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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.

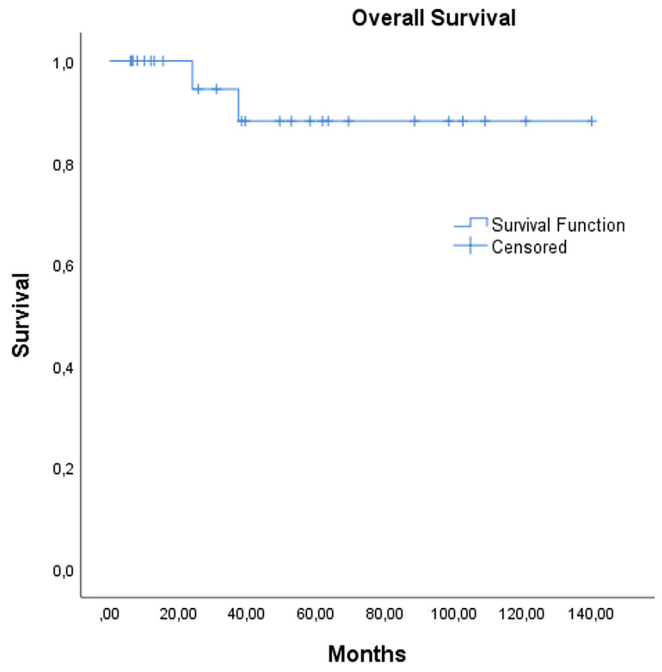

Figure 1. Overall survival of the study cohort

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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