidities.

All procedures involving human participants in this study adhered to the ethical standards set by the institutional and/or national research committee, as well as the guidelines outlined in the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. Approval was obtained from the Hacettepe University Ethics Committee for the study (decision no: 2022/15-54, date: 04.10.2022).

Statistical Analysis

Where appropriate, baseline characteristics were presented as percentages, means, and standard deviations. The chi-square test was employed to assess the baseline patient characteristics of the GemCis group and the other treatment group. Survival analyses were conducted using the Kaplan-Meier method and Cox regression analyses. A p value less than 0.05 was considered statistically significant. The multivariate Cox regression analysis included parameters with p-values below 0.05. For these analyses, the Statistical Package for Social Sciences (SPSS, IBM, New York, USA) version 22 was utilized.

Results

In our study, 49 patients were involved. The patients' mean age was 59.29±11.77 years. Thirty-one patients were male, and all patients had an ECOG of 0 or 1. There were 18 patients with gallbladder cancer and 31 with bile duct cancers. The tumor stage was 2 in 24 patients, and the lymph node stage was 0 in 29 patients. Negative surgical margins were found in 41 patients, while positive microscopic surgical margins were found in 8 patients. The most commonly used treatments were GemCis combinations and capecitabine. Adjuvant radiotherapy was administered to 19 patients, while no radiotherapy was administered to the remaining 30 patients. Anemia and hypoalbuminemia appeared in 19 and 17 of the patients, respectively. Table 1 presents the demographic, pathological, and clinical characteristics of the patients.

Thirty patients died during their follow-up. mOS was 44.8±7.32 months [95% confidence interval (CI): 30.47-59.19]. Kaplan-Meier analysis was used to examine the factors that influence survival. Women had an mOS of 54.76±5.48 months (95% CI: 44.00-65.52), and men had an mOS of 36.3±4.43 months (95% CI: 27.63-45.03) (p=0.132). mOS times were found to be comparable in patients aged ≥65 (43.5±1.74 months, 95% CI: 40.08-46.91) and patients aged <65 (44.8±12.89 months, 95% CI: 19.56-70.10), with a p value of 0.324). The mOS for gallbladder cancer is 42.2±2.01 months (95% CI: 38.31-46.22), while for bile duct cancers, it is 54.7±19.63 months (95% CI: 16.28-93.24) (p=0.803). The mOS time was found to be lower as the T stage increased 71.5 months (95% CI: 55.31-87.74), 36.3 months (95% CI: 22.08-50.58), 35.5 months (95% CI: 16.45-54.54), respectively; T2, T3, and T4, p=0.024). Those who did not have lymph node metastases had a longer mOS than those who did 61.9 months (95% CI: 34.35-89.45) and 26.6 months (95% CI: 10.09-43.23), respectively; p=0.013).

Tumor, node, metastasis (TNM) stage 2 patients had a longer mOS than TNM stage 3 patients 71.5±30.18 months (95% CI: 12.317-130.69) and 35.5±5.95 months (95% CI: 23.82-47.17); p=0.002.

When compared to other treatments, patients receiving the GemCis combination had a longer mOS 71.5±33.62 months (95% CI: 5.63-137.43) and 41.8±4.07 months (95% CI: 33.84-49.82); p=0.033. The relationship between treatment regimen and mOS is shown in Figure 1.

Positive surgical margins, adjuvant radiotherapy, anemia, hypoalbuminemia, and mOS had no correlation (p=0.869, p=0.208, p=0.738, and p=0.699).

Table 1. Baseline clinical and laboratory features of patients

		No	%
Age (mean ± standard deviation)	59.29±11.77		
Age	>65	13	26.5
	<65	36	73.5
Sex	Female	18	36.7
	Male	31	63.3
ECOG score	0	47	95.9
	1	2	4.1
Tumor localization	Gallbladder cancer	18	36.7
	Intrahepatic cholangiocarcinoma	13	26.6
	Extrahepatic cholangiocarcinoma	18	36.7
Primary tumour classification	2	24	49
	3	22	44.9
	4	3	6.1
Lymph node status	0	29	59.2
	1	15	30.6
	2	5	10.2
Pathological tumour stage	2	23	44.9
	3	26	55.1
Resection margin	R0	41	83.7
	R1	8	16.3
Chemoterapy regimen	Gemcitabine plus cisplatin	26	53.3
	Gemcitabine plus fluoropyrimidine	5	10.2
	Gemcitabine	7	14.2
	Capecitabine	11	22.3
Adjuvant radiotherapy	Present	19	38.8
	Absent	30	61.2
Anemia	Present	19	38.8
	Absent	30	61.2
Hipoalbuminemia	Present	17	34.7
	Absent	32	65.3

ECOG: Eastern Cooperative Oncology Group

The parameters associated with survival in univariate analysis were included in the multivariate Cox regression analysis (T stage, N stage, TNM stage, and treatment agents). The GemCis combination treatment (HR: 2.38, 95% CI: 1.042-5.466; p=0.040) and presence of stage 3 disease (HR: 3.32, 95% CI: 1.491-7.402) were independent risk factors for mOS. Univariate and multivariate analysis results are shown in Table 2. It was found that younger patients were given the GemCis combination, whereas adjuvant radiotherapy was used more frequently in patients who received other chemotherapy. Table 3 compares the demographic, clinical, and pathological characteristics of patients receiving GemCis treatment with those receiving other therapies.

Discussion

In our retrospective study, being diagnosed at an advanced stage and receiving treatment other than GemCis were identified as independent risk factors.

BTCs encompass various components, including gallbladder, intrahepatic bile duct, and extrahepatic bile duct cancers. Due to their rarity, they are evaluated in clinical studies [10-12]. The BILCAP study compared adjuvant capecitabine treatment to observation alone. The mOS was reported as 51 months in the capecitabine arm and 36 months in the observation arm [21]. This study indicated a greater contribution of adjuvant treatment in stage 2 tumors, compared to other stages. The lower survival time observed in our study, in comparison to the BILCAP study, can be attributed to the exclusion of stage 1 patients from our analysis. The lack of statistically significant recurrence-free survival (RFS) analysis after 24 months in the BILCAP study underscores the need for alternative treatments to capecitabine. In our study, the mOS in the capecitabine arm was determined as 42.26 months (95% CI: 29.18-55.34). The lower survival time compared to the BILCAP study was due to the exclusion of stage 1 patients in our study. It is noteworthy that although capecitabine is the preferred option, the National Comprehensive Cancer Network guidelines continue to recommend a gemcitabine-based chemotherapy regimen [22].

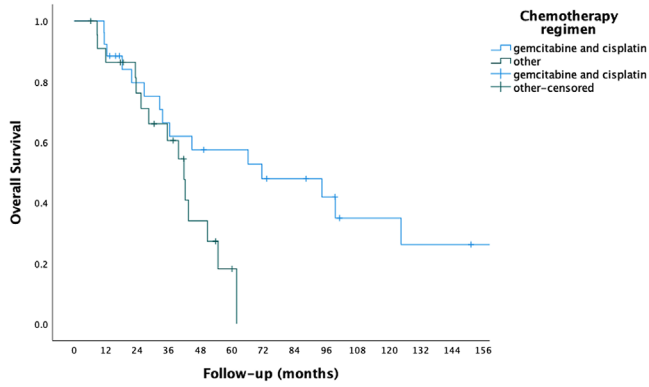

Figure 1. Overall survival according to adjuvant chemotherapy regimen

Single-agent gemcitabine therapy or combination regimens containing gemcitabine have been explored in the treatment of BTCs, drawing from the successful results seen in pancreatic cancer [23,24]. However, a study comparing adjuvant gemcitabine treatment to observation alone failed to demonstrate a survival benefit, as both arms exhibited a 60-month survival rate [12]. In the PRODIGE 12-ACCORD 18 study, the administration of adjuvant gemcitabine-oxaliplatin prolonged the mOS, but the difference was not statistically significant [11]. A meta-analysis that included the PRODIGE 12-ACCORD 18 study and the BCAT study also failed to demonstrate the contribution of gemcitabine-based adjuvant therapy [25]. The mOS in the gemcitabine arm was reported as 75 months, while it was approximately 50 months in the follow-up arm. In our study, the mOS was 43.5 months when gemcitabine was administered alone and 34.5 months when gemcitabine was combined with capecitabine.

Table 2. Univariate and multivariate analysis of factors associated with median overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% confidence interval	p	HR	95% confidence interval	p
T status (2 vs. 3-4)	2.827	1.298-6.159	0.009	2.062	0.312-13.639	0.441
N status (negative vs. positive)	2.467	1.184-5.141	0.016	1.567	0.571-4.304	0.383
Treatment (G+C vs. other)	2.395	1.050-5.462	0.038	2.386	1.042-5.466	**0.040**
TNM stage (2 vs. 3)	3.333	1.497-7.420	0.002	3.322	1.491-7.402	**0.003**

TNM: Tumor, node, metastasis, HR: Hazard ratio

Table 3. Baseline clinical and laboratory features of patients according to treatment

		Gemcitabine plus cisplatin	Others	p value
Mean age		55.27±9.76	63.84±12.38	
Age	>65	3 (11.5%)	10 (43.5%)	**0.021**
	<65	23 (88.5%)	13 (56.5%)	
Sex	Female	8 (30.8%)	10 (43.5%)	0.390
	Male	18 (69.2%)	13 (56.5%)	
ECOG score	0	25 (96.2%)	22 (95.7%)	1.00
	1	1 (3.8%)	1 (4.3%)	
Tumor localization	Gallbladder	7 (26.9%)	11 (47.8%)	0.239
	Intrahepatic	9 (34.6%)	4 (17.4%)	
	Extrahepatic	10 (38.5%)	8 (34.8%)	
Tumor stage	2	14 (53.8%)	10 (43.5%)	0.664
	3	11 (42.3%)	11 (47.8%)	
	4	1 (3.8%)	2 (8.7%)	
Lymph node stage	0	14 (52%)	15 (65.2%)	0.422
	1	10 (40%)	5 (21.7%)	
	2	2 (8%)	3 (13%)	
TNM stage	2	12 (46.2%)	10 (43.5%)	1.00
	3	14 (53.8%)	13 (56.5%)	
Resection margin	R0	21 (80.8%)	20 (87.0%)	0.706
	R1	5 (19.2%)	3 (13.0%)	
Radiotherapy	Present	4 (15.4%)	15 (65.2%)	**<0.001**
	Absent	22 (84.6%)	8 (34.8%)	
Anemia	Present	8 (30.8%)	12 (52.2%)	0.155
	Absent	18 (69.2%)	11 (47.8%)	
Hipoalbuminemia	Present	7 (28%)	10 (43.5%)	0.247
	Absent	19 (72%)	13 (56.5%)	

ECOG: Eastern Cooperative Oncology Group, TNM: Tumor, node, metastasis

Following the identification of a survival benefit with the GemCis combination, it has become the standard treatment for metastatic BTCs [26,27]. Building on its efficacy in advanced disease, studies have been conducted to evaluate its effectiveness in earlier stages. The STAMP study compared the GemCis combination with capecitabine treatment in extrahepatic bile duct cancers and found no significant difference in mOS, with both arms exhibiting an mOS of approximately 35 months [28]. In contrast to this study, real-life data have demonstrated the efficacy of the GemCis combination [25]. In our study, patients with BTC who received the GemCis combination had a remarkable mOS of 71 months. These patients were on average eight years younger, had a lower incidence of anemia, and represented a more select group. The ACTICCA-1 study, which compares adjuvant GemCis combination with capecitabine treatment in BTCs, has the potential to impact the standard treatment approach [20]. Based on our study findings, the GemCis combination yielded impressive results.

Although the OS curves for the two treatment groups were similar in the early follow-up period, a notable divergence emerged after approximately 36 months. Specifically, patients in the GemCis group showed better long-term survival, while survival rates in the other treatment group declined more rapidly. This pattern suggests that the benefit of GemCis may become more evident in the mid-to-late follow-up period, rather than in the early post-treatment phase. Therefore, the time-dependent nature of the treatment effect should be considered when interpreting the survival outcomes.

Study Limitations

We acknowledge that our study has certain limitations. Being retrospective and conducted in a single center, the patient groups may not be homogeneous, and the sample size may be insufficient. The administration of GemCis treatment to a relatively younger group of patients with better overall health may introduce bias when comparing different treatment options. Additionally, the small patient population in our study results from the inclusion of only those patients who underwent surgery at our center and subsequently received treatment and follow-up. Another important limitation of our study is the lack of RFS data for most patients, which prevented us from performing a meaningful RFS analysis. These limitations should be taken into consideration when interpreting the results of our study.

Conclusion

While capecitabine is currently considered the standard treatment for operated BTCs, our study revealed impressive results with a mOS of 71 months in young patients who were in good general condition, and received the GemCis combination. Additionally, the observed late divergence in survival curves suggests a time-dependent treatment effect, which may not be fully captured by conventional statistical methods such as the log-rank test.

These findings suggest that the GemCis combination may be a potential candidate for treatment if supported by prospective randomized controlled trials. Further research and validation through rigorous clinical trials are necessary to establish the efficacy and safety of this treatment approach in a larger patient population.

Ethics

Ethics Committee Approval: Approval was obtained from the Hacettepe University Ethics Committee for the study (decision no: 2022/15-54, date: 04.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Original Article

Survival Outcomes in Epithelial Ovarian Cancer: The Role of the Ovarian Cancer-specific Comorbidity Index

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ABSTRACT

Aim: Epithelial ovarian cancer (EOC) is a gynecologic malignancy that is often diagnosed at an advanced stage and is associated with a high mortality rate. Comorbidities may significantly influence treatment planning and survival outcomes in these patients. This study aimed to evaluate the impact of comorbidity on survival in EOC patients using the Ovarian Cancer-Specific Comorbidity Index (OCCI).

Methods: This retrospective study included patients with newly diagnosed EOC. Demographic and clinical data, comorbidities, and treatment strategies were recorded. Patients were classified into low-, moderate-, and high-risk groups based on the OCCI, and the associations between progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: Significant differences in survival were found among the risk groups. Taking the low-risk group as a reference, hazard raios (HRs) for PFS were 2.02 (p=0.002) in the moderate-risk group and 3.41 (p<0.001) in the high-risk group; for OS, HRs were 3.05 (p=0.001) and 5.63 (p<0.001), respectively. OCCI, Eastern Cooperative Oncology Group (ECOG) status, and the International Federation of Gynecology and Obstetrics (FIGO) stage were independent predictors of PFS. In contrast, OCCI, FIGO stage, and cytoreductive surgery were independent predictors of OS.

Conclusion: OCCI is a valuable tool for predicting survival and informing clinical decision-making in patients with EOC. The burden of comorbidities can significantly influence treatment choices and survival, particularly in elderly and advanced-stage patients. Incorporating OCCI into clinical practice may support the development of personalized and multidisciplinary treatment strategies, ultimately enhancing treatment outcomes.

Keywords: Epithelial ovarian cancer, Ovarian Cancer-Specific Comorbidity Index (OCCI), geriatric population, FIGO stage, ECOG performance status

Introduction

Ovarian cancer is among the most common gynecologic malignancies worldwide and remains the leading cause of gynecologic cancer-related mortality [1]. Approximately 95% of ovarian malignancies are epithelial ovarian cancers (EOC), for which the standard treatment approach includes cytoreductive surgery, platinum-based chemotherapy, and, in some instances, radiotherapy [2]. Despite advances in targeted therapies, long-term survival in EOC remains poor, with most patients experiencing recurrence within 15-18 months [3,4]. The disease primarily affects older adults with multiple comorbidities, further complicating treatment and prognosis [5].

Comorbidities-defined as the coexistence of additional physical or psychological conditions alongside a primary disease-are increasingly prevalent with advancing age and have a substantial impact on cancer treatment outcomes and tolerance, particularly in aggressive therapies like chemotherapy [6,7]. In EOC, where the majority of patients are elderly, comorbidities play a critical role in treatment decisions and prognosis [8,9]. However, there is no consensus on the optimal method for assessing comorbidity in oncology, and commonly used tools such as the Charlson Comorbidity Index, Elixhauser Comorbidity Index, National Cancer Institute Comorbidity Index, and Adult Comorbidity Evaluation-27 are not explicitly designed for cancer [10-14]. To address this gap, a study based on the Danish Gynecologic Cancer Database

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developed and validated the age-specific Ovarian Cancer Comorbidity Index (OCCI), which offers a practical and rapid means to stratify mortality risk in EOC patients [7]. Its utility has since been supported by secondary validation in a U.S. population [15].

Clarifying the role of comorbidities in EOC prognosis could enhance risk stratification and inform more personalized treatment approaches. Despite this, limited data exist regarding the prognostic utility of comorbidity indices, and no prior research has evaluated the clinical applicability of the OCCI within a Turkish patient population. Therefore, this study aimed to assess the impact of pre-chemotherapy comorbidity risk assessment using OCCI, on survival outcomes in newly diagnosed EOC patients.

Methods

This cohort study included patients diagnosed with EOC between January 2019 and January 2023 who were followed in the medical oncology department of our institution. Demographic data, clinical characteristics, comorbid conditions, treatment modalities, Eastern Cooperative Oncology Group (ECOG) performance status, histopathological subtypes, and International Federation of Gynecology and Obstetrics (FIGO) stages were retrospectively collected from patient files and digital hospital records. Additionally, treatment protocols (adjuvant, neoadjuvant, or palliative chemotherapy), surgical cytoreduction status, and treatment responses were analyzed. Patients were grouped based on whether they underwent surgery or not.

Due to the real-world design of the study, patients with varying disease stages and treatment intents were included. This includes early-stage patients undergoing curative surgery and stage 4 patients receiving palliative chemotherapy, which may introduce clinical heterogeneity.

The study was conducted in accordance with the principles of ethics. It was approved by the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/59, date: 17.04.2025). The ethics committee waived the requirement for informed consent due to the study's retrospective nature.

The study population consisted of patients aged 18 years or older with a new diagnosis of EOC, no prior systemic treatment, an evaluable ECOG performance status, and clinically adequate liver, renal, and cardiac function. The analysis included patients treated with a standard chemotherapy regimen administered every 21 days, comprising paclitaxel at a dose of 175 mg/m² and carboplatin (area under the curve 4-6) calculated according to creatinine clearance [16]. Demographic characteristics and comorbidity status before chemotherapy were used as the basis for analysis, and patients who received bevacizumab during chemotherapy or a poly (ADP-Ribose) polymerase (PARP) inhibitor as maintenance therapy were excluded. Patients who received bevacizumab during chemotherapy or PARP inhibitors as maintenance therapy were excluded from the study. This decision was based on the limited and inconsistent use of these agents during the study period, as well as the incomplete availability of data regarding maintenance treatments. Excluding these patients allowed for a more homogeneous cohort and minimized potential confounding effects arising from significant survival differences between patients receiving maintenance therapy and those who did not. Additional exclusion criteria were a history of another malignancy, incomplete diagnosis or comorbidity data, pregnancy or lactation, insufficient follow-up or loss of follow-up.

Evaluation of comorbidities was carried out using the OCCI, as proposed by Noer and colleagues. [7] This scoring system incorporates patient age and the presence of five specific comorbidities: hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and dementia. The OCCI score for each patient was calculated using the following formula: $OCCI = \sum(RCi \times i)$

In this formula, *i* represents the presence (1) or absence (0) of each comorbidity, and *RCi* denotes the regression coefficient assigned to each comorbidity (Table 1).

Based on the total OCCI score, patients were stratified into low-, moderate-, and high-risk groups for subsequent analyses (Table 2).

Statistical Analysis

Categorical variables were summarized as counts and percentages. Based on the OCCI, patients were stratified into three risk categories: low, moderate, and high. Continuous variables were analyzed between groups using either the independent t-test or the Mann-Whitney U test, depending on data distribution. Categorical comparisons were performed using the chi-square or Fisher's exact test, as appropriate. Progression-free survival (PFS) was defined as the interval from the initiation of treatment to disease progression, death from any cause, or the date of last contact. Overall survival (OS) refers to the time from initial diagnosis to death or last follow-up. Survival analyses were performed using the Kaplan-Meier method, with comparisons between groups evaluated using the log-rank test. Variables identified as significant in univariate analyses were included in a Cox proportional hazards model to determine independent prognostic indicators. All statistical tests were two-tailed, with a significance threshold set at $p<0.05$. Analyses were conducted using International Business Machines Corporation (IBM) Statistical Package for the Social Sciences Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 212 patients were included, with 33.0% categorized as low-risk, 47.2% as moderate-risk, and 19.8% as high-risk according to the OCCI. ECOG performance status differed significantly among groups ($p=0.013$); ECOG 0 was more common in moderate-risk patients, whereas ECOG 2 was more frequent in the high-risk group. FIGO stage distribution also varied significantly ($p<0.001$), with early-stage disease

(1-2) being more prevalent in low-risk patients, and stage 4 dominating the high-risk group. Cytoreductive surgery was more frequently performed in low-risk patients (76.1%) and less frequently in high-risk patients (20.0%) (p<0.001). Palliative chemotherapy was administered more often in the high-risk group (80.0%) compared to others (p<0.001). Other significant differences were observed in histologic subtypes, primary tumor site, and chemotherapy approach (Table 3).

Among the comorbid conditions, COPD (p=0.031) and dementia (p<0.001) showed statistically significant differences across OCCI risk groups. Both conditions were notably more prevalent in the high-risk group, with dementia observed in 20.0% and COPD in 23.8% of these patients. Other comorbidities such as hypertension, coronary artery disease, and diabetes mellitus did not differ significantly between groups (Table 4).

In PFS and OS analyses, univariate analysis revealed significantly worse outcomes in patients aged ≥65 years [PFS: hazard ratio (HR)=2.22, p<0.001; OS: HR=1.95, p<0.001]. However, no significant difference was found in multivariate analysis. According to risk stratification, the median PFS was 13.70 months in the low-risk group, 11.30 months in the moderate-risk group, and 7.92 months in the high-risk group (p<0.001, Figure 1).

Similarly, median OS was 49.20, 34.14, and 21.78 months, respectively (p<0.001, Figure 2). Multivariate analysis also showed significantly worse PFS and OS in the moderate- and high-risk groups (p<0.001).

In univariate analysis, patients with ECOG scores of 2 and 3 had significantly shorter PFS compared to those with ECOG scores of 0 (HR=2.89, p<0.001, and HR=2.77, p=0.023, respectively). However, no significant difference was found in ECOG performance status in the multivariate analysis. Increasing FIGO stage was associated with significantly worse PFS and OS in univariate analysis (p<0.001). However, in multivariate analysis, only OS remained significantly worse (p=0.018).

Patients receiving neoadjuvant or palliative chemotherapy had significantly shorter PFS and OS compared to those receiving adjuvant chemotherapy in univariate analysis (p<0.001). In multivariate analysis, PFS remained markedly worse in the palliative chemotherapy group (p=0.003) (Tables 5, 6).

Table 1. Variables and their corresponding weights derived from multivariate analysis for OCCI scoring

Comorbidity	RC (95% CI)
Hypertension	-0.29 (-0.43 to -0.15)
Coronary artery disease	0.46 (0.23 to 0.67)
Chronic obstructive pulmonary disease	0.56 (0.28 to 0.82)
Diabetes mellitus	0.40 (0.17 to 0.66)
Dementia	0.81 (0.34 to 1.28)

Regression coefficients adapted from Noer et al. [9].
OCCI: Ovarian cancer-specific comorbidity index, CI: Confidence interval, RC: Regression coefficient

Table 2. Cut-off values for OCCI risk stratification based on patient age groups

Age group	Low risk	Moderate risk	High risk
16-44 years	Score <1.21	1.21≤ score <3.64	Score ≥3.64
45-54 years	Score <0.28	0.28≤ score <1.74	Score ≥1.74
55-64 years	Score <-0.22	-0.22≤ score <1.12	Score ≥1.12
65-74 years	Score <-0.57	-0.57≤ score <0.53	Score ≥0.53
≥75 years	Score <-1.20	-1.20≤ score <-0.31	Score ≥-0.31

Age-stratified index scores from Noer et al. [9].
OCCI: Ovarian Cancer-Specific Comorbidity Index

Table 3. Comparison of demographic and clinical features across OCCI risk groups

Factor	Total n=212	Low risk n=70 (33.0%)	Moderate risk n=100 (47.2%)	High risk n=42 (19.8%)	p value
Age-year					0.417
<65	130 (61.3%)	40 (57.1%)	66 (66.0%)	24 (57.1%)	
≥65	82 (38.7%)	30 (42.9%)	34 (34.0%)	18 (42.9%)	
ECOG performance status					0.013*
0	62 (29.2%)	14 (20.0%)	34 (34.0%)	14 (33.3%)	
1	112 (52.8%)	44 (62.9%)	50 (50.0%)	18 (42.9%)	
2	32 (15.1%)	12 (17.1%)	10 (10.0%)	10 (23.8%)	

Table 3. Continued

Factor	Total n=212	Low risk n=70 (33.0%)	Moderate risk n=100 (47.2%)	High risk n=42 (19.8%)	p value
3	6 (2.8%)	0 (0.0%)	6 (6.0%)	0 (0.0%)	
FIGO stage					<0.001*
1	28 (13.2%)	20 (28.6%)	8 (8.0%)	0 (0.0%)	
2	26 (12.3%)	18 (25.7%)	8 (8.0%)	0 (0.0%)	
3	102 (48.1%)	26 (37.1%)	66 (66.0%)	10 (23.8%)	
4	56 (26.4%)	6 (8.6%)	18 (18.0%)	32 (76.2%)	
Histology					0.009*
High-grade serous	164 (77.4%)	58 (82.9%)	72 (72.0%)	34 (81.0%)	
Low-grade serous	10 (4.7%)	0 (0.0%)	6 (6.0%)	4 (9.5%)	
Endometrioid	16 (7.5%)	8 (11.4%)	8 (8.0%)	0 (0.0%)	
Clear cell	12 (5.7%)	2 (2.9%)	10 (10.0%)	0 (0.0%)	
Other or unknown	10 (4.7%)	2 (2.9%)	4 (4.0%)	4 (9.5%)	
Cytoreductive surgery					<0.001*
Yes	140 (66.0%)	70 (76.1%)	66 (66.0%)	4 (20.0%)	
No	72 (34.0%)	22 (23.9%)	34 (34.0%)	16 (80.0%)	
Primary site					0.020*
Ovarian carcinoma	174 (82.1%)	60 (85.7%)	82 (82.0%)	32 (76.2%)	
Primary peritoneal carcinoma	22 (10.4%)	8 (11.4%)	12 (12.0%)	2 (4.8%)	
Fallopian tube carcinoma	16 (7.5%)	2 (2.9%)	6 (6.0%)	8 (19.0%)	
Chemotherapy					<0.001*
Adjuvant	54 (25.5%)	26 (28.3%)	28 (28.0%)	0 (0.0%)	
Neoadjuvant	86 (40.6%)	44 (47.8%)	38 (38.0%)	4 (20.0%)	
Pallative	72 (34.0%)	22 (23.9%)	34 (34.0%)	16 (80.0%)	

*Significant.
OCCI: Ovarian Cancer-Specific Comorbidity Index, ECOG: Eastern Cooperative Oncology Group, FIGO: International Federation of Gynecology and Obstetrics

Table 4. Prevalence of selected comorbidities across OCCI-defined risk groups

Factor	Total n=212	Low risk n=70 (%)	Moderate risk n=100 (%)	High risk n=42 (%)	p value
Hypertension					0.162
Yes	86 (40.6%)	34 (37.0%)	40 (40.0%)	12 (60.0%)	
No	126 (59.4%)	58 (63.0%)	60 (60.0%)	8 (40.0%)	
Coronary artery disease					0.084
Yes	46 (21.7%)	16 (17.4%)	22 (22.0%)	8 (40.0%)	
No	166 (78.3%)	76 (82.6%)	78 (78.0%)	12 (60.0%)	
Chronic obstructive pulmonary disease					0.031*
Yes	26 (12.3%)	8 (11.4%)	8 (8.0%)	10 (23.8%)	
No	186 (87.7%)	62 (88.6%)	92 (92.0%)	32 (76.2%)	
Diabetes mellitus					0.129
Yes	52 (24.5%)	16 (22.9%)	30 (30.0%)	6 (14.3%)	
No	160 (75.5%)	54 (77.1%)	70 (70.0%)	36 (85.7%)	
Dementia					<0.001*
Yes	8 (3.8%)	4 (4.3%)	0 (0.0%)	4 (20.0%)	
No	204 (96.2%)	88 (95.7%)	100 (100.0%)	16 (80.0%)	

Table 4. Continued

Factor	Total n=212	Low risk n=70 (%)	Moderate risk n=100 (%)	High risk n=42 (%)	p value
Hypertension					0.162
Yes	86 (40.6%)	34 (37.0%)	40 (40.0%)	12 (60.0%)	
No	126 (59.4%)	58 (63.0%)	60 (60.0%)	8 (40.0%)	
Coronary artery disease					0.084
Yes	46 (21.7%)	16 (17.4%)	22 (22.0%)	8 (40.0%)	
No	166 (78.3%)	76 (82.6%)	78 (78.0%)	12 (60.0%)	
Chronic obstructive pulmonary disease					0.031*
Yes	26 (12.3%)	8 (11.4%)	8 (8.0%)	10 (23.8%)	
No	186 (87.7%)	62 (88.6%)	92 (92.0%)	32 (76.2%)	
Diabetes mellitus					0.129
Yes	52 (24.5%)	16 (22.9%)	30 (30.0%)	6 (14.3%)	
No	160 (75.5%)	54 (77.1%)	70 (70.0%)	36 (85.7%)	
Dementia					<0.001*
Yes	8 (3.8%)	4 (4.3%)	0 (0.0%)	4 (20.0%)	
No	204 (96.2%)	88 (95.7%)	100 (100.0%)	16 (80.0%)	

*Significant.
OCCI: Ovarian Cancer-Specific Comorbidity Index

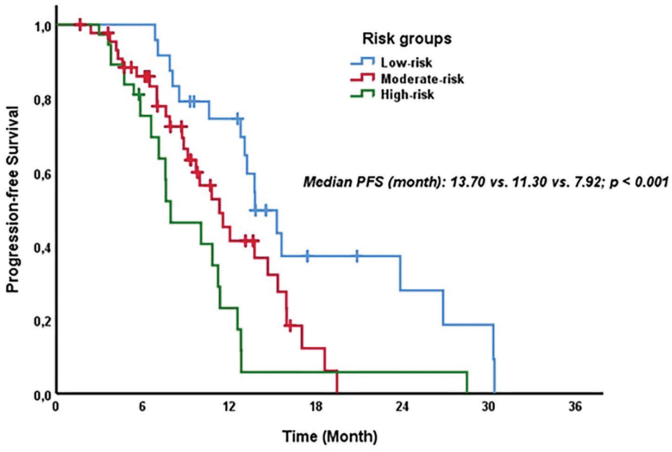

Figure 1. Kaplan-Meier curve of PFS according to risk groups of the ovarian cancer-specific comorbidity index
PFS: Progression-free survival

Time (months)	0	6	12	18	24	30
Low risk	70	67	41	17	9	2
Moderate risk	100	64	24	3	0	0
High risk	42	27	3	1	1	0

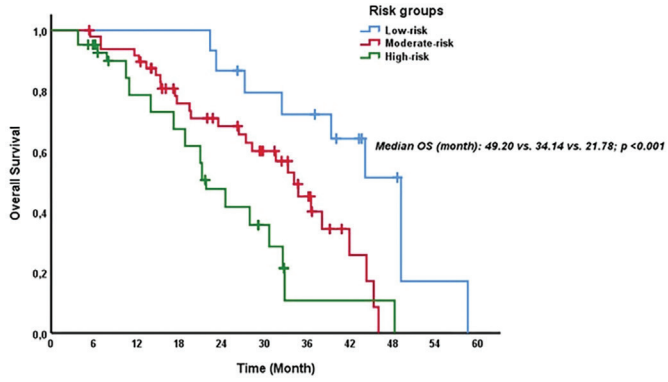

Figure 2. Kaplan-Meier curve of OS according to risk groups of the ovarian cancer-specific comorbidity index
OS: Overall survival

Time (months)	0	12	24	36	48	60
Low risk	70	70	60	47	19	0
Moderate risk	100	86	52	16	0	0
High risk	42	28	14	2	0	0

Table 5. Univariate analysis of progression-free survival and overall survival in patients with EOC

Factor	PFS	p value	OS	p value
	HR (95% CI)		HR (95% CI)	
Age-year				
<65	1		1	
≥65	2.22 (1.6-3.08)	<0.001*	1.95 (1.37-2.76)	<0.001*
Risk groups				
Low risk	1		1	
Moderate risk	2.02 (1.29-3.17)	0.002	3.05 (1.61-5.78)	0.001
High risk	3.41 (2.20-5.28)	<0.001*	5.63 (2.99-10.60)	<0.001*
ECOG performance status				
0	1		1	
1	1.43 (0.96-2.12)	0.077	1.06 (0.69-1.63)	0.791
2	2.89 (1.73-4.82)	<0.001*	1.93 (1.12-3.31)	0.017*
3	2.77 (1.15-6.70)	0.023*	3.53 (1.45-8.57)	0.005*
FIGO stage				
1	1		1	
2	6.01 (2.79-12.96)	<0.001*	2.48 (1.17-5.27)	0.018*
3	17.71 (8.34-37.63)	<0.001*	3.92 (2.09-7.34)	<0.001*
4	33.90 (15.12-76.02)	<0.001*	11.16 (5.45-22.84)	<0.001*
Histology				
High-grade serous	1		1	
Low-grade serous	2.82 (1.22-6.52)	0.015*	1.22 (0.53-2.79)	0.639
Endometrioid	1.12 (0.64-1.95)	0.700	0.97 (0.53-1.77)	0.911
Clear cell	1.58 (0.83-2.99)	0.164	0.75 (0.33-1.71)	0.490
Other or unknown	0.79 (0.38-1.64)	0.523	0.84 (0.41-1.76)	0.650
Cytoreductive surgery				
No	1		1	
Yes	0.36 (0.25-0.52)	<0.001*	0.40 (0.28-0.59)	<0.001*
Primary site				
Ovarian carcinoma	1		1	
Primary peritoneal carcinoma	0.91 (0.50-1.64)	0.749	0.87 (0.48-1.59)	0.658
Fallopian tube carcinoma	2.06 (1.08-3.95)	0.030*	1.77 (0.92-3.40)	0.090
Chemotherapy				
Adjuvant	1		1	
Neoadjuvant	6.19 (3.79-10.12)	<0.001*	2.52 (1.58-4.03)	<0.001*
Palliative	7.93 (4.84-12.99)	<0.001*	4.28 (2.60-7.02)	<0.001*

*Significant.
EOC: Epithelial ovarian cancer, PFS: Progression-free survival, OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, FIGO: International Federation of Gynecology and Obstetrics, HR: Hazard ratio, CI: Confidence interval

Table 6. Multivariate analysis of progression-free survival and overall survival in patients with EOC

Factor	PFS	p value	OS	p value
	HR (95% CI)		HR (95% CI)	
Age-year				
<65	1		1	
≥65	0.47 (0.19-1.15)	0.098	0.82 (0.36-1.85)	0.635
Risk groups				
Low risk	1		1	
Moderate risk	3.17 (1.79-5.62)	<0.001*	2.55 (1.31-4.97)	0.006*
High risk	15.70 (5.35-46.13)	<0.001*	4.55 (1.67-12.39)	0.003*
ECOG performance status				
0	1		1	
1	1.55 (0.093-2.60)	0.092	0.74 (0.44-1.25)	0.255
2	1.98 (1.01-3.89)	0.047*	0.66 (0.34-1.28)	0.218
3	1.11 (0.40-3.07)	0.836	1.00 (0.39-2.59)	0.996
FIGO stage				
1	1		1	
2	3.49 (1.66-7.35)	0.001*	1.73 (0.77-3.86)	0.184
3	3.02 (1.12-8.18)	0.029*	3.36 (0.84-13.50)	0.087
4	6.16 (2.02-18.77)	0.001*	8.59 (1.97-37.54)	0.004*
Cytoreductive surgery				
No	1		1	
Yes	1.72 (0.58-5.09)	0.327	0.33 (0.13-0.83)	0.018*
Primary site				
Ovarian carcinoma	1		-	
Primary peritoneal carcinoma	0.56 (0.28-1.10)	0.091	-	
Fallopian tube carcinoma	2.34 (1.07-5.12)	0.034*	-	
Chemotherapy				
Adjuvant	1		1	
Neoadjuvant	1.98 (0.78-5.03)	0.151	0.67 (0.16-2.74)	0.577
Palliative	5.51 (1.79-16.94)	0.003*	0.27 (0.06-1.35)	0.111

*Significant.
EOC: Epithelial ovarian cancer, PFS: Progression-free survival, OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, FIGO: International Federation of Gynecology and Obstetrics, CI: Confidence interval

Discussion

This study highlights the clinical relevance of the OCCI in chemotherapy-naive patients newly diagnosed with EOC. Our findings demonstrate that higher OCCI scores are significantly associated with poorer PFS and OS, especially among high-risk patients. Multivariate analyses identified OCCI, ECOG performance status, and FIGO stage as independent prognostic factors for PFS, while OCCI, FIGO stage, and cytoreductive surgery independently predicted OS. These results underscore the critical role of comorbidity burden in the management and prognosis of EOC.

Previous studies on the impact of comorbidities in EOC have yielded mixed results, possibly due to differences in study design, comorbidity indices used, and patient populations [8,17,18]. For instance, Minlikeeva et al. [8] found no significant impact of comorbidities on survival, possibly reflecting the inherently poor prognosis of EOC. Nonetheless, our findings support the importance of accurate comorbidity assessment, as demonstrated by the significant association between OCCI risk groups and survival outcomes. Retrospective analyses from Denmark also identified age, comorbidity, and FIGO stage as independent risk factors for mortality in gynecologic malignancies, emphasizing the need for personalized treatment in elderly patients with high comorbidity burdens [19]. Other studies confirmed comorbidity as an independent prognostic factor even after adjusting for tumor characteristics, with comorbid patients having a 1.31 to 1.50-fold higher risk of death [20-23]. Additionally, the age-adjusted Charlson Comorbidity Index has been shown to predict postoperative

complications and OS in advanced EOC [21], and several investigations have reported negative impacts of comorbidities on survival [22,23].

The prognostic influence of comorbidity extends beyond OS to cancer-specific mortality, especially in elderly populations, although the magnitude varies by cancer type [24]. Some studies highlight that comorbidities significantly affect treatment response and long-term survival, and serve as strong predictors of outcomes beyond their impact on postoperative complications [25]. Moreover, this effect cannot be fully explained by treatment selection or healthcare delays, suggesting the presence of complex underlying mechanisms [8]. Thus, thorough evaluation of patients' comorbidities is essential for clinical decision-making and preoperative risk stratification. The validation of OCCI in diverse populations further supports its applicability for international clinical use [7,15,17].

In our cohort, OCCI outperformed the Charlson Comorbidity Index in predicting survival outcomes, suggesting that disease-specific comorbidity tools may better guide risk assessment and treatment planning in EOC. Consistent with previous studies, including Vranes et al. [15] validation in a U.S. population, OCCI proved effective. Comorbidities influence treatment decisions, although some reports indicate that comorbidity does not significantly alter surgical choices, which are mainly driven by disease stage and performance status [19]. Our multivariate analyses reinforced advanced age and higher FIGO stage as significant prognostic factors alongside comorbidity scores, reflecting their established roles in disease aggressiveness and treatment limitations [26,27].

Regarding treatment modalities, cytoreductive surgery showed a significant positive effect on OS, aligning with established literature emphasizing its prognostic importance in EOC [28]. However, surgical planning for patients with substantial comorbidities requires caution due to increased perioperative risks, underscoring the necessity of multidisciplinary evaluation. While age was associated with survival in univariate analysis, this relationship did not persist in multivariate analysis, likely due to confounding by comorbidity prevalence and reduced treatment tolerance among elderly patients. This aligns with Danish data indicating increased median diagnosis age alongside rising comorbidity prevalence in EOC [22]. The well-established worsening of survival with advancing FIGO stage and the positive impact of cytoreductive surgery on OS observed in our study further validate these prognostic factors [7]. The pronounced survival decline in advanced-stage patients highlights the need for more intensive therapeutic strategies. Furthermore, the positive influence of successful cytoreduction supports its critical role in long-term outcomes.

Study Limitations

This study has several limitations. First, its retrospective design and single-center setting may lead to missing data, introduce selection bias, and limit the generalizability of the findings. Second, the inclusion of patients with markedly heterogeneous disease stages and treatment intents-ranging from early-stage patients undergoing primary surgery to *de novo* stage 4 patients receiving only palliative chemotherapy-may have introduced confounding effects that complicate the interpretation of survival outcomes. Third, patients treated with maintenance therapies such as anti-vascular endothelial growth factor agents or PARP inhibitors were excluded due to limited access and incomplete records. Although this exclusion may reduce the applicability of findings to contemporary clinical practice and potentially bias survival estimates, it also allowed for a more homogeneous study population by minimizing treatment-related variability. In addition, the proportional hazards assumption underlying the Cox regression models was not formally tested, which constitutes a methodological limitation that may affect the interpretation of hazard ratios over time. Finally, several important confounders-such as socioeconomic status, nutritional condition, and psychosocial factors-were not captured in the analysis, which could influence both comorbidity burden and clinical outcomes. Future prospective, multicenter studies that include broader patient characteristics and contemporary therapies are warranted to validate and expand upon these findings.

Conclusion

This study demonstrates that the OCCI is a valuable tool for prognostic assessment in patients newly diagnosed with EOC. The significantly lower survival rates observed in patients with higher comorbidity scores underscore the importance of carefully evaluating these individuals during treatment and follow-up planning. Incorporating the OCCI into clinical practice may contribute to optimizing both treatment responses and quality of life. In this context, the development of multidisciplinary approaches and personalized treatment strategies represents a crucial step toward improving outcomes in EOC care. Future research should focus on how the OCCI can inform treatment decisions, identify patients who may require more intensive therapy, and determine which specific comorbidities have the most significant prognostic value. Additionally, comparative studies are needed to evaluate the advantages and limitations of the OCCI relative to other comorbidity indices. These efforts may ultimately lead to more effective treatment strategies and improved survival outcomes for patients with EOC.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of ethics. It was approved by the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/59, date: 17.04.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.K., Concept: İ.K., Design: İ.K., P.K., Data Collection or Processing: İ.K., P.K., Analysis or Interpretation: İ.K., Literature Search: K.D., Writing: İ.K., P.K.

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

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Original Article

The Retrospective Analysis of Patients with Primary Immune Thrombocytopenia: The Associated Factors with Bleeding and The Factors with Treatment Response

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ABSTRACT

Aim: Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia and is twice as common in women as in men. Although severe bleeding is rare, identifying risk factors for bleeding can guide treatment decisions. This study aimed to evaluate the relationships between age, platelet count, hemoglobin level, mean platelet volume (MPV), and bleeding in ITP patients. Additionally, the impact of variables such as age, gender, platelet count, bone marrow megakaryocyte count, MPV, intravenous immunoglobulin (IVIG) response (in splenectomized patients), and remission duration on treatment response was investigated.

Methods: We retrospectively analyzed the medical records of 101 patients (81 females, 20 males) diagnosed with ITP and followed at the Hematology Outpatient Clinic of Karadeniz Technical University Farabi Hospital between 2008 and 2011. Statistical analysis was performed to assess the relationship between clinical/laboratory variables and bleeding, first-line treatment response, and splenectomy outcomes.

Results: Low platelet count and elevated MPV were significantly associated with bleeding ($p<0.05$). MPV elevation was also a favorable factor in predicting first-line treatment response. Among splenectomized patients, a positive response to IVIG was associated with better splenectomy outcomes ($p<0.05$). Furthermore, longer remission durations were significantly correlated with favorable splenectomy responses ($p<0.01$).

Conclusion: MPV may serve as a useful marker for both bleeding risk and treatment response in ITP. A favorable IVIG response may predict splenectomy success. The association between remission duration and splenectomy response adds valuable insight to individualized management strategies in ITP.

Keywords: Immune thrombocytopenia, mean platelet volume, splenectomy

Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia due to accelerated platelet destruction and impaired platelet production. It has an incidence of 40-160/1,000,000 and is twice as common in women as in men. Although rare, severe bleeding may occur in patients with platelet counts below 20-30x10^9/L. Despite low platelet counts in patients with ITP, the low rate of severe bleeding may be explained because the available platelets are more functional despite their low number. It has been found that advanced age and a history of previous bleeding are risk factors for severe bleeding in patients with ITP [1,2]. Mean platelet volume (MPV) is higher when accompanied by young, larger than normal platelets. High MPV indicates the appearance of platelets which are thought to be more active in terms of hemostasis-providing effect compared to young-large volume and normal platelets. In this study, we aimed to investigate the relationship between age, hemoglobin level, platelet count, and MPV and severe bleeding in patients with ITP.

In this study, we aimed to retrospectively analyze the factors affecting treatment response in patients treated with steroid, intravenous immunoglobulin (IVIG), splenectomy, and rituximab. For this purpose, it was planned to investigate the effects of age, sex, peripheral blood platelet count, bone

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marrow megakaryocyte count, MPV, response to IVIG (in splenectomized patients), and disease duration on treatment response.

Methods

The study included 101 patients, of whom 81 were female and 20 were male. Our study was conducted by retrospectively analyzing the files of patients who were examined and treated, with the diagnosis of ITP, in the Hematology Outpatient Clinic of Karadeniz Technical University Faculty of Medicine Farabi Hospital between 2008 and 2011. The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the Ethics Committee of Karadeniz Technical University Faculty of Medicine (decision no: 2012/95, date: 23.07.2012).

Exclusion criteria for ITP patients:

- Physical examination is characterized by features other than bleeding findings,

- Abnormalities in peripheral smear and complete blood count other than thrombocytopenia,

- Hepatitis B surface antigen, hepatitis C virus (HCV), human immunodeficiency virus (HIV), antinuclear antibody (ANA), anti-double stranded DNA be positive,

- Abnormalities in chest radiography,

- Impairment in thyroid function tests and complete urine analysis,

- The emergence of findings in bone marrow aspiration and biopsy that exclude ITP.

In this study, we planned to investigate the relationship between age, platelet count, hemoglobin level, MPV, and bleeding in patients with ITP. We planned to investigate the effects of age, gender, peripheral blood platelet count, bone marrow megakaryocyte count, MPV, response to IVIG (in splenectomized patients), and duration of remission on the next treatment response in relapsed patients.

Treatment Response Criteria

In accordance with the American Society of Hematology (ASH) 2019 guidelines, treatment response was categorized as follows: complete response (CR): platelet count ≥100×10^9/L and no bleeding. Response: platelet count ≥30×10^9/L and at least a twofold increase from baseline without bleeding. No response: platelet count <30×10^9/L or less than a twofold increase from baseline, or manifestation of bleeding. These criteria were adopted to evaluate the first-line and second-line treatment efficacy in our study cohort.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as number and percentage. Group comparisons were conducted using the independent samples t-test for continuous variables. A p value of less than 0.05 was considered statistically significant.

Results

Eighty-one female and 20 male patients were included in our study. The mean age of patients with no or mild bleeding (n=82) was 43±16 years. The mean age of patients with moderate or severe bleeding (n=19) was 49±21 years (p=0.29). The platelet count was 40469±32160 in patients with no or mild bleeding and 16900±12485 in patients with moderate or severe bleeding (p=0.001) ; a significant difference was found (Figure 1). MPV mean value was 10.1±1.4 in patients with no or mild bleeding and 8.7±1.3 in patients with moderate or severe bleeding (p=0.001). A significant difference was found (Figure 2). The mean hemoglobin value was 13.2±1.6 in patients with no or mild bleeding and 12.8±1.6 in patients with moderate or severe bleeding (p=0.34) (Table 1).

Treatment was indicated in 65 of 101 patients. Among the 65 patients with treatment indication, 31 patients received

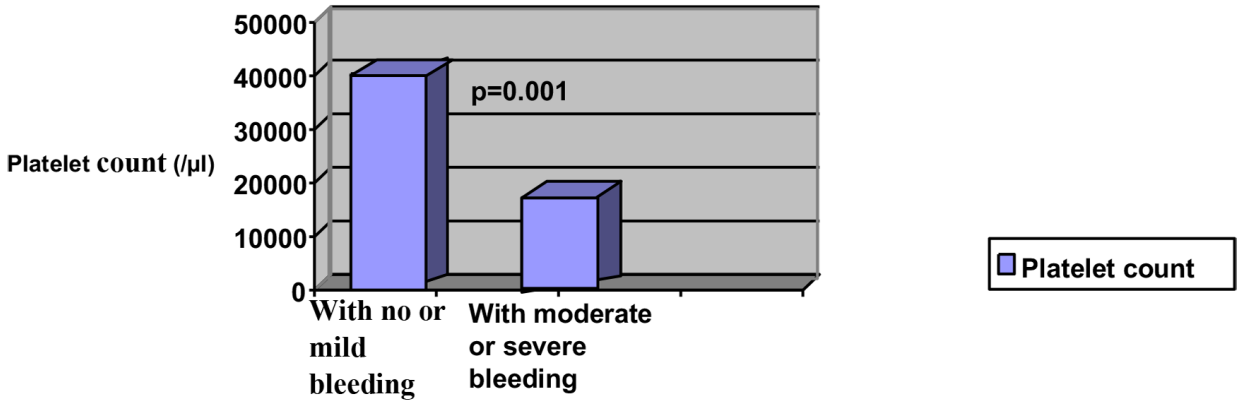

Figure 1. Relationship between platelet count and bleeding in ITP patients
ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume

only steroid treatment (1 mg/kg methylprednisolone), and 16 patients received only IVIG treatment (1 g/kg/day for 2 days). Eighteen patients received IVIG treatment together with steroids. Treatment responses of the patients were analyzed. Of the 49 patients who received steroids (steroid only and steroid + IVIG), 29 responded, while 20 did not respond. Of 34 patients who received IVIG (IVIG only and steroid + IVIG), 21 responded and 13 were non-responders. Overall, 41 patients responded to first-line treatment, while 24 patients were non-responders. The mean age of patients who did not respond to first-line treatment was 45±20 years, while the mean age of patients who responded was 45±17 years (p=0.9). The mean platelet count of first-line treatment non-responders was 16,583±1360, while the mean platelet count of responders was 16,820±1600 (p=0.9). The mean number of bone marrow megakaryocytes in first-line treatment-naive patients was 6±2.6, while the mean number of bone marrow megakaryocytes in responders was 6.3±2.1 (p=0.5). The MPV was found to be 10±1.4/fL in first-line treatment responders and 8.8±1.4/fL in non-responders (p=0.002) (Table 2, Figure 3).

Splenectomy was performed as second-line treatment. Of the 28 patients who underwent splenectomy by laparotomy, 21 had a complete response (CR) (71%), while 8 (29%) were non-responders. There was no significant difference between responders and non-responders in terms of platelet count, age, and MPV (Table 3). Since the existence of an IVIG response before splenectomy may indicate a good response to the procedure, we examined the response status to IVIG treatment

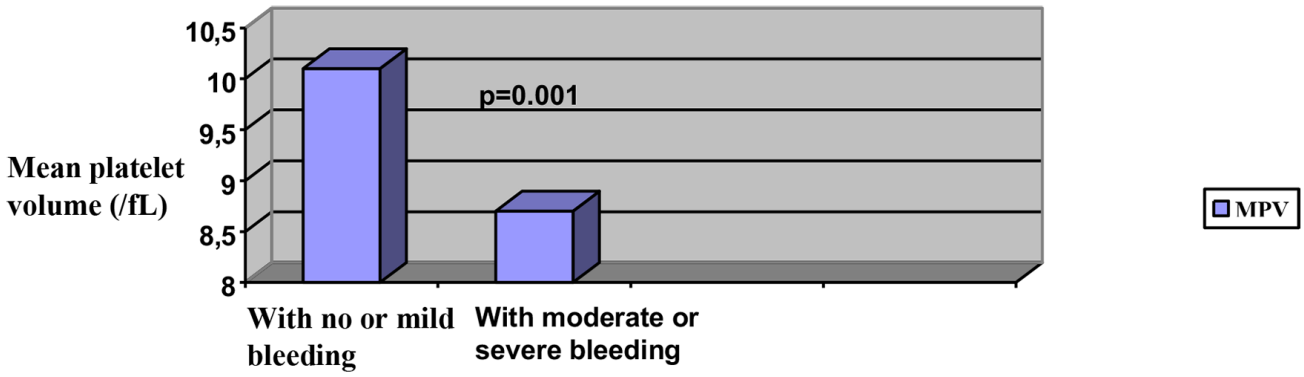

Figure 2. Relationship between MPV and bleeding in ITP patients
ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume

Table 1. The associated factors with bleeding in ITP patients

	With no or mild bleeding (n=82)	With moderate or severe bleeding (n=19)	p
Age	43±16	49±21	0.29
Platelet count	40469±32160	16900±12485	0.001
MPV	10.1±1.4	8.7±1.3	0.001
Hemoglobin	13.2±1.6	12.8±1.6	0.34

ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume

Table 2. The associated factors with first line treatment response in ITP patients

	Non-responders (n=24)	Responders (n=41)	p
Age	45±20	45±17	0.9
Platelet count	16583±1360	16820±16000	0.9
Megakaryocytes	6±2.6	6.3±2.1	0.5
MPV	8.8±1.4	10±1.4	0.002

ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume

Table 3. Factors associated with splenectomy treatment response in ITP

	Non-responder (n=8)	Responder (n=21)	p
Age	46±21	44±17	NS
Platelet count	22222±19227	14250±7949	NS
MPV	9.7±0.97	9.5±1.85	NS
Duration of remission	200±126	113±101	0.04

ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume, NS: Not significant

of patients who underwent splenectomy. It was found that 11 of 13 patients who received IVIG as first-line treatment before splenectomy and were found to be non-responders underwent splenectomy as second-line treatment. Of these 11 patients, 5 (45.5%) responded while 6 were non-responders. Splenectomy was performed as second-line treatment in 5 of 21 patients, who received IVIG as first-line treatment before splenectomy and responded to this treatment. All of these 5 (100%) patients responded to splenectomy (p=0.93).

The mean duration of remission was 176±124 (25-500) days in patients who received first-line treatment, and had a treatment response, but who were then indicated for second-line treatment due to relapse. The mean duration of remission after first-line treatment was 200±126 days in patients who received second-line treatment and had a treatment response, and 113±101 days in those patients who had no treatment response (p=0.04) (Figure 4).

Discussion

Our results are in agreement with recent findings in the literature. Ahmad et al. [3] emphasized the bleeding risks associated with ITP, while Ghanima et al. [4] reviewed the clinical efficacy and safety of thrombopoietin receptor agonists. Provan et al. [5] discussed predictors of bleeding severity, and Cooper and Ghanima [6] proposed updated therapeutic frameworks. Consistent with the ASH 2019 guidelines and these contemporary studies, MPV has emerged as a clinically relevant biomarker not only for platelet activity, but also as a predictor of bleeding tendency and treatment response in patients with ITP. Our data showing an inverse correlation between MPV and bleeding severity, and a positive correlation with treatment response, support this position.

In this study, we analyzed the factors affecting bleeding and treatment response in patients with ITP. Of the 101 patients included in our study, 81 (80.2%) were female; 20 (19.8%) were male and the P/E ratio was found to be 4.05. Adult ITP is

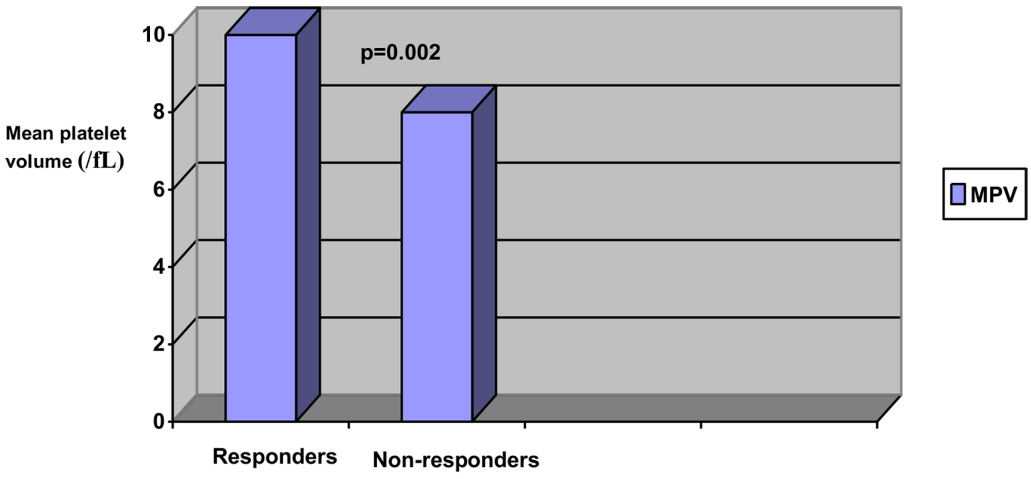

Figure 3. Relationship between MPV and treatment response in ITP patients
ITP: Immune thrombocytopenic purpura, MPV: Mean platelet volume

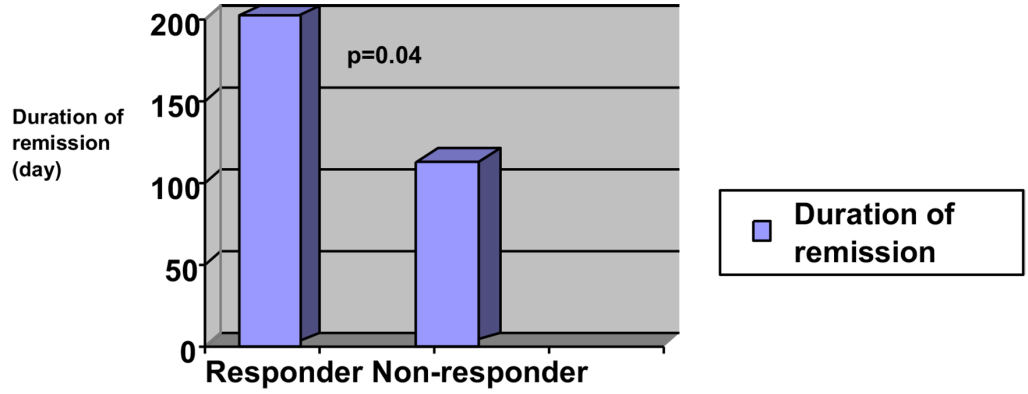

Figure 4. Relationship between splenectomy response and remission duration in ITP patients
ITP: Immune thrombocytopenic purpura

reported more common in women in studies and guidelines,. In a series of 162 cases (122 females, 40 males) conducted by Yenerel et al. [7] from İstanbul University, the F/M ratio was found to be 3/1. In a study conducted by Reid [8] in the United States of America between 1995 and 2001, the F/M ratio was found to be 4/1. In a retrospective study conducted by Kaya et al. [9] in 2011 and covering the years 1993-2009, the F/M ratio was found to be 3.1 in 110 patients, 83 of whom were female and 27 of whom were male. In a retrospective study conducted at Dicle University in 2012, in which 109 patients with splenectomy were examined, 88 (80.7%) of the patients were female and 21 (19.3%) were male. The M/F ratio was found to be 4.19 [10]. ITP was reported to be observed more frequently in females, ranging from two to four times, according to the literature, and our study was found to be compatible with the literature in this respect.

Of the patients included in our study, 82 (81.2%) had no/light bleeding and 19 (18.8%) had moderate/severe bleeding. In a series of 162 cases by Yenerel et al. [7] from İstanbul University, the rate of patients with moderate/severe bleeding was 17.3% and the rate of patients with no/light bleeding was 82.7%, which was similar to those in our study. In our study, age was examined among the factors affecting bleeding, and the median age was found to be 43±16 years in patients with no/mild bleeding and 49±21 years in patients with moderate/severe bleeding. Although the median age of patients with mild/no bleeding was lower, there was no significant statistical difference in terms of age between patients with mild/no bleeding and those with moderate/severe bleeding. There are publications showing that the risk of bleeding increases with increasing age. In one study, the 5-year fatal bleeding risk predicted for patients over the age of 60 years with a platelet count below $30x10^9$/L was 48%, while this rate was 2.2% in patients younger than 40 years, [11]. In our study, a statistically significant difference was found between the two groups in terms of platelet count among the factors affecting bleeding. The platelet count was found to be 40,469±32,160 in patients with no/mild bleeding and 16,900±12,485 in patients with moderate/severe bleeding (p=0.001). Accordingly, platelet count is significantly lower in patients with moderate/severe bleeding. In the ASH 2011 ITP guideline, it was stated that the increase in bleeding risk became evident below 20 or $30x10^9$/L in different studies, and the treatment limit was $30x10^9$/L, although there was no definite limit [12]. The statistical difference identified in our study was found to be compatible with the literature.

When we analyzed MPV, one of the factors affecting bleeding, we found a significant difference between the two groups as MPV: 10.1±1.4/fL in patients with no/light bleeding and MPV: 8.7±1.3/fL in patients with moderate/severe bleeding (p=0.001). High MPV indicates platelets are thought to be more active in terms of their hemostasis effect compared to young, large-volume, and normal platelets. This may indicate that high MPV is a protective factor in terms of bleeding risk. When we looked at hemoglobin levels among the possible factors that may increase the risk of bleeding, we found that they were not associated with the risk of bleeding in patients with ITP.

One hundred and eleven patients (81.2%) received steroids, IVIG, or both as first-line treatment. Twenty patients (19.8%) were followed up without treatment. In our study, 29 (59%) of 49 patients who received steroid treatment responded. In a study by Kaya et al. [9], 11 of 110 patients (10%) were followed up without treatment. The results of the study were similar to those of previous studies in terms of treatment-free follow-up. In the study by Kaya et al. [9], 71.7% of the patients who were started on steroids responded, while 28.2% were found to be unresponsive. Aydoğdu et al. [13], obtained a CR in 34 (58%) of 62 chronic ITP patients, with standard 1 mg/kg corticosteroid treatment. In a study conducted on 125 adult patients with ITP, approximately 40% achieved a permanent response lasting 2.5 years with steroid treatment [14]. Mazzucconi et al. [15] summarized 2 cohort studies and reported high response rates with dexamethasone. Our study is compatible with the literature in this respect.

When we analyzed the factors affecting first-line treatment, no significant difference was found between responders and non-responders in terms of age, platelet count, and megakaryocyte count. A statistically significant difference was found with a mean MPV of 10±1.4 fL in responders and 8.8±1.4 fL in non-responders (p=0.002). No study analyzing the effect of MPV elevation on treatment response was found in the available literature. Elevated MPV indicates the increase in the volume of platelets in the peripheral blood and may be an indicator of the high compensatory capacity of the bone marrow. Therefore, elevated MPV may be a positive marker for first-line treatment response.

We examined the second-line treatment responses of the patients. We found that 21 (71%) of 28 patients who underwent splenectomy through the laparotomy method had a CR and 8 were non-responders. We could not detect a significant difference in terms of platelet count, age, and MPV between patients who had a CR to secondary treatment and non-responders. Numerous studies have shown that two-thirds of the patients usually responded within days to splenectomy [12]. Parameters to predict splenectomy success have been studied, and it was observed that young age may serve as a preliminary indicator. In our study, although the age of patients who responded to splenectomy was slightly lower, no statistically significant difference was found. In a study by Önder et al. [10], splenectomy was performed in 109 patients and 82.6% of these patients had CR, and 12.8% had partial response. One patient (0.9%) died. In this study, a very high response rate was achieved when the literature was considered. In a study by McMillan [16], the CR rate to splenectomy was found to be 70%. In a study by Kaya et al. [9], the response rate to splenectomy was found to be 75%. Our study was consistent with the literature in terms of response rate to splenectomy. We investigated whether demonstrating a response to IVIG treatment before splenectomy is an indicator of a good response to splenectomy. Some studies in the literature indicate that IVIG response is a positive indicator

for splenectomy response [17,18]. However, other studies indicate that a response after IVIG is not an indicator that remission will be achieved with splenectomy [19-21]. In our study, all 5 patients (100%) with an IVIG response achieved a CR to splenectomy, whereas only 5 of 11 patients (45.5%) without an IVIG response did so . However, this difference was not statistically significant in our study, probably due to the insufficient number of patients (p=0.93). There are no data in the literature on the effect of time to relapse on splenectomy response. In our study, although response rates to splenectomy were higher in patients with late relapse after first-line treatment, age still seems to be the most objective criterion for response to splenectomy.

Study Limitations

This study has some limitations. Its retrospective and single-center design may limit the generalizability of the results and introduce selection bias. Due to the nature of retrospective data, not all confounding variables could be controlled. The relatively small sample size, especially in subgroups such as splenectomized patients, may have reduced the statistical power. Also, the absence of long-term follow-up data prevents assessment of sustained treatment outcomes.

Conclusion

This retrospective analysis suggests that low platelet count and decreased MPV are significantly associated with increased bleeding risk in patients with ITP. Furthermore, elevated MPV may serve as a predictive marker for favorable response to first-line therapy. Although no statistically significant association was found between pre-splenectomy IVIG response and splenectomy outcomes, a trend toward improved response in IVIG responders was observed. The observed correlation between longer remission duration and splenectomy success warrants further investigation. These findings highlight the potential clinical utility of MPV as a prognostic parameter in both bleeding risk stratification and therapeutic response prediction in ITP.

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 Karadeniz Technical University Faculty of Medicine (decision no: 2012/95, date: 23.07.2012)

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.K., Concept: T.K., Design: T.K., M.Y., Data Collection or Processing: T.K., Analysis or Interpretation: T.K., M.Y., Literature Search: T.K., M.Y., Writing: T.K., M.Y.

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

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Original Article

Characteristics and Outcomes of Patients with Acute Promyelocytic Leukemia: A Single-center Experience

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ABSTRACT

Aim: Acute promyelocytic leukemia (APL) is defined by the t(15;17) chromosomal translocation, resulting in the promyelocytic leukemia-retinoic acid receptor alpha fusion gene. The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has led to survival rates surpassing 90%. This study evaluated the clinical features and outcomes of APL patients managed at our center.

Methods: A retrospective review was conducted on 27 APL patients treated between January 2010 and February 2022.

Results: The median patient age was 41 years (range: 18-82). Risk classification identified 14 low-risk (51.9%), 10 intermediate-risk (37.0%), and three high-risk (11.1%) patients. Induction treatment involved ATRA plus chemotherapy (CT) in 21 cases and ATRA plus ATO in six cases. All patients achieved complete remission. At a median follow-up of 49 months (6-140), neither median overall survival nor progression-free survival had been reached. Relapse occurred in five patients (18.5%); four underwent successful salvage therapy followed by autologous transplantation. One patient with CNS relapse achieved remission after intrathecal therapy but later died due to cerebral hemorrhage during transplant preparation. Major non-hematologic toxicities included infections (66.6%) and differentiation syndrome (48.1%). Neutropenic fever and thrombocytopenia were the most frequent grade 3-4 hematologic events. No deaths were attributed to treatment-related adverse events.

Conclusion: Newly diagnosed APL remains a curable malignancy with high response rates when treated with ATRA-based regimens involving CT or ATO.

Keywords: Acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide, treatment outcome

Introduction

Acute promyelocytic leukemia (APL) accounts for roughly 5-10% of all acute myeloid leukemia (AML) diagnoses and aligns with the M3 subtype in the French-American-British classification [1,2]. At the cytogenetic level, APL is marked by a specific reciprocal translocation between chromosomes 15 and 17, namely t(15;17) (q22; q12), resulting in the promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) fusion gene [1,2]. This *gene* product forms a chimeric oncoprotein that interferes with normal RARα function, disrupting hematopoietic differentiation and shaping the distinctive clinical and molecular features of APL [3].

Before the introduction of targeted therapies, conventional chemotherapy (CT) regimens-comprising agents such as daunorubicin, idarubicin, and cytarabine-led to complete remission (CR) in approximately 75-80% of patients with newly diagnosed APL. Nevertheless, the median remission duration ranged from 11 to 25 months, and long-term cure was achieved in only 35-45% of cases [3-5].

A paradigm shift in APL management emerged in the 1990s with the recognition of the remarkable therapeutic potential of all-trans retinoic acid (ATRA, or tretinoin) and arsenic trioxide (ATO). These agents act by overcoming the differentiation arrest characteristic of APL, thereby promoting

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gradual cellular maturation and contributing significantly to treatment success [6-8].

The combination of ATRA with anthracycline-based CT has markedly improved outcomes in patients with APL, resulting in CR rates exceeding 90% and long-term survival rates of 70-80% [3-5]. APL, now considered one of the most curable forms of hematologic malignancy, is primarily treated with CT regimens incorporating ATRA and/or ATO [9]. Treatment protocols utilizing ATRA and ATO alone have demonstrated CR rates above 90% and cure rates surpassing 80% [2].

In this context, the current study aimed to analyze the clinical characteristics and real-world outcomes of 27 APL patients managed at our center.

Methods

This study received ethical approval from the Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital (decision no: 2022-03/1692, date: 09.03.2022), in accordance with national regulations and the principles outlined in the Declaration of Helsinki (1964) and its later amendments.

A retrospective cohort analysis was conducted on 27 patients with a newly diagnosed, and previously untreated APL between January 2010 and February 2022. Patients harboring APL variants involving RARα fusion with genes other than PML were excluded from the analysis. Clinical records were reviewed to obtain data on demographics, baseline laboratory findings, genetic mutations at diagnosis, bone marrow histopathology, treatment regimens, clinical responses, adverse events, relapse status, and stem cell transplantation, among patients aged 18 and above.

APL diagnosis was established through the identification of the t-(15;17) translocation via cytogenetic testing or the identification of PML-RARα fusion using reverse transcriptase-polymerase chain reaction (RT-PCR). Bone marrow morphology, cytogenetic profiles, and quantitative RT-PCR analyses for PML-RARα were assessed post-induction and after each consolidation phase, followed by monitoring every three months for a period of three years. Additional molecular evaluations included screening for mutations in *NPM1, WT1, FLT3-ITD*, and *FLT3-TKD genes*.

Patients were stratified into three risk categories based on the Sanz scoring system: (1) low-risk [white blood cell (WBC) $\leq 10 \times 10^9$/L, platelets $>40 \times 10^9$/L], (2) intermediate-risk (WBC $\leq 10 \times 10^9$/L, platelets $\leq 40 \times 10^9$/L), and (3) high-risk (WBC $>10 \times 10^9$/L). Patients in the low- and intermediate-risk groups generally share a white blood cell count below 10,000/μL, whereas high-risk individuals present with elevated WBC levels at diagnosis. An increased Sanz risk score is associated with poorer outcomes and a greater likelihood of early mortality [10].

Treatment Protocols

All patients received ATRA either alone or in combination with CT.

a) In the standard ATRA-idarubicin induction protocol, patients were administered ATRA at a dose of 45 mg/m²/day in two divided oral doses until hematologic remission was achieved. Idarubicin was administered intravenously at 12 mg/m² on days 2, 4, 6, and 8. Consolidation therapy consisted of three cycles of anthracycline-based CT-idarubicin (5-7 mg/m²/day for 4 days), mitoxantrone (10 mg/m²/day for 3 days), or idarubicin (12 mg/m²/day for 1-2 days)-along with ATRA (45 mg/m²/day orally for 15 days in each cycle). For maintenance, low- and intermediate-risk patients received ATRA (45 mg/m²/day orally, for 15 days every 3 months), while high-risk patients received a combination of 6-mercaptopurine (50 mg/m²/day), methotrexate (15 mg/m² weekly), and ATRA two years [11].

b) In the ATRA plus ATO regimen, induction involved oral ATRA at 45 mg/m²/day (divided doses) for up to 60 days, alongside daily intravenous ATO at 0.15 mg/kg until CR. Consolidation included ATRA administered in 2-week on/off cycles for 9 months, and ATO, given five days per week for 4 weeks, repeated every other month (80 doses).

c) In the ATRA +3+7 protocol, induction therapy consisted of idarubicin (12 mg/m² 4 on days 1-3) and cytarabine (100 mg/m² continuous 4 infusion on days 1-7), combined with ATRA (45 mg/m²/day in two divided oral doses), until hematologic remission.

Supportive care included transfusion of blood products to maintain platelet and coagulation parameters according to treatment guidelines.

Definitions and Study Endpoints

Hematologic CR was evaluated based on the criteria established by the International Working Group on AML, which outlines standardized definitions for diagnosis, response, outcomes, and reporting in therapeutic trials [12]. Molecular remission was defined as the complete absence of detectable PML-RARα transcripts. Hematologic relapse refers to the reappearance of blasts with or without promyelocytes or the emergence of extramedullary involvement. Molecular relapse was characterized by the re-detection of PML-RARα transcripts in patients previously testing negative. Early death was defined as mortality occurring within 36 days of initiating tretinoin therapy during induction. Overall survival (OS) was calculated from the start of tretinoin treatment to death from any cause or the last date of follow-up.

Differentiation syndrome was diagnosed when at least two of the following were present: dyspnea, unexplained fever, weight gain >5 kg, hypotension without known cause, acute renal impairment, and radiographic evidence of pulmonary infiltrates or pleuropericardial effusion. A single symptom alone was not sufficient to confirm the diagnosis [13]. An elevated disseminated intravascular coagulation (DIC) score-calculated based on increased fibrin-related markers (e.g., D-dimer, FDP), prolonged partial thromboplastin (PT), reduced platelet count, and fibrinogen level-was associated with poorer outcomes. A DIC score ≥5 indicated overt DIC [14]. Pseudotumor cerebri was defined by the presence of one or more of the following: intense headache, nausea, vomiting, papilledema, retinal hemorrhages, or visual disturbances [9].

Statistical Analysis

All statistical evaluations were performed using Statistical Package for the Social Sciences software (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median values along with their minimum and maximum ranges, while categorical data were summarized as frequencies and percentages. Survival analysis, including OS and CR duration, was carried out using the Kaplan-Meier method, with comparisons between groups made using the log-rank test. Differences in response rates across categories were assessed using the chi-square (χ^2) test.

Results

Patient Characteristics

At diagnosis, the median age of the cohort was 41 years, with a range between 18 and 82 years. Of the 27 patients, 12 (44.4%) were female and 15 (55.6%) were male. Three individuals (11.1%) were identified as having therapy-related APL. Among these, two had a prior history of breast cancer, and one had previously been treated for colon cancer.

According to the Sanz risk stratification system, 14 patients (51.9%) were categorized as low risk, 10 (37.0%) as intermediate risk, and 3 (11.1%) as high risk. At initial presentation, one patient (3.7%) showed extramedullary involvement, specifically with bone infiltration.

DIC with a score of ≥5 was observed in 21 patients (77.8%), indicating overt DIC. Bleeding manifestations at diagnosis were reported in 8 patients (29.6%), including epistaxis in 2 (7.4%), gingival bleeding in 5 (18.5%), and gastrointestinal bleeding in 1 patient (3.7%).

Regarding molecular abnormalities, WT1 mutations were identified in 9 patients (33.3%), FLT3-ITD mutations in 4 patients (14.8%), FLT3-TKD mutations in 1 patient (3.7%), and NPM1 mutations in 1 patient (3.7%). A detailed summary of the demographic and clinical features of the patients is presented in Table 1.

Treatment and Patient Response

Induction therapy, consisting of ATRA combined with CT, was administered to 21 out of the 27 patients. Of these, 17 received the standard ATRA plus idarubicin protocol; while four were treated with the ATRA plus 3+7 regimen. The remaining six patients underwent induction with a combination of ATRA and ATO. CR was achieved in all patients following induction treatment, and no early mortality was recorded during this period.

At a median follow-up duration of 49 months (range: 6-140 months), neither median OS nor median progression-free survival (PFS) had been reached. The OS curve is illustrated in Figure 1.

Relapse occurred in 5 patients (18.5%), with one case involving extramedullary disease in the central nervous system (CNS). The median time to relapse was 9 months. Four relapsed patients underwent salvage treatment, achieved CR again, and subsequently underwent autologous stem cell transplantation. These individuals remain in remission under ongoing follow-up. The patient with CNS relapse also entered remission following intrathecal therapy; however, this patient died from cerebral hemorrhage during pre-transplantation preparation. A detailed summary of treatment responses and clinical outcomes is presented in Table 2.

Adverse Events

The most frequently encountered serious non-hematologic adverse events during treatment were infections and differentiation syndrome. A detailed list of other severe non-hematologic toxicities is presented in Table 3. Differentiation syndrome was diagnosed in 13 patients (48.1%), with the condition occurring predominantly in those treated with ATRA plus ATO (83.3%), while it was observed in only 38% of patients receiving ATRA in combination with CT.

Most cases of differentiation syndrome emerged during the induction phase (40.7%), with only two patients (7.4%)

Table 1. Demographic and clinical characteristics of the 27 patients

Gender	n (%)
Female	12 (44.4)
Male	15 (55.6)
Median age, years (range)	41 (18-82)
Type of APL	
De novo	24 (88.9)
Therapy-related	3 (11.1)
ECOG performance status	
0	10 (37.0)
1	10 (37.0)
2	7 (25.9)
Sanz risk score	
Low	14 (51.9)
Intermediate	10 (37.0)
High	3 (11.1)
Bleeding/hemorrhage	8 (29.6)
Concomitant mutation	15 (55.4)
FLT3-ITD positive	4 (14.7)
FLT3 TKD positive	1 (3.7)
WT1 positive	9 (33.3)
NPM1 positive	1 (3.7)
DIC score ≥5 (overt DIC)	21 (77.8)
Value	Median (range)
WBC ($\times10^9$/L)*	1550 (260-29.330)
ANC ($\times10^9$/L)*	650 (87-16.780)
Hb (g/L) †	9.1 (4.4-13.6)
Plt count ($\times10^9$/L)*	27.000 (5.000-187.000)
Blasts in bone marrow	85 (40-90)

*Before platelet transfusion, †Before erythrocyte transfusion, ECOG: Eastern Cooperative Oncology Group, ITD: Internal Tandem duplications, TKD: Tyrosine kinase domain, WBC: White blood cell, ANC: Absolute neutrophil count, Hb: Hemoglobin, Plt: Platelet, DIC: Disseminated intravascular coagulation

experiencing it during the consolidation period. All affected individuals were promptly initiated on dexamethasone at a dose of 10 mg twice daily. Temporary interruption or dose reduction of ATRA was necessary in four patients during induction and in one patient during consolidation. All cases responded favorably to the intervention, with complete resolution of symptoms.

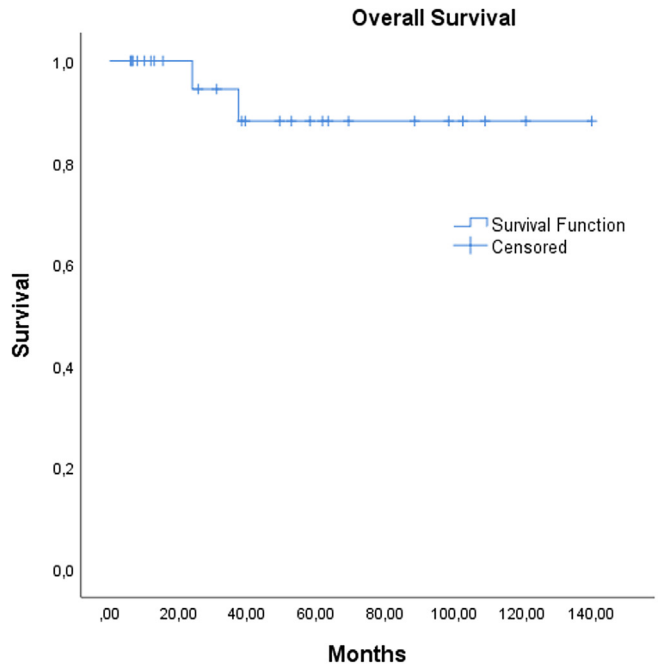

Figure 1. Overall survival of the study cohort

Table 2. Treatment responses and clinical outcomes

	n (%)
CR	27 (100%)
Relapse disease	5 (18.5%)
Follow-up, month, median (min-max)	49 (6-140)
PFS	Not reach
OS	Not reach

CR: Complete response, PFS: Progression-free survival, OS: Overall survival, min-max: Mininmum-maximum

Table 3. Severe non-hematologic toxicities observed during therapy

Severe infection	n (%)
Sepsis	3 (11.1)
Pneumonia	9 (33.3)
Fungal lung infection	3 (11.1)
Anal abscess	3 (11.1)
Pseudotumor cerebri	1 (3.7)
Differentiation syndrome	13 (48.1)
Supraventricular tachycardia	1 (3.7)
Pulmonary hemorrhage	1 (3.7)
Grade 3 hepatotoxicity	1 (3.7)

Pseudotumor cerebri was observed in one patient (3.7%) during both induction and consolidation phases. Among grade 3-4 hematologic adverse effects, neutropenic fever and cytopenias were the most prevalent. A comprehensive overview of grade 3-4 hematologic toxicities is shown in Table 4. Importantly, no treatment-related deaths occurred due to adverse events.

Discussion

In this study, we analyzed the clinical, hematologic, and therapeutic profiles of 27 patients diagnosed with APL at our institution. The median age of our cohort was 41 years, which is consistent with the general literature. This indicates that APL tends to occur at a younger age compared to other AML subtypes, whose median onset is typically higher [15].

The pathogenesis of APL is driven by the PML- RARα fusion gene, which promotes leukemogenesis by blocking differentiation and sustaining the self-renewal capacity of leukemic progenitors [16]. For molecular confirmation, conventional cytogenetic analysis, fluorescence *in situ* hybridization, and RT-PCR are employed. Real-time quantitative PCR (RQ-PCR) is also applied. Among these, RQ-PCR provides the added advantage of identifying distinct PML-RARα isoforms and quantitatively monitoring minimal residual disease, which is critical for evaluating treatment response and early relapse detection [17]. In our study, RQ-PCR was utilized both at diagnosis and throughout follow-up for disease monitoring.

Mutations involving FLT3, WT1, NRAS, and KRAS are frequently identified in newly diagnosed cases of APL; however, their prognostic implications remain inconclusive [18,19]. Among these, FLT3 mutations are notably more prevalent in APL compared to other AML subtypes [20]. Prior studies have reported FLT3 mutations in approximately 43% of APL patients [21], whereas our cohort demonstrated a lower incidence, with FLT3 mutations detected in 18.4% of cases. Particularly, FLT3-ITD mutations have been associated with hematologic features such as increased leukocyte counts at presentation. Despite these associations, the definitive impact of FLT3-ITD mutations on prognosis in APL remains uncertain and requires further investigation [22-24].

Table 4. Grade 3-4 hematologic adverse events observed during treatment

	Induction therapy (n, %)	Consolidation therapy (n, %)
Anemia Grade 3	 23 (85.2)	 12 (40.4)
Neutropenia Grade 3 Grade 4	 NA 27 (100)	 2 (7.4) 23 (85.2)
Thrombocytopenia Grade 3 Grade 4	 1 (3.7) 26 (96.4)	 7 (25.9) 12 (40.4)
FEN	27	10 (37)

FEN: Febrile neutropenia, NA: Not available

In our study, the proportion of high-risk APL patients was relatively low (11.1%) compared to rates reported in previous Turkish studies, which documented high-risk patient proportions of 21% and 35%, respectively [25,26]. Additionally, a national study by Çelik et al. [27] reported a high-risk APL rate of 12.5%, which is more consistent with our findings. These discrepancies in high-risk patient proportions may stem from various factors such as differences in referral patterns, earlier diagnosis in more recent years, institutional diagnostic criteria, or selection bias related to study inclusion. Further multicenter data may help clarify these variations in clinical presentation across different cohorts. Other international studies have typically reported high-risk classification rates ranging from 30% to 40% [28-30].

Recent research has confirmed the therapeutic efficacy of combining ATRA with either CT or ATO in the management of APL [31]. In line with these findings, all patients in our cohort who were treated with ATRA-based protocols-whether combined with CT or ATO-achieved CR after induction therapy.

While earlier studies have reported relapse rates in APL ranging from approximately 11.76% to 12.4%, our study demonstrated a slightly elevated relapse incidence of 18.5% [10,32]. Specifically, five of the 27 patients experienced disease recurrence, including one case involving extramedullary relapse in the CNS.

In a previously published study, the estimated 12-year event-free survival (EFS), OS, and disease-free survival rates were reported as 80.9%, 87.4%, and 89.1%, respectively, at a median follow-up duration of 83 months [33]. Another study demonstrated a 5-year EFS rate of 89.2% and an OS rate of 91.7% across all patients. Among those who achieved CR, the 5-year relapse-free survival rate was 94.8%, while the OS reached 97.4%. Despite successful remission, 5% of these patients experienced relapse [34]. In comparison, within our cohort, monitored for a median of 49 months, the median OS and PFS had not yet been reached at the time of analysis.

Timely diagnosis, proactive supportive interventions, and the effective management of therapy-related complications are fundamental to successful APL treatment [35]. A significant challenge in managing APL remains the high rate of early mortality, estimated at 20-30%, primarily due to DIC and hemorrhagic events, which may occur before or during the initiation of induction therapy [2]. The coagulopathy inherent to APL involves complex mechanisms, including both primary and secondary fibrinolysis, and consumptive coagulopathy. Consequently, intracranial and pulmonary hemorrhages are frequently reported as the leading causes of early death, particularly around the time treatment begins. Although thrombotic manifestations can sometimes dominate the clinical picture, they are less frequently observed [6,31].

In our cohort, a DIC score ≥5 was observed in 77.8% of patients. Hypofibrinogenemia (fibrinogen <150 mg/dL) was present in 11 patients (40.7%), and bleeding at diagnosis was noted in 29.6% of cases. By contrast, earlier studies reported bleeding manifestations at diagnosis in approximately 67% to 90% of patients [36,37].

In our center, several supportive care strategies were implemented during the induction phase to minimize early mortality. ATRA was initiated immediately upon clinical and morphological suspicion of APL, even before cytogenetic confirmation, in accordance with international guidelines [15]. Platelet transfusions were administered to maintain counts above 30,000/μL, and fresh frozen plasma or cryoprecipitate was used to manage coagulopathy. Febrile neutropenia was addressed with broad-spectrum antibiotic prophylaxis, and antifungal agents were used in cases of prolonged neutropenia. DIC was closely monitored and treated with aggressive fibrinogen replacement when necessary. These proactive and intensive supportive measures likely contributed to the absence of early deaths during induction in our cohort. Only one patient died during follow-up. Despite achieving remission following intrathecal therapy for CNS relapse, the patient succumbed to cerebral hemorrhage during transplantation preparation.

In a previously published study, 57.4% of patients diagnosed with APL presented with infections at admission. By contrast, only 3.7% of our patients exhibited signs of infection at diagnosis. This notably lower rate may reflect earlier presentation to healthcare facilities in our cohort. During induction therapy, all patients developed neutropenic fever, which necessitated empirical antibiotic treatment. Despite this, microbiological evaluations, including cultures, did not reveal any clinically significant pathogens. Importantly, no early mortality due to infection was recorded. Vaid et al. [38] reported a neutropenic fever incidence of 62.5% among patients during therapy, while another study cited a rate of 91%; attributing the increase to delays in initiating treatment [32].

Regarding hepatotoxicity, Mandegary et al. [39] observed elevated liver enzymes in APL patients receiving ATO, aspartate aminotransferase levels increased in the 45% of cases, alanine aminotransferase levels in the 60%, and bilirubin in the 40% of cases. Conversely, a separate study on APL patients treated with ATRA reported grade 3-4 hepatic adverse events in 3% of patients [36]. In our study, no grade 3 or 4 hepatic toxicities were observed. Temporary elevations in liver enzyme levels resolved upon interruption of therapy, and liver function parameters returned to normal in all patients.

In our cohort, pseudotumor cerebri was identified in one patient (approximately 3.7%), a rate that is slightly higher than the 2% reported by Mandelli et al. [36]. Management of this condition included the discontinuation of ATRA, administration of strong analgesics such as codeine or morphine sulfate, and the use of dexamethasone at 10 mg every 12 hours for a minimum of three days, in combination with furosemide [9].

Differentiation syndrome remains one of the most critical and potentially fatal complications associated with APL therapy, particularly in patients treated with ATRA and/or ATO. Reported incidence rates in the literature range widely, likely due to differences in induction protocols (e.g., CT-based vs. ATO-based regimens), variations in ATRA dosing, and the application of prophylactic corticosteroids, ranging from 2.5% to 63% [13,36,39,40]. In our study, the incidence of differentiation

syndrome was 48.1%, which is consistent with the findings of Dayama et al. [32]. This relatively high rate may be partially explained by the diagnostic criteria used, which require only two clinical signs or symptoms for confirmation, regardless of severity. Additionally, differences in induction therapy protocols and the nature of supportive care may also account for variability in reported rates. Given the life-threatening potential of fully developed differentiation syndrome, we initiated prompt treatment with dexamethasone (10 mg twice daily) at the first indication of clinical symptoms [15]. Importantly, no treatment-related mortality was observed in our cohort.

Study Limitations

The primary limitation of this study is the relatively small sample size, which reflects the rarity of APL as a hematologic malignancy. Moreover, the retrospective design and the single-center nature of the study may restrict the generalizability of the findings. To better elucidate prognostic factors and validate clinical outcomes, future prospective studies involving larger, multicenter cohorts are warranted.

Conclusion

APL is a medical emergency that requires early diagnosis and timely treatment to reduce the risk of early death. In this study, all patients achieved CR after receiving ATRA combined with either anthracycline-based CT or ATO. Our findings support the notion that newly diagnosed APL is a highly treatable disease when appropriate therapy and supportive care are provided.

Ethics

Ethics Committee Approval: This study received ethical approval from the Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital (decision no: 2022-03/1692, date: 09.03.2022), in accordance with national regulations and the principles outlined in the Declaration of Helsinki (1964) and its later amendments.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., B.A.C., E.B., Concept: S.S., B.A.C., D.İ., M.K.Ç., Design: S.S., Data Collection or Processing: S.S., B.A.C., E.B., S.Y., B.U.U., T.Y., D.İ., M.K.Ç., Analysis or Interpretation: S.S., B.A.C., E.B., Literature Search: S.S., B.A.C., E.B., B.U.U., Writing: S.S., B.A.C., E.B., S.Y., B.U.U., T.Y., D.İ., M.K.Ç.

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Original Article

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Second-line Chemotherapy for Advanced Bladder Cancer: Taxanes Versus Vinflunine

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ABSTRACT

Aim: Second-line chemotherapy in advanced urothelial carcinoma (UC) remains a significant clinical challenge, with limited high-level evidence guiding regimen selection. Vinflunine is the only agent approved by the European Medicines Agency for this setting, while taxanes are widely used off-label based on phase 2 data.

Methods: We conducted a retrospective analysis of patients with metastatic bladder cancer treated at Aydın Adnan Menderes University between 2013 and 2022. Eligible patients had received at least three months of second-line chemotherapy with either vinflunine or taxane-based regimens (docetaxel or paclitaxel). Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events were compared between groups.

Results: Among 38 patients receiving second-line therapy, 25 (65.8%) were treated with taxanes and 13 (34.2%) with vinflunine. Median PFS was significantly longer in the taxane group (4.9 vs. 2.2 months; p=0.001). Median OS favored taxanes numerically (13.2 vs. 4.33 months) but did not reach statistical significance (p=0.068). ORR was higher in the taxane group (52% vs. 23.1%), but the difference was not statistically significant (p=0.87). Adverse event profiles were consistent with known toxicities.

Conclusion: This single-center retrospective study suggests that taxane-based regimens may offer superior PFS compared to vinflunine in the second-line treatment of advanced UC, despite the lack of statistically significant OS benefit. Given limitations in access to immunotherapy and targeted agents, cytotoxic chemotherapy remains essential, underscoring the need for further prospective trials to define optimal second-line strategies.

Keywords: Urothelial carcinoma, second-line chemotherapy, taxanes, vinflunine

Introduction

Metastatic bladder urothelial carcinoma (UC) responds well to chemotherapy; therefore, systemic chemotherapy combined with immunotherapy is a preferred treatment. Few studies exist for second-line treatment [1]. Currently, enfortumab-vedotin with pembrolizumab has replaced avelumab immunotherapy maintenance after platinum-sensitive treatment, achieving a 32-month overall survival (OS), with a 68% objective response rate (ORR) [2]. Disease typically advances after 13 months, with the effectiveness of cisplatin-based second-line therapy remaining uncertain. Due to reimbursement issues, cisplatin-based therapies remain first-line treatments. Cisplatin-based treatments like gemcitabine with cisplatin (GC), or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) show survival benefits with 40-70% response rates [3].

Chemotherapy treatments after cisplatin-based therapy failure are usually single-agent therapies, with an ORR of 5-20% and

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median progression-free survival (PFS) of 3-4 months [4,5]. The US Food and Drug Administration has not approved any cytotoxic chemotherapy drugs for second-line treatment. Vinflunine was approved in the second-line treatment by the European Medicines Agency (EMA) in 2009, providing a 2.3-month OS advantage over best supportive care (BSC) [6]. Both docetaxel and paclitaxel are widely used in second-line settings, based on phase 2 data. A study involving 76 patients treated with weekly single-agent paclitaxel reported an ORR of 5-10% and a median OS ranging from 6.9 to 7.2 months [7,8]. In a randomized trial conducted by Choueiri et al. [9], patients receiving docetaxel at a dose of 75 mg/m^2 every three weeks had a median OS of 7 months. Nonetheless, 19% of these patients experienced grade 3/4 hematologic side effects, while 25% encountered grade 3/4 non-hematologic toxicity, including fatigue, infection, and electrolyte imbalances. Recent data indicate that, although immunotherapy agents provide a survival benefit in second-line treatment, they are effective in only about 20% of patients [10].

In second-line treatment, studies have only been conducted against BSC owing to characteristics such as advanced age, comorbidities, and poor performance status of patients. The effectiveness of the treatments used was unclear when compared with each other. The purpose of this research is to assess and contrast the effectiveness of paclitaxel and vinflunine, which are commonly chosen for second-line therapy in advanced bladder cancer.

Methods

Patients diagnosed with advanced-stage bladder cancer who were followed up at the Clinic of Medical Oncology at Aydın Adnan Menderes University Training and Research Hospital between 2013 and 2022 were retrospectively analyzed. The study included patients over the age of 18 years who had been diagnosed with metastatic disease and had received at least three months of second-line chemotherapy. Patient data were retrospectively recorded by reviewing the hospital database and follow-up files. Data on demographics, clinicopathological characteristics, response rates, and survival outcomes were collected in a retrospective manner. Individuals were excluded if they had incomplete data, were lost to follow-up, could not be assessed for response, had a secondary cancer, or had herbal or alternative treatments.

According to RECIST criteria, the time from the initiation of subsequent chemotherapy until radiological progression or date of death was considered PFS. The duration from the start of subsequent treatment to either the final follow-up or the date of death was defined as OS. Adverse events related to drugs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.Patients were grouped into those receiving vinflunine (n=13) and those receiving taxane-based treatment (docetaxel or paclitaxel) (n=25). The treatment groups were compared in terms of OS, PFS, and ORR.

Following the Declaration of Helsinki guidelines, the Clinical Research Ethics Committee at the Aydın Adnan Menderes University Faculty of Medicine granted approval for the study. (decision no: E-53043469-050.04-764721, date: 11.07.2025).

Statistical Analysis

Data analysis was performed using International Business Machines Corporation Statistical Package for the Social Sciences (SPSS) version 22, a software developed by SPSS Inc.. Clinical and demographic patient characteristics were examined using descriptive analysis. Numerical and categorical variations are presented as percentages (%) and numbers (n). When dealing with continuous data that adhere to a normal distribution, the findings are presented as the mean along with the standard deviation. For data with other distributions, results are presented as median and range. The Kaplan-Meier method was utilized to determine PFS and OS. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox regression model. Group differences were evaluated using the log-rank test. A p value of less than 0.05 was deemed statistically significant for all analyses.

Results

Out of 102 patients who underwent initial chemotherapy, 38 individuals (37.2%) proceeded to receive a second round of treatment. Among those who underwent second-line chemotherapy, 34 (89.5%) were male. The participants in the study had a median age of 68, ranging from 48 to 82. Only three (7.9%) patients had no history of smoking. Eighteen (47.4%) patients did not receive local treatment and were classified as *de novo* metastatic. The most common visceral organ metastasis was in the lung (n=19). Twelve (31.6%) patients had no other comorbidities. The most commonly used first-line treatment regimen (89.5%) was platinum plus gemcitabine. As a second-line treatment, 25 (65.8%) patients received taxane, and 13 (34.2%) patients received vinflunine. Table 1 presents the baseline characteristics of the patient cohort.

The median OS in the entire treatment group was found to be 6.26 months (standard error=2.99, 95% CI: 0.39-12.13). In the taxane group, the median OS was 13.2 months (standard error=6.23, 95% CI: 0.98-25.4), while in the group receiving vinflunine, the median OS was 4.33 months (standard error=1.07, 95% CI: 2.22-6.44). There was no statistically significant difference in OS between the treatment groups (p=0.068) (Figure 1A). In the entire patient group, the median PFS was determined to be 3.96 months (standard error=0.881, 95% CI: 2.24-5.69). In the taxane group, the median PFS was 4.9 months (standard error=0.687, 95% CI: 3.55-6.24), while in the vinflunine group, the median PFS was 2.2 months (standard error=0.399, 95% CI: 1.42-2.98). The groups exhibited a statistically significant difference (p=0.001) (Figure 1B).

The overall response rate was 42.1% in all patients who received second-line treatment. In the taxane and vinflunine groups, the ORR was 52% (13/25) and 23.1% (3/48), respectively. The

ORR did not show a notable difference in the groups receiving taxane and vinflunine treatments (p=0.87). In the taxane group, the disease control rate was 68% (17 out of 25), whereas in the vinflunine group, it was 23.1% (3 out of 13). The groups did not show any statistically significant differences (p=0.305). After progression on the current treatment, 44.7% (n=17) of the patients received systemic chemotherapy. Table 2 displays the response characteristics of the treatment groups

All individuals initially received platinum-based therapy and were platinum-resistant. For second-line treatment, only patients who received vinflunine (n=13) and taxane (n=25) were compared. The groups treated with taxane and vinflunine demonstrated a statistically significant difference in PFS, with median PFS values of 4.9 months and 2.2 months, respectively (p=0.001). There was no statistically significant difference observed between the groups regarding OS. The median OS was 13.2 months for participants given taxane and 4.33 months for those given vinflunine (p=0.068). The rate of anemia of any grade was 88% and 100% in the taxane and vinflunine groups, respectively. The rates of grade 3-4 anemia were 12% and 0%, respectively (Table 3).

Table 1. Demographic and clinicopathological features of the patients

	All patients n (%)	**Taxan n (%)**	**Vinflunine n (%)**
Gender Female Male	 4 (10.5%) 34 (89.5%)	 23 (92%) 2 (8%)	 11 (84.6%) 2 (15.4%)
Age (median) Min-max	68 (48-82)	69 (50-82)	66 (48-80)
Smoking Yes No	 31(92.1%) 3 (7.9%)	 23 (92%) 2 (8%)	 12 (92.3%) 1 (7.7%)
ECOG PS 0 1 2	 1 (2.6%) 33 (86.8%) 4 (10.5%)	 0 (0%) 22 (88%) 3 (12%)	 1 (7.7%) 11(84.6%) 1 (7.7%)
Comorbid disease Yes No	 26 (68.4%) 12 (31.6%)	 19 (76%) 6 (24%)	 7 (53.8%) 6 (46.2%)
Comorbid disease HT Type-2 DM CAD COPD	 23 (60.5%) 3 (7.9%) 8 (21.1%) 8 (21.1%)	 17 (44,7%) 1 (2.6%) 7 (18.5%) 4 (10.5%)	 6 (15.8%) 2 (5.3%) 1 (2.6%) 4 (10.5%)
Histopathology urothelial carcinoma other	 36 (94.7%) 2 (5.3%)	 24 (96%) 1 (4%)	 12 (92.3%) 1 (7.7%)
De novo metastasis Yes No	 18 (47.4%) 20 (52.6%)	 11 (44%) 14 (56%)	 7 (53.8%) 6 (46.2%)
Metastatic sites Lung Liver Bone Distant lymph node Other	 19 (50%) 4 (10.5%) 14 (36.8%) 33 (86.8%) 5 (13.2%)	 12 (31.5%) 2 (5.3%) 8 (21.1%) 21 (55.2%) 5 (13.2%)	 7 (18.5%) 2 (5.3%) 6 (15.8%) 12 (31.6%) 0 (0%)
First-line CT type Platinum+gemcitabin Platinum+taxan Gemcitabin Other	 34 (89.5%) 1 (2.6%) 1 (2.6%) 2 (5.3%)	 22 (88%) 0 (0%) 1 (4%) 2 (8%)	 12 (92.3%) 1 (7.7%) 0 (0%) 0 (0%)
Second-line CT type Taxan Vinflunine	 25 (65.8%) 13 (34.2%)	 25 (100%)	 13 (100%)

ECOG PS: Eastern Cooperative Oncology Group performance status, CT: Chemotherapy, HT: Hypertension, Type 2 DM: Type 2 diabetes mellitus COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease

Discussion

Although there are only a few phase 3 studies on second-line treatments for locally advanced and metastatic UC, no chemotherapy regimen has proven to be better than the others. This study aimed to share real-world data from a retrospective, single-center experience.

Although an enhanced understanding of molecular pathways in carcinoma treatment has introduced targeted agents, immunotherapies, and antibody-drug conjugates into second-line therapy in recent times, their use remains limited due to countries' reimbursement policies. Therefore, chemotherapy agents are used in a large number of patients. Various chemotherapeutic drugs have been investigated for second-line treatment. Pemetrexed has undergone evaluation in two phase 2 studies. While one study showed a positive response

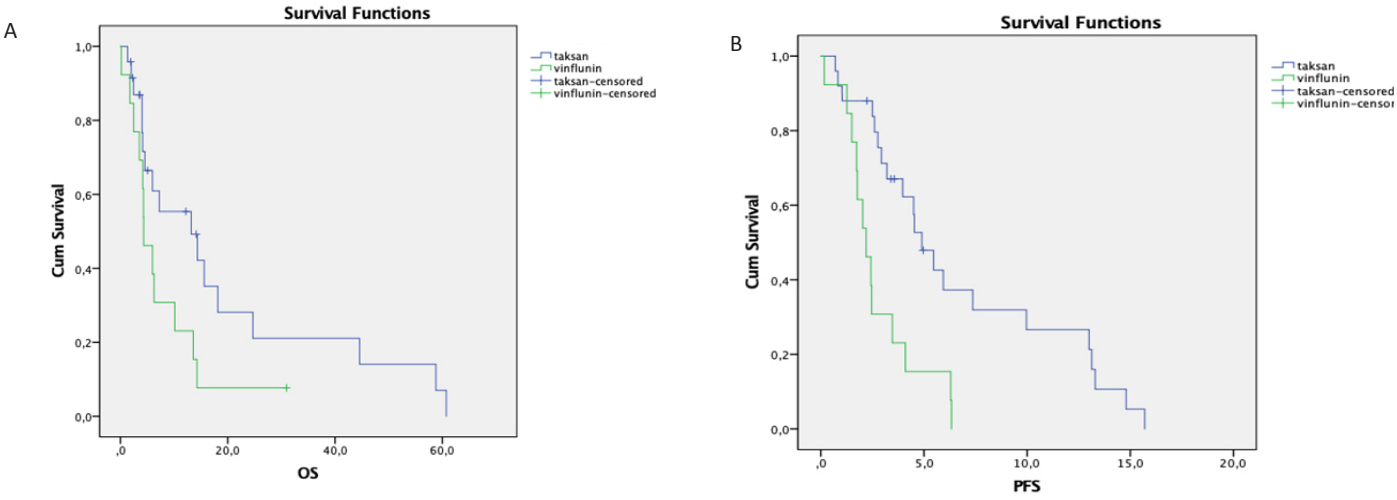

Figure 1. (A) Overall survival curves. B) Progression-free survival curves

Table 2. Objective tumor responses

		Taxan n (%)	Vinflunine n (%)	p
Best response	Complete response	4 (16%)	1 (7.7%)	
	Partial response	9 (36%)	2 (15.4%)	
	Stable response	4 (16%)	0 (0%)	
	Progressive disease	8 (32%)	10 (76.9%)	
Objective response rate		13 (52%)	3 (23.1%)	0.87
Disease control rate		17 (68%)	3 (23.1%)	0.305

Table 3. Most common treatment-related adverse events and hematologic abnormalities

	Taxan				Vinflunine			
Adverse Event	Overall incidence No. of patients (%)		Grade 3 or 4 No. of patients (%)		Overall incidence No. of patients (%)		Grade 3 or 4 No. of patients (%)	
Anemia	22	88	3	12	13	100	0	0
Neutropenia	11	44	0	0	2	15.4	0	0
Thrombocytopenia	8	32	0	0	3	23.1	0	0
Nausea	20	80	0	0	5	38.5	0	0
Diarrhea	17	68	1	4	1	7.7	0	0
Stomotitis	12	48	0	0	1	7.7	0	0
Hepatic enzymes elevation	4	16	1	4	2	15.4	0	0
Rash	0	0	0	0	4	30.8	1	7.7
Neuropathy	17	68	0	0	1	7.7	0	0

(response rate 28% and OS 9.8 months), a negative response were obtained in the other [11,12]. Other chemotherapy agents (such as irinotecan, oxaliplatin, nab-paclitaxel, ixabepilone, ifosfamide, gemcitabine, and combinations like paclitaxel-gemcitabine) have also been studied, resulting in a 10-20% ORR, median PFS ranging from 2 to 3 months, and median OS between 6 and 9 months [13].

Vinflunine is considered an appropriate choice. In a phase 3 second-line study involving 370 patients with advanced or metastatic UC, vinflunine demonstrated an improvement in survival compared to BSC, achieving the primary endpoint with a median survival of 6.9 months versus 4.6 months (HR 0.88, 95% CI: 0.69-1.12) and attained a 9% ORR [6]. It was approved by the EMA and started to be used as second-line therapy. Subsequently, a phase 2/3 cabazitaxel study with vinflunine in the opposite arm was planned. The study began with phase 2, which included 70 patients. The patient characteristics were comparable across both study groups, with neither group exhibiting a complete response to the treatment. A partial response was observed in three patients (13%) receiving cabazitaxel and six patients (30%) receiving vinflunine. The median PFS for cabazitaxel was 1.9 months, whereas for vinflunine, the difference in PFS was statistically significant, with a median of 2.9 months (p=0.039). However, although there was a trend in favor of vinflunine for OS (7.6 vs. 5.5 months), it was not significant, so it could not proceed to phase 3 [14]. In our study, a similar PFS rate (2.2 months) was observed in patients receiving vinflunine.

Taxanes were widely used in Europe as a second-line treatment prior to vinflunine approval, despite the limited responses observed in small phase 2 studies. Paclitaxel was investigated in three phase 2 studies with small patient numbers. In a cohort of 31 patients, the ORR was found to be 10% while the median OS was 7.2 months. However, in the other two studies, the ORR was lower (5-7%) [7]. In a phase 2 trial, docetaxel was assessed; showing an ORR of 13% and a median OS of 9 months [15]. Although no study in the literature directly compares vinflunine to taxanes as second-line treatment, they remain the two most used agents in daily practice. In our study, a statistically significant PFS advantage was observed in patients who received taxanes. Although OS was numerically in favor of taxanes, it was not significant (13.2 months vs. 4.33 months, p=0.068).

Over the past few years, with the increasing use of immunotherapy and targeted therapies, many drugs have been approved for second-line therapy of advanced-stage bladder cancer. For platinum-resistant patients who have not received immunotherapy, pembrolizumab, nivolumab, avelumab, enfortumab vedotin, erdafitinib, and trastuzumab-deruxtecan have been approved by the FDA for use as second-line therapies [16-22]. In a phase 2 trial involving nivolumab, the ORR was 20%, showing no dependence on programmed cell death ligand 1 (PD-L1) expression levels. With a median follow-up period of seven months, the study revealed a notable and enduring OS advantage, with a median OS of nine months for the entire group. Specifically, for participants with PD-L1 expression levels below 1% and those at or above 1%, the median OS was six months and eleven months months, respectively. Additionally, the treatment had a manageable safety profile [16]. The KEYNOTE-045 study evaluated pembrolizumab against randomized chemotherapy options, including paclitaxel, docetaxel, or vinflunine, in patients with advanced UC who had experienced progression after treatment with platinum-resistant therapies. Compared with chemotherapy, pembrolizumab improved OS with a median follow-up of approximately 28 months (mOS 10 vs. 7 months; HR 0.70, 95% CI: 0.57-0.85). The PFS was comparable between the two treatment groups, with median PFS being two months versus three months, and a HR of 0.96 (95% CI: 0.79-1.16). Moreover, the pembrolizumab group experienced fewer adverse side effects [17]. Similarly, an ORR of up to 24% was achieved with avelumab [18].

The effectiveness of enfortumab vedotin, previously confirmed in other research, was assessed in a phase 3 clinical trial (EV-301) involving patients with metastatic UC. The study design was similar to that of the pembrolizumab study. The control arm consisted of investigator-chosen chemotherapy regimens. The results showed that enfortumab vedotin improved both mOS (13 vs. 9 months, HR 0.70) and mPFS (6 vs. 4 months, HR 0.63) [19]. Nevertheless, individuals who experienced progression following maintenance with avelumab were excluded from the study. The incidence of grade ≥3 toxicity for any adverse event was comparable between the two treatment groups, with rates of 52% and 51%, respectively. In a study evaluating erdafitinib, an fibroblast growth factor receptor (FGFR) inhibitor, it was found to be effective compared to chemotherapy in patients with FGFR mutations. Moreover, this study included patients who had previously received immunotherapy. After a median follow-up period of 16 months, erdafitinib demonstrated superior OS and PFS compared to chemotherapy, with a median OS of 12 months versus 8 months (HR 0.64) and a median PFS of 6 months versus 3 months (HR 0.58). Additionally, erdafitinib showed higher ORR (46% compared to 12% with chemotherapy) and complete response rates (7% compared to 1% with chemotherapy) [20]. In another cohort of the study, erdafitinib was compared with pembrolizumab in patients who had not previously received immunotherapy. Similar survival outcomes were observed, with a median follow-up period of 33 months, a median OS of 11 months for each group, and a HR of 1.18 [21]. Fam-trastuzumab deruxtecan was assessed in a basket study involving patients with human epidermal growth factor receptor-2 (HER2) expression.With a median observation of 13 months, the ORR was 39% in 41 patients with advanced bladder cancer. Moreover, patients with IHC 3+ disease exhibited higher ORRs than those with IHC 2+ disease, with rates of 56% compared to 35% [22].

Despite the benefits of antibody-drug conjugates, immunotherapy, and targeted therapies, the need to find effective cytotoxic agents for second-line treatment persists because of limited access to these drugs. Our research underscores this gap in the existing literature by evaluating taxane, a treatment with potential efficacy, against vinflunine,

which is already sanctioned and regarded as the standard treatment. We confirmed the safety profiles of both taxanes and vinflunine and did not detect any novel safety signals.

Study Limitations

Our study is subject to certain limitations. Firstly, its single-center and retrospective nature may introduce biases. The limited patient cohort, the absence of standardized treatment transitions, and the lack of a significant difference in OS despite the observed advantage in PFS may contribute to these biases. To accurately assess OS, larger, prospective, and randomized controlled trials are warranted. In future research, stringent control of treatment transitions is crucial to minimize confounding effects. Additionally, conducting subgroup analyses to identify specific patient populations that may derive greater benefit from this treatment is advantageous.

Conclusion

Although chemotherapy regimens do not show superiority over each other in terms of survival, taxanes have demonstrated a significant PFS benefit over vinflunine administration. The agents used in second-line treatment have only been shown to provide a survival benefit against BSC. For this reason, systemic therapy is recommended as a second-line treatment for all patients with good performance status.

Ethics

Ethics Committee Approval: Following the Declaration of Helsinki guidelines, the Clinical Research Ethics Committee at the Aydın Adnan Menderes University Faculty of Medicine granted approval for the study. (decision no: E-53043469-050.04-764721, date: 11.07.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Pratices: B.D., O.Y.B., Concept: B.D., A.A., Ö.A., Design: B.D., O.Y.B., Data Collection or Processing: A.A, G.Ç., Ö.A., Analysis or Interpretation: B.D., A.A., O.Y.B., Literature Search: B.D., G.Ç., Ö.A., Writing: B.B., G.Ç.

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