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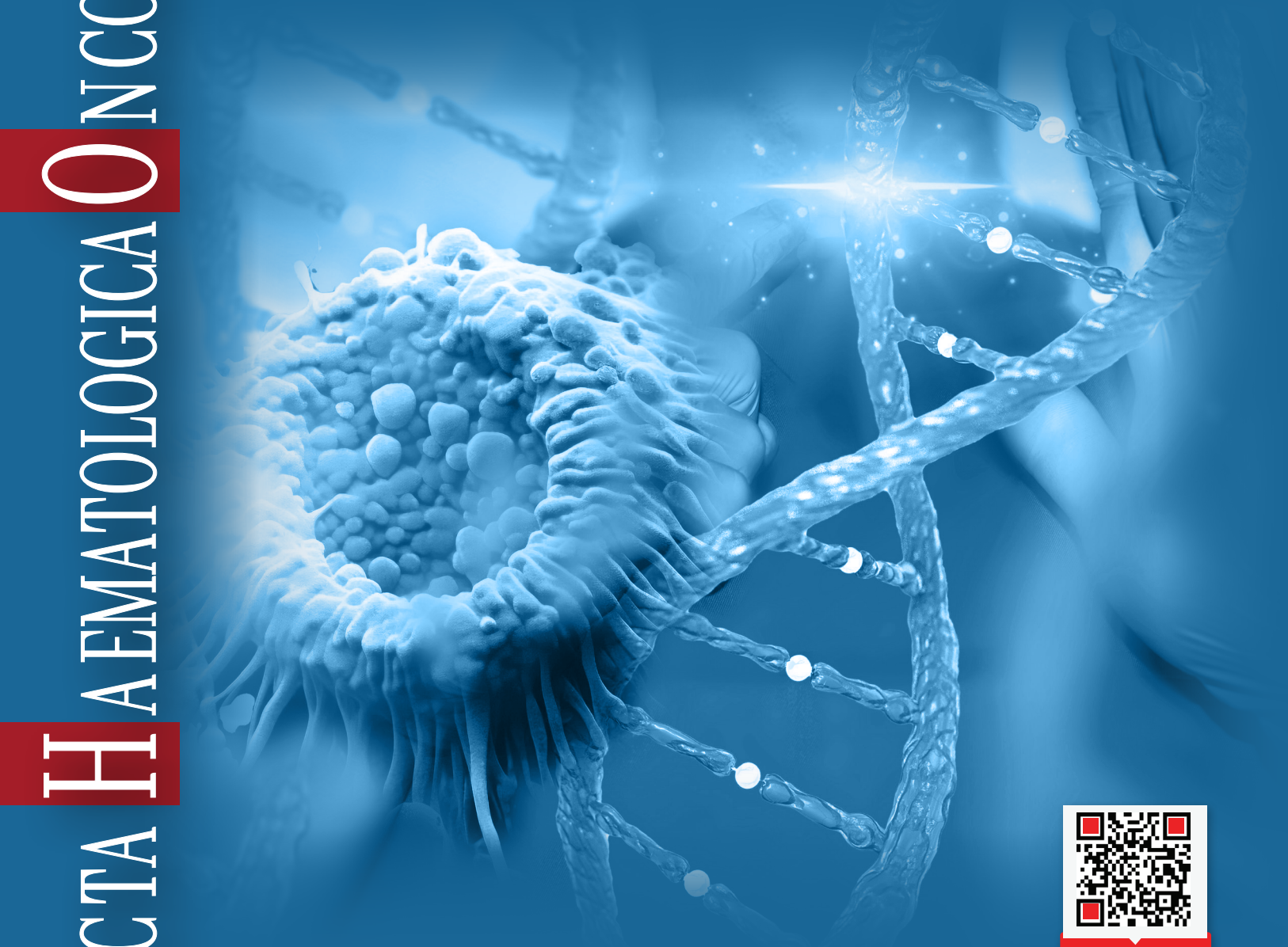

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Original Article

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Isolated Vaginal Metastases of Endometrial Cancer and Their Role in Adjuvant Brachytherapy

Varol Gülseren[1], İlker Çakır[2], Gamze Aköz[3], Aykut Özcan[2], Muzaffer Sancı[2], Zübeyde Emiralioğlu Çakır[2], Aykut Özdemir[4], Pınar Tuğçe Özer[2], Kemal Güngördük[5]

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ABSTRACT

Aim: This study aimed to investigate the effect of adjuvant vaginal brachytherapy (VBT) after initial surgery on local recurrence, disease-free survival, and overall survival (OS) in patients with endometrial cancer (EC).

Methods: The data of patients diagnosed with EC at the gynecological oncology clinic between 1998 and 2021 were retrospectively analyzed. Patients who underwent total hysterectomy with negative surgical margins were included in the study.

Results: Fifty-six patients who were treated for EC and subsequently developed isolated vaginal metastases (IVM) were evaluated. In the treatment of vaginal recurrence, 20 patients were treated with resection+VBT±external beam radiotherapy (EBRT)±chemotherapy and 36 patients were treated with VBT+EBRT±chemotherapy. The 5-year OS rates for patients who received resection+VBT treatment were 78.8% and 35.8% for patients who received EBRT+VBT treatment (p=0.023). The recurrence time did not significantly differ depending on whether or not adjuvant VBT was given (p=0.463). The mean 5-year OS rates were 49.4% and 62.5% in patients who did and did not receive VBT, respectively (p=0.521). As a result of the evaluation of risk factors that may affect OS in patients with IVM, according to Cox regression analysis, none of the prognostic factors were found to have a significant effect.

Conclusion: This study found that adjuvant VBT did not affect local recurrence time and OS rate in patients with EC.

Keywords: Vaginal metastasis, endometrial cancer, brachytherapy, lymph node

Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract and is the fourth most common cancer in women [1]. There has been an increase in the incidence of EC in both premenopausal and postmenopausal women because of changes in environmental and nutritional factors (obesity, nulliparity, estrogen replacement therapy) [2]. Although the prognosis is generally excellent, recurrence occurs in approximately 15% of cases [3]. Relapses usually occur within 3 years of initial treatment. Unfortunately, the 5-year survival rate of patients with recurrence is significantly reduced, with salvage therapy success rates of around 16-40% [4,5]. For treatment management purposes, EC patients are subdivided according to their risk of recurrence, taking into account patient age, tumor size, International Federation of Gynecology and Obstetrics (FIGO) staging, histological type and grade, and lymphovascular space involvement (LVSI) [4]. The overall 5-year survival rate is 55% for pelvic and 17% for extrapelvic recurrences [2]. Half of the recurrences in early-stage patients are confined to the pelvis, with the remainder being isolated extrapelvic metastases (25%) or both pelvic and extrapelvic (25%) recurrences [2]. Early detection of recurrent

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disease is critical and may affect survival because it is more suitable for localized disease treatment.

The term recurrent disease central to the vaginal wall or vaginal cuff refers to local recurrence. The treatment approach depends on the specific site of recurrence, duration of disease-free period, the patient's general health, and whether or not they have received prior adjuvant radiotherapy [2]. Although adjuvant radiotherapy reduces the risk of local recurrence, recurrence can limit treatment options and prolong survival [6]. Conventional external radiotherapy, intracavitary brachytherapy, and surgical excision are acceptable treatment options for vaginal recurrence [2]. Pelvic exenteration is usually considered in patients with localized recurrence who do not improve after radiation [2]. The aim of this study was to investigate the effect of adjuvant vaginal brachytherapy (VBT) after initial surgery on local recurrence, disease-free survival (DFS), and overall survival (OS) in patients with EC.

Methods

The data of patients diagnosed with EC at the gynecological oncology clinic between 1998 and 2021 were analyzed. Fifty-six cases of local recurrence were retrospectively evaluated. Patients who underwent total hysterectomy with negative surgical margins were included in the study. Patients with distant or multiple organ metastases were excluded from the study. The study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Local Ethics Committee (date: 09.12.2022, decision no: 2022/11-44). All procedures were performed in compliance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its subsequent amendments or comparable ethical standards.

The FIGO 2023 staging system was used [7]. Surgical procedures, adjuvant treatment methods, and survival status of patients were investigated. LVSI, tumor size, depth of myometrial invasion, cervical involvement, adnexal involvement, and lymph node status were analyzed from pathological reports. The diagnosis of vaginal metastasis was made by evaluating the results of speculum and biopsy examinations. Distant organ metastasis was evaluated by computed tomography, magnetic resonance imaging, or positron emission tomography.

All surgical procedures were performed by experienced specialists in the field of gynecological oncology surgery. Abdominal exploration was done in detail. After entering the peritoneal cavity, peritoneal washing was performed for cytology. Exploration of the abdominal cavity included systematic examination of the peritoneal surfaces, omentum, colon, small intestine, and paracolic, pelvic, mesenteric, and para-aortic regions, as well as palpation to identify suspicious lesions. The procedures included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, and omentectomy. Systematic complete pelvic para-aortic lymphadenectomy was performed in the presence of deep myometrial invasion, cervical involvement, non-endometrioid histological type, and grade 3 tumor. Pelvic lymphadenectomy consisted of removal of lymphatic tissue over the external and common iliac vessels and in the obturator fossa. Para-aortic LN dissection was defined as removal of the aorta starting from the bifurcation, above the inferior vena cava, and below the left renal vein.

The adjuvant VBT dose and fractionation regimen is 3 fractions of 7.0 Gy (21 Gy total dose) prescribed to a vaginal depth of 0.5 cm. Vaginal cylinder diameters can vary between 2.5 and 3.5 cm. VBT was administered when adequate vaginal cuff healing occurred. Care was taken to ensure no longer than 8 weeks between surgery and the first brachytherapy fraction. Brachytherapy was performed on an average of 14 days. According to the FIGO 2023 staging system, patients between stages 1B-2C were recommended adjuvant VBT. Brachytherapy may be considered for stage 3C patients. After obtaining the information, patients made a decision.

All patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. In the control group, the vagina was evaluated using a speculum, and the pelvis was examined using ultrasonography. At least once a year, cytology was evaluated using a smear of the vagina. Computed tomography or magnetic resonance imaging was performed annually. DFS was defined as the time from the date of primary surgery until the detection of recurrence or last observation. Total survival (OS) was defined as the duration from the date of primary surgery until death or last observation.

Statistical Analysis

Nominal parameters were expressed as mean±standard deviation and analyzed using one-way ANOVA. Categorical data, which were evaluated as numbers and percentages, were compared using the chi-square test. Pearson's chi-square test was used if the proportion of groups with less than 5 numbers was <20%. Fisher's precision test was used if the proportion of groups with less than 5 numbers was >20% and the minimum number of evoked signals was less than 5. Survival analysis was performed using the Kaplan-Meier method, and results were compared using the log-rank test. Cox regression analysis was used to identify factors affecting survival, and the results are presented as hazard ratios. Data recording and statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 17, SPSS, Inc, Chicago, IL). A p value of <0.05 was set to indicate statistical significance.

Results

Fifty-six patients who were treated for EC and subsequently developed isolated vaginal metastases (IVM) were evaluated. Mean ages were calculated as 59.1±10.1 and 65.6±8.6, respectively, in patients who did not receive adjuvant VBT at the initial diagnosis (p=0.097). Tumors of 8 (22.2%) patients in the group who were not administered adjuvant VBT and in 8 (40.0%) patients in the group who were administered VBT were of the non-endometrioid histological type. Deep myometrial invasion was present in 8 (22.2%) patients in the group who

were not administered VBT and in 14 (70.0%) patients in the group who were administered VBT (p=0.019). The presence of LVSI was more common in the VBT group (p=0.039). Demographic data and clinical characteristics of patients with EC and vaginal recurrence according to the groups that received and did not receive adjuvant VBT are presented in Table 1. For the treatment of vaginal recurrence, 20 patients were treated with resection+VBT±external beam radiotherapy (EBRT)±chemotherapy and 36 patients were treated with VBT+EBRT±chemotherapy. The 5-year OS rates for patients who received resection+VBT treatment were 78.8% and 35.8% for patients who received EBRT+VBT treatment (p=0.023).

The median duration of vaginal recurrence in patients who did not receive adjuvant VBT was 20 (3-104) months, and the median time to recurrence in patients who received VBT was 19.5 (6-72) months. The recurrence time did not significantly differ depending on whether or not adjuvant VBT was given (p=0.463). The mean 5-year OS rates were 49.4% and 62.5% in patients who did and did not receive VBT, respectively (p=0.521) (Figure 1).

As a result of the evaluation of risk factors that may affect OS in patients with IVM, according to Cox regression analysis, none of the prognostic factors were found to have a significant effect (Table 2). Univariate regression analysis identified lymph node involvement as a negative risk factor for OS (odds ratio=4.9, 95% confidence interval=1.2-19.8).

Discussion

In this study, patients with EC with isolated local recurrence were examined. When the relapse development time was examined, adjuvant VBT was found to not have a significant effect. In addition, adjuvant VBT had no effect on OS. Although VBT was given for local control, it was disappointing that it did not affect our main expectation of survival. In the treatment of isolated vaginal recurrence, the survival of patients who underwent resection in addition to radiotherapy and chemotherapy was significantly higher.

EC is usually diagnosed at an early stage and has a good prognosis; however, the 5-year OS rate for patients who relapse is between 20% and 50% [8]. The most common site of recurrence is the vagina (30%) [9]. Relapses usually occur within the first three years [10]. For patients with local recurrence, the 3-year probability of survival was 34-64% [9]. IVM can be successfully treated with radiotherapy and/or surgery [11]. Patients who received radiotherapy for local recurrence had a 5-year OS of 75% [12]. More extensive

Table 1. Clinical and pathological features of patients with endometrial cancer and vaginal recurrence

	VBT not performed (n=36)	VBT performed (n=20)	p
Age (years), mean±SD	59.1±10.1	65.6±8.6	0.097
CA125, mean±SD	29.9±27.2	22.0±19.4	0.424
Hemoglobin (gr/dL), mean±SD	12.1±1.9	11.9±1.0	0.761
Histological type - Endometrioid - Non-endometrioid	 28 (77.8%) 8 (22.2%)	 12 (60.0%) 8 (40.0%)	0.284
High grade	12 (33.3%)	12 (60.0%)	0.167
Tumor size (cm), mean±SD	3.8±2.1	4.4±1.3	0.439
Pelvic lymph node dissection	28 (77.8%)	16 (80.0%)	0.205
Para-aortic lymph node dissection	20 (55.6%)	12 (60.0%)	0.312
Deep myometrial invasion	8 (22.2%)	14 (70.0%)	0.019
Cervical stromal involvement	8 (22.2%)	4 (20.0%)	0.642
Adnexal involvement	-	2 (10.0%)	0.357
Lymphovascular space invasion	10 (27.8%)	14 (70.0%)	0.039
Adjuvant external beam radiotherapy	8 (22.2%)	12 (60.0%)	0.046
Adjuvant chemotherapy	12 (33.3%)	6 (30.0%)	0.600
Short-term disease-free interval (≤12 month)	12 (33.3%)	4 (20.0%)	0.454
Stage - 1A2 - 1B - 2B - 3C - 3C1 - 3C2	 18 (50.0%) 2 (5.6%) 4 (11.1%) 4 (11.1%) 2 (5.6%) 6 (16.7%)	 - 4 (20.0%) 8 (40.0%) 4 (20.0%) - 4 (20.0%)	0.084
Recurrence treatment - Resection+VBT±EBRT±CT - VBT+EBRT±CT	 12 (33.3%) 24 (66.7%)	 8 (40.0%) 12 (60.0%)	0.519

SD: Standard deviation, VBT: Vaginal brachytherapy, EBRT: External beam radiotherapy, CT: Chemotherapy

surgery, such as pelvic exenteration, is usually reserved for patients with localized recurrences who do not improve after radiotherapy [2]. The incidence of complications related to the exenteration procedure is around 30-48% and the 5-year OS is around 40-73% [13,14]. In our cohort, the 5-year OS rates for patients who received resection+VBT treatment were 78.8% and 35.8%, respectively, for patients who received external radiotherapy+VBT treatment (p=0.023). Due to the small number of patients, we could not compare the recurrence treatment options between patients who did and did not receive adjuvant VBT therapy. More valuable information can be obtained by performing more homogeneous subgroup analyses with a larger number of patients and prospective studies.

Although adjuvant RT significantly reduces the risk of vaginal and intrapelvic recurrence, it does not improve OS [11,15,16].

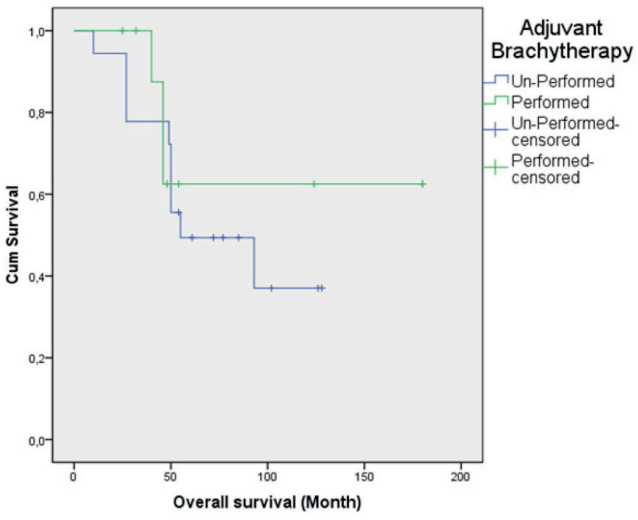

Figure 1. Effect of adjuvant vaginal brachytherapy on overall survival according to Kaplan-Meier curve

Patients with local recurrence who did not receive adjuvant radiation had a better 5-year OS than those who received adjuvant radiotherapy (65% vs. 43%) [6]. In our study, we analyzed whether there was no difference in the mean 5-year OS between patients who received and did not receive VBT (p=0.521), and the rates were 49.4% and 62.5%, respectively. It has been shown in the literature and in our study that adjuvant VBT treatment does not have a positive effect on OS. Therefore, we think that it is appropriate to give it to selected patients with more consideration when adjuvant VBT treatment is given. In the literature, patients with a long disease-free interval have been shown to have better OS [11]. In the present study, Cox regression analysis showed that a short disease-free interval did not have a significant effect on OS. When VBT doses and fractions were evaluated, according to multivariate regression analysis, there was no difference in the risk of vaginal recurrence between the 7.0 Gy 3 fractions prescribed at a 0.5 cm depth, the 6.5 Gy 3 fractions prescribed at a 0.5 cm depth, or the 6.0 Gy 5 fractions [17].

Study Limitations

There are some shortcomings in our study. First, it can be said to be of a retrospective nature. Depending on this, there may be difficulty in remembering and/or missing information in files. Second, it can be concluded that the number of patients was small. Despite these, we believe that our study with a homogeneous case group, such as isolated vaginal recurrence in EC, which is not common, provides important results.

Conclusion

In conclusion, adjuvant VBT did not affect the local recurrence time or OS rate of patients with EC. Considering that the side effects that may occur due to brachytherapy and its deterioration in quality of life are considered, it is recommended not to be given to every patient but to selected patients with

Table 2. Evaluation of risk factors that may affect overall survival among patients with vaginal recurrent endometrial cancer using Cox regression analysis

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Recurrence therapy (resection)	0.5	0.1-1.8	0.312	0.3	0.1-7.1	0.930
Lymph node involvement	4.9	1.2-19.8	0.026	5.1	0.1-17.6	0.367
Deep myometrial invasion	2.3	0.7-7.2	0.126	6.2	0.1-9.8	0.184
Cervical stromal invasion	2.3	0.6-9.0	0.212	3.9	0.1-12.4	0.568
Adnexal invasion	0.1	0.1-10.2	0.899	0.4	0.1-11.4	0.893
Lymphovascular space invasion	1.8	0.5-5.5	0.299	2.5	0.2-5.8	0.126
Vaginal brachytherapy	0.6	0.1-2.4	0.535	6.0	0.4-7.9	0.100
High CA125 (>35)	2.4	0.8-7.6	0.112	2.3	0.1-8.7	0.203
Non-endometrioid type	0.8	0.2-3.2	0.835	0.8	0.1-12.6	0.984
High-grade (3)	1.0	0.6-1.9	0.781	1.3	0.1-14.2	0.920
Stage 2-3	1.6	0.5-5.1	0.393	1.9	0.1-11.3	0.804
Short-term disease-free interval	1.4	0.4-4.8	0.408	2.0	0.1-10.6	0.724

OR: Odds ratio, CI: Confidence interval

a high risk of recurrence, considering its limited effect on OS. In addition, patients who do not receive adjuvant radiotherapy have an additional tool for treatment when recurrence occurs.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Local Ethics Committee (date: 09.12.2022, decision no: 2022/11-44).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Özd., Concept: G.A., P.T.Ö., Design: İ.Ç., Data Collection or Processing: Z.E.Ç., Analysis or Interpretation: K.G., Literature Search: A.Ö., M.S., Writing: V.G.

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Original Article

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Relationship Between Neoadjuvant Chemoradiotherapy Response and Mesorectum Volume in Rectum Cancer

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ABSTRACT

Aim: To investigate the relationship between changes in mesorectum volume (MRV) following neoadjuvant chemoradiotherapy (nCRT) and pathological and clinical response in patients with locally advanced rectum cancer (LARC).

Methods: The study included 39 patients who received nCRT for LARC and underwent surgery between January 2016 and April 2019. The MRV was measured on magnetic resonance imaging (MRI) before and after nCRT. Patients were separated into two groups based on an increase or decrease in MRV following nCRT. The relationships were examined between the 2 groups and the pathological T and N statuses, pre- and post-nCRT T and N statuses, and the degree of MRI regression and pathological regression.

Results: A retrospective analysis was performed on 39 patients, consisting of 19 males and 20 females, with a mean age of 59.3 years (range, 27-80 years). The mean MRV was 116.8 mm^3 (range, 49.9-253.9) before and 115.5 mm^3 (50.9-196.7) after nCRT. There was an increase in MRV in 21 patients and a decrease in 18 patients. In the MRI evaluation, there was no response to nCRT in 4 patients, and in the pathological evaluation, a response could not be determined in 9 patients.

Conclusion: Because this study is one of the first in the literature to investigate the relationship between changes in MRV and response to nCRT, further studies are needed to reach more meaningful results.

Keywords: Rectum cancer, neoadjuvant treatment, mesorectum volume

Introduction

The World Health Organization statistics revealed colorectal cancer to be the second most common malignancy in women (after breast cancer) and the third most common malignancy in men, with a total annual death toll of 861,700 worldwide [1]. One-third of colorectal cancers are rectal cancers. Mesorectal excision after neoadjuvant chemoradiotherapy (nCRT) is the standard treatment for mid- and lower locally advanced rectum cancer (LARC) (T3-4 and/or N+) [2].

The main benefit of nCRT for LARC is to downsize and downstage the tumor to increase the chance of complete resection and obtain better local control [3]. However, several clinical studies have shown extreme variability in the response of LARC to nCRT [4,5]. Although a full pathological and clinical response is achieved with nCRT in approximately 20-30% of patients with rectum cancer, a significant proportion of patients do not respond to nCRT [6-8]. There are many regression grading systems to evaluate the pathological response to nCRT, such as the American Joint Committee on Cancer TRG, Mandard, Dworak, and Ryan Tumor Regression Grading system [9,10]. The Modified Ryan Scheme for Tumor Regression Score is recommended for routine use by the College of American Pathologists [11].

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Another advantage of nCRT is that when a clinical full response occurs, the "watch-and-wait" treatment protocol can be applied as a nonsurgical option [12]. Therefore, recent studies have aimed to radiologically estimate pathological responses [13-16]. Of all the suitable imaging methods, magnetic resonance imaging (MRI) is considered the most appropriate because of its broad routine clinical application in the evaluation of rectum cancer, high soft-tissue resolution, and lack of radiation exposure. Some traditional and functional MRI methods have been reported to show advantages in the prediction of tumor response to nCRT [17-19]. Although it has been reported that T and N status affect the response to nCRT, [20-22] there are few studies have investigated other factors that might have an effect. Therefore, the identification of markers that predict response to nCRT is an important issue in the management of LARC.

Since the variables that determine the response of LARC to neoadjuvant therapy are still unknown, variables that affect the response to therapy are still being investigated. The aim of this study was to investigate the relationship between changes in the mesorectum volume (MRV) measured by MRI before and after nCRT and pathological and radiological response in patients with LARC.

Methods

A retrospective screening was performed for patients who received nCRT and underwent surgery at the Konya Training and Research Hospital due to LARC between January 2016 and April 2019. The study included 39 patients (20 females and 19 males, with a mean age of 59.3 years (range, 27-80 years). The inclusion criteria were sufficient quality of MRIs to evaluate MRV and the T and N statuses before and after nCRT, surgery in the Konya Training and Research hospital after nCRT, and were not determined with distant organ metastasis on thoracoabdominal computed tomography (CT).

The first MRI was performed at the time of diagnosis (pre nCRT) and the second MRI (post nCRT) within 1 week before surgery. Grading of the patients was made using the T and N evaluation criteria on MRI. T3 was evaluated as tumor invasion through the muscularis propria into the subserosa or into non-peritonealized perirectal tissues without reaching the mesorectal fascia or adjacent organs, and T4 was evaluated as tumor invasion directly into other organs or structures and/or perforating the visceral peritoneum. Lymph nodes with unfavorable morphology and diameter >5 mm were evaluated as lymph node involvement. N0 was evaluated as no lymph nodes, N1 as 1-3 suspicious nodes, and N2 as ≥4 suspicious nodes. Thoracoabdominal CT examinations were performed in all patients to evaluate distant organ metastasis.

All patients received the same nCRT protocol. For nCRT 6 cycles of FOLFOX therapy are administered. The external beam radiotherapy dose was 50 Gy delivered in 25 daily fractions of 2 Gy five days a week. Concomitant chemotherapy consisted of oral 5-fluorouracil-derivative capecitabine, 825 mg/m^2 b.i.d. Changes in MRV were evaluated using MRI. Patients were separated into 2 groups according to an increase or decrease in MRV. The statistical relationships were investigated by comparing the changes in MRV with the degree of MRI tumor regression and pathological regression.

MRI Evaluation

The MRIs of the patients before and after nCRT were evaluated by an experienced radiology specialist who was blinded to the clinical information of the patients.

All MRIs were acquired on a 1.5T unit (Magnetom aera, Siemens Healthcare, Germany). MRI scans were performed following a standard protocol with a 16-channel phase array pelvic-receiver coil. The MRI tumor regression grade (MrTRG) was used to evaluate regression on MRI (Table 1). TRGs were evaluated on coronal, axial, and sagittal T2W1 MRIs.

Pathology Evaluation

Tissue samples were processed and embedded in paraffin blocks. Slices 5 m thick were cut from the blocks and stained with hematoxylin and eosin. Using the modified Ryan scheme for histopathological examination, the regression scores were evaluated by an independent, experienced pathology specialist (Table 2).

Mesorectum Volume Evaluation

The MRIs were evaluated by an experienced radiation oncologist using the Eclipse Treatment Planning System version 9.8. The mesorectum contours from the piriformis muscle to the level of peritoneal reflection were drawn manually on axial slices to measure the MRV. The net MRV was calculated by subtracting the rectum volume defined in the same way from the defined volume, and the value was recorded as mm^3.

Statistical Analysis

Data obtained in the study were statistically analyzed using Statistical Package for the Social Sciences version 23.0 software (IBM, Armonk, NY, USA). Continuous measurements were presented as mean±standard deviation, median, minimum, and maximum values, and categorical variables were presented as number (n) and percentage (%). For comparisons

Table 1. Magnetic resonance imaging tumor regression classification

Grade	Definition	Response status
1	No tumor signal, only linear scar	Full response
2	A small amount of residual tumor, but predominant fibrotic low signal intensity	Good response
3	Low signal fibrosis and mixed signal density areas moderate but without tumor predominance	Moderate response
4	Mainly signal intensity and minimal fibrotic low signal intensity	Mild response
5	Fibrosis is not evident; only a tumor signal is present	No response

of categorical variables, the chi-squared test or the Fisher's test was used. Agreement between the pre- and post-nCRT MRI results and the pathological results was evaluated using the intraclass correlation coefficient (ICC), interpreted as r ≥0.91: high correlation, 0.90-0.71: good correlation, 0.70-0.51: moderate correlation, 0.50-0.31: low correlation, and ≤0.30: no correlation. The level of statistical significance was accepted as 0.05 for all tests.

Results

The retrospective analysis included 39 patients (20 females and 19 males, with a mean age of 59.3 years (range, 27-80 years). Rectal cancer was present in the distal section in 19 (48.7%) of the patients, in the mid-section in 14 (35.9%), and in the proximal section in 6 (15.4%). The time from nCRT to surgery was ≤12 weeks in 76.9% (30) of the patients and >12 weeks in 23.1% (9). Mesorectal excision was performed in 29 patients, abdominoperineal resection in 9 patients, and abdominoperineal resection together with vaginectomy in 1. The mean MRV was measured as 116.8 mm^3 before nCRT and as 115.5 mm^3 after nCRT. MRV was found to decrease in 18 patients and increase in 21 (Table 3).

When the pathological regression scores were examined, full response was determined to be full response in 4 patients, and no pathological response in 9. Examination of the MrTRG values revealed almost complete response in 5 patients and no response in 4. Pathological regression evaluations according to the modified Ryan scheme and the MrTRG classifications are shown in detail in (Table 4).

The relationships between radiological T and N status and postoperative T and N status were examined using the ICC values. Agreement with the MRI evaluations was low before nCRT (0.19 and 0.42; 0.50-0.31) and moderate after nCRT (0.63 and 0.64; 0.70-0.51) (Table 5).

Table 2. Modified Ryan scheme

Grade	Definition	Response status
0	No viable cancer cells	Full response
1	Single cells or occasional small groups of	Almost full response
2	Residual cancer with evident tumor regression, but greater than single cells or occasional small groups of cancer cells	Partial response
3	Extensive residual cancer with no evident tumor regression	Poor response or no response

Table 3. Demographic and clinical characteristics of patients

	Mean±SD	Median (minimum-maximum)
Age (years)	59.3±11.6	59 (27-80)
	n (%)	
Gender		
Female	20 (51.3)	
Male	19 (48.7)	
Location		
Distal	19 (48.7)	
Middle	14 (35.9)	
Proximal	6 (15.4)	
Surgical interval (weeks)		
<12	30 (76.9)	
>12	9 (23.1)	
Surgery performed		
TME	29 (74.4)	
APR	9 (23.1)	
APR+vaginectomy	1 (2.6)	
MRV		
Decreased	18 (46.2)	
Increased	21 (53.8)	
	Mean±SD	**Median (minimum-maximum)**
Pre-nCRT MRV (mm^3)	116.8±43.7	110.8 (49.9-253.9)
Post-nCRT MRV (mm^3)	115.5±36.9	108.4 (50.9-196.7)
MRV difference	-1.36±28.6	2.7 (-72-62.4)

SD: Standard deviation, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy

The relationships were examined of the increase or decrease in MRV after nCRT with gender, tumor localization, time to surgery, pathological T and N statuses, pre- and post-nCRT MRI T and N statuses, modified Ryan scores and MrTRG were examined. No statistically significant correlation was observed between the variables examined and the changes in MRV ($p>0.05$). The findings are shown in detail in (Table 6).

The relationship between pre- and post-nCRT MRV values and the pathological and radiological response was evaluated by re-classifying patients with grades 0, 1, and 2 in the modified Ryan scheme as pathological response present, and no response in those with grade 3, and radiological response present in patients with grades 1, 2, 3, and 4, and no response in those with grade 5. No statistically significant differences were found between pre- and post-nCRT MRV and pathological response. The relationship between pre- and post-nCRT MRV values and radiological response was found to be more significant than the pathological response, but at $p=0.2$, the difference was not statistically significant in either group (Table 7).

Table 4. Distribution of MrTRG and modified Ryan scores of patients

	n (%)
Modified Ryan score	
0	4 (10.3)
1	8 (20.5)
2	18 (46.2)
3	9 (23.1)
MrTRG	
1	5 (12.8)
2	7 (17.9)
3	13 (33.3)
4	10 (25.6)
5	4 (10.3)

MrTRG: Magnetic resonance imaging tumor regression grade

Discussion

Predicting the pathological response to nCRT in the preoperative period is important for determining which patients can be followed up without surgery under a "watch-and-wait" protocol. In surgeries performed after nCRT, a temporary or permanent ostomy is opened in most patients, which has negative effects on quality of life. Various clinical parameters were used to estimate the pathological response to nCRT. There are studies in the literature that have examined the relationship of response to nCRT with clinical parameters, such as tumor size, distance to the anal verge, and T and N status [20-25]. Although various studies have found a relationship between tumor size and response to nCRT, different methods were used in those studies to evaluate tumor size such as endorectal ultrasound, digital rectal examination and flexible endoscopy [20-24]. The relationship between distance to the anal verge and response to nCRT has not been fully clarified, and its value as a predictive marker is unclear [25,26]. Although a full clinical and pathological response after nCRT has been observed more frequently in T1-2 tumors, this rate has been shown to be lower in lymph node positivity [20-22]. Moreover, only examining T and N status is insufficient for individual patient response evaluation.

There are studies in the literature that have aimed to predict which patients will respond to nCRT with imaging methods in LARC. MRI radionic features of mesorectal fat can be used to predict pathological complete response, local and distant recurrences, and T and N categories after treatment [14,15]. To the best of our knowledge, this study is one of the first to investigate the role of MRV changes in the estimation of pathological response to nCRT in the treatment of LARC.

In a previous study that evaluated the relationship between mesorectal fatty tissue volume and response to nCRT, it was shown that when MRV exceeded 69.4 mL, the rates of pathological response increased [13]. In that study, the median MRV value was found to be 85.7 mm^3 (21.2-269.0), whereas in the current study, the MRV values measured with

Table 5. Compatibility of pathology data with MRI evaluations before and after nCRT

	Pathology	Pre-nCRT MRI	Post-nCRT MRI	Interclass correlation (95% CI)	
	n (%)	n (%)	n (%)	Pat&PreMR	Pat&PostMR
T					
T0	7 (17.9)	-	4 (10.3)	0.19 (-0.51-0.58)	0.63 (0.29-0.80)
T1	4 (10.3)	-	7 (17.9)		
T2	9 (23.1)	11 (28.2)	16 (41.0)		
T3	16 (41.0)	25 (64.1)	11 (28.2)		
T4	3 (7.7)	3 (7.7)	1 (2.6)		
N					
N0	28 (71.8)	9 (23.1)	26 (66.7)	0.42 (-0.10-0.70)	0.64 (0.30-0.81)
N1	6 (15.4)	22 (56.4)	9 (23.1)		
N2	4 (10.3)	8 (20.5)	4 (10.3)		
N3	1 (2.6)	-	-		

MRI: Magnetic resonance imaging, CI: Confidence interval, nCRT: Neoadjuvant chemoradiotherapy

Table 6. Relationships between variables and increase/decrease in mesorectum volume

	MRV decreased	MRV increased	p
	n (%)	n (%)	
Gender			
Female	10 (55.6)	10 (47.6)	0.751
Male	8 (44.4)	11 (52.4)	
Tumor localization			
Distal	11 (61.1)	8 (38.1)	0.356
Mid	5 (27.8)	9 (42.9)	
Proximal	2 (11.1)	4 (19.0)	
Surgical interval (weeks)			
<12	12 (66.7)	18 (85.7)	0.255
>12	6 (33.3)	3 (14.3)	
ypT			
ypT0	4 (22.2)	3 (14.3)	0.962
ypT1	2 (11.1)	2 (9.5)	
ypT2	4 (22.2)	5 (23.8)	
ypT3	7 (38.9)	9 (42.9)	
ypT4	1 (5.6)	2 (9.5)	
ypN			
ypN0	15 (83.3)	13 (61.9)	0.132
ypN1	2 (11.1)	4 (19.0)	
ypN2	0 (0.0)	4 (19.0)	
ypN3	1 (5.6)	0 (0.0)	
Modified Ryan score			
0	3 (16.7)	1 (4.8)	0.619
1	4 (22.2)	4 (19.0)	
2	7 (38.9)	11 (52.4)	
3	4 (22.2)	5 (23.8)	
MrTRG			
1	2 (11.1)	3 (14.3)	0.601
2	5 (27.8)	2 (9.5)	
3	6 (33.3)	7 (33.3)	
4	4 (22.2)	6 (28.6)	
5	1 (5.6)	3 (14.3)	
MRI T before nCRT			
T2	4 (22.2)	7 (33.3)	0.617
T3	13 (72.2)	12 (57.1)	
T4	1 (5.6)	2 (9.5)	
MRI N before nCRT			
N0	5 (27.8)	4 (19.0)	0.388
N1	11 (61.1)	11 (52.4)	
N2	2 (11.1)	6 (28.6)	
MRI T after nCRT			
T0	2 (11.1)	2 (9.5)	0.352
T1	5 (27.8)	2 (9.5)	
T2	5 (27.8)	11 (52.4)	
T3	6 (33.3)	5 (23.8)	
T4	0 (0.0)	1 (4.8)	
MRI N after nCRT			
N0	11 (61.1)	15 (71.4)	0.301
N1	6 (33.3)	3 (14.3)	
N2	1 (5.6)	3 (14.3)	

MrTRG: Magnetic resonance imaging tumor regression grade, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy

MRI were 110.8 mm^3 before nCRT and 108.4 mm^3 after nCRT. The difference between the values in these two studies was attributed to the measurement with MRI in the current study and with CT in the previous study, and no clear criteria have been determined for MRV measurement.

Some studies have shown that surgical outcomes after colon cancer surgery are related to the visceral fatty area rather than BMI [27-30]. In a study that investigated the clinical importance of mesorectal fatty tissue, it was shown that as the mesorectal fatty area (cm^2) increased, survival increased [31]. Survival analysis was not performed in the current study, and as the mesorectal surface area was not considered to be more important, the MRV measurement was performed as a 3-dimensional measurement.

As the number of patients in this study was low in each of the MrTRG grade and modified Ryan grade groups, the patients were classified as those with and without a pathological response, and the relationship between the MRI findings and the increase or decrease in MRV was evaluated. However, there was still not found to be any statistically significant relationship between the groups.

A moderate-level correlation was determined between the pathological ypT and ypN values and the T and N statuses evaluated by MRI after nCRT. It can be considered that future studies with larger patient populations will be able to reach higher correlation values, and thus, statistically significant results will emerge.

Although no statistically significant difference was found in this study, it is important to examine the relationship between changes in MRV and both postoperative T and N status, as well as the clinical regression grade values (MrTRG and Ryan regression grade).

Table 7. Relationship of MRV with pathological and radiological response

	Pathological response (+) Mean±SD	Pathological response (-) Mean±SD	p	MRI response (+) Mean±SD	MRI response (-) Mean±SD	p
Pre-nCRT MRV (mm^3)	118.3±43.8	111.9±45.3	0.7	119.9±44.9	89.3±103	0.2
Post-nCRT MRV (mm^3)	117.6±39.6	108.3±26.9	0.5	117.8±38.1	94.6±13.5	0.2

MrTRG: Magnetic resonance imaging (MRI) tumor regression grade, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy SD: Standard deviation

Study Limitations

The limitations of this study could be said to be that there was no analysis of total body fat volume, subcutaneous fat volume, visceral fat volume, and BMI values, the patient population was small, there is no standardization in MRV measurements, and it will be better to have two reviewers who can independently evaluate the MRIs and pathologies.

Conclusion

In conclusion, although no significant relationship was determined between the increase or decrease in MRV and the response to nCRT, this is the first study to investigate this subject. There is a need for further studies with larger patient groups and using different imaging techniques, which will help overcome the limitations of this study and better reflect the importance of changes in MRV.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Konya Training and Research Hospital (decision no: 27-08, date: 04.07.2019) and conformed to the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: R.S.K., E.E., O.D., Design: R.S.K., E.E., O.D., Data Collection or Processing: R.S.K., E.E., M.S., Analysis or Interpretation: İ.K., Literature Search: R.S.K., E.E., M.S., İ.B., B.T., Writing: R.S.K., E.E.

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Original Article

Cognitive Impairment in Caregivers of Cancer Patients: A Cross-sectional Study

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ABSTRACT

Aim: Cancer caregivers (CCG) is crucial in well-being of patients with cancer. They are responsible for making cognitively demanding decisions that affect patients' welfare. In this study, we aimed to evaluate the cognitive impairment of CCG and compare with non-CCG.

Methods: This cross-sectional study focused on CCG and non-CCG patients at a university hospital. Caregiver-reported outcomes were measured by mini-mental state examination (MMSE).

Results: A total of 217 caregivers were included. 122 (56.3%) were in the CCG group and 95 (43.7%) were in the non-CCG group. The median age of the caregivers was 46.6 (20-76) years, and 56.6% were female. Education level was significantly higher among CCG (64.7 vs 29.5%, p<0.001). Mean MMSE scores were 27.9 and 24.2 for the non-CCG and CCG groups, respectively, corresponding to 0% and 40.1% of caregivers in the non-CCG and CCG groups with cognitive impairment. The mean difference in MMSE scores was statistically significant in all areas of cognitive function (p<0.001). In the CCG group with cognitive impairment, 15 and 40 patients had mild and moderate cognitive impairment. Cognitive impairment based on the MMSE was significantly associated with old age (p=0.006) and lower education level (p=0.001).

Conclusion: This study revealed that cognitive impairment in CCGs is not uncommon. Because caregivers are decision makers during most of the disease processes of patients with cancer, any deterioration in their cognitive reserve should be checked to maintain optimal care for patients.

Keywords: Caregiver, cancer, cognitive impairment, mini-mental state examination

Introduction

The survival rate of cancer is increasing daily with the introduction of new treatment modalities. Patients live longer due to the psychological, social, and physical burden of the disease and treatment. Informal caregivers are non-professional, unpaid caregivers of patients who share this burden. They are usually individuals from the family setting or friends who take on different roles secondary to physical or cognitive impairment of the patient [1]. According to a caregiving report in the United States published in May 2020, cancer is the 2nd common illness for which a caregiver is needed [2].

Informal caregivers of patients with chronic diseases take on many responsibilities, such as cooking, traveling, scheduling, hospital policies, and economic difficulties, and, most importantly, deciding between treatment options. It has been found that cancer caregivers (CCG) are more likely to co-reside with patients and provide care for approximately 33 hours weekly and help in different types of activities of daily living (getting in and out of a bed, chair, or toilet and feeding) [3,4]. Thus, it is important to evaluate informal caregivers' cognitive abilities to determine whether they are capable of making decisions on behalf of patients with cancer [5]. Their health can be affected in the long term because of increasing stress, causing changes in neurohormonal and inflammatory

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processes [6]. When caregivers' quality of life deteriorates, especially their mental health, optimal support and long-term care may be compromised. This may even affect patient treatment. Since the course of a disease differs among cancer patients and clinical deterioration can progress more rapidly, caregiving may differ from other chronic diseases [7].

The mini-mental state examination (MMSE) is one of the most widely used screening tests for identifying cognitive impairment. It was first developed by Folstein et al. [8] in 1975 and has since been widely used in research and clinical settings. Although designed for identifying cognitive impairment, it is mostly used in clinical practice to identify dementia and Alzheimer disease. To our knowledge, no previous studies have evaluated the cognitive status of caregivers using the MMSE.

Herein, we aimed to evaluate the cognitive impairment of cancer caregivers and compare it with that of caregivers of patients with a chronic disease other than cancer (non-CCG) using the MMSE.

Methods

Study Design

This prospective cross-sectional study was conducted at a university hospital. The Acıbadem University Local Ethics Committee approved the study protocol on 17.09.2020 (approval number: ATADEK-2020-20/5, date: 17.09.2020). Caregivers and patients were informed about the study. After receiving informed consent from the volunteering caregivers, questionnaires were conducted face-to-face by clinical nurses under supervision of a doctor in the hospital's daily chemotherapy and endocrinology clinic.

Participants

The eligibility criteria for cancer caregivers were as follows; aged <18 years; caring for a patient with cancer under treatment; not having any hearing abnormalities, any known psychological or central nervous system disorder, or any history of cancer; and not undergoing active treatment that could influence cognitive abilities. The control group, caregivers of patients receiving treatment for a chronic endocrinological disorder were included. Information about the caregivers was obtained from the caregivers themselves. The demographic and clinical characteristics of the patients and their treatment schedules were obtained from their medical records.

In the cancer group, targeted treatments received by patients were defined as anti-vascular endothelial growth factor therapy, anti-endothelial growth factor therapy, and anti-HER2 therapy. Hormone treatment was defined as antiandrogen and antiestrogen therapy. The endocrinological group comprised patients with hypothyroidism, diabetes mellitus, adrenal insufficiency, and Cushing's syndrome.

Assessments and Tools

Cognitive performance was assessed using the MMSE. A validated Turkish version of the MMSE was used [9]. The MMSE comprises 11 questions. It measures registration, attention, calculation, recall, language, and orientation functions. Administration of the test takes 5-10 minutes. Cognitive impairment was defined as an MMSE score 24. Severe, moderate, and mild cognitive impairment were defined as MSSE scores under 9, 10-18, and 19-23, respectively.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 25.0 (IBM, Armonk, New York, USA). Continuous variables were compared using the independent samples t-test and Mann-Whitney U test. Binary logistic regression analysis was performed to determine the odds ratio for predictive factors. Pearson's correlation test was used to evaluate correlations between continuous variables. P value of <0.05 was accepted as indicative of statistical significance.

Results

A total of 217 caregivers were included in the study. Of these, 122 (56.3%) were classified into the CCG group, and 95 (43.7%) were classified into the non-CCG group. The median age of the caregivers was 46.6 (20-76) years, and 56.6% were female. The detailed demographic and clinical characteristics of the caregivers are presented in Table 1. Education level was significantly higher among CCG (64.7 vs 29.5%, p<0.001). A total of 64.7% of patients in the CCG group and 29.5% of patients in the non-CCG group had a university degree or higher. Most of the relatives of patients with cancer were spouses (35.2%) or children (29.5%), whereas in the non-CCG group, the majority were spouses (45.3%) and parents (24.2%) (p<0.001). Patients were mainly diagnosed with breast cancer (n=39, 31.9%), gastrointestinal cancer (n=28, 22.9%), and lung cancer (n=23, 18.8%). The time since diagnosis was less than a year for most of the patients (n=59, 48.3%), and most patients had stage 4 disease (n=78, 63.9%). The Eastern Cooperative Oncology Performance Status of patients were 0-1 for 76% of the patients. The demographic and clinical characteristics of patients with cancer are presented in Table 2.

The mean MMSE scores were 27.9 and 24.2 in the non-CCG and CCG groups, respectively. Cognitive impairment was not observed in the non-CCG group, whereas 40% of the CCG group exhibited cognitive impairment. The mean difference in MMSE scores was statistically significant in all areas of cognitive function (p<0.001, Table 3). Figure 1 shows boxplots of scores according to MMSE components. Language subscale scores were significantly different between the two groups.

Regarding the CCG group with cognitive impairment, 40 patients had mild impairment (MCI) while 15 had moderate cognitive impairment. According to the univariate analysis, cognitive impairment based on the CCG on the MMSE was statistically associated with old age (p=0.006) and lower education level (p=0.001, Table 4). Multivariate analysis was performed to identify independent predictors of cognitive impairment. Education level (p=0.009) was found to be the only predictor of cognitive impairment.

Table 1. Demographic and clinical characteristics of caregivers

	Non-CCG (n=95)	CCG (n=122)	p
Age (min.-max.)	47.2 (20-76)	46.2 (20-72)	0.724
Sex			
Female	48 (50.5%)	75 (61.5%)	0.106
Male	47 (49.5%)	47 (38.5%)	
Social status			
Single/divorced	18 (19%)	32 (26.2%)	0.448
Married	77 (81.1%)	90 (73.8%)	
Level of education			
Uneducated	1 (1.1%)	3 (2.5%)	**<0.001***
Primary school	29 (30.5%)	7 (5.7%)	
Secondary school	8 (8.4%)	9 (7.4%)	
High school	29 (30.5%)	24 (19.7%)	
University	25 (26.3%)	63 (51.6%)	
Postgraduate	3 (3.2%)	16 (13.1%)	
Occupation			
Employed/student	36 (37.9%)	50 (41%)	0.644
Unemployed/retired	59 (62.1%)	72 (59%)	
Chronic disease			
Present	26 (27.4%)	22 (18%)	0.100
Absent	64 (72.6%)	100 (82%)	
Relationship with the patient			**<0.001***
Parents	23 (24.2%)	7 (5.7%)	
Siblings	5 (5.3%)	14 (11.5%)	
Children	14 (14.7%)	36 (29.5%)	
Partners	43 (45.3%)	43 (35.2%)	
Others	10 (10.5%)	22 (18.0%)	

*p value <0.05.
CCG: Cancer caregivers, Min.-max.: Minimum-maximum

Table 2. Demographic and clinical characteristics of patients with cancer

		n (%)
Age (years)	Min.-max.	56 (28-80)
Sex	Female	75 (61.4)
	Male	47 (38.5)
Time since diagnosis	≤12 months	59 (48.3)
	12-24 months	21 (17.2)
	≥24 months	42 (34.4)
ECOG	0	46 (37.7)
	1	46 (37.7)
	2	27 (22.1)
	3	3 (2.4)
Stage	1	14 (11.4)
	2	16 (13.1)
	3	14 (11.4)
	4	78 (63.9)
Treatment type	Chemotherapy	72 (59)
	Chemotherapy+targeted therapy	18 (14.7)
	Immunotherapy	6 (4.9)
	Hormone treatment	13 (10.6)
	Targeted therapy	13 (10.6)

ECOG: Eastern Cooperative Oncology Group, Min.-max.: Minimum-maximum

Table 3. MMSE scores of caregivers

	Non-CCG (n=95)	CCG (n=122)	p
Orientation	9.99±0.103	9.24±1.068	**<0.001***
Registration	3.04±0.459	2.67±0.787	**<0.001***
Attention and calculation	4.68±0.593	3.20±1.872	**<0.001***
Recall	2.83±0.519	2.22±0.838	**<0.001***
Language	8.96±0.202	6.84±1.410	**<0.001***
Total	29.40±1.086	24.17±4.111	**<0.001***
CI (total score <24)	0 (0%)	49 (40.1%)	**<0.001***

*p value <0.05.
CI: Cognitive impairment, MMSE: Mini-mental state examination, CCG: Cancer caregivers

The variables were further analyzed using binomial logistic regression models to understand their predictive value for MCI among cancer caregivers. Patients with a university degree or higher education were 59% less likely to have cognitive impairment. Caregivers that were children were 92% less likely to suffer from cognitive impairment. Chemotherapy was associated with a 71% decreased risk of MCI among the different treatment modalities.

Discussion

In this study, we aimed to assess cognitive impairment among cancer caregivers. The MMSE was used to evaluate cognitive impairment, which, to our knowledge, is the first study to use the mini-mental test as a screening tool among caregivers. The MMSE scores of cancer caregivers were lower than those of non-cancer caregivers in all aspects, indicating higher cognitive impairment among CCGs. Most patients in the CCG group suffered from mild cognitive impairment, with scores between 19 and 24. Language was the most impaired area in the MMSE scores of CCGs. Education and age were found to be predictors of cognitive impairment.

The MMSE is a commonly preferred test to screen cognitive mental status in the elderly population, with an estimated sensitivity and specificity of 85-92% and 85-93%, respectively [10]. Although it cannot be used for making formal diagnoses, it is used as the first step in detecting cognitive impairment [11]. Cognitive impairment is defined as trouble concentrating, learning new things, and making everyday life decisions. Although impairment has been proven in caregivers of patients with dementia or stroke, cognitive dysfunction in CCGs is a less frequently examined field [12,13]. In our study, MCI seen in 40% of CCGs is noteworthy. The statistically significant difference in MMSE scores between the two caregiver groups also demonstrates the high disease burden on CCGs. Unlike non-CCGs, CCGs spend approximately 35

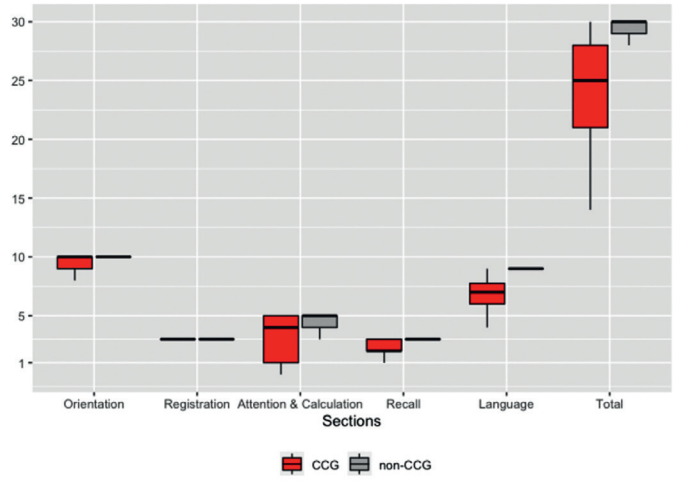

Figure 1. Boxplots of MMSE scores in the CCG and non-CCG groups
MMSE: Mini-mental state examination, CCG: Cancer caregivers

Table 4. Predictive factors of cognitive impairment in the CCG group

	Score ≤24 (n=55)	Score >24 (n=67)	p
Age (years)**	49.7±11.5	43.4±12.8	**0.006**
Sex (male)**	18 (32.7%)	29 (43.3%)	0.233
Marital status**	43 (78.2%)	47 (70.1%)	0.136
Education level of university students**	27 (49.1%)	52 (77.6%)	**0.001**
Comorbidities**	14 (25.5%)	8 (11.9%)	0.053
Relatedness (first degree)**	13 (23.6%)	30 (44.8%)	**0.015**
Sex (male)***	21 (38.2%)	25 (37.3%)	0.922
Age (years) ***	54 (23%)	57 (21%)	0.265
Stage 4 disease	35 (66.1%)	43 (64.2%)	0.832
ECOG***	22 (40%)	24 (35%)	0.459
Mean time after diagnosis*** (month)	14 (29%)	12 (34%)	0.451
Polypharmacy***	6 (10.9%)	14 (20.9%)	0.138

*p<0.05.
ECOG: Eastern Cooperative Oncology Group**, Characteristics of caregivers*** Characteristics of patients, CCG: Cancer caregivers

hours a week on the patient's daily activities [14]. This may cause them to withdraw from social life, have a negative impact on relationships, experience loss of communication, and thus weaken their cognitive functions. Therefore, the mild and moderate cognitive impairment observed among cancer caregivers may be the result of caregiver burden, leading to decreased quality of life and interference with the capacity of caregivers to provide optimal care [15]. High cortisol levels and stress, which are used to explain cognitive dysfunction in patients with dementia, may also affect CCG levels [16].

The effect of MMSE scores on dementia prediction is well known. However, cognitive dysfunction, apart from dementia, may be a primary indicator of functional impairment in major depressive disorder [17]. The global prevalence of depression among CCGs across studies was 42.08%, and a subgroup analysis showed that the pooled prevalence of depression in studies that used a cross-sectional study design (42%), like our study, was higher than that in studies with a longitudinal study design (34%) [18]. Sleep disturbances and fatigue may also affect cognitive impairment, which can be observed in CCGs. However, when the secondary causes of cognitive dysfunction are excluded, cognitive dysfunction becomes a core component of depressive disorder. Thus, learning, memory, executive functioning, processing, and attention/concentration may be significantly impaired [19]. Antidepressants and/or pharmacotherapy can improve residual cognitive function [20]. Thus, caregivers diagnosed with cognitive impairment may be referred for treatment.

Education level and age were found to be predictors of cognitive impairment. Studies have shown that mild cognitive impairment affects quality of life [21]. In a study by Decadt et al. [22], caregiver age and education level were not associated with decreased quality of life or increased stress. However, the relationship between patient and patient's diagnosis were significantly related to distress levels. In contrast, Kilic and Oz [23] found that gender, education level, and relationship to the patient were significantly associated with quality of life. Education level and employment status are closely related to an individual's ability to communicate and cope with stress. Unemployed caregivers spend more time with patients, affecting their cognitive status and mood and increasing their susceptibility to depression. Finding age as a predictor of cognitive impairment was expected because cognitive changes occur even with normal aging. This also explains the decreased risk of impairment observed when the caregiver is the child of the patient.

Study Limitations

The study has several limitations. The MMSE scores were not interpreted in consideration of age and education norms. The MMSE also has several disadvantages, such as a lack of exploration of all cognitive domains. The possible reasons for the low MMSE scores in the CCG group, such as depression, sleep problems, and dementia, were not examined. Owing to the cross-sectional study design, potential changes over time may be confounding factors of lower MMSE scores among CCGs. Longitudinal studies are needed to understand how caregiver outcomes evolve. Third, the disease burden of the control group may be lower than that of patients with cancer, which may interfere with the reliability of the comparison. Lastly, the sample size is small, which may explain the lack of influence of patient factors on cognitive impairment among caregivers.

Our results are worth attention for healthcare professionals to better address cancer caregivers that are in need of support during patient's active treatment. The MMSE, which is an easily applicable test, can be incorporated into caregiver distress screening methods because cognitive impairment can be a sign of depression.

Conclusion

Most patients with cancer seek physical or psychological support, which is generally provided by their informal caregivers. Thus, the cognitive functioning of CCGs is significant because they make many decisions on behalf of the patient. Our study, which is the first to use MMSE in caregivers, emphasizes that cognitive assessment among caregivers is worth noting because cognitive impairment in CCGs is not an uncommon symptom and may interfere with the well-being of patients. Interventions should be developed to reduce the psychosocial and psychological burden of caregiving that causes cognitive decline in CCG patients.

Ethics

Ethics Committee Approval: The Acıbadem University Local Ethics Committee approved the study protocol on 17.09.2020 (approval number: ATADEK-2020-20/5, date: 17.09.2020).

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

Authorship Contributions

Surgical and Medical Practices: A.Y., Ö.O., Concept: A.Y., Design: A.Y., Data Collection or Processing: A.Y., M.K., E.S., B.O., G.B., Ö.S., S.Y.H., Ö.O., Analysis or Interpretation: A.Y., Ö.O., Literature Search: E.Ş.T., Writing: E.Ş.T.

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Original Article

Evaluation of Patients with *Staphylococcus aureus* Bacteriuria Over a Three-year Period in an Oncology Hospital

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ABSTRACT

Aim: *Staphylococcus aureus* bacteriuria (SABU) is encountered in patients with long-term care, urologic abnormalities, older age, and comorbidities. SABU may be caused by contamination, colonization, asymptomatic bacteriuria, urinary tract infection (UTI), or invasive disease, but its clinical relevance and therapy are unclear. This study evaluated individuals with *S. aureus* isolated via urine culture at an oncology hospital.

Methods: Eighty-two patients with *S. aureus* urine isolation were studied retrospectively. Age, sex, clinical data, and laboratory results were evaluated. Concurrent *S. aureus* bacteremia (SAB) development was also determined.

Results: Of the patients, 52% were male and 48% were female. Overall, 63.4% of the patients had cancer. Among these patients, 39.02% had genitourinary cancer, 8.53% had gastrointestinal cancer, 6.09% had breast cancer, 2.43% had respiratory tract cancer, 2.43% had lymphoma, 1.21% had acute myeloid leukemia, and 3.65% had other cancers (brain, bone, and soft tissue). Moreover, 68.2% of the patients had urological abnormalities, and 18.2% had urinary catheters. Moreover, 39.02% of *S. aureus* were resistant to methicillin. The average C-reactive protein level in SABU patients was 62.17 mg/L and procalcitonin was 0.3656 ng/mL. Five of the SABU patients (6.09%) had simultaneous *S. aureus* in their blood cultures, and all of the infections were secondary to bacteriuria and seeding following urological instrumentation/catheterization.

Conclusion: Urological abnormalities/cancers and urinary catheter use were significant underlying factors of SABU. The differential diagnosis of SABU should be based on clinical/laboratory data and presence of pyuria. To avoid unnecessary antibiotic use, repeated urine and blood cultures may be useful for guiding clinicians about the use of SABU.

Keywords: *Staphylococcus aureus,* bacteriuria, methicillin resistance

Introduction

Staphylococcus aureus infections are a significant cause of mortality and morbidity in immunosuppressed patients. *S. aureus* is present in about 20-30% of the nose and skin of healthy adults. These percentages are higher for hospitalized patients and hospital staff. *S. aureus* infections range from mild to life-threatening infections, including skin infections, abscesses, bacteremia, endocarditis, osteomyelitis, and pneumonia. *S. aureus* can also accumulate and cause biofilm formation on medical devices, including artificial heart valves or joints, heart pacemakers, and catheters [1].

S. aureus is also a rare cause of urinary tract infection (UTI). According to the literature, *S. aureus* bacteriuria (SABU) is isolated in approximately 0.2-4% of urinary cultures. SABU is encountered in patients with long-term care, catheterization, urologic abnormalities and procedures, older age, and comorbidities [1]. It is not clear the clinical significance of SABU and the treatment decision due to the possibility that it may be caused by contamination, colonization, asymptomatic

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bacteriuria, primary UTI, or the manifestation of an invasive disease. There is a relationship between SABU and *S. aureus* bacteremia (SAB) and invasive staphylococcal disease [1]. The management of SABU was an unrecognized entity. For this reason, this study aimed to evaluate patients with *S. aureus* isolated via urine cultures in an oncology hospital and to contribute to appropriate therapy or control of *S. aureus* UTIs with or without bacteremia.

Methods

Our study included 82 adult (≥18 years old) with *S. aureus* urine isolation who were admitted or hospitalized at University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 1, 2020, and July 1, 2023. Patient data were analyzed retrospectively. This study was conducted with the permission of the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Local Ethics Committee (research no.: 2023-12/128, date: 11.01.2024). Demographic characteristics (age, gender) and clinical data (presence of hospital or community acquired infection, comorbidity, cancer, urinary stone history, urinary catheter use), and laboratory reports [bacterial culture, antibiogram, serum C-reactive protein (CRP) and procalcitonin levels] of the patients were analyzed. Antibiotic sensitivities to *S. aureus* and the number of leukocytes in the complete urinalysis were also evaluated. Data were collected on blood cultures obtained within three months from urine samples and any positive blood cultures obtained within one year. Among patients with more than one culture positivity, only the first positive sample was included in this study. Patients with signs of infection other than SABU and/or SAB infection were excluded from the study.

Urine and nephrostomy samples were sent to the microbiology laboratory and inoculated into 5% sheep blood agar and eosin methylene blue agar media and evaluated after overnight incubation by detecting bacterial colony numbers (CFU/mL). Blood samples were inoculated into blood culture bottles and incubated in an Autobio BC120 device (Autobio-diagnostic, China). An automated system (VITEK, Biomerioux, France) and conventional methods were used for the typing of microorganisms and antibiotic susceptibility tests. The antibiotic susceptibility results were evaluated according to European Committee on Antimicrobial Susceptibility Testing criteria [2]. SABU was defined as "the detection of *S. aureus* in a urine sample, independent of co-detected pathogens" [1,3]. The analyses of the contingency tables were performed using the chi-square test.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) (version 26) (SPSS Inc., Chicago, IL, USA) and expressed as numbers, percentages, medians, minimums, and maximums.

Results

S. aureus was isolated from the urine of 82 patients. Among the included patients, 43 (52%) were male and 39 (48%) were female. The age of the patients ranged from 0 to 90 years old, and the average age was 53.84. The sample distribution was as follows: 74 (90.25%) mid-stream urine samples and eight (9.75%) nephrostomy samples. Among the included patients, 22 (26.82%) were inpatients and 60 (73.17%) were outpatients. The antibiotic susceptibilities of the patients are presented in Table 1.

All inpatients (n=22, 26.82%) had health care-related infections according to the Centers for Disease Control and Prevention criteria [4]. In total, 43 (52%) patients had a symptomatic UTI.

The comorbidity status of the 82 patients was evaluated: 24 (29.26%) had bladder or kidney disease (hydronephrosis, ureter anomalies, ureteral stones, bladder stones), 20 (24.39%) had benign prostatic hyperplasia, 13 (15.85%) had hypertension, 10 (12.19%) had a history of kidney stones, nine (10.97%) had diabetes mellitus, three (3.65%) had renal cysts, and two (2.43%) had a central catheter. The immunosuppressive status of the patients was as follows: 17.07% (14/82) prostate cancer, 8.53% (7/82) bladder malignant neoplasm, 7.31% (6/82) cervix cancer, 6.09% (5/82) breast cancer, 3.65% (3/82) ovary cancer, 3.65% (3/82) stomach cancer, 2.43% (2/82) kidney cancer, 2.43% (2/82) rectum/colon cancer, 2.43% (2/82) lymphoma, 1.21% (1/82) esophagus malignant neoplasm, 1.21% (1/82) acute myeloid leukemia, 1.21% (1/82) anal canal malignant neoplasm, 1.21% (1/82) soft tissue tumor, 1.21% (1/82) lung cancer, 1.21% (1/82) brain tumor, 1.21% (1/82) larynx tumor, 1.21% (1/82) bone and connective tissue tumor. In total, 63.4% (52/82) of the patients had cancer. A total of 56 (68.2%) of the patients had urological abnormalities, and 15 patients (18.2%) had urinary catheter use.

Colony counts were $>10^5$ CFU/mL in 45% (37/82) of the urine samples. Among the *S. aureus* isolates from urine, 39.02% (32/82) were resistant to methicillin. Antibiotic susceptibilities were as follows: benzyl penicillin, 11.11% (4/36); levofloxacin, 77.27% (34/44); fosfomycin, 85.71% (42/49); ciprofloxacin, 85.29% (29/34); nitrofurantoin, 96.49% (55/57), trimethoprim-sulfamethoxazole 97.53% (79/81); and linezolid, 100% (64/64). All isolates were susceptible to vancomycin and teicoplanin.

The urinalysis results of patients with SABU indicated that white blood cell count ranged between 0 and 220.6 white blood cell/HPF; the mean was 152.46. The serum CRP levels ranged from 0.38 to 299.25 mg/L; the average was 62.17. Patients' procalcitonin levels in serum ranged from 0.019 to 6.31 ng/mL, (average 0,3656). SABU+SAB patients' CRP levels in serum ranged from 66.06 to 208 mg/L, (average 142.6). Patients' procalcitonin levels in serum ranged from 0.146 to 6.31 ng/mL, (average 1.43). Patients with symptomatic UTI were more likely to have significant pyuria than those who were asymptomatic (p=0.013).

Of the 82 patients with *S. aureus* in their urine samples, five hospitalized patients (6.09%) had simultaneous *S. aureus* growth in their blood cultures. All cases (5/5) occurred after urological instrumentation or catheterization and is considered secondary to seeding from bacteriuria. The characteristics of patients with simultaneous S. aureus infection in their blood cultures are presented in Table 2.

Table 1. Antibiotic susceptibility of patients according to distribution to patient situation (inpatient/outpatient)

Patient situations	Benzyl penicillin (%)	Levofloxacin (%)	Fosfomycin (%)	Ciprofloxacin (%)	Nitrofurantoin (%)	Trimethoprim-sulfamethoxazole (%)	Linezolid (%)	Vancomycin (%)	Teicoplanin (%)
Inpatient	3/22 (13.63)	8/12 (66.66)	12/14 (85.71)	8/12 (66.66)	13/15 (86.66)	20/22 (90.90)	20/20 (100)	22/22 (100)	22/22 (100)
Outpatient	1/14 (7.14)	26/32 (81.25)	30/35 (85.71)	21/22 (95.45)	42/42 (100)	59/59 (100)	44/44 (100)	60/60 (100)	60/60 (100)
Total	4/36 (11.11)	34/44 (77.27)	42/49 (85.71)	29/34 (85.29)	55/57 (96.44)	79/81 (97.53)	64/64 (100)	82/82 (100)	82/82 (100)

Table 2. Characteristics of patients with *Staphylococcus aureus* bacteriuria and simultaneous *S. aureus* growth in blood cultures

No	Age	Gender	Comorbidity	Cancer	Urinary catheter	CRP (mg/L)	Procalcitonin (ng/mL)	WBC urine (WBC/HPF)	Methicillin susceptibility
1	42	Female	History of stones	Cervix neoplasm	Yes	146.47	0.264	11	Susceptible
2	68	Male	No	Bladder malignant neoplasm	Yes	66.06	0.279	40	Susceptible
3	69	Female	History of diabetes and urinary stones	No	Yes	197	6.31	312	Susceptible
4	78	Male	Hypertension	Prostat malignant neoplasm	Yes	208	0.176	24	Resistant
5	87	Female	Renal cyst	No	Yes	95.53	0.146	128	Resistant

CRP: C-reactive protein, WBC: White blood cell

Discussion

S. aureus is a major cause of hospital- and community-acquired bloodstream infections. The mortality rate associated with SAB might reach 40%. In patients receiving antibiotic therapy and prolonged hospitalization, *S. aureus* can cause complex infections, such as endocarditis. *S. aureus* is an infrequent cause of bacteriuria. The presence of *S. aureus* in urine samples can be attributed to contamination, colonization, UTI, bacteremic seeding from another location or SAB. Urinary colonization or infections caused by *S. aureus* were frequently observed in individuals who received indwelling catheters or recent urinary tract instrumentation. The reported prevalence of *S. aureus* isolates from UTIs ranges from 0.5% to 1% [5].

Limited guidance is available regarding the examination and treatment of SABU. Schuler et al. [3] identified urinary tract catheterization as the primary contributor to SABU, accounting for 63-82% of cases. Other factors include urinary tract obstruction, invasive procedures, the recent hospitalization, old age, and male gender [3]. On the other hand, *S. aureus* is often found on both the skin and mucous membranes at the same time in people with SABU, indicating a higher risk of contamination during sampling (66-75%) [1]. Our investigation of patients with SABU found no statistically significant differences between male and female patients with SABU. In our study, 26.82% of the SABU patients were admitted as inpatients, whereas 73.17% received treatment as outpatients. The patients in our study had several comorbidities, and half of our patients had cancers. 18.2% of SABU patients had urinary catheters, while 68.2% had urologic abnormalities. These data recognized that urologic abnormalities and urinary catheters were significant underlying factors in SABU patients; measures for such patients, including decolonization, antibiotic treatment, and catheterization, may be beneficial.

According to the literature, SAB may be a cause or a result of SABU. SABU may serve as the focal site for future bacteremia and invasive infection [6]. The incidence of concurrent SAB in patients with SABU ranges from 8% to 27% and is associated with poor outcomes. The established risk factors associated with simultaneous SAB include male sex, hospitalization, signs of systemic infection, urinary tract abnormalities, and diabetes [1]. In a study conducted by Mason et al. [1], it was found that bacteremia developed in four of six patients who underwent urological instrumentation in the SABU group [1]. Arpi and Renneberg [7] found that out of 132 hospitalized patients with SABU, 8.3% experienced the development of SAB. They hypothesized that the development of secondary SAB to SABU was linked to urinary catheterization, urologic abnormalities, and instrumentation [7]. According to a study conducted by Al Mohajer et al. [8], among 326 patients with SABU, SAB occurred in 22% of patients with MRSA SABU and 8.4% of patients with MSSA SABU within 12 months. The risk factors for developing invasive disease were absence of UTI symptoms and admission as an inpatient [8]. A meta-analysis conducted by Schuler et al. [3] found that simultaneous SABU was recorded in 7.8-39% of SAB patients [3]. Additionally, the study group conducted a combined analysis and discovered a strong correlation between SABU and infections in bones and joints, as well as the occurrence of septic embolism in the

spleen, kidneys, or central nervous system [3]. Furthermore, SABU could occur as a consequence of SAB, and this was identified as an independent risk factor for mortality. If there are no identifiable risk factors for colonization, the presence of SABU might indicate the presence of an invasive illness, such as infective endocarditis. The presence of SABU in infective endocarditis can be a more severe result and may indicate the spread of vasculitis manifested by renal microabscesses [1]. In our study, we found that 6.9% of patients with SABU had SAB. Additionally, four out of the five patients with both SABU and SAB had urinary catheters, which correlates with the information reported in the literature. We proposed that the probability of SAB development was greater in patients undergoing genitourinary operations (catheterization) and malignancy. Pre-emptive antibiotic treatment in patients prior to instrumentation has been recommended in previous studies [1]. We propose that extensive clinical trials should involve a greater number of patients.

There was a lack of clear instructions regarding the investigation and management of SABU, including the most effective antibiotic treatment. In Mason et al.'s [1] study, 37% of patients with SABU showed symptoms of UTI, although 57% were prescribed antibiotics [1]. In our study, 52% of patients had a symptomatic UTI, and 56% received antibiotic treatment. Within a 3-month period, none of the patients exhibited a recurrence of *S. aureus* based on urine culture results after a positive initial test. These data indicated that the selection of antibiotic treatment for SABU was a significant problem. The differential diagnosis of asymptomatic bacteriuria, colonization, UTI and bacteriuria potentially linked with bacteremia should rely on clinical evidence and the presence of pyuria in patients with various risk factors. To limit inappropriate antibiotic administration, we recommend repeated urine and blood culture for individuals with suspected asymptomatic SABU.

Effective medicines for MSSA include intravenous cefazolin or flucloxacillin. Effective treatment options for MRSA include vancomycin, linezolid, and daptomycin [3]. In our study, 39.02% of *S. aureus* isolates from urine were resistant to methicillin. Among the group of patients with SABU+SAB (n=5) in our investigation, two were found to have MRSA SABU. Although MRSA SABU appeared to have a stronger connection with SAB than MSSA SABU, our investigation demonstrated that patients infected with MSSA were susceptible to both SABU and SAB. We recommend that the selection of antibiotics should be based on the local susceptibility patterns of each hospital. In our study, there was low resistance to usual first-line antibiotics.

Studys Limitations

The retrospective nature of our research and the small sample size are its limitations.

Conclusion

In conclusion, our study revealed that the investigation and management of SABU are challenging. Further studies with larger sample sizes are necessary. Urological abnormalities, cancers, and urinary catheters are significant underlying factors in SABU patients; measures for such patients, including decolonization, antibiotic treatment, and avoidance of catheterization, may be beneficial. Pre-emptive antibiotic treatment in patients prior to instrumentation is recommended. The differential diagnosis of asymptomatic bacteriuria, colonization, UTI, and bacteriuria potentially associated with bacteremia should be based on clinical data and the presence of pyuria. To avoid unnecessary antibiotic use, we recommend repeated urine and blood culture for patients with SABU. The microbiology results may be useful for guiding clinicians about SABU.

Ethics

Ethics Committee Approval: This study was conducted with the permission of the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Local Ethics Committee (research no: 2023-12/128, date: 11.01.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.B, T.U, G.İ, M.D, A.P., Concept: M.D, T.D., Design: M.D, T.D., Data Collection or Processing: M.D, T.D., Analysis or Interpretation: M.D, T.D., Literature Search: İ.M, S.S.Y, A.S.G, N.İ., Writing: M.D, T.D, A.S.G.

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Original Article

Factors Influencing Intensive Care Unit Outcomes in Elderly Patients with Solid Organ Tumors

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ABSTRACT

Aim: The increasing incidence of cancer in the older population presents challenges in intensive care units (ICU) due to age-associated complications and critical illness. Despite advancements in cancer treatment, the management of patients in the ICU remains complicated, with conflicting reports on outcomes. Therefore, in this study, we aimed to investigate the factors influencing ICU outcomes to guide the management and overall care of this vulnerable patient population.

Methods: This retrospective cohort study was conducted in a 9-bed tertiary medical ICU of Gazi University Hospital from July 2019 to January 2023 to investigate factors influencing ICU outcomes in elderly patients with solid organ tumors. The primary outcome measure of the study was ICU mortality.

Results: Among 123 critically ill elderly patients with solid organ tumors, the ICU mortality rate was 58%. ICU non-survivors had higher rates of metastatic disease (85% vs. 33%, p<0.01), underlying chronic obstructive pulmonary disease (45% vs. 27%, p=0.03), higher Acute Physiology and Chronic Health Evaluation II (APACHE II) [27 (24-34) vs. 15 (12-19), p<0.01], Sequential Organ Failure Assessment [10 (6-15) vs. 4 (2-5), p<0.01] and lower Glasgow Coma Scale scores [13 (10-15) vs. 15 (13-15), p=0.01]. ICU non-survivors also had higher rates of sepsis (72% vs. 50%, p=0.01) and shock (80% vs. 35%, p<0.01) and lower albumin levels (2.3±0.5 vs. 2.6±0.6, p=0.03) at ICU admission. Sepsis at ICU admission [odds ratio (OR) 95% confidence interval (CI): 5.5 (1.8-17.4), p<0.01], presence of metastasis [OR (95% CI): 2.12 (1.41-4.32), p<0.01], APACHE II score [OR (95% CI): 1.8 (1.29-2.51), p<0.01] and invasive mechanical ventilation [OR (95% CI): 1.56 (1.14-2.01), p=0.01] were found as independent risk factors for ICU mortality in this patient population.

Conclusion: Metastasis, sepsis upon ICU admission, APACHE II score, and requirement for invasive mechanical ventilation were independent risk factors for ICU mortality in elderly patients with solid organ tumors. Future studies should validate these findings in larger cohorts and focus on disease states and treatment modalities.

Keywords: Solid organ tumors, intensive care unit, mortality, outcome

Introduction

As the world population ages, the incidence of cancer also increases. Cancer is a leading cause of morbidity and mortality worldwide, with approximately 70% of cancer-related deaths occurring in individuals aged 65 years and older [1]. With advancements in medical care, more elderly patients with solid organ tumors are being admitted to intensive care units (ICU), where they manage disease-related complications and critical illness.

The decision to admit elderly patients with cancer to the ICU is influenced by various factors, such as the patient's performance status, comorbidities, treatment methods, and the status of the underlying malignancy [2]. Despite advancements in cancer treatment, managing elderly patients with solid organ tumors in the ICU presents several challenges, including compromised physiological reserves, increased susceptibility to infections, and increased risks of treatment-related toxicities [3]. On the other hand, although mortality rates tend to increase with age,

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some elderly individuals admitted to the ICU have outcomes comparable to those of younger patients [4]. Thus, comorbid conditions and frailty, rather than age as just a number should have priority in assessing ICU requirements [4,5].

Understanding the outcomes of elderly patients with solid tumors in the ICU is crucial for optimizing care and making clinical decisions. While some studies have reported favorable outcomes and improved survival rates among this patient population, others have emphasized the high mortality rates and poor prognosis associated with critical illness in elderly patients with cancer [5-7]. While prior research has contributed to our understanding of the prognosis of these patients, there is a need to gather diverse and up-to-date data to guide future advancements in patient care [5,8].

Therefore, in this study, we aimed to investigate the factors influencing ICU outcomes to guide the management and overall care of this vulnerable patient population.

Methods

Study Design and Setting

This retrospective cohort study was conducted in the nine-bed tertiary medical ICU of Gazi University Hospital between July 2019 and January 2023. The research protocol complied with the Declaration of Helsinki and was approved by the Gazi University Local Ethics Committee (number: 2024-507, date: 03.04.2024). The primary outcome measure of the study was ICU mortality.

Participants

Patients were included if they were ≥65 years old and had a confirmed diagnosis of solid organ tumor. Patients were excluded if they were terminally ill, stayed less than 24 hours, or were transferred from other ICUs.

Data Collection

Epidemiological and laboratory data were obtained from electronic hospital records and medical archives. Demographic information including age, sex, malignancy type, presence of metastasis, and clinical severity scores like the Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Risk, Injury, Failure Loss, and End-stage kidney disease (RIFLE) score, and admission laboratory parameters [C-reactive protein (CRP), procalcitonin, and albumin levels] were collected. Additionally, data regarding the cause and clinical parameters related to ICU admission, comorbidities, need for hemodialysis, invasive procedures, nosocomial infections, and ICU mortality rates were documented. Sepsis was defined using the Sepsis-3 criteria [9]. Acute kidney injury (AKI) was diagnosed according to the RIFLE criteria upon ICU admission. The GCS, APACHE II, RIFLE, and SOFA scores were computed within 24 hours of ICU admission to assess the severity of the illness.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation or median with interquartile range based on their distribution. Categorical variables are presented as frequencies and percentages. Patients were divided into two groups according to ICU survival, and data were compared between ICU survivors and non-survivors. The Mann-Whitney U test or independent samples t-test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables. Logistic regression analysis was used to identify independent risk factors for ICU mortality. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences version 22.0 software (IBM Corp, New York, NY).

Results

ICU mortality was 58% (n=71) in 123 critically ill elderly patients with solid organ tumors. Detailed information regarding baseline characteristics, ICU admission, and follow-up data of the patients is presented in Tables 1 and 2. ICU non-survivors had higher rates of metastatic disease (85% vs. 33%, p<0.01) and underlying chronic obstructive pulmonary disease (COPD) (45% vs. 27%, p=0.03) than ICU survivors. ICU non-survivors also had higher APACHE II [27 (24-34) vs. 15 (12-19), p<0.01] and SOFA [10 (6-15) vs. 4 (2-5), p<0.01] scores, lower GCS scores [13 (10-15) vs. 15 (13-15), p=0.01], higher rates of sepsis (72% vs. 50%, p=0.01) and shock (80% vs. 35%, p<0.01), and lower albumin levels (2.3±0.5 vs. 2.6±0.6, p=0.03) at ICU admission (Table 1). Moreover, ICU non-survivors had higher rates of invasive mechanical ventilation (92% vs. 33%, p<0.01), renal replacement therapy (65% vs. 10%, p<0.01), central venous catheterization (86% vs. 48%, p<0.01), vasopressor requirement (97% vs. 37%, p<0.01), and more frequent nosocomial infections (58% vs. 29%, p<0.01) than ICU survivors during the ICU follow-up (Table 2). Sepsis at ICU admission [odds ratio (OR) 95% confidence interval (CI): 5.5 (1.8-17.4), p<0.01], presence of metastasis [OR (95% CI): 2.12 (1.41-4.32), p<0.01], APACHE II score [OR (95% CI): 1.8 (1.29-2.51), p<0.01], and invasive mechanical ventilation [OR (95% CI): 1.56 (1.14-2.01), p=0.01] were found as independent risk factors for ICU mortality in this patient population (Table 3).

Discussion

The findings of our study highlight the essential factors influencing ICU outcomes in elderly patients with solid organ tumors. In summary, ICU mortality was high, and ICU non-survivors had higher rates of metastatic disease, underlying COPD, and worse prognostic scores at ICU admission. Moreover, ICU non-survivors had higher rates of invasive mechanical ventilation, renal replacement therapy, central venous catheterization, and vasopressor therapy requirement and more frequent nosocomial infections during the ICU follow-up than ICU survivors. In addition to worse prognostic

scores and IMV requirement, metastasis was found to be an independent risk factor for ICU mortality.

One of the key observations of our study was the significantly higher prevalence of metastatic disease among ICU non-survivors. The presence of metastasis was also an independent risk factor for ICU mortality. These findings are consistent with the existing literature highlighting the detrimental impact of advanced disease states on ICU outcomes in patients with cancer [10,11]. Metastatic disease, in particular, has been identified as a significant predictor of poor prognosis and

Table 1. Baseline characteristics and ICU admission data of elderly patients with solid organ tumors

Characteristics	All patients (n=123)	Survivors (n=52) (42%)	Non-survivors (n=71) (58%)	p value
Age (years)*	70 (69-77)	70 (66-73)	70 (69-74)	0.56
Female, n (%)	43 (35)	20 (38)	23 (32)	0.31
Solid organ tumor, n (%)				
Gastrointestinal	37 (30)	16 (31)	21 (30)	0.52
Lung	35 (28)	12 (23)	23 (32)	0.18
Genitourinary	26 (21)	11 (21)	15 (21)	0.58
Head and neck	8 (7)	4 (8)	4 (6)	0.46
Breast	12 (10)	7 (13)	5 (7)	0.19
Rare tumors	6 (5)	4 (8)	2 (3)	0.21
Metastasis	77 (63)	17 (33)	60 (85)	**<0.01**
Additional comorbidities, n (%)				
Hypertension	75 (61)	30 (58)	45 (63)	0.35
COPD	46 (37)	14 (27)	32 (45)	**0.03**
Diabetes mellitus	36 (29)	18 (35)	18 (25)	0.18
Neurological disease	21 (17)	9 (17)	12 (17)	0.56
Severity and organ failure scores				
APACHE II score	25 (20-31)	15 (12-19)	27 (24-34)	**<0.01**
SOFA score*	8 (4-10)	4 (2-5)	10 (6-15)	**<0.01**
Glasgow Coma Scale	13 (6-15)	15 (13-15)	13 (10-15)	**0.01**
Laboratory parameters				
C-reactive protein*	142 (81-242)	112 (87-277)	149 (79-242)	0.53
Procalcitonin*	1.4 (0.4-4)	1.34 (0.3-3.7)	1.9 (0.4-5.9)	0.11
Albumin (mean±SD)	2.4±0.5	2.6±0.6	2.3±0.5	**0.03**
AKI upon ICU admission, n (%)	69 (56)	28 (54)	41 (58)	0.40
Sepsis upon ICU admission, n (%)	77 (63)	26 (50)	51 (72)	**0.01**
Shock upon ICU admission, n (%)	75 (61)	18 (35)	57 (80)	**<0.01**

*Median (interquartile range).
n: Number, SD: Standard deviation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, AKI: Acute kidney injury

Table 2. ICU follow-up data of elderly patients with solid organ tumors

Characteristics	All patients, (n=123)	Survivors, (n=52) (42%)	Non-survivors, (n=71) (58%)	p value
Mechanical ventilation, n (%)				
Non-invasive	34 (28)	16 (31)	18 (25)	0.34
Invasive	82 (67)	17 (33)	65 (92)	**<0.01**
Length of ICU stay (days)*	15 (8-25)	16 (11-25)	15 (8-25)	0.25
New onset AKI, n (%)	28 (23)	12 (23)	16 (23)	0.46
Renal replacement therapy, n (%)	41 (33)	34 (65)	7 (10)	**<0.01**
Central venous line, n (%)	86 (70)	25 (48)	61 (86)	**<0.01**
Vasopressor requirement, n (%)	88 (72)	19 (37)	69 (97)	**<0.01**
Blood product replacement, n (%)	63 (51)	22 (42)	41 (58)	0.06
Parenteral nutrition, n (%)	24 (20)	10 (19)	14 (20)	0.61
Nosocomial infection rate, n (%)	56 (46)	15 (29)	41 (58)	**<0.01**

*Median (interquartile range).
n: Number, AKI: Acute kidney injury, ICU: Intensive care unit

Table 3. Independent risk factors for ICU mortality in elderly patients with solid organ tumors

Factor	Odds ratio (95% CI)	p value
Sepsis at ICU admission	5.5 (1.8-17.4)	**<0.01**
Metastasis	2.12 (1.41-4.32)	**<0.01**
APACHE II score	1.8 (1.29-2.51)	**<0.01**
Invasive mechanical ventilation	1.56 (1.14-2.01)	**0.01**

ICU: Intensive care unit, APACHE II: Acute Physiology and Chronic Health Evaluation II, CI: Confidence interval

increased mortality in critically ill patients with cancer [12]. A study by Soares et al. [11] found that metastatic cancer was associated with increased mortality among patients admitted to ICUs, corroborating our observation of higher ICU mortality among elderly patients with metastatic disease. Furthermore, Darmon et al. [10] reported similar findings, emphasizing the adverse impact of metastasis on short-term outcomes in critically ill patients with cancer. By explicitly examining this relationship in elderly patients with solid organ tumors, our study contributes to the factors influencing ICU outcomes in this population.

Furthermore, our study confirmed the association between underlying COPD and ICU mortality. The higher mortality rate observed in patients with COPD may be attributed to the higher incidence of lung cancer, which is a common etiological factor among these patients, primarily due to smoking. In our study, ICU non-survivors had higher APACHE II and SOFA scores and lower GCS scores, indicating greater physiological derangement and organ dysfunction at ICU admission. These findings are consistent with previous studies demonstrating the prognostic value of severity scoring systems in predicting mortality among critically ill patients [13,14].

The higher prevalence of sepsis and shock among ICU non-survivors highlights the critical role of systemic inflammatory response and hemodynamic instability in determining outcomes in this patient cohort. Sepsis, in particular, has been identified as a significant contributor to mortality in critically ill patients with cancer, highlighting the importance of early recognition and aggressive management of sepsis and its complications [15,16].

According to our results, CRP and procalcitonin levels did not significantly differ between ICU survivors and non-survivors. This result may seem at odds with the existing literature, which mainly highlighted the association between procalcitonin and mortality risk in critically ill patients [17]. On the other hand, considering the influence of tumor-related inflammation, it is important to interpret this finding cautiously [18]. Solid organ tumors can modulate the host immune response and release proinflammatory mediators, which may affect biomarker profiles. Although procalcitonin is commonly used as a marker of infection, its use in patients with cancer can be complicated by tumor-induced inflammation. Moreover, considering the relationship between procalcitonin level alterations and organ failure, the high incidence of sepsis and AKI in our cohort may further complicate the interpretation of these results.

Additionally, the current study highlights the impact of therapeutic interventions on ICU outcomes. Non-survivors in the ICU were more likely to require invasive mechanical ventilation, renal replacement therapy, central venous catheterization, and vasopressor therapy, reflecting the higher burden of organ support and resuscitative measures in this subgroup. These findings are consistent with those of previous studies demonstrating an association between invasive interventions and increased mortality in critically ill patients with cancer [19,20].

In this single-center experience, our study contributes to the existing body of literature by identifying critical independent risk factors for ICU mortality among elderly patients with solid organ tumors. Our finding of sepsis at ICU admission is consistent with previous data highlighting the detrimental impact of septic complications on outcomes in ICU patients with solid organ tumors [15,19]. Similarly, the association between the APACHE II score and ICU mortality highlights the prognostic value of severity scoring systems in this population. This is consistent with prior research demonstrating their use in predicting outcomes in ICU patients with various underlying conditions [14,21]. Furthermore, our observation of invasive mechanical ventilation as a risk factor was similar to the findings of studies on critically ill patients with cancer, emphasizing the significance of respiratory support in determining patient outcomes [10,11].

Study Limitations

The results of this study have significant findings related to identifying factors related to ICU outcomes in elderly patients with solid organ tumors. However, it is important to acknowledge several limitations of our study, including its retrospective nature and reliance on a single-center cohort. Moreover, our study lacks data regarding the timing and regimen of oncological treatment methods before ICU admission. Additionally, we only had data on whether the patient had metastatic disease. We did not have detailed information regarding the stages of solid organ tumors. Future studies should aim to validate our results in larger prospective cohorts and to focus more on disease status and cancer treatment modalities.

Conclusion

Our study identified metastatic disease, COPD, severity scoring, organ failure assessment systems, sepsis, and therapeutic

interventions as significant determinants of ICU outcomes in elderly patients with solid organ tumors. These findings emphasize the importance of early recognition and tailored management strategies to improve outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Gazi University Local Ethics Committee (number: 2024-507, date: 03.04.2024).

Informed Consent: Retrospective cohort study.

Authorship Contributions

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

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Letter to the Editor

Acute Myocardial Infarction in a Patient with Hodgkin Lymphoma After ABVD Treatment

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Keywords: ABVD, cardiotoxicity, Hodgkin lymphoma, myocardial infarction

Dear Editor,

A 23-year-old male patient was diagnosed with nodular sclerosis classic Hodgkin lymphoma. He was diagnosed with lymphadenopathy in his left inguinal region for 6-7 months from the excisional biopsy. The patient had no B symptoms at diagnosis. He had no other known diseases or medications in his medical history, but he was a smoker. There was a history of nasopharyngeal cancer in his father and uncle in his family history. The patient underwent positron emission tomography (PET). PET was performed, and the patient was staged as Ann Arbor stage 3A. Echocardiography (ECHO), electrocardiography (ECG), and cardiological examination were requested before starting chemotherapy. The cardiological examination detected no pathology, and the ECHO and ECG results were evaluated as normal. The patient's weight was 95 kg, and his height was 185 cm. The patient was started on doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy by calculating the body surface area based on the corrected body weight. The patient received chemotherapy in the outpatient chemotherapy unit without any problems, and he was called for control 5 days later for a blood count. However, the patient applied to the emergency department because of chest pain 4 days after receiving chemotherapy. The patient was diagnosed with acute myocardial infarction (MI) as a result of examinations, and angiography was performed. The ECG image is shown in Figure 1 when the patient presents to the emergency department with chest pain. A stent was inserted during angiography. The patient was discharged after the procedure and was followed up. Chemotherapy was interrupted for approximately 1 month. After MI, dosage adjustments were made according to the patient's chemotherapy protocol. The patient continued cardiology follow-up after MI. At follow-up, no sequelae were noted. The ejection fraction increased to the normal range. Chemotherapeutic drugs, such as anthracycline, are frequently used to treat various malignant cancers. The use of these drugs is severely limited by cardiotoxicity, which is classified as type I cardiotoxicity and characterized by cardiomyocyte death leading to permanent harm and a 50% 1-year mortality rate [1,2]. The most frequent side effect of anthracycline is left ventricular systolic dysfunction, which is primarily caused by myocyte destruction and fibrous tissue replacement [3]. The reports that are now available imply that anthracycline-induced cardiac damage develops over time and occurs throughout exposure. Although HF and arrhythmias might appear suddenly (within weeks of exposure), most patients who come months to years after exposure to anthracycline develop HF and problems from LV systolic dysfunction (congestion, cardiogenic shock) (4). Our patient exhibited some differences from previous reports. First, the patient received ABVD chemotherapy for the first time and did not have cumulative dose accumulation. The patient was 23 years old, and he had no etiology other than smoking, which would increase the risk of cardiovascular disease. Second, the ECG, ECHO, and cardiological examination performed before the start of chemotherapy were completely normal. As a

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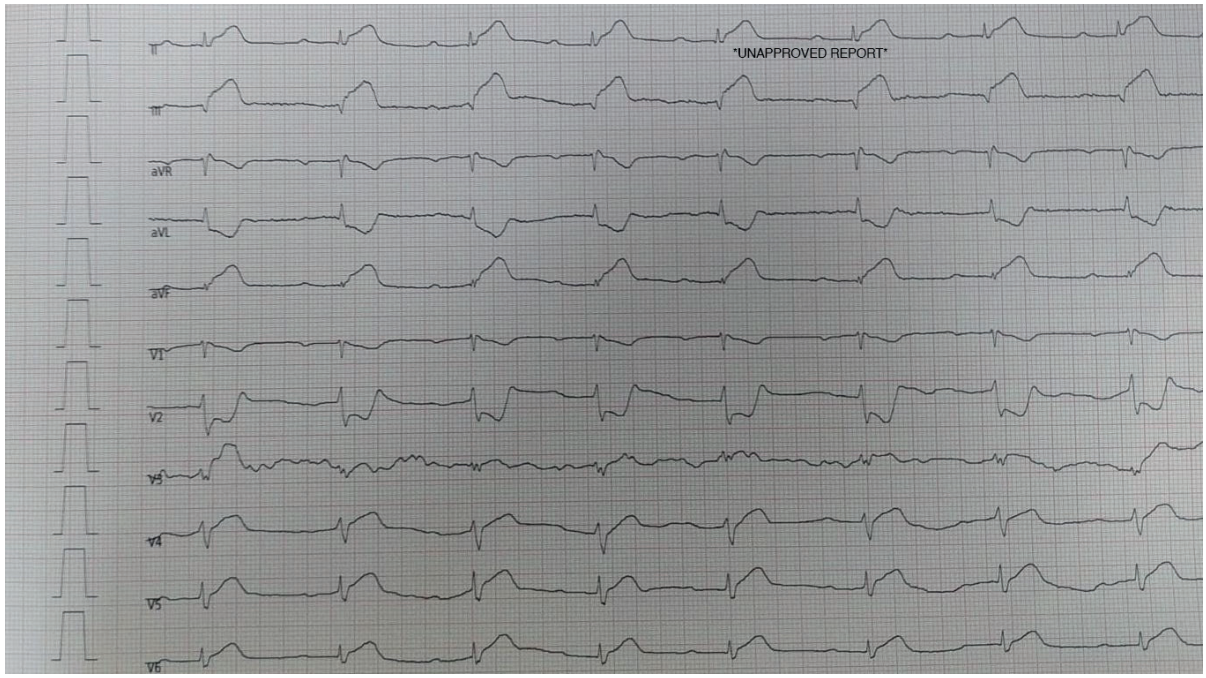

Figure 1. ECG image when the patient presented to the emergency room with chest pain and ST elevation in the inferior leads D2, D3, and AFV, accompanied by ST depression in V1 and V2, inferior-posterior myocardial infarcts, and hyperacute period
ECG: Electrocardiography

result, although anthracycline-based chemotherapy regimens often cause advanced cardiotoxicity, it should be kept in mind that they may cause cardiac diseases, such as MI, in the acute period.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

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

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