Original Article

The Predictive Value of FDG PET/CT in the Evaluation of Bone Marrow Involvement in Lymphoma Patients

Lenfoma Hastalarında Kemik İliği Tutulumunu Değerlendirmede FDG PET/BT'nin Prediktif Değeri

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ABSTRACT

Introduction: The aim of the current study was to determine the role of PET-CT in the evaluation of bone marrow (BM) involvement during initial staging in patients with newly diagnosed lymphoma.

Methods: A retrospective analysis was made of 104 patients who were admitted to our Hematology Department between January 2010 and September 2016 and were diagnosed with lymphoma. Patients were classified as Hodgkin (HL) and Non-Hodgkin Lyphoma (NHL). NHL patients were evaluated in two subgroups as aggressive and indolent.

Results: The patients comprised 54 (51.9%) males and 50 (48.1%) females and were classified as 24 patients with HL and 80 with NHL. BM biopsy showed BM involvement in 40 patients (38.5%) and there was no pathological finding in 64 (61.5%) patients. BM involvement was detected on PET-CT in 41 (39.4%) of the whole patient group, of which 26 (63.4%) cases had diffuse infiltration and the remaining 15 (36.6%) cases had patchy infiltration. For all lymphoma patients, sensitivity of PET-CT was 80% and specificity was 85.9%. Sensitivity and specificity of PET-CT was 92.3% and 81.8% for HL patients and 74.1% and 86.8% for NHL patients, respectively. For only aggressive NHL patients, PET-CT sensitivity was 81.8% and specificity was 87.75%.

Discussion and Conclusion: PET-CT is an effective method for assessing BM involvement with a higher sensitivity especially for HL and aggressive NHL patients in detecting patchy involvement. The fact that it is non-invasive and easy to apply may support that it can be used instead of BM biopsy.

Keywords: Lymphoma, Bone Marrow Involvement, Biopsy, PET-CT

ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, yeni tanı konmuş lenfoma hastalarında ilk evreleme sırasında kemik iliği (BM) tutulumunun değerlendirilmesinde PET-BT'nin rolünü belirlemektir.

Yöntem ve Gereçler: Ocak 2010-Eylül 2016 tarihleri arasında Hematoloji Bölümümüze başvuran ve lenfoma tanısı alan 104 hastanın retrospektif analizi yapıldı. Hastalar Hodgkin (HL) ve Hodgkin Dışı Lenfoma (HDL) olarak sınıflandırıldı. HDL hastaları da agresif ve yavaş seyirli olmak üzere iki alt grupta değerlendirildi.

Bulgular: Hastaların 54'ü (%51.9) erkek ve 50'si (%48.1) kadındı ve 24 HL'li ve 80 HDL olarak sınıflandırıldı. Kemik iliği (Kİ) biyopsisi 40 hastada (%38,5) Kİ tutulumu gösterdi ve 64 (%61,5) hastada patolojik bulgu görülmedi. PET-BT ile tüm hasta grubunun 41'inde (%39,4) Kİ tutulumu saptandı, bunların 26'sında (%63,4) yaygın infiltrasyon, kalan 15'inde (%36,6) yamalı infiltrasyon vardı. Tüm lenfoma hastaları için PET-BT'nin duyarlılığı %80 ve özgüllüğü %85.9'du. PET-BT'nin duyarlılığı ve özgüllüğü HL hastaları için sırasıyla %92,3 ve %81,8 ve NHL hastaları için %74,1 ve %86,8 idi. Sadece agresif HDL hastaları için PET-BT duyarlılığı %81.8 ve özgüllük % 87.75 idi.

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Tartışma ve Sonuç: PET-BT, yamalı tutulumun saptanmasında özellikle HL ve agresşf HDL hastalarında Kİ tutulumunu daha yüksek bir duyarlılıkla değerlendirmek için etkili bir yöntemdir. Non-invaziv ve uygulanmasının kolay olması BM biyopsisi yerine kullanılabileceğini destekleyebilir.

Anahtar Kelimeler: lenfoma, kemik iliği tutulumu, biyopsi, PET-BT

Introduction

Lymphomas are clonal tumors originating from lymphocytes (T and B) or NK (natural killer) cells from immune system cells. They have different morphological, immunological and clinical features depending on the differentiation stage of the cell from which they originate [1]. The Ann-Arbor classification is used for lymphoma staging [2]. Correct staging is essential for effective treatment planning [3, 4]. While computed tomography (CT) is the most commonly used imaging method for initial staging in Non-hodgkin Lymphoma (NHL) patients, PET-CT, which combines positron emission tomography (PET) and computed tomography (CT), shows involvement more effectively than CT, especially in aggressive lymphomas. [5]. PET-CT is now the standard method for HL and aggressive NHL staging, but it has low diagnostic value in slow-progressive lymphomas [6, 7].

Bone marrow (BM) involvement is of great importance in the staging of lymphoma and thus in determining treatment and prognosis. [8]. BM involvement is present in approximately 25-40% of NHLs and 5-14% of HLs [9, 10]. Unilateral BM biopsy of the dorsal iliac crest is accepted as the gold standard in routine evaluation of BM involvement and is routinely performed [2]. However, it has some limitations such as being an invasive painful procedure and bypassing limited involvement. PET-CT has been evaluated as useful in demonstrating BM involvement in various studies [3, 4, 11, 12], and has therefore been accepted as a complementary study for BM biopsy [13, 14].

The aim of the current study is to determine the predictive value of PET-CT in comparison with BM biopsy results in the evaluation of BM involvement in HL and NHL patients.

Patients and methods

This study included 24 HL and 80 NHL patients admitted to Necmettin Erbakan University Hematology Department between January 2010 and September 2016 who were diagnosed with HL and NHL. All patients underwent both PET-CT and BM biopsy for initial staging. In the clinical staging, physical examination, laboratory tests, PET-CT results, and unilateral BM biopsy results were recorded. Stage, presence of B symptoms, histopathological diagnosis and demographic information were obtained from patient files. The PET-CT findings of the patients were re-evaluated and recorded with SUV (Standardized Uptake Value) max measurements from the right lobe mid-segment segment 7-8, spleen parenchyma and dorsal iliac wing region where BM biopsy was performed. Spleen parenchyma and BM areas with a higher SUVmax measurement than liver parenchyma were accepted as involvement. Cases with increased diffuse bone marrow activity in PET-CT were evaluated as involvement and recorded. Cases with irregular, non-diffuse increase in metabolic activity were defined as patchy BM involvement and recorded. BM biopsy was accepted as the gold standard in demonstrating involvement, and sensitivity-specificity tables were made according to the results of biopsy and PET-CT. According to these tables, the sensitivity, specificity, positive and negative predictive values of PET-CT in demonstrating BM involvement were calculated.

Statistical Analysis

Statistical analysis was performed using SPSS version 16 software and Excel 2013. The conformity of the variables to normal distribution was examined with the Kolmogorov Smirnov and Shapiro-Wilk tests. Data with normal distribution were presented

as mean±standard deviation, and data without normal distribution as median (minimum-maximum) values.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for this cross sectional study was granted by Necmettin Erbakan University Faculty of Medicine Ethics Committee (Number: 2016/680 Date: 30.09.2016)

Results

All patients

Twenty four HL and 80 NHL patients were included in the study. The most common subtypes were Nodular Sclerosis among HL (n=17, 16.3%) and Diffuse Large B Cell Lymphoma (n=56, 53.8%) among NHL patients. All subtypes are shown in Table 1. The patients comprised 54 (51.9%) males and 50 (48.1%) females with a median age of 60.5 years (range, 20-90 years). Advanced stage disease was present in 75 patients (72.2%) and 47 patients (45.2%) had B symptoms at the time of diagnosis. The total mortality rate was 24% (n=25) at the final follow-up time. The demographic and disease characteristics are shown in Table 2.

The BM biopsy results revealed that 40 patients (38.5%) had involvement and 64 patients (61.5%) had no involvement. BM involvement was detected on PET-CT in 41 (39.4%) of all patients, 26 (63.4%) of which were diffuse and the remaining 15 (36.6%) were patchy (Table 3). The sensitivity and specificity of PET-CT were 80% and 85.9%, respectively. The positive predictive value (PPV) of PET-CT in the assessment of BM involvement was 78% and the negative predictive value (NPV) was 87.3% (Table 3).

HL patients

Twenty four HL patients with a median age of 46 years [range, 20-70 years] were evaluated (Table 2). BM biopsy showed involvement in 13 (54.2%) patients and no involvement in 11 (45.8%) patients. On PET-CT, BM involvement was detected in 14 (58.3%) patients and no involvement in 10 (41.7%) patients. Of these involvements, two(14.3%) were patchy, and 12 (85.7%) showed diffuse involvement. The demographic and disease characteristics and BM involvement results of HL patients are shown in Table 2. In HL patients, the PET-CT sensitivity to BM involvement was 92.3% and specificity was 81.8%. The PPV of PET-CT was 85.7% and the NPV was 90% in HL patients (Table 3).

NHL patients

Eighty (76.9%) NHL patients with a median age of 64 [range, 21-90 years] were evaluated (Table 2) BM biopsy revealed involvement in 27 (33.7%) patients, and no involvement in 53 (66.3%) patients. On PET-CT, BM involvement was not detected in 53 (66.3%) patients and was observed in the remaining 27 (33.7%) patients. Of these, 13 (48.1%) were patchy and 14 (51.9%) had diffuse involvement. The demographic and disease characteristics and BM involvement results of NHL patients are shown in Table 2. The sensitivity of PET-CT for detecting BM involvement in NHL patients was 74.1% and specificity was 86.8%. PET-CT had a PPV of 74.1% and a NPV of 86.8% (Table 3).

In the evaluation of 71 aggressive NHL patients, BM biopsy showed involvement in 22 (31.0%) patients and 49 (69.0%) patients had no BM involvement. On PET-CT, 24 (33.8%) patients had involvement while 47 (66.2%) patients had no involvement (Table 3). The sensitivity and specificity of PET-CT for aggressive NHL patients was 81.8% and 87.75%, respectively. The PPV of PET-CT was 75% and the NPV was 91.5%.

In the evaluation of 9 NHL patients with an indolent course, five (55.6%) patients had involvement in the BM biopsy, and four (44.4%) patients had no involvement. When evaluated with PET-CT, involvement was observed in three (33.3%) patients and no involvement was observed in six (66.7%) patients.

Table 1. Diagnostic subgroups of the patients

Diagnosis	Subgroup	n (%)
Hodgkin Lymphoma	Nodular Sclerosis HL	17 (%16,3)
	Lymphocyte Rich HL	3 (%2,9)
	Mixed Cellularity HL	3 (%2,9)
	Lymphocyte Depleted HL	1 (%1)
Non-Hodgkin Lymphoma	Diffuse Large B-cell Lymphoma	56 (%53,8)
	Mantle cell Lymphoma	5 (%4,8)
	Peripheral T-cell lymphoma	5 (%4,8)
	Angioimmunoblastic T cell lymphoma	2 (%1,9)
	Anaplastic large cell lymphoma	2 (%1,9)
	Marginal Zone Lymphoma	6 (%5,8)
	Follicular lymphoma grade I and II	2 (%1,9)
	Follicular Lymphoma Grade III	1 (%1)
	Small Lymphocytic Lymphoma	1 (%1)
All		104 (100)

Table 2. General demographic findings and bone marrow involvement

	HL (N=24)	NHL (N=80)	All (N=104)
Age Median [min-max.]	46.0 [20-70]	64 [21-90]	60.5 [20-90]
Gender			
Male	12 (%50,0)	38 (%47,5)	50 (%48,1)
Female	12 (%50,0)	42 (%52,5)	54 (%51,9)
Stage and B symptoms			
I / IB	1(4,2%) / 1(100%)	7(%8,8) / 0(0%)	8 (%7,7) / 1(12,5%)
II / IIB	5(20,8%) / 2(40%)	16(20,0%) / 7(43,7%)	21 (20,2%) / 9(42,8%)
III / IIIB	5(20,8%) / 1(20%)	30(37,5%) / 16(53,3%)	35(33,7%) / 17(48,5%)
IV / IVB	13(54,2%) / 8(61,5%)	27(33,7%) / 12(44,4%)	40(%38,5) / 20(50%)
BM Involvement in PET-CT (n)			
Patchy	2 (8,3%)	13 (16,2%)	15 (14,4%)
Diffuse	12 (50,0%)	14 (17,5%)	26 (25,0%)
Patients' survival			
Survivors	22 (91,7%)	57 (71,3%)	79 (76,0%)
Nonsurvivors	2 (8,3%)	23 (28,7%)	25 (24,0%)

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, BM: Bone marrow

Table 3. Evaluation of bone marrow involvement in all patients

	Overall (n=104)		HL (n=24)		NHL (n=80)	
	BMB (+)	BMB (-)	BMB (+)	BMB (-)	BMB (+)	BMB (-)
PET CT (+)	32	9	12	2	20	7
PET CT (-)	8	55	1	9	7	46
Total	40	64	13	11	27	53

BMB: Bone marrow biopsy, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

Discussion

Correct staging of the disease is of great importance in follow-up and survival in patients with lymphoma [3, 4]. PET with radioactive fluorine-18-labeled glucose analogue 18F-Fluorodeoxyglucose (FDG) is increasingly used in the evaluation of various malignant tumors, including lymphoma. [15-18]. The most important advantage of PET-CT is the ability to distinguish between active tumoral tissue and necrosis and fibrosis [19-21]. Anemia, infections, G-CSF use, chemo-therapy (CT) use that may cause bone marrow activation during PET-CT scan may cause false positives but do not exclude BM involvement. [4, 22].

BM biopsy is the gold standard method for BM involvement. However, it is an invasive method and there are also some difficulties in achieving certain standards in terms of efficiency during implementation. According to a study by Brain, the minimum length of the biopsy material was determined as 16 mm [23], while 20mm was the minimum length of unilateral biopsy required by Campbell et al [24]. As this procedure is quite painful and it is difficult to obtain adequate sampling, the search for other non-invasive tests has increased. In many studies, it has been shown that PET-CT and BM biopsy are compatible with BM biopsy results, which is the most important step in the staging of lymphoma patients. In the current study, the correlation between PET-CT and patients with BM involvement was 80%. These results were found to be compatible with the 78% and 80% correlation reported by Carr et al. and Pakos et al., respectively [8, 25].

In the current study, lymphoma patients were evaluated under the headings of HL and NHL, and the NHL patients were further analyzed as aggressive or indolent. Previous studies have reported that BM involvement is seen in 5-14% of HL [26] and 30-50% of NHL [27, 28], whereas when the subgroups are evaluated, BM involvement is seen in 18-36% of aggressive NHL and in 40-90% of indolent NHL [29]. In the current study, BM involvement was found in 54.2% of the HL patients, which was a higher rate than in recent reports in literature. Such a difference may have occurred because the number of HL patients included in this study was low. In the NHL patients, BM involvement was found in 33.7%, which was a similar rate to those previously reported. According to the subgroup evaluation, BM involvement was seen in 31% of the aggressive NHL group and in 55.6% of the indolent NHL group.

In the current study, BM biopsy detected involvement in eight patients where PET-CT showed no involvement. Of these 8 patients, one was HL, four were aggressive NHL and three were indolent NHL. Previous studies have shown that PET-CT has very low sensitivity to show BM involvement in Mantle Cell Lymphoma with low FDG uptake regardless of aggressive or indolent NHL grouping [14]. In the current study, three patients were followed up with the diagnosis of indolent group NHL and two patients with Mantle Cell Lymphoma. However, BM involvement can be missed on PET-CT in lymphomas with low density (10-20%) [30]. This may have been the cause of inconsistency in the remaining three patients.

In nine patients, BM involvement was determined with PET-CT while BM biopsy revealed no involvement. Of these patients, two were HL, 6 were aggressive NHL and one was indolent NHL. In recent studies, it has been reported that BM involvement may be in a diffuse pattern or it may exhibit patchy involvement [31, 32]. In the absence of FDG uptake in the biopsy area, involvement in BM biopsy may not be observed. In the current study, patchy involvement was observed in four patients who had no involvement on BM biopsy but had PET-CT involvement and the SUVmax values in the posterior iliac wing region were found to be relatively low. Although obtained in accordance with the literature, it is thought that the biopsy material of the remaining 5 patients who did not show involvement in BM biopsy was not sufficient for definitive diagnosis. [33-35]. It has been reported in another study that even if sufficient and bilateral biopsy was performed,

accuracy could only be increased by 10-50%. [25].

In a meta-analysis by Pakos et al., which discussed the role of PET-CT in demonstrating BM involvement in 13 studies with 587 patients, the sensitivity and specificity for detecting BM involvement were evaluated as 51% and 91%, respectively. It was shown that half of 12 patients who had BM involvement on PET-CT but not on biopsy showed BM involvement when the BM biopsy was repeated. [25]. Muslimani et al. reported PET-CT sensitivity as 79% and specificity as 91%. Sensitivity and specificity rates were lower in the NHL group, but there was no statistically significant difference [36].

In the current study, when all the patients were evaluated, sensitivity was found to be 80%, specificity 85.9%, PPV 78%, and NPV 87.3%. When the subgroups were evaluated, the highest sensitivity was 92.3% in HL patients. According to these results, PET-CT to show BM involvement; they are an effective method for HL patients and less effective for NHL patients. When sensitivity and selectivity were evaluated for the NHL subgroups, PET-CT appears to be more effective in the evaluation of BM involvement in aggressive NHL patients than in all NHL patients and indolent NHL patients.

Conclusion

In the evaluation of BM involvement in lymphoma patients, PET-CT is a very useful but not perfect method. Although it is a non-invasive method, the increase in cost should also be considered. In order to evaluate BM involvement effectively, BM biopsy can be performed after PET-CT, especially for the determination of BM involvement in lymphomas with patchy involvement. The efficacy of PET-CT in HL and aggressive NHL patients is quite high, and although there is still no substitute for BM biopsy, these methods complement each other. As PET-CT activity is low in indolent lymphomas, it cannot replace biopsy. Further larger patient-based studies are needed to evaluate the value of PET-CT for BM involvement instead of biopsy.

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Original Article

Diagnostic Value of 1.5 Tesla Multiparametric MRI in Prostate Cancer

1.5 Tesla Multiparametrik MRG'nin Prostat Kanserinde Tanısal Değeri

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ABSTRACT

Introduction: Although prostate biopsy is still the gold standard in diagnosis of prostate cancer (PC), multi-parametric MRI (MpMRI) applied with 1.5 Tesla (T) or 3T systems has become an indispensable method in diagnosis. We aimed to compare "Prostate Imaging-Reporting and Data System version2" (PI-RADSv2) scores with pathology of patients who underwent MpMRG (1.5T) for the suspicion of PC.

Methods: Between January 2017 and January 2020, 52 patients (26 benign, 26 malignant patients) who underwent MpMRI followed by biopsy in our center due to suspicion of PC were included in our study. Age, prostate volume, blood PSA (prostate specific antigen) value, density and pathology of these cases were analyzed. The PI-RADSv2 assessment category was assigned for each patient by an experienced radiologist. The "Chi-square" test and "Student-t" test were used for statistical analysis.

Results: The mean prostate volume of benign group (96.4±77.7) was significantly higher than patients with cancer (47.4±17.3) (p=0.003). Mean PSA value and PSA density in patients with malignancy (PSA value, 13.7±16.5 ng/ml; PSA density, 0.33±0.46 ng/ml/cc) were significantly higher than benign group (PSA value, 6.8±3.3 ng/ml; PSA density, 0.09±0.05 ng/ml/cc, p<0,05). The sensitivity, specificity, negative predictive value and positive predictive value of MpMRI applied with 1.5 T system in detection of significant PC was 73.08%, 84.62%, 82.61% and 75.86%, respectively.

Discussion and Conclusion: Considering the high negative predictive value of negative MpMRI findings for significant PC due to PI-RADSv2, MRI can reduce unnecessary biopsy.

Keywords: Multiparametric magnetic resonance imaging, prostate biopsy, prostate cancer, Prostate Imaging–Reporting and Data System

ÖZET

Giriş ve Amaç: Prostat kanseri tanısında prostat biyopsisi halen altın standart tetkik olmakla birlikte 1,5 Tesla (T) ya da 3 T cihazlarla uygulanan multi-parametrik MRG (MpMRG), tanıda vazgeçilmez bir tetkik haline gelmiştir. Bu çalışmada; prostat kanseri şüphesiyle 1,5 T cihaz ile MpMRG yapılan hastaların, Prostat Görüntüleme Raporlama ve Bilgi Sistemi versiyon2 (PI-RADSv2) skorlarını, prostat biyopsisi patoloji sonuçlarıyla karşılaştırmayı amaçladık.

Yöntem ve Gereçler: Çalışmamıza kliniğimizde Ocak 2017-Ocak 2020 tarihleri arasında prostat kanser şüphesi nedeniyle MpMRG ve ardından prostat biyopsisi yapılmış 52 hasta (26 benign, 26 malign) dahil edildi. Bu olguların yaşı, prostat hacmi, kan PSA (prostat spesifik antijen) değeri, yoğunluğu ve patoloji sonuçları analiz edildi. Deneyimli bir radyolog tarafından her bir hasta için PI-RADSv2 skorlama sistemine göre kategorizasyon yapıldı. İstatistiksel analizde "Ki kare" testi ile "Student-t" test kullanıldı.

Bulgular: Benign hasta grubunun (96,4±77,7) ortalama prostat hacmi malign gruptan (47,4±17.3) anlamlı olarak daha yüksektir (p=0,003). Ortalama PSA değeri ve yoğunluğu malign hastalarda (PSA değeri, 13,7±16,5 ng/ml; PSA yoğunluğu, 0,33±0,46 ng/ml/cc) benign hasta grubundan (PSA değeri, 6,8±3,3 ng/ml; PSA yoğunluğu, 0,09±0,05 ng/ml/cc; p<0,05) daha yüksektir. 1,5T cihaz ile uygulanan MpMRG'nin anlamlı prostat kanseri saptamadaki sensitivitesi %73,08, spesifitesi %84,62 pozitif prediktif değeri %82,61 iken negatif prediktif değeri ise %75,86 olarak hesaplandı.

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Tartışma ve Sonuç: PI-RADSv2'ye göre negatif MpMRG'nin yüksek negatif prediktif değeri göz önüne alındığında MRG gereksiz biyopsi oranını azaltabilir.

Anahtar Kelimeler: Multi-parametrik manyetik rezonans görüntüleme, prostat biyopsisi, prostat kanseri, Prostat Görüntüleme Raporlama ve Bilgi Sistemi versiyon2

Introduction

Prostate cancer is the most frequently diagnosed disease among men worldwide [1]. It is the second most frequent cause of deaths due to malignant tumors [2]. Digital rectal examination (DRE) and prostate-specific antigen (PSA) are used in prostate cancer screening [3]. Prostate biopsy continues to be the gold standard diagnostic technique for the detection of prostate cancer. However, some patients are subjected to unnecessary biopsies because of false-positive results. Even though clinically insignificant cancers can be detected with biopsy, clinically significant cancers are sometimes missed. Furthermore, trans-rectal ultrasound (TRUS) biopsy may carry significant morbidity and cause life-threatening sepsis [4]. In recent prospective studies, the sensitivity of prostate biopsy in the diagnosis of cancer was reported to be 70% [1]. For this reason, non-invasive tests that will reduce unnecessary biopsies by predicting negative results are considerable [5]. In recent years, magnetic resonance imaging (MRI) has stood out as a non-invasive technique that can be used for the evaluation of the prostate and its surrounding tissues. Initially, prostate MRI was based on morphologic assessment using T1-weighted (T1W) and T2-weighted (T2W) images. It had limited capability to distinguish benign pathological tissue and clinically insignificant prostate cancer from clinically significant cancer. To enhance diagnostic accuracy, anatomic T2W was combined with functional sequences including diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) MRI, and MR proton spectroscopy under the title of multiparametric MRI (MpMRI). For standardization of evaluation and reporting in prostate MpMRI examinations, a scoring system called the Prostate Imaging Reporting and Data System (PI-RADS) was developed in 2012, which demonstrates the cancer risk probability and aggressiveness obtained by multiparametric (morphological-functional) examination of the prostate. The PI-RADS scoring system was revised as PI-RADSv2 in 2015. In PI-RADSv2, the dominant technique was defined based on lesion location. Accordingly, DWI was defined as the dominant technique in the evaluation of peripheral zone lesions and T2W images as the dominant technique in the evaluation of transitional zone lesions. A simplified interpretation of DCE-MRI evaluation was added. According to that, an area of rapid enhancement matching an abnormality in DWI or T2W sequences was considered positive or negative on the basis of qualitative evaluation. MR spectroscopic examination is no longer used in the PI-RADSv2 system [6]. The likelihood of the presence of prostate cancer was determined based on an overall combination of the results obtained from T2W, DWI, and DCE-MRI using a 5-point "Likert" scale (1: very low level of suspicion; 2: low level of suspicion; 3: equivocal; 4: cancer probable; 5: definitely cancer) [7]. In PI-RADSv2, clinically significant cancer was defined as cancers meeting the criteria of Gleason pattern of ≥ 4 and/or cancer core length of ≥ 6 mm and/or tumour volume of ≥ 0.5 cc and/or extra-prostatic spread. This definition aims to standardize the reporting of MpMRI and the correlation with pathology for clinical and research applications [6,8].

In this study, the PI-RADSv2 scores of the patients who underwent 1.5 Tesla MpMRI for suspected prostate cancer in our clinic were compared with the results of the prostate

biopsies performed under TRUS, and the literature was reviewed. The diagnostic performance of 1.5 Tesla MpMRI was evaluated in cancer diagnosis.

Material and Method

Our retrospective study was approved by the Institutional Review Board of 'Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital' (Decision number and date: 2021-04/1096 and 21.04.2021). We retrospectively analysed a total of 245 MpMRI obtained in our hospital between January 2017 and January 2020. Patients who did not have histopathological results and those who were diagnosed with prostate cancer after prostate biopsy prior to MRI were excluded from the study. As a result, 93 patients (67 benign, 26 malignant) who underwent cognitive prostate biopsy along with MpMRI and TRUS due to a total PSA value of 4 ng/ml and/or suspicious findings in DRE were included in the study. To be able to make a comparison between the groups which included 67 benign pathologies and 26 malignant pathologies, the number of patients in the groups were equalized. In line with this purpose, 26 benign patients were selected from the group consisting of 67 benign patients by simple random sampling method and as a result, 26 malignant and 26 benign patients were included in the study. Age, prostate volume, the value and density of blood PSA were recorded for these patients. The examination was performed with 1.5 Tesla MRI (GE Optima 360) using an 8-channel torso coil. In the protocol, 3 plans were included: T2W, DCE-MRI and DWI. The DWIs were obtained on b=50, 1000 and 1400. Scoring was carried out according to the PI-RADSv2 scoring system by a 12-year experienced radiologist. As a result of histopathological evaluation, Gleason grades were recorded for the cases with prostate carcinoma. MpMRI results were considered clinically significant but negative for cancer for PI-RADS 1 and 2 lesions, whereas they were regarded positive for PI-RADS 3, 4, 5 lesions. Statistical analyses were performed using the SPSS (version 22.0, SPSS). The Kolmogorov-Smirnov test was used to analyze the normal distribution of data. Continuous variables were presented as mean ± standard deviation. Patients were compared in terms of differences in age, total PSA value, PSA density and the mean prostate volume using the "Student T" test. Categorical variables were described as numbers and percentages, and tested by Chi-square test. The "p" value less than 0.05 was considered to show a significant difference. The parameters of diagnostic accuracy including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with corresponding 95% confidence intervals.

Results

There was no statistically significant difference between the two groups regarding the mean age with the mean age of the malignant patient group being 65.7±8.7 years and the mean age of the benign patient group being 61.6±6.5 years (p=0.064). The mean prostate volume of the benign patient group was significantly higher compared to the malignant group (p=0.003). While the mean total PSA of the malignant patient group was 13.7±16.5 ng/ml, the mean total PSA of the benign patient group was 6.8±3.3 ng/ml. The mean total PSA of the malignant group was significantly higher than that of the benign group (p=0.041). The mean PSA density of the malignant patient group was 0.33±0.46 ng/ml/cc, whereas that of the benign patient group was 0.09±0.05 ng/ml/cc. The mean PSA density of the malignant group was

Table 1: The comparison of patient characteristics between benign and malignant groups

	Benign patients (n = 26)	Malignant patients (n = 26)	P value
Age (mean±SD)	61,6±6,5	65,7± 8.7	0,064
Prostate volume (mean±SD)	96,4±77,7	47,4±17,3	0,003
Total PSA value (ng/ml) (mean±SD)	6,8±3,3	13,7±16,5	0,041
PSA density (ng/ml/cc) (mean±SD)	0,09±0,05	0,33±0,46	0,013

SD, standard deviation; PSA, prostate spesific antigen; n, number of cases.

Table 2. PI-RADS v2 scores of patients due to histopathologic results

PI-RADS v2 score	Histopathologic Results Benign patient group (n = 26)	Malignant patient group (n = 26)
PI-RADS 2	22	7
PI-RADS 3	4	6
PI-RADS 4	0	7
PI-RADS 5	0	6

n, number of cases; PI-RADSv2; Prostate Imaging Reporting and Data System version 2

Table 3: Diagnostic performance of multi-parametric MRI

	Results
Sensitivity	73.08%
Specificity	84.62%
Positive predictive value	82.61%
Negative predictive value	75.86%
Accuracy	78.85%

significantly higher as compared to the benign group (p=0.013). Table 1 shows the differences between the variables.

Table 2 shows the PI-RADSv2 scores of the malignant and benign groups obtained with MpMRI. The benign patient group was scored as PI-RADS 2 (n=22) and PI-RADS 3 (n=4) according to MpMRI. On the other hand, the malignant patient group was scored as PI-RADS 2 (n=7), PI-RADS 3 (n=6), PI-RADS 4 (n=7) and PI-RADS 5 (n=6) according to MpMRI. 19 of 26 malignant patients scored ≥3 in PI-RADS (Table 2). It was indicated that MpMRI had a sensitivity of 73.08% and a specificity of 84.62% in the diagnosis of prostate cancer. (Table 3). In cases with suspected prostate cancer, the PPV of the PI-RADSv2 score reported as a result of MpMRI was 82.61%, while its NPV was calculated as 75.86% (Table 3). The accuracy rate was found to be 78.85%. Figure 1 shows PI-RADSv2 categories by the Gleason score of the cases. Half of the cases (4/8) was scored as PI-RADS 2 in Gleason 3+3. In Gleason 4+3, however, half of the cases (3/6) was scored as PI-RADS 4 while the other half (3/6) was scored as PI-RADS 5.

Discussion

In this study, the PI-RADS scores of patients who underwent MpMRI with 1.5 Tesla for suspected prostate cancer in our clinic were retrospectively compared with the results of TRUS-guided prostate biopsies. The mean age, mean PSA value, mean PSA density, and prostate volumes of the patients were analysed. The diagnostic performance of MpMRI in the diagnosis of clinically significant cancer was evaluated.

In our study, the mean total PSA value and the mean PSA density of the malignant patient group were significantly higher compared to the benign patient group (p=0.013). It was demonstrated in the study by Shakir et al. that targeted biopsy with MRI increases diagnostic accuracy in patients with high PSA values [9].

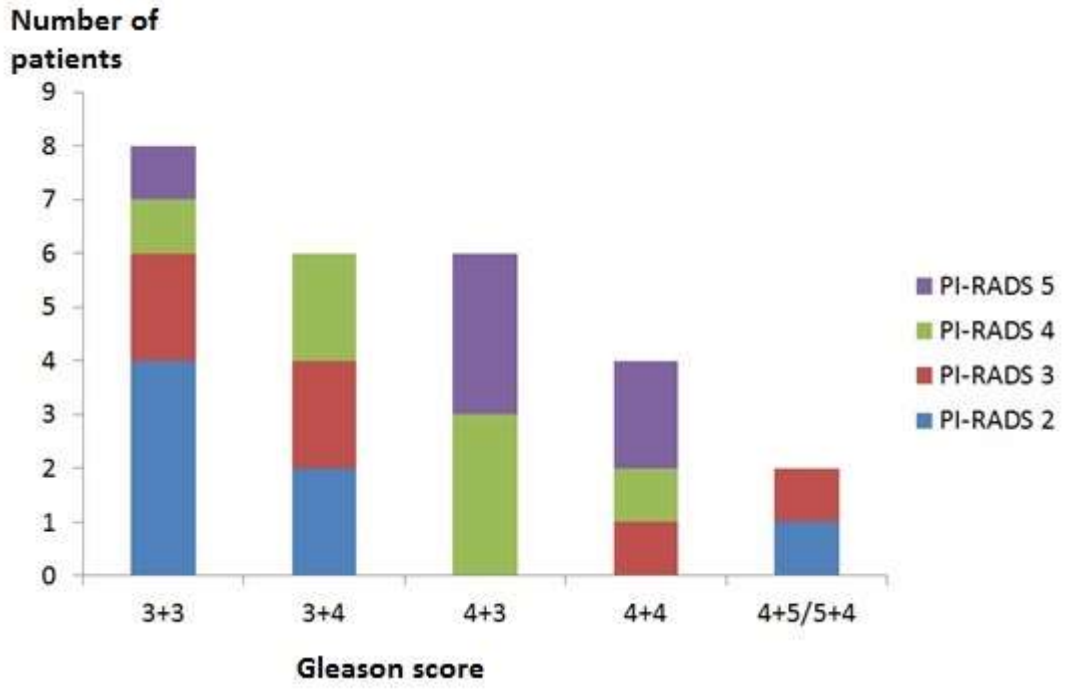

Figure1: Gleason scores of patients due to PI-RADSv2 category

In Shakir et al., the rate of diagnosed clinically significant prostate cancer was 56.2% in 1003 patients who underwent targeted and 12-quadrant TRUS-guided biopsies. In comparison with 12-quadrant systematic biopsy, targeted biopsy was able to detect a higher rate of clinically significant cancer. Furthermore, this diagnostic accuracy rate increased even more in patient groups with PSA values between 4 and 10 ng/ml and in those with PSA values >10 ng/ml. It was demonstrated that in patients with a total PSA of ≥ 5.2 ng/ml, targeted biopsy increases the accuracy of clinically significant prostate cancer diagnosis compared to conventional biopsy. In this study, we found the mean total PSA value as 13.7±16.5 ng/ml in malignant patients. In our study, the accuracy of TRUS biopsy is higher compared to the study conducted by Shakir et al. [9]. However, this may be due to the fact that there was a small number of patients in our study and that we did not make comparisons by dividing patients into subgroups according to PSA values.

In our study, we evaluated the accuracy of MpMRI in the diagnosis of clinically significant prostate cancer. As a result of histopathological examination, cognitive biopsy performed after MpMRI with 1.5 T torso coil to detect significant prostate cancer had a sensitivity of 73.08%, a specificity of 84.62%, a PPV of 82.6%, and a NPV of 75.86% with an accuracy rate of 78.85%. As Tamada et al. found in their retrospective study conducted on 50 patients with a total PSA value ranging from 4-10 ng/ml that MpMRI performed with 1.5 T had a sensitivity of 83%, a specificity of 80%, PPV of 91%, and NPV of 67%, and an accuracy rate of 82% in the diagnosis of prostate cancer similar to our results [10]. In the study Tanimoto et al. retrospectively investigated 83 patients with high PSA values using a 1.5 T system, the sensitivity, specificity and accuracy rate of MpMRI were found to be 95%, 74% and 86%, respectively [11]. Compared to our study, the diagnostic performance of MpMRI was higher than the study of Tanimoto et al. [11]. Although there are some minor differences in the diagnostic performance of MRI among the studies performed with a 1.5 T MRI device in the literature, MpMRI is a non-invasive technique

with high accuracy rates in the diagnosis of prostate cancer as stated in our study.

Sertdemir et al. reported that prostate cancer could be better distinguished from chronic prostatitis at 3 T MRI compared with 1.5 T MRI [12]. Another study in which Ulrich et al. made a comparison between 1.5 T MRI and 3 T MRI revealed that the signal-to-noise ratio (SNR) and the contrast-to-noise ratio (CNR) were similar in T2W images at both magnetic field strengths (p=0.7-1); however, SNR and CNR were significantly lower in DWIs obtained with 1.5 T MRI compared to 3 T MRI (p<0.01) [13]. When DWI is important in the evaluation of clinically significant cancers in the peripheral zone, 3 T MRI may be preferred. Using a 1.5 T device may have affected the sensitivity and specificity in our study, leading to relatively lower accuracy rates compared to previous studies with 3 T.

Our study has some limitations that should be noted. Our study was designed with a retrospective design. Performing TRUS-guided cognitive biopsy in MpMRI instead of using MRI-guided in-bore biopsy or MRI/TRUS fusion-guided biopsy for lesions suspected to have cancer may have affected our accuracy rates. Recent studies have demonstrated that compared to systematic biopsy, MRI-guided biopsy improves diagnostic performance in detecting clinically significant cancers [14]. Furthermore, although anterior prostate cancer represents a considerable part of all prostate cancer types, systematic TRUS biopsy may be insufficient in the diagnosis of such lesions. Turkbey et al. reported that anterior prostate cancer could be detected higher in fusion biopsy as compared to systematic TRUS biopsy [15]. Moreover, it was revealed that MRI and subsequent MRI/US-fusion biopsy increased the diagnosis rate of lesions that were missed by systematic biopsy [9, 15]. Another limitation is that as the measurements were carried out by a single radiologist, we were not able to conduct an analysis for inter-observer agreement. To evaluate the diagnostic performance of 1.5 T MpMRI, it is necessary to conduct studies on larger patient groups that include risk factors.

Conclusion

This study demonstrated the ability of 1.5 T MpMRI performed in our institution to predict the results of TRUS biopsy. Even though our results have lower accuracy rates compared to the studies performed with 3 T MRI in the literature, it can be concluded considering the high NPV of 1.5 T MRI in our study that MpMRI can prevent unnecessary biopsy in patients with high PSA. Performing biopsy for the suspicious area determined by MpMRI in patients with high PSA will increase biopsy performance and diagnostic accuracy.

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Original Article

Long-Term Oncological Outcomes for Patients Treated with Oncoplastic Breast-Conserving Surgery

Onkoplastik Meme Cerrahisi Uygulanan Hastalarda Uzun Dönem Onkolojik Sonuçlar

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ABSTRACT

Purpose: Oncoplastic breast surgery is a safe and effective surgical technique that improves aesthetic outcomes and broadens the indication for breast-conserving surgery for larger tumors. The purpose of this study was to assess the long-term oncological results of oncoplastic breast-conserving surgery in breast cancer patients.

Methods: This is a retrospective study of 230 breast cancer patients who underwent volume displacement oncoplastic breast surgery techniques between 2007 and 2014. We did not limit our data due to the tumor stage to analyze all and see if tumor size affects the safety of this technique.

We explored patient and tumor characteristics, surgical treatments, surgery-related complications, and pathological outcomes. Moreover, disease-free survival, overall survival, and local recurrence rates of 10 years follow-up were also estimated.

Results: The median follow-up time was 73 months (range 7–149 months). The 10-year disease free survival (DFS) rate was 74.4%, and 10-year overall survival (OS) was 80.0%. The 10-year local recurrence rate was 1.7%. The early complication rate was 22.6%.

Conclusions: The oncoplastic breast-conserving surgery is a method that can be applied safely without unfavorable effects on local relapse and survival rates, even for large tumors.

Keywords: Breast Cancer, Breast-Conserving Surgery, Oncoplastic Breast Surgery

ÖZET

Amaç: Onkoplastik meme cerrahisi, büyük tümörlerde bile iyi estetik sonuçlarla meme koruyucu cerrahi imkanı sağlayan bir tekniktir. Bu çalışma, onkoplastik meme cerrahisi ile tedavi edilmiş hastalarda uzun dönem onkolojik sonuçların değerlendirilmesini amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada, 2007-2014 yılları arasında hastanemizde onkoplastik meme cerrahisi teknikleri kullanılarak opere edilmiş 230 meme kanseri hastasına ait veriler retrospektif olarak değerlendirilmiştir. Bu alanda yapılmış benzer çalışmaların çoğunda erken evre meme kanseri hastalarına ait veriler bulunmaktadır. Biz böyle bir kısıtlama yapmadan tüm hastalarımıza ait verileri değerlendirerek, tümör boyutunun bu tekniğin güvenilirliğini etkileyip etkilemediğini araştırdık.

Ayrıca, hasta ve tümör özellikleri, uygulanan cerrahi yöntem, cerrahi komplikasyonlar, patolojik sonuçlar ile lokal nüks ve sağkalım özellikleri incelendi.

Bulgular: Median takip süresi 73 ay (aralık 7–149 ay) idi. 10 yıllık hastalıksız sağkalım oranı %74.4 ve 10 yıllık toplam sağkalım oranı %80.0 olarak bulundu. 10 yıllık lokal nüks oranı %1.7 idi. Erken komplikasyon oranı %22.6 olarak tespit edildi.

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Sonuç: Onkoplastik meme cerrahisi, büyük tümörü olan hastalarda bile komplikasyon, lokal nüks ve sağkalım oranlarında olumsuzluğa neden olmadan güvenle uygulanabilir bir yöntemdir.

Anahtar kelimeler: Meme kanseri, Onkoplastik meme cerrahisi, Meme koruyucu cerrahi

Introduction

The main objective during breast-conserving surgery (BCS) is to remove the tumor with negative surgical margins (SM) and maintain local control [1,2]. Rather poor cosmetic results could be observed in patients, particularly when a wide excision is performed. The purpose of BCS is increasingly shifting to cosmetic outcomes and patient satisfaction. Although the use of wide excisions contributes to maintaining local disease control, satisfactory results can be achieved via oncoplastic breast-conserving surgery (OBCS). These approaches allow large tumors in large breasts to be removed with improved cosmetic results [3].

BCS with adjuvant radiotherapy (RT) has been established as oncologically safe [4-7]. One of the most important advantages of OBCS is that postoperative RT planning is more manageable for patients with macro-mastia; in addition, treatment with low doses can be maintained.

In general, OBCS includes two types of techniques. Volume displacement techniques involve glandular or dermoglandular trans-position after resection, whereas volume replacement techniques involve autologous tissue or implants.

In this study, we evaluated data from patients who were surgically treated using volume displacement techniques. The aim of this study is to explore long-term oncological outcomes.

Materials and methods

In this study, data of 230 patients treated using several OBCS techniques at Ankara Oncology Hospital between 2007 and 2014 were retrospectively analyzed. The data were collected from the hospital database and operation room records.

Patient selection: Patients treated with classical BCS were not included in this study. In addition, patients with systemic metastases or another primary malignancy and patients who had neoadjuvant chemotherapy were excluded. Patients whose records could not be reached were also excluded.

Most of the similar studies had evaluated only patients with early-stage breast tumors. We did not limit our data due to the tumor stage to analyze all and see if tumor size affects the safety of this technique.

We explored patient and tumor characteristics (age, pathological subtypes, receptor status, pathological tumor size, axillary status, and pathological status), performed surgical technique, surgery-related complications, and pathological outcomes. We noted the excised tissue amounts from the operating room records, as all tissue weights were measured with a kitchen scale at the time of the surgery. Moreover, disease-free survival, overall survival, and local recurrence rates of 10 years follow-up were also estimated.

A local recurrence was defined as a tumor recurrence in the same breast with similar morphological characteristics as the primary tumor. Regional recurrence was registered as an event in the ipsilateral lymph nodes, including axillary, infra-clavicular region, intramammarian, or internal mammarian chain.

Surgical techniques: There are different volume displacement techniques involving glandular or dermoglandular transposition after tumor resection. Glandular tissue reshaping involves covering the parenchymal

defect by undermining the surrounding glandular tissues and suturing adjacent glandular tissues or by transposing glandular tissues surrounding the defect [8].

The method that was applied was determined based on the breast volume and tumor location. Applied techniques in our clinic were inferior and superior pedicle wise–pattern mammaplasty, an upper-outer quadrantectomy-racket excision, batwing, and round block (doughnut mastopexy) techniques [9-10]. Through these methods, the nipple-areolar complex and dermo-glandular flap could be safely supplied with blood through a virtual pedicle (superior, medial or inferior), and a significant amount of breast tissue and excessive skin could also be removed.

The inferior pedicle technique (wise–pattern mammaplasty) was primarily preferred for tumors located in the superior quadrants of the breast. The superior pedicle technique was preferred for the tumors located in the lower pole of the breast.

Batwing and round block techniques were preferred for tumors located in the central part of the breast and above the nipple-areola complex (NAC).

An upper-outer quadrantectomy-racket excision technique was preferred for upper-outer quadrant tumors. Radial fusiform racket incisions were planned to include the skin over the tumor bed in the upper-outer quadrant of the breast. These incisions were extended from the areola to the axillary hairy skin. A fusiform excision including subcutaneous tissue and pectoral fascia was performed. This technique allows us to perform a sentinel lymph node biopsy (SLNB) and axillary dissection (AD) using the same incision [11].

Contralateral breast symmetrization operations were performed, based on the patients' decisions, in the same session.

There is no standard definition for surgical margin positivity [1,12-16]. However, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines [17] for breast cancer define the positive margins after BCS as "ink on tumor" for both invasive cancer and DCIS and recommend re-excision for positive margins. In contrast, for patients with pure DCIS, at least a 2 mm resection margin width is associated with a reduced risk of ipsilateral breast tumor recurrence. In our study, surgical margin positivity was evaluated as margins <1 mm for invasive tumors and ≥2 mm for DCIS.

Statistical analysis: Patient characteristics were given as numbers and percentages, continuous data as median (minimum-maximum). The Pearson Chi-square test and Fisher's exact test were used to analyze categorical variables, and an independent sample t-test analysis was used to analyze continuous variables. P values <0.05 were considered statistically significant. The Kaplan-Meier method was used to determine the breast cancer recurrence rate and survival. All analyses were performed with SPSS software (version 15.0; SPSS Inc., Chicago, IL).

Ethical consideration: The data were collected retrospectively and approved by the Institutional Review Board of "University of Health Sciences Dr AY Ankara Oncology Health Application and Research Center" (Approval Code: 2021-05/1182). This study was conducted in accordance with the ethical standarts stated by the 1964 declaration of Helsinki.

Results

Patient and tumor characteristics:

The median age was 50 years (range 27-82). The median follow-up time was 73 months (range 7-149).

Table 1.—Tumor characteristics

Tumor characteristics	N (%)
Pathological subtypes	
Invasive ductal	166 (72.2%)
Invasive lobular	7 (3.0%)
Mixed	10 (4.3%)
DCIS	25 (10.9%)
Other*	22 (9.6%)
ER	
Positive	179 (77.8%)
Negative	51 (22.2%)
PR	
Positive	162 (70.4%)
Negative	68 (29.6%)
C erb B2†	
Positive	17 (7.4%)
Negative	187 (81.3%)
N/A	26 (11.3%)
Tumor size	
Tis	25 (10.9%)
T1	77 (33.5%)
T2	114 (49.6%)
T3	14 (6.1%)
Axilla	
N0	154 (67.0%)
N1	53 (23.0%)
N2	16 (7.0%)
N3	7 (3.0%)

**tubular, medullary, papillary, mucinous, metaplastic carcinoma, small cell carcinoma, †only invasive tumors, N/A not available*

Most of the patients had stage-2a tumors (35.3%). There were 14 (6.1%) patients who had T3 tumors. Besides, 76 patients (33.0%) had lymph node metastases. In total, 166 patients (72.2%) were pathologically diagnosed with invasive ductal carcinoma, and 108 of these patients (65%) had extensive intraductal components. We found 22 patient tumors at grade (G)1, while 117 were G2 and 91 were G3. The final pathological evaluation results are summarized in Table 1.

Symmetrization and pathological outcomes:

A symmetrization mammoplasty procedure was performed on 53 patients (23.0%). Three (5.7%) invasive tumors, 3 (5.7%) ductal carcinoma in-situ (DCIS) and 8 (15.1%) atypical ductal hyperplasia were recorded by pathological evaluation of contralateral breast tissue. All patients who were diagnosed with occult invasive tumors of the contralateral breast had invasive ductal tumors at the primary tumor side.

Surgical treatment:

We performed the inferior pedicle technique on 87 patients (37.8%), superior pedicle technique on 28 patients (12.2%), racket excision technique on 92 patients (40%), and batwing and round block techniques on 23 patients (10%).

The removed tissue amounts were <100 gr for 17 patients (7.4%), 100-500 gr for 106 patients (46.1%), 501-1000 gr for 81 patients (35.2%) and >1000 gr for 26 patients (11.3%).

A highly significant relationship was noted between the removed tissue and surgical technique applied ($p<0.001$) (Table 2). The largest amounts of tissue were removed with the inferior pedicle technique.

There is no standard definition for surgical margin positivity [1,10-14]. In our study, surgical margin positivity was evaluated as margins <1 mm for invasive tumors and ≥2 mm for DCIS. Although a minimum of 198 patients had negative resection margins (86.1%), the tumor distances to resection margins were closer than supposed to be for 32 patients (13.9%).

Reoperation was performed for 19 patients (8.3%). Specifically, 6 of these patients (18.8%) underwent re-excision, and 13 patients (40.6%) underwent a mastectomy. Nevertheless, as we mentioned before, we identified 32 patients who had positive resection margins. Thirteen patients rejected the re-excission offer and had RT. Two patients who refused re-excision and two others who had completed their treatment procedures had local recurrences (LR). We found a significant relationship between LR and SM positivity ($p=0.035$).

We found a significant relationship between SM positivity and tumor size ($p=0.008$). In particular, SM positivity was detected more

Table 2. Relationship between removed tissue amount, surgical technique and surgical margins

Surgical technique	Removed tissue (gr)	n (%)	Negative SM n (%)	Positive SM n (%)
Inferior pedicle	<100 g	1 (1.1%)	1 (1.1%)	0 (0%)
	100-500 g	20 (23.0%)	19 (21.8%)	1 (1.1%)
	500-1000 g	50 (57.5%)	43 (49.4%)	7 (8.0%)
	>1000 g	16 (18.4%)	13 (14.9%)	3 (3.4%)
Superior pedicle	<100 g	0 (0%)	0 (0%)	0 (0%)
	100-500 g	11 (39.3%)	9 (32.1%)	2 (7.1%)
	500-1000 g	14 (50.0%)	12 (42.9%)	2 (7.1%)
	>1000 g	3 (10.7%)	3 (10.7%)	0 (0%)
Intraglandular flap	<100 g	15 (16.3%)	12 (13.0%)	3 (3.3%)
	100-500 g	57 (62.0%)	47 (51.1%)	10 (10.9%)
	500-1000 g	14 (15.2%)	14 (15.2%)	0 (0%)
	>1000 g	6 (6.5%)	5 (5.4%)	1 (1.1%)
Other*	<100 g	1 (4.3%)	1 (4.3%)	0 (0%)
	100-500 g	18 (78.3%)	15 (65.2%)	3 (13.0%)
	500-1000 g	3(13.0%)	3 (13.0%)	0 (0%)
	>1000 g	1 (4.3%)	1 (4.3%)	0 (0%)

SM: surgical margin
**Batwing and round block techniques*

Table 3. The relationship between the need for reoperation and pathological subtype *(p<0.001)*

	Reoperation		
	Yes	No	Total
Pathological subtype			
DCIS	6 (24.0%)	19 (76.0%)	25 (100%)
Inv ductal	15 (9.0%)	151 (91.0%)	166 (100%)
Inv lobular	3 (42.9%)	4 (57.1%)	7 (100%)
Mixed	5 (50.0%)	5 (50.0%)	10 (100%)
Other	4 (18.2%)	18 (81.8%)	22 (100%)
TOTAL	33 (14.3%)	197 (85.7%)	230 (100%)

Table 4.—Survival rates according to pathological stage

Stage	N (%)	10-year disease-free survival	10-year overall survival
0	25 (10.8%)	95,0%	100%
1	59 (25.4%)	89.6%	77.1%
2a	82 (35.3%)	87.0%	73.8%
2b	38 (16.4%)	73.8%	72.0%
3a	21 (9.1%)	71.4%	41.7%
3c	7 (3.0%)	68.6%	42.9%
TOTAL	230 (100%)		

often among patients who had T2 tumors (n=18). There was also a significant relationship between the pathological subtype and SM positivity (p=0.003). Fifteen patients diagnosed with invasive ductal carcinoma had positive SM. No significant relationship was observed with the excised tissue weight and surgical technique in regard to SM positivity. Eleven of 87 patients (12.6%) who underwent the inferior pedicle technique, 5 of 28 superior pedicle patients (14.3%), 14 of 92 intraglandular flap patients (15.2%), and 3 of 23 patients who had other techniques were SM-positive (Table 2).

No significant relationship could be established between the reoperation need and applied surgical technique, pathological stage or removed tissue weight; however,

reoperation need was significantly related to pathological subtypes ($p<0.001$). Reoperation was required more frequently for patients with mixed (50%) and invasive lobular carcinoma (42.9%) (Table 3).

SLNB was performed on 203 patients who had clinically negative axilla before surgery. In addition, 60 patients with a metastatic sentinel lymph node and 27 patients who had clinically positive axilla before surgery were also subjected to AD.

Adjuvant therapy:

Although 73% (n= 168) of patients were administered adjuvant chemotherapy, 79.6% (n= 183) of patients received hormonal therapy. Adjuvant whole breast RT was planned and applied for all patients.

Complications:

Wound complications during the early postoperative period were observed in 52 patients (22.6%). In particular, 13% of patients (n=30) exhibited wound separation, 5.7% of patients (n=13) exhibited infection, and the remaining patients (n=9) experienced rarely observed complications such as areola or skin necrosis.

Survival rates:

Four patients (1.7%) experienced LR at a median follow-up time of 73 months. The median interval between the primary breast cancer diagnosis and LR was 47 months (range, 33–57 months). For one of these patients, the inferior pedicle mammoplasty technique was performed, while the other three underwent superior pedicle mammoplasty. There were no significant differences in the LR rates among oncoplastic techniques ($p=0.35$).

Two patients had axillary recurrences. One patient developed axillary recurrence seven months after surgery; their SLNB was negative, and the patient underwent AD. The other patient experienced LR at the 42nd month and axillary recurrence at the 80th month after surgery. She also had AD with BCS.

In contrast, distant metastases were observed in 24 patients (10.4%). There was no significant relationship between distant metastasis with either surgical margin positivity or surgical technique.

We found no significant relationship between pathological stage and LR or OS in our series (Table 4).

The 10-year breast cancer-specific DFS rate was 74.4%, and 10-year OS rate was 80.0%. The 10-year LR rate was 1.7%, and the regional recurrence [RR] rate was 2.2%.

Discussion

The most important thing for breast cancer patients when administering BCS is applying primary oncologic surgical principles. Therefore, maintaining appropriate SM and achieving local control with a wide excision is critical and essential.

There is no universal definition of what constitutes a negative microscopic margin. For example, the NCCN guidelines [17] recommend re-excision for “ink on tumor”, whereas other guidelines suggest that adequate margins for DCIS should be ≥2 mm after BCS [1,15-17].

In a meta-analysis, Losken et al. [4] reported positive margins in 12.4% of OBCS and 20.6% for BCS alone. In another meta-analysis, Chen et al. [18] reported that the positive-margin rate showed differences between the BCS-alone and OBCS groups. In contrast, the re-excision rate was significantly lower in the OBCS group, which indicated a better therapeutic effect of OBCS than BCS alone. OBCS techniques allow large tumors in large breasts to be removed with improved cosmetic results [19,20].

In our study, we determined that 33 patients (14.2%) had positive resection margins. Most of the studies evaluated only patients with early-stage breast tumors. We did not limit our results to evaluate all of the OBCS experiences. The number of positive margins in our results may be related to not excluding patients with larger tumors. Furthermore, as we pointed out, 47% of patients (n=108) had invasive ductal carcinoma with an extensive intraductal component, which is a factor associated with close or positive SM leading to re-excision [17,21].

Macromastia has typically been a relative contra-indication to BCS due to difficulties with postoperative RT. However, this issue is no longer a problem for patients because OBCS causes decreases in breast volume. Our study determined that all of the patients had postoperative RT without compromise for macromastia.

Early and late complication rates were 22.6% and 21.8%, respectively. More late complications occurred in patients treated using the inferior pedicle technique. This may be explained by the fact that the largest amounts of tissue were removed with this technique.

Another advantage of OBCS is the capacity to maintain symmetrization in the opposite breast using the same technique. In 11.4% of patients, incidental malignancy was discovered, and high-risk lesions were found in 15.1% of 53 patients. These results remind us that the contralateral breast of a woman with breast cancer is at high risk for a new tumor, and underscores the importance of a routine pathological examination of contralateral breast specimens in breast cancer patients [22].

There are few studies reporting LR rates of OBSC [23-26]. A systematic review [3] that analyzed 88 articles focused on OBCS published between 2000-2011 reported LR in 0% to 7% of the patients. In a meta-analysis [19] comparing OBSC and BCS alone, LR rates were similar in both groups. Similarly, Kelemen et al. [27] found no difference in LRs between OBCS and conventional BCS. In another meta-analysis comparing OBCS and BCS, there was no significant difference in recurrence and reoperation rates [28]. Park et al. [29] evaluated the influence of margin status on LR at BCS. They found patients with close margins and those with negative margins both had an LR rate of 7% at 8 years. Similarly, Niinikoski et al. [30] found no differences in the positive SM or reoperation rates between OBCS and BCS. The LR rate was 1.7% in our series, which Is compatible with literature data. Two of the four patients had surgical margin positivity, and as we mentioned before, there was no significant relationship between LR and positive SM.

The DFS rate was 74.4% for a ten-year period, which is acceptable compared with the corresponding rates for BCS as a whole [28, 31]. De Lorenzi et al. [32] reported DFS rates of 69% in the OBCS group and 73.1% in the BCS-alone group at ten years.

Based on our long-term results, OBCS is a method that can be applied safely without increasing complications, local relapse, or survival rates even with large tumors.

The cosmetic concerns of women with breast cancer diagnosis should not be forgotten. We know that improved cosmetic results can be obtained without compromising oncological principles with OBCS.

OBCS is a method that can be applied safely and broadens the indication for BCS towards larger tumors.

We believe that the reliability of this method will be understood more clearly via studies involving longer follow-up periods. In addition, as mentioned before, as a result of the first international consensus conference on

standardization of oncoplastic BCS, there is a need for prospective multicenter studies to optimize patient selection and for standardized criteria to qualify and accredit OBCS training centers. Therefore, we expect OBCS to become increasingly common over time.

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Original Article

Evaluation of Effect and Side Effects of Pemetrexed in Patients with Advanced-Stage Lung Adenocarcinoma

İleri Evre Akciğer Adenokarsinom Hastalarında Pemetrexed'in Etki ve Yan Etki Değerlendirmesi

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ABSTRACT

Objectives: The purpose of this study was to evaluate the effectiveness and dose-limiting side effects of pemetrexed use in patients with advanced-stage non-small-cell lung adenocarcinoma.

Materials and Methods: This study was conducted retrospectively by examining the files of patients who received treatment between 2017 and 2019. The dose-limiting side effects of the patients were evaluated by looking at the blood tests taken before each cycle and the notes in their files. All toxicities were classified by using the Common Terminology Criteria for Adverse Events verison 5.

Findings: The most common dose-limiting side effect was neutropenia, which developed in 50% of the patients. Side effects that affecting all blood series were observed in 28,1% of patients. The incidence of side effects of platinum given with pemetrexed was similar. Longer median survival was statistically correlated within patients receiving pemetrexed + platinum combination chemotherapy in the second and subsequent lines ($p<0.05$).

Conclusions: Pemetrexed is an easily tolerated and effective chemotherapy agent in advanced-stage non-small-cell lung carcinomas.

Keywords: Lung cancer, chemotherapy, pemetrexed, side-effects, efficacy

ÖZET

Amaç: Bu çalışmada ileri evre akciğer adenokarsinomu hastalarında pemetrexed kullanımının etkinliğini ve doz kısıtlayıcı yan etkilerini değerlendirmek amaçlanmıştır.

Materyal ve metod: Bu çalışma 2017–2019 yılları arasında tedavi almış hastaların dosyaları retrospektif olarak incelenerek yapılmıştır. Hastaların gelişmiş olan doz kısıtlayıcı yan etkileri, her kür öncesi alınan kan tetkikleri ve dosyalarındaki notlara bakılarak değerlendirildi. Tüm toksisiteler Common Terminology Criteria for Adverse Events version 5 kullanılarak sınıflandırıldı.

Bulgular: Hastalarda en sık doz kısıtlayıcı yan etki 50% hastada gelişen nötropeni oldu. Hastaların 28,1%'inde tüm kan serilerini etkileyen yan etki görülmüştür. Pemetrexedle birlikte verilen platinlerin yan etki insidansları benzerdi. Pemetrexed platin kombinasyon kemoterapisini ikinci ve sonraki basamaklarda alan hastalarda daha uzun median sağkalımla saptandı ($p<0,05$).

Sonuç: Pemetrexed ileri evre akciğer adenokarsinomunda kolay tolere edilebilen, etkili bir kemoterapi ajanıdır.

Anahtar Kelimeler: Akciğer kanseri, Kemoterapi, Pemetrexed, Yan Etki, Etkinlik

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Introduction

Non-small-cell lung cancer is still among the leading causes of cancer-related death in both males and females worldwide. Platinum-based chemotherapy improves survival compared to palliative care in metastatic non-small-cell lung cancer patients with good performance scores. Platinum-based combined therapies including immunotherapy are among the standard treatments in first-line treatment in patients without driver mutation [1]. Of the two platinum used in lung cancer, cisplatin is superior to carboplatin in terms of survival, while carboplatin is a more tolerable treatment option [2].

As an antifolate metabolite, pemetrexed is a well-tolerated and effective cytotoxic agent in advanced-stage lung adenocarcinomas. Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase enzymes. As a result, RNA and DNA synthesis is inhibited. As used in non-small-cell lung adeno-carcinomas, it has been proven to be effective in malignant mesothelioma. It has recently been shown that the combination of pemetrexed and platinum-based chemo-therapy with pembrolizumab prolongs survival compared to chemotherapy regardless of PD-L1 level [3].

This study aimed to examine the effectiveness and toxicity profile of platinum + pemetrexed combination in patients with advanced-stage lung adenocarcinoma.

Materials and Methods

This study was conducted retrospectively by examining the medical records of the patients with advanced-stage lung adenocarcinoma treated in Medical Oncology Department of Sanlıurfa Mehmet Akif Inan Training and Research Hospital. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before the study, ethical approval was obtained from the Harran University clinical research ethics committee (Desicion number: HRU /21.07.27 Date: 29 March 2021).

Patients

Advanced-stage non-small cell lung cancer patients with a histologically confirmed diagnosis of adenocarcinoma who received treatment between January 1, 2017 and December 31, 2019 were included in the study. Inclusion criteria for the study were defined as being 18 years or older, before treatment having a platelet count of $100x10^9$ cells/L, a neutrophil count of more than $1.5x10^3$ cells/L, a total bilirubin level less than two times the upper limit of normal, aspartate aminotransferase (AST) level is less than three times the upper limit of normal or less than five times of normal in those with liver metastases, glomerular filtration rate (GFR) calculated with the Cockcroft-Gault formula being more than 45 ml/min, and an ECOG performance score being two or less.

Study Design

The histological diagnosis date of all patients was determined as the starting point. All patient's height, weight, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, total leukocyte count, neutrophil count, and platelet count were recorded before treatment. Body mass index (BMI) was calculated from height and weight values.

Patients with bone, liver, and brain metastases were identified. It was determined in which line pemetrexed was used and which platinum agent it was given with (cisplatin or carboplatin). During the treatment, patients who were given erythrocyte suspension were determined due to the decrease in hemoglobin value (below 10g/dl), and symptoms such as

tachycardia and dizziness they showed. The patients who developed neutropenia (neutrophil count below $1.5x10^3$ cells/dl) and thrombopenia (platelet count below $100x10^9$ cells/L) during treatment were determined. Nephrotoxicity was defined as a decrease of 25% or more from the baseline glomerular filtration rate (GFR). Those with AST levels were higher than three times the upper limit of normal or in patients with liver metastases, those with a value higher than five times the upper limit of normal were evaluated as hepatotoxicity. Toxicity assessments were made by examining blood tests taken before each treatment and were classified using the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5).

Treatments

All patients received treatment at a dose of 500 mg/m^2 pemetrexed every 21 days. Before the treatment, 400 µg folic acid supplementation was provided to all of them daily. All patients were given 1000 µg of vitamin B12 before treatment and repeated every nine weeks. The treatment scheme was continued until disease progression or development of unacceptable toxicity. Cisplatin, together with pemetrexed was given at a dose of 75 mg/m^2 every 21 days. Carboplatin was calculated according to the area under curve ((GFR+25)*AUC) Calvert formula and was given every 21 days. Platinums were not given after 6 cycles and pemetrexed was applied alone. All patients received routine premedication and supportive treatments such as antiemetics.

Statistical analysisThe Statistical Package for Social Sciences (SPSS) for Windows 21.0 program was used for the statistical analysis of the findings of the study. The Shapiro-Wilk test was used for the normality distribution analysis of independent samples. Continuous variables presented as mean+SD. Independent sample T-test was used for parametric data and Mann Whitney U test was used for the analysis of non-parametric data. Kaplan Meier analysis and Log-rank (mantel-cox) analysis were performed for survival analysis. The results were evaluated at the $p<0.05$ level and 95% confidence interval.

Findings

There were 32 patients in this study. The average age was 57.9±1.9 overall (range, 34 to 77 years), while it was 59±2 in males (n=27), and 52.2±6 in females (n=5). The average BMI of all patients was found to be 25.4±0.8, the mean BMI of male patients was 24.8±0.8, and the mean BMI of female patients was 28.5±2.4.

There were eight patients with bone metastases and nine patients with brain metastases. There were no bone and brain metastases in 18 patients. There was no patient with liver metastasis. The characteristics of the patients are given in Table 1.

The mean neutrophil count of the patients before the first cycle was 6400±2700/mm^3 (minimum 1990/mm^3, and maximum 11670/mm^3). The mean lymphocyte was found to be 2000±1000/mm^3 (minimum 310/mm^3, and maximum 6556/mm^3). Neutropenia did not develop in 16 patients during the treatment, and grade 1-4 neutropenia (<1500/mm^3) developed at least once in 16 patients. Grade 1-2 neutropenia developed in six patients, while grade 3-4 neutropenia developed in ten patients. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of development of neutropenia (p=0.296).

The mean hemoglobin value of the patients before treatment was 12.8±2.5 g/dl (minimum 7.42 g/dl, and maximum 16.58 g/dl). While taking pemetrexed and platinum combination, 11 patients did not need transfusion throughout the treatment. At least one unit of

Table 1: Characteristics of patients

Characteristics of patients	n (%)
Age	
≤60	20(61,3%)
>60	12(38,7%)
Sex	
Male	27(84,4%)
Female	5(15,6%)
Driver Gene Mutation	
Yes	4(12,6%)
No	28(87,4%)
Sites of Metastates	
Bone	8 (25%)
Brain	9(28,1%)
Liver	0(0%)
Bone+Brain	3(9,3%)
Pemetrexed+Platinum	
Cisplatin	15(46,9%)
Carboplatin	17(53,1%)
The Line of Using Pemetrexed	
First-Line	22(68,8%)
Second and Subsequent Lines	10(31,2%)
Toxicities (Grade 1-4)	
Anemia	11(34,4%)
Neutropenia	16(50%)
Thrombocytopenia	12(37,5%)
Anemia+ Thrombocytopenia+ Neutropenia	9(28,1%)
Without Hematological Toxicity	8(25%)
Nefrotoxicity	7(21,9%)
Hepatotoxicity	2(6,3%)

erythrocyte suspension was transfused to 21 patients. All the hemoglobin decreases that developed were at the level of grade 1-2. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of the development of anemia (p=0.909).

The mean platelet count of the patients before treatment was 283000±110000 /mm^3. While taking pemetrexed and platinum combination, thrombocytopenia (<100,000/mm^3) did not develop in 20 patients, but it did develop in 12 patients. Grade 3-4 thrombocytopenia developed in two patients, and grade 1-2 in ten patients. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of thrombocytopenia development (p=0.242). There was no statistically significant difference between those taking cisplatin and carboplatin in terms of any hematological toxicity development (p=0.546).

The mean AST level of the patients was 21.9±11.5 and the mean ALT level was 25.9±27. During the treatment period, hepatotoxicity developed in two patients, but not in 30 patients and all hepatotoxicity cases that developed were grade 1-2. Hepatotoxicity developed in two patients receiving carboplatin. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of hepatotoxicity development (p=0.177).

The mean GFR of the patients was found to be 89.5±18, the lowest GFR was 53 ml/min, the highest GFR was 120 ml/min. During the treatment period, nephrotoxicity developed in seven patients, but not in 25 patients. No patient developed renal failure requiring dialysis. All nephrotoxicities were at a level that could be treated with fluid replacement. Nephrotoxicity developed in five patients receiving ciplatin and two patients receiving carboplatin. There was no statistically significant difference between those taking

Table 2: Distribution of advers event in first and second or subsequent lines treatments

Advers event	First line treatment n(%)	Second or next line treatment n(%)	p
Any hematological toxicity	14(63,6%)	10(100%)	0.035
Need of transfusion	12(54,5%)	9(90%)	0,106
Neutropenia	7(31,8%)	9(90%)	0.006
Thrombocytopenia	6(27,3%)	6(60%)	0.119
Nephrotoxicity	5(22,7%)	2(20%)	1
Hepatotoxicity	1(4,5%)	1(10%)	0,534

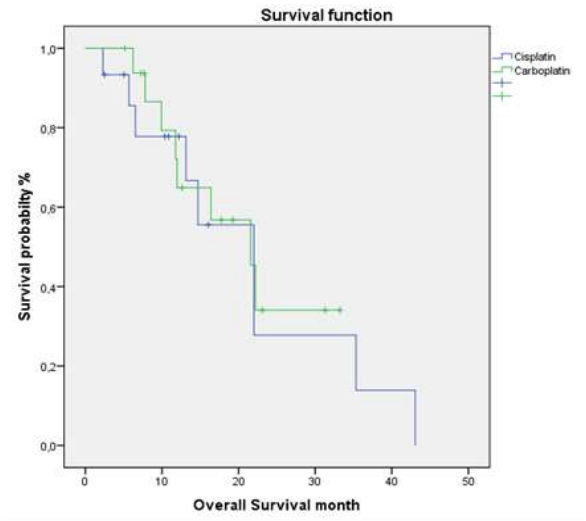

Figure 1: Analysis of overall survival among patients receiving Cisplatin or Carboplatin

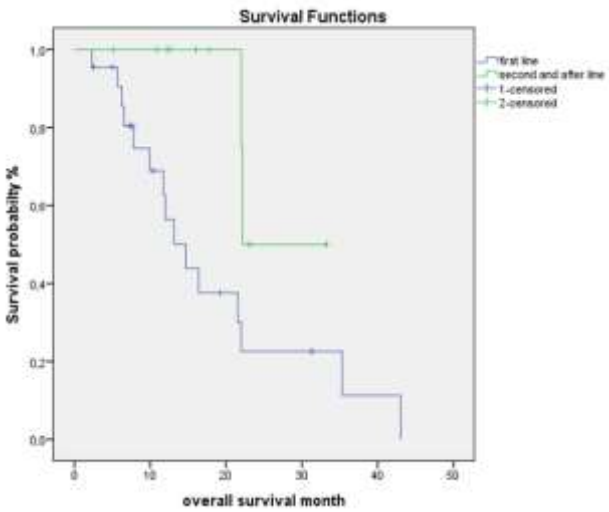

Figure 2: Relationship between pemetrexed use treatment line and overall survival analysis

cisplatin and carboplatin in terms of development of nephrotoxicity (p=0.147). There was no correlation between BMI measured before treatment and nephrotoxicity (p=0.618) The incidence of advers event in the first line treatment and second or subsequent lines treatments are given in Table 2.

While 15 patients were treated with the combination of cisplatin and pemetrexed, 17 patients were treated with the combination of carboplatin and pemetrexed. All patients received an average of 6.5±6.7 cycles of treatment (minimum of 1 and a maximum of 38 cycles of treatment). The median overall survival time of the patients was 12.41 months (95% CL 2.30-43.77 months). The median survival time from the start of pemetrexed was calculated as 8.86 months (95% CI 1.00-43.03 months). The median overall survival of those receiving cisplatin was 12.2 months (95% CI 2.3-43.07 months), and the median overall survival of those receiving carboplatin was 12.63 months (95% CI 5.13-33.13 months) as illustrated in Figure 1.

The combination of pemetrexed + platinum (cisplatin or carboplatin) was used in 22 patients in the first-line and in ten patients in the second or later lines. A median survival of 11.06 months (95% CI 2.3-43.07months) was

achieved in patients used in first-line. The median survival was found to be 16.9 months (95% CI 5.13-33.23 months) in patients used in the second and subsequent lines. The survival of patients who received pemetrexed in the second or later lines was statistically significantly longer than those who received it in the first-line ($p<0.05$), as illustrated in Figure 2.

Discussion

Non-small-cell lung cancer is the leading cause of cancer-related death worldwide. According to the 2016 report of national cancer statistics, the most common cancer in male at all ages is lung cancer [4]. While current treatment guidelines are category 1 option for all metastatic non-small-cell lung cancers, they also recommend examining PDL-1 for an immunotherapy option and molecular testing to detect driver mutations in non-adenocarcinoma types. Treatment is directed according to the results from these molecular tests.

In today's modern treatment protocols, tyrosine kinase inhibitors are the primary treatment option in patients with driver mutations. Immunotherapy is also a treatment option that has proven itself with its effectiveness in recent years and has come to the fore with its safe side-effect profile compared to chemotherapy. In recent years, the addition of chemotherapy to these treatment protocols has been investigated and a difference in survival is observed [3]. Surely, the addition of new generation agents to combination therapies changes the incidence, type, and degree of side effects. In this case, the evaluation of the side effects and knowing the agent causing the side effects are crucial in the management of the patients.

As a folate antagonist, pemetrexed is among the treatment options in nonsmall-cell nonsquamous lung cancer and malignant mesothelioma, and its effectiveness has been proven in all treatment lines [5]. Pemetrexed has side effects such as fatigue, nausea, vomiting, loss of appetite, and diarrhea due to folic antagonism. In addition to these, there are potentially serious side effects such as hepatotoxicity, nephrotoxicity, and hematological toxicities. These side effects are either limit the use or require a dose change.

Pemetrexed-associated hepatotoxicity is usually mild. It is associated with low-to-moderate liver serum enzyme elevations, but the findings are usually mild and transient. There is no jaundice and no accompanying symptoms. Enzyme elevations are more than three times the upper limit of normal in only 1-6% of patients. It is usually treated with dose intensity variation. Rarely, dose modification or discontinuation of treatment is required. No cases of significant liver injury attributed to pemetrexed have been reported. The mechanism of liver damage develops mostly as a result of folate metabolism. The hepatic metabolism of pemetrexed is minimum, it is mostly excreted by the kidneys [6]. Pemetrexed-associated hepatotoxicity is more common in patients with pre-existing liver injury. In our study, hepatotoxicity developed in 6.3% (n=2) patients and was found to be compatible with the literature. In this study, liver dysfunction was found at grade 1-2 level. Severe hepatic impairment did not develop in any of the patients. In cases where hepatotoxicity is encountered in patients using pemetrexed, other causes must be investigated. During this period, treatments should be delayed until the values return to normal.

Pemetrexed is excreted by renal elimination. 70-90% of the drug is excreted unchanged by the kidney in the first 24 hours. Previous studies have shown that its pharmacokinetics are directly related to creatinine clearance. Therefore, pemetrexed should be recommended to those with adequate renal function. Greater exposure with decreased creatinine clearance is known to be associated

with hematological toxicity. It is not recommended if the glomerular filtration rate is below 45 ml/min [7,8].

Cancer patients are usually patients with comorbid diseases and using many nephrotoxic drugs. These patients are likely to develop nephrotoxicity and, like all other drugs, chemotherapeutic agents should be chosen carefully [9]. Nephrotoxicity is an important treatment-limiting effect for pemetrexed therapy and a significant problem in patients who receive and respond to pemetrexed combination chemotherapy. In the Paramount study, it is reported that 7.8% of the patients encountered renal toxicity, and 4% had to stop the treatment. Moreover, they mentioned the cumulative effect of kidney toxicity in the treatment arm [10]. In our study group, the rate of nephrotoxicity was found to be 21.9% (n=7). Taking cisplatin or carboplatin with pemetrexed did not change the risk of developing nephrotoxicity. There was no relationship between BMI measured before treatment and the development of nephrotoxicity. While this nephrotoxicity may be due to pemetrexed, reasons such as higher GFR due to sarcopenia developing in cancer patients and insufficient hydration due to loss of appetite should be considered. Although the causes of nephrotoxicity development in our study were different, there may be a different actual result than the calculated value because the patients were gathered on a common ground. In order to determine the risk of developing nephro-toxicity, a research can be done with the data obtained by following the patients throughout the treatment.

Most clinical studies have reported pemetrexed-related hematological toxicities. Its effect on folate metabolism is shown as the cause. Vitamin B12 and folic acid supplementation is recommended to reduce pemeterexed-related hematological toxicities. All three series are affected by pemetrexed toxicity. When toxicity develops, the dose of pemetrexed should be reduced by 50% if the platelet count is below 50,000; if the platelet count is between 50,000-100,000 and the neutrophil count is below 500 mm^3/dl, the pemetrexed dose should be reduced by 25% [11,12]. In our study group, anemia developed in 11 patients, neutropenia in 16 patients, and thrombocytopenia in 12 patients. Nine patients were affected by all three series. No hematological toxicity was observed in eight patients. In general, hematological toxicities are more common than other toxicities, but they can be easily managed. While giving treatment, it should be remembered that hematologic toxicities can be seen in most patients.

The combination of pemetrexed and platinum has been tested at various lines in many studies. Scagliotti et al. compared the effect of pemetrexed with gemcitabine/cisplatin and pemetrexed/cisplatin combinations in first-line [12]. In Scagliotti et al. study, median overall survival was found to be 12.6 months in lung adenocarcinoma patients receiving pemetrexed. In a phase III randomized study by Grønberg et al., the combination of pemetrexed + carboplatin was tested in the first line. In that study, a median survival of 7.3 months was reached [13]. In a randomized phase III study conducted by Hanna et al. in 2004, pemetrexed and docetakel were compared in the second-line. The median survival for pemetrexed was found to be 8.3 months [14].

Although the number of patients in our study was very small for evaluation of efficacy and survival, our results were found to be consistent with the literature. In this study, patients who received pemetrexed in second or subsequent lines had better survival. This seems like a surprising result at first view. However, there were only 10 patients receiving pemetrexet in the second or subsequent series and four of them had a driver mutation. These are the patients who received targeted therapy in the first series and

has already a better survival than patients without a mutation. It should also be noted that lung cancer has a very short survival, especially in patients without a driver mutation. Patients who can receive second-line therapy may have a possibly slower course of disease or they may have a good responded to the first line treatment. As a result, we think that the better survival of those who received pemetrexed in the 2nd line may be related to these factors. We cannot present this data as the drug was more effective in the second lines.

The first limitation of this study was small number of patients. Secondly, because it was a retrospective study, we could not present the side effects that we could observe clinically, such as nausea, vomiting, and fatigue. The positive aspect of our study was that we were able to document side effects with detailed and closely followed laboratory tests.

Conclusions

In our study, pemetrexed combinations used in all treatment lines were beneficial in patients with advanced-stage lung adenocarcinoma. The combination of pemetrexed and platinum has an acceptable toxicity profile. The toxicity profile did not change with the platinum selection. The most common toxicity is hematological toxicities, primarily neutropenia. Another significant and frequent side effect is nephrotoxicity. Early detection and management of toxicities seems possible with close clinical and laboratory evaluation.

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Original Article

Contribution of Diffusion-Weighted Imaging and Ultrasound Elastography to the Diagnosis of Breast Cancer

Meme Kanserinde Difüzyon Ağırlıklı Görüntüleme ve Ultrason Elastografinin Tanıya Katkıları

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ABSTRACT

Introduction: The firmness of breast lesions helps to differentiate malignant masses from benign masses. Tissue stiffness can be evaluated quantitatively and objectively by magnetic resonance imaging (MRI) and ultrasonography (USG) using the apparent diffusion coefficient (ADC) and ultrasound elastography techniques, respectively. We aimed to determine the strain ratio (SR) and ADC and their contribution to the diagnosis in malignant breast masses using US elastography and diffusion MR sequences.

Methods: Our study included 50 lesions in 50 female patients over 18 years of age who had invasive breast cancer proven histopathologically by tru-cut biopsy and had breast US elastography and breast MRI examinations before biopsy in the Radiology clinic archive. Sonoelastographic studies were performed with a 13-18 Mhz linear high resolution volumetric probe (Toshiba Aplio 400, Japan, 2014). Imaging and measurements were made by a single practitioner with 10 years of experience in breast radiology. ADC values were measured from different parts of the lesion, not including cystic, necrotic and hemorrhagic areas, using 10-40 mm^2 ROI on ADC maps and the lowest ADC value was selected.

Results: A significant correlation between the SR and sizes of the masses ($p<0.001$). A correlation between the mass ADC and the size was found to be inversely proportional to each other, but suggesting statistically low significance ($p<0.031$). The highest SR and ADC were 92.79 in a single case with mixed intracystic mucinous and ductal carcinoma and $1.49x10^{-3}$ mm^2/s in a single case with mucinous carcinoma, respectively.

Discussion and Conclusion: Sonoelastography and DWI are relatively new non-invasive methods with high sensitivity and specificity. The use of these methods together with basic methods in breast diseases increases the diagnostic performance in the differentiation of benign and malignant breast lesions.

Keywords: breast cancer, diffusion weighted imaging, US elastography

ÖZET

Giriş ve Amaç: Meme lezyonlarının sertliği, malign kitleleri benign kitlelerden ayırmaya yardımcı olur. Doku sertliği, sırasıyla görünür difüzyon katsayısı (ADC) ve ultrason elastografi teknikleri kullanılarak manyetik rezonans görüntüleme (MRG) ve ultrasongrafi (US) ile kantitatif ve objektif olarak değerlendirilebilir. Bu çalışmada US elastografi ve difüzyon MR sekanslarını kullanarak malign meme kitlelerinde strain ratio (SR) ve görünür difüzyon katsayısı değerlerinin (ADC) ve tanıya katkılarını belirlemeyi amaçladık.

Yöntem ve Gereçler: Çalışmamıza İstanbul Eğitim veAraştırma Hastanesi Radyoloji Kliniği'nde Kasım 2013-Nisan 2014 tarihleri arasında, tru-cut biyopsi ile histopatolojik olarak kanıtlanmış invaziv meme kanseri olan ve Radyoloji kliniği arşivinde, biyopsi ve tedavi öncesi meme US elastografi ve

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meme MRG incelemeleri bulunan 18 yaş üzeri 50 kadın olguda 50 lezyon dahil edildi. Sonoelastografik incelemeler 13-18 Mhz lineer yüksek rezolüsyonlu volümetrik prob ile gerçekleştirildi (Toshiba Aplio 400, Japan, 2014). Görüntüleme ve ölçümler 10 yıl meme radyoloji tecrübesi olan tek uygulayıcı tarafından yapılmıştır. MR görüntüleri pron pozisyonda, bilateral 16 kanallı phased-array meme koili kullanılarak 1.5-Tesla MR cihazı (Signa HDi; GE Healthcare, Milwaukee, WI) ile gerçekleştirilmiştir. ADC haritalarında 10-40 mm^2 ROI kullanılarak lezyonun farklı bölgelerinden, kistik, nekrotik ve hemorajik alanları içermeyecek şekilde ADC değerleri ölçüldü. Bu değerler arasından en düşük ADC değeri seçildi.

Bulgular: Kitlelerin SR değerleri ile boyutları arasında birbiriyle doğru orantılı ve istatistiksel olarak orta derecede anlamlı ilişki izlenmektedir ($p<0.001$). Kitle ADC değeri ile boyut arasında ise birbiriyle ters orantılı ancak istatistiksel olarak düşük anlamlılık düşündüren korelasyon bulundu ($p<0.031$). Kitle ADC ve SR değerleri arasında anlamlı korelasyon izlenmedi ($p>0.05$). En yüksek SR değeri, mikst intrakistik müsinöz ve invazif duktal karsinom tanılı tek olguda 92.79 ve en yüksek ADC değeri ise müsinöz karsinom tanılı tek olguda $1.49x10^{-3}$ mm^2/s olarak elde edilmiştir.

Tartışma ve Sonuç: Ultrason Elastografi ve difüzyon ağırlıklı görüntüleme yüksek duyarlılık ve özgüllüğü olan invazif olmayan nisbeten yeni yöntemlerdir. Bu yöntemlerin meme hastalıklarında temel yöntemler ile birlikte kullanılması benign ve malign meme lezyonun ayrımında diagnostik performansı artırmaktadır.

Anahtar Kelimeler: meme kanseri, difüzyon ağırlıklı görüntüleme, US elastografi

Introduction

Breast cancer is currently the most frequently diagnosed cancer in women and the leading cause of cancer death worldwide [1]. Early and reliable diagnosis is the most effective method of reducing breast cancer-related deaths [2]. Although the early diagnosis rates of breast cancer increase with the widespread use of mammography (MG) and ultrasonography (US), these examinations may be insufficient to differentiate benign and malignant breast lesions. Therefore, magnetic resonance imaging (MRI) is increasingly used as a complementary and problem-solving method [2,3].

The firmness of breast lesions helps to differentiate malignant masses from benign masses. Tissue stiffness can be evaluated quantitatively and objectively with MRI and USG using the apparent diffusion coefficient (ADC) and ultrasound elastography techniques, respectively [4]. Previously, both techniques have been proven to be non-invasive imaging techniques that are beneficial in determining the malignancy risk of breast masses [5].

Diffusion-weighted imaging (DWI) is an MRI technique based on thermal energy-induced random motion (Brownian motion) of water molecules in biological tissues, and its quantitative parameter is ADC. In malignant tissue, low ADC values are expected due to the relatively reduced extracellular space due to increased cellularity, limited fluid diffusion, and increased nucleus/cytoplasm ratio. In many studies comparing ADC in malignant and benign lesions of the breast, significantly lower ADC values and diffusion restriction were observed in malignant lesions [6,7].

Elastography is a non-invasive imaging method used in combination with US. In elastography, the strain (elasticity) map of the compressed tissues is created. The basis of this technique is that tumor tissues are harder than normal tissues due to desmoplastic reaction and fibrosis, and hard tissues are more resistant to compression. Harder areas are seen in darker and blue tones on the strain map [8,9]. One of the elastography methods is the measurement of strain ratio, which is a semi-quantitative value. In this method, the average stiffness index of the mass, normal

glandular tissue or breast adipose tissue (strain index) is obtained by the device and the mass stiffness index is compared with the stiffness indices of the normal glandular tissue or breast adipose tissue with a special software. This ratio obtained is the strain ratio (SR) [8,10].

In this study, we aimed to determine the contribution of SR and ADC values to the diagnosis of malignant breast masses using US elastography and DWI methods.

Material and Method

Approval for the study was obtained from the Ethics Committee of Istanbul Training and Research Hospital, with the decision numbered 468.

Patient Selection

Our study was conducted in İstanbul Training and Research Hospital Radiology Clinic between November 2013 and April 2014. 50 lesions in 50 female patients with invasive breast cancer proven histopathologically by tru-cut biopsy and who had breast US elastography and breast MRI examinations were included. All of the MRI examinations were obtained before biopsy and treatment. A voluntary consent form was obtained from all patients.

Ultrasonographic B-mode and Elastography Evaluation

Ultrasonographic examinations were performed with a 13-18 Mhz linear high resolution volumetric probe (Toshiba Aplio 400, Japan, 2014). Imaging and measurements were made by a single practitioner with 10 years of experience in breast radiology. In the examination, all quadrants of the breast were scanned in different planes. The dimensions of the detected masses were measured and their longest diameters were included in the study.

Strain US elastography was performed in cases with a mass detected in B-mode US examination, by applying a one-second interval, repetitive compression at constant power, perpendicular to the lesion. Images with the same morphology and wave spectrum at least 5 times were analyzed. After the elastographic images were obtained, the strain values of the mass and adjacent adipose tissue were measured numerically with the ROIs placed on a static elastographic image, and the strain ratio (SR) values were obtained automatically by the device. Considering the color map obtained, the hardest areas without cystic, necrotic and calcification areas were selected for ROIs placed in the mass.

MRI Technique

MR images were performed in prone position with a 1.5-Tesla MR device (Signa HDi; GE Healthcare, Milwaukee, WI) using bilateral 16-channel phased-array breast coils. A standard protocol including contrast and diffusion-weighted imaging (DWI) sequences was used in all examinations. For DWI sequence, fat-suppressed pre-contrast axial single-shot echo planar imaging (EPI) sequence with b values of 0 and 800 s/mm^2 was used. Automatically generated ADC maps from DWIs with a special software were created on the GE advantage workstation (Figure 1). ADC values were measured by manually placing 20-40 mm^2 ROIs (region of interest) from different regions of the lesions on these maps, not including cystic, necrotic and hemorrhagic areas. Among these values, the lowest ADC values were selected.

Statistical Method

Descriptive statistics were presented as mean, standard deviation, and percentage. The mean of the two groups was compared with the t-test for independent groups. The mean of more than two groups was compared with one-way anova comparison methods. In the statistical evaluation, the correlation of the distribution of quantitative variables with each other and categorical features with each

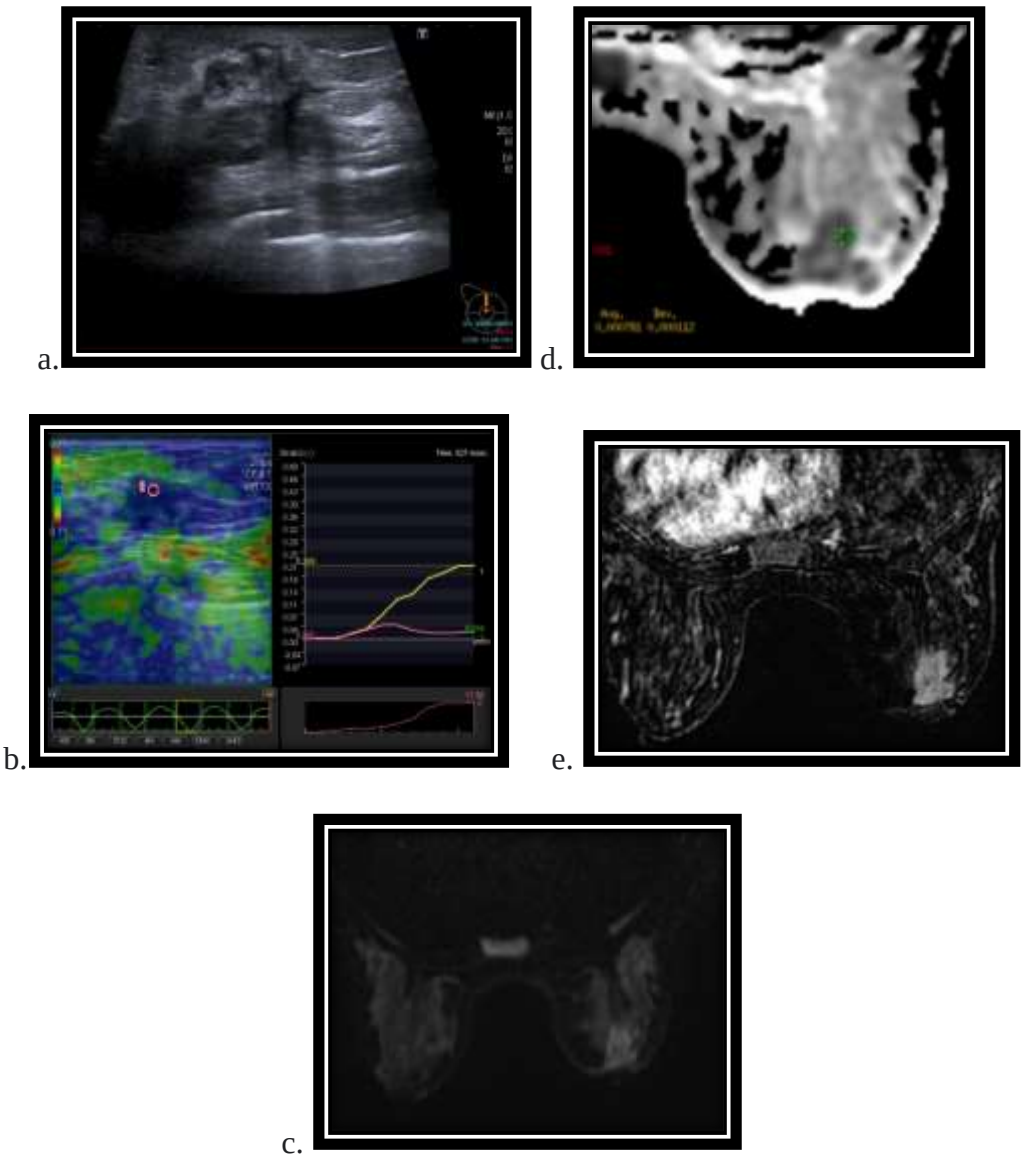

Figure 1. Retroareolar area of the right breast with gray scale USG (a) with irregularly defined lobulated contour, (b) SR value of 11.55 on US elastography, diffusion restriction on DWI (c), peripheral hypointensity on ADC map (d) and dynamic Contrast-enhanced examination (e) reveals a mass lesion with heterogeneous contrast-enhancing malignant character.

other was calculated using the Pearson test. Statistical analyzes were performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) package program. The significance level was accepted as 0.05 in all tests.

Results

A total of 50 patients and 50 lesions were included in the study. The ages of the cases were between 21 and 89, and the mean age was calculated as 53.38±13.2.

In the evaluation of the localization of the lesions, 20 lesions (40%) were located in the right breast and 30 lesions (60%) were located in the left breast.

In the evaluation made according to the localization of the lesions in the breast, quadrant localization; Each breast was divided into five quadrants and a retroareolar area. The distribution of the lesions according to their localization is given in Table 1.

Table 1. Distribution of lesions by localization

Localization	n	%
Upper outer quadrant	22	44.0
Lower outer quadrant	8	16.0
Upper medial quadrant	10	20.0
Lower medial quadrant	5	10.0
Retroareolar region	5	10.0
Total	50	100.0

Table 2. Descriptive statistical data of the size, strain ratio and ADC values of the lesions

	n	min	max	median	SD
Size (mm)	50	8.00	80.00	23.48	12.73
SR	50	4.42	92.79	20.60	20.21
ADC value (10^{-3} mm^2/s)	50	0.24	1.49	0.82	0.26

min:minimum, max:maximum, SD:standart deviation

Table 3. Data on the evaluation of the relationship between patient age, lesion dimensions and strain ratios with Pearson's test

		Age	Size	Strain ratio
Size (mm)	r	0.052		
	p	0.722		
	N	50		
Strain ratio	r	0.133	0.594	
	p	0.356	<0.001	
	N	50	50	
ADC value (10^{-3} mm^2/s)	r	0.055	-0.305	-0.154
	p	0.702	0.031	0.287
	N	50	50	50

ductal carcinomas (with no subcategories specified), one mixed invasive cribriform carcinoma and invasive tubular carcinoma, one mixed intracystic mucinous carcinoma and invasive ductal carcinoma, one mixed invasive ductal and invasive mucinous carcinoma, and one mucinous (N=50).

Descriptive statistical data of the size, strain ratio and ADC values of the lesions are given in Table 2.

The relationships between patient age, lesion sizes, strain ratios and ADC values were evaluated with the Pearson test, and the data are shown in Table 3.

A directly proportional and statistically moderately significant ($p<0.001$) (Figure 2) relationship is observed between the SR values and sizes of the masses. A correlation was found between the mass ADC value and the size, which was inversely proportional to each other, but was statistically insignificant ($p<0.031$). Bilateral relationships between age and strain ratio and between age and ADC value were not significant (Table 3). No statistically significant correlation was found between strain ratio and ADC value ($p>0.05$). Comparisons were made by side with the t-test to determine the connections between independent groups, but no statistically significant difference was found between the right and left sides.

In Figure 3, the distribution of ADC values according to the number of cases is shown in the form of histogram graph. For example, the lowest ADC value of $0.24x10^{-3}$ includes 2% of the cases. The highest ADC value was obtained as $1.49x10^{-3}$ mm^2/s in a single case with mucinous carcinoma.

Discussion

Breast cancer is the second most common type of cancer in all humans, after lung cancer, and the most common in women. Although breast MRI has a sensitivity of 89-100% in detecting invasive breast cancers, its specificity is around 72% [11].

Other advantages of DWI over contrast-enhanced MRI are that it can show microscopic cellular changes with high sensitivity without the need for contrast material, it provides numerical information about cellularity, and the scanning time is short [12]. While normal tissue shows intense signal loss on DWI, these areas appear bright because tumor cells restrict the movement of

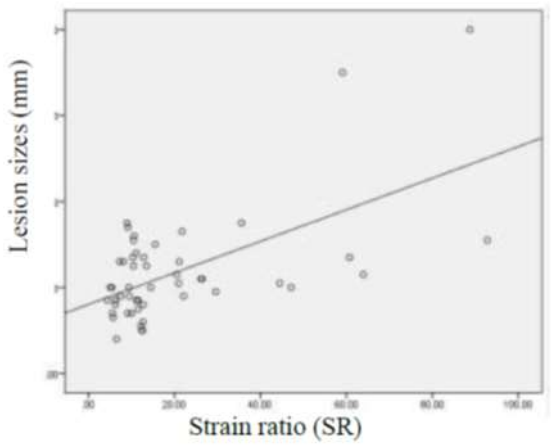

Figure 2. Scatterplot showing the relationship between SR values and sizes of the masse

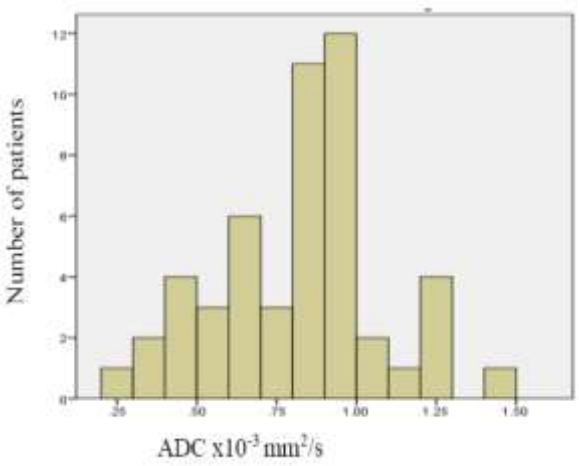

Figure 3. Histogram graph showing the distribution of mass ADC values according to the number of cases

molecules. DWI is basically obtained by adding the diffusion weight gradient known as the "b value" to the T2-weighted images. T2-weighted signal effect is more prominent in examinations performed with low b value (T2 shine through effect). Although the diffusion weight is more pronounced in the examinations used with a high b value, the are lower signal-noise (SNR) ratios. This affects the image quality [9,12,13].

The ADC value is the measurable numerical equivalent of the diffusion of water molecules in the tissues and can be represented as an ADC map showing the ADC of each voxel in each slice based on DWI. There is an inverse ratio between the ADC value and the cellular density of malignant breast masses. Lower ADC values were found in malignant breast masses with high cellularity [9].

The inclusion of DWI in breast MRI protocols is becoming widespread all over the world. DWI using ADC mapping can detect breast cancer with sensitivity up to 96% and specificity up to 100%. The main goal in the use of DWI is to distinguish between benign and malignant lesions in order to prevent unnecessary breast biopsies [14].

Being sensitive to tissue microstructure and cellularity, DWI provides quantitative information that can be used for lesion characterization. It has also been shown in multicenter studies that improved lesion characterization reduces the number of unnecessary biopsies [15]. Another factor affecting the ADC is the 'b value' used during shooting. The microperfusion effect of the tissue affects the ADC value and leads to higher values in the shots made using a low b value. However, there is no consensus in the literature on which b value is more suitable for breast diffusion studies.

Pereira et al. [12] reported that ADC values measured with 0 and 750 b values were slightly more reliable than other b values in the differentiation of malignant and benign breast masses. In our study, the b values used in DWIs were 0 and 850 s/mm^2.

It has been reported in the literature that malignant breast masses have lower ADC values compared to benign masses [9,12]. Chen et al. [16], in their meta-analysis study including 13 studies, reported that the mean ADC values of malignant breast masses varied between 0.87 and 1.36×10^{-3} mm^2/s, and the mean ADC values of benign breast lesions varied between 1.00 and 1.82×10^{-3} mm^2/s.

In our study, Kitajima et al. study [17], a low significant and inversely proportional correlation was found between mass ADC value and size ($p<0.031$). However, a study of Partridge et al. [18], using b values 0 and b 600 s/mm^2, reported that the size of the lesion had no effect on the ADC value.

Guo et al. [19], found that lesions with an ADC value of $1.30x10^{-3}$ mm^2/s and less were considered breast cancer, the sensitivity of DWI was reported as 93%, specificity 88%, and overall accuracy 91%. In our study, when the threshold value was $1.30x10^{-3}$ mm^2/s, 98% (n=49) of the masses were classified as malignant. The only case in our study that remained above this threshold value was mucinous carcinoma, and the ADC value was measured as $1.49x10^{-3}$ mm^2/s. Because mucinous cancers contain low cellularity and mucin islets, they show less diffusion restriction and higher ADC values compared to other malignant breast masses [20]. A study of Satake et al. [9] with 115 BIRADS (Breast Imaging-Reporting and Data System) category 4 and 5 breast masses, reported that the ADC value of mucinous cancer masses were greater than the threshold value and this finding is compatible with our study.

In the literature, the mean ADC value of malignant breast masses has been defined in many different studies: $0.75x10^{-3}$ mm^2/s [7], $0.907x10^{-3}$ mm^2/s (masses diagnosed only with invasive ductal carcinomas) [21], $0.97x10^{-3}$ mm^2/s [22], $1.09x10^{-3}$ mm^2/s [23]. In our study, the mean ADC value of malignant lesions was calculated as $0.82x10^{-3}$ mm^2/s. Considering that almost all of the lesions in our study were invasive ductal carcinoma, this value is compatible with the literature.

Itoh et al. [24] reported that there is a good correlation between real-time US elasto-graphy and histological analysis, and that this method has high sensitivity and specificity in the differentiation of benign and malignant masses.

Different SR values have been reported in the literature to differentiate benign and malignant masses. Mousa et al. [25], Zhi et al. [26] and Ueno et al. [27] reported the SR threshold value as 3.6, 3.05 and 4.8 in their study, respectively.

With all of the SR threshold values mentioned above, 100% of the masses in our study were classified in the malignant category, which is consistent with these studies. We think that these differences in SR values are due to the different pressures of the practitioners, the reference strain index being fibroglandular tissue or fatty tissue, the depth of the reference ROI and the difference in USG devices.

In many studies in the literature, it has been reported that there is a significant difference between the mean SR values of malignant and benign breast masses. Kim et al. [28] evaluated 157 lesions with US elastography, and reported the mean SR value of malignant lesions as 5.69±1.63 and benign lesions as 2.69±1.40. In our study, the mean SR value of malignant masses was 20.6±20.2, which is higher than literature. This may be because of the absence of in situ ductal or lobular carcinom cases in our study, unlike other studies.

In our study, it was shown that the SR values of the masses increased in direct proportion to their size. In parallel with our findings, in a multicenter study conducted with 1562 cases, it was shown that the stiffness of fibro-adenomas and malignant tumors was correlated with increasing lesion size, but there was no correlation between size and stiffness in other solid and cystic lesions of the breast and in-situ ductal cancers [29]. There are few studies in the literature evaluating the relationship between SR values and mass sizes in malignant masses.

The use of strain elastography as an elastography technique in our study can be considered as a limitation in terms of practitioner dependency, but we think that we

minimized this limitation by performing all measurements by a single practitioner with 10 years of breast radiology experience. In recent years, studies comparing the effectiveness of shear wave elastography and strain elastography with simultaneous applications have also shown that these elastography techniques have similar diagnostic performance [30,31]. In addition, the relatively small number of samples is among the limitations of our study.

Conclusion

US elastography and DWI are new non-invasive methods with high sensitivity and specificity. The use of these methods together with basic methods in breast diseases increases the diagnostic success in the differentiation of benign and malignant breast lesions.

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Original Article

Analysis of Demographic and Disease Characteristics of Patients with Chronic Myeloid Leukemia: A Single Centre Retrospective Analysis

Kronik Miyeloid Lösemili Hastaların Demografik ve Hastalık Özelliklerinin Analizi: Tek Merkezli Retrospektif Bir Analiz

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder, characterized by overproduction of cells of the myeloid series with the presence of the Philadelphia chromosome (Ph). With the development of tyrosine kinase inhibitors (TKIs), treatment options for CML have changed significantly. A key role in assessing the survival and prognosis of CML patients is the reduction of the BCR-ABL burden with appropriate treatment in defined time. The aim of this study was to analyze the clinical and demographic characteristics of CML patients, as well as their treatment efficacy, side-effect profiles, treatment resistance and survival.

Patients and methods: This retrospective study was conducted on patients diagnosed with BCR-ABL positive CML in the Hematology Department of our hospital between 2010 and 2020. The clinical and demographic characteristics of CML patients were analyzed together with treatment efficacy, side-effects, resistance to treatment, possible complications and survival.

Results: Evaluation was made of a total of 59 patients, with the mean age of 55.59±14.48 years, and median total follow-up period of 33.9 [0.2-172.0] months. All patients were given imatinib as the first-line treatment. Two patients were included in a trial of imatinib cessation at another center. At 12 months after imatinib treatment, 53.3% patients achieved major molecular response (BCR ABL <0.1). As second generation TKIs, dasatinib was preferred in 14 (46.7%) patients and nilotinib was preferred in 15 patients (50%). At 12 months after 2nd line TKI treatment, 77.8% patients achieved major molecular response (BCR ABL <0.1). Blastic transformation was detected in three patients during follow-up.

Conclusion: The results of the current study demonstrated that treatment options, response rates and side-effects were all comparable with the results of other real-world studies. Larger patient-based studies are needed to cover the course of the disease and to better manage these patients.

Key words: CML, management, treatment

ÖZET

Amaç: Kronik miyeloid lösemi (KML), Philadelphia kromozomunun (Ph) varlığı ve miyeloid serideki hücrelerin aşırı üretimi ile karakterize klonal miyeloproliferatif bir hastalıktır. Tirozin kinaz inhibitörlerinin (TKİ'ler) gelişmesiyle, KML için tedavi seçenekleri önemli ölçüde değişmiştir. KML hastalarının sağkalımını ve prognozunu değerlendirmede anahtar rol, BCR-ABL yükünün, uygun tedavi ile tanımlanan zaman ve değerde azalmasıdır. Bu çalışmanın amacı, KML hastalarının klinik ve demografik özelliklerinin yanı sıra tedavi etkinliklerini, yan etki profillerini, tedavi dirençlerini ve sağkalımlarını analiz etmekti.

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Gereç ve Yöntem: Bu retrospektif çalışma, 2010-2020 yılları arasında hastanemiz hematoloji bölümünde BCR-ABL pozitif KML tanısı alan hastalar üzerinde gerçekleştirilmiştir. KML hastalarının klinik ve demografik özellikleri, tedavi etkinliği, yan etkiler, tedaviye direnç, olası komplikasyonlar ve sağkalım parametreleri ile birlikte analiz edildi.
Bulgular: Bu çalışmaya toplam 59 hasta dahil edildi. Ortalama yaş 55.59±14.48 (yıl) ve medyan toplam takip süresi 33.9 [0.2-172.0] aydı. Tüm hastalara ilk tedavi olarak imatinib verildiği görüldü. Başka bir merkezdeki imatinib kesilme çalışmasına iki hasta dahil edildi. İmatinib tedavisinden 12 ay sonra, hastaların %53.3'ünde majör moleküler yanıt elde edildi (BCR ABL <0.1). İkinci kuşak TKİ olarak 14 (%46,7) hastada dasatinib, 15 hastada (%50) nilotinib tercih edildi. İkinci basamak TKİ tedavisinden 12 ay sonra, hastaların %77.8'i majör moleküler yanıt elde etti (BCR ABL <0.1). Üç hastada, takipte blastik transformasyon saptandı.
Sonuç: Mevcut çalışmanın sonuçları, tedavi seçeneklerinin, yanıt oranlarının ve yan etkilerin, mevcut literatür sonuçlarıyla karşılaştırılabilir olduğunu göstermiştir. Hastalıkların seyrini daha iyi yönetmek ve tedavilerini düzenlemek için daha geniş popülasyonlu çalışmalara ihtiyaç vardır.

Anahtar kelimeler: KML, yönetim, tedavi

Introduction

Chronic myeloid leukemia (CML) is a malignant hematological disorder that usually begins as a chronic phase (CP) and then reaches the accelerated phase (AP) and blastic phase (BP) within a short time if not treated and ends with death after the overproduction of clonal myeloproliferative cells due to the Philadelphia chromosome (Ph) effect [1, 2]. The incidence has been reported as 1-2 / 100,000 cases and 15% of all newly diagnosed leukemia cases. Since tyrosine kinase inhibitors (TKIs) came into use as the main treatment strategy, it was found that life expectancy approached that of the general population and there was a significant improvement in survival [3, 4]. Until the early 2000s, the treatment protocols planned for CML were extremely limited, consisting of toxic, non-specific, and non-promising agents such as busulfan, hydroxyurea, and interferon-alfa. Although there has been great progress in CML treatment with the use of TKIs, allogeneic-hematopoietic stem cell transplantation (allo-HSCT) is still an important therapeutic alternative for TKI-resistant patients [5, 6]. The key point in evaluating the survival and prognosis of CML is that the BCR-ABL burden has decreased in the defined time and value with appropriate treatment [7]. There are many different TKIs that can be used for the treatment of chronic phase CML by evaluating comorbidity, intolerance, mutation status or loss of efficacy [8].

The International Randomized Study of Interferon and STI571 (IRIS) has shown that imatinib, a tyrosine kinase inhibitor, is effective in newly diagnosed chronic phase chronic myeloid leukemia (CML-CP). In the same study, 343 patients were followed cytogenetically for 18 months and it revealed that patients treated with imatinib achieved a higher and sustained response than patients treated with interferon (IFN) plus cytarabine. The rate of complete cytogenetic response (CCyR) was 76% in imatinib arm and 15% in interferon (IFN) plus cytarabine arm [9].

Second-line therapy with nilotinib, dasatinib or bosutinib may provide high response rates in patients who have insufficient response to imatinib or who have been discontinued due to imatinib intolerance [10-12]. Ponatinib is a 3rd generation TKI option that is effective against all other TKI-resistant mutants including the BCR-ABL1 T315I mutation, which is also accepted as "gatekeeper", but can only be used in selected patients due to its high serious side-effects [13].

Table 1. Distribution of demographic characteristics and blood parameters of the patients

(N=59)	
Gender n (%)	
Female	29 (%49,2)
Male	30 (%50,8)
Age (year) Median [Min-Max]	55,0 [25,0-89,0]
Comorbidity n (%)	
No	36 (%61,0)
Yes	23 (%39,0)
Number of Comorbidities Median [Min-Max]	1,0 [1,0-4,0]
Hemoglobin (g/dL) Median [Min-Max]	11,3 [4,1-17,0]
WBC (×10^3/mm^3) Median [Min-Max]	68100,0 [5100,0-576500,0]
Neutrophil (×10^3/mm^3) Median [Min-Max]	52100,0 [3200,0-393000,0]
Platelet (×10^3/mm^3) Median [Min-Max]	298000,0 [64000,0-3803000,0]
Basophil (×10^3/mm^3) Median [Min-Max]	270,0 [0,0-25310,0]
Monocyte (×10^3/mm^3) Median [Min-Max]	2200,0 [200,0-28440,0]
LDH (/l) Median [Min-Max]	547,0 [152,0-2287,0]
Ferritin (ng/mL) Median [Min-Max]	69,5 [2,2-1119,0]
Vitamin B12 (pmol/L) Median [Min-Max]	925,5 [76,0-2000,0]

WBC:white blood cell, LDH: lactate dehydrogenase

The aim of this study was to analyze the clinical and demographic characteristics of CML patients, as well as treatment efficacy, side-effects, resistance to treatment, possible complications, and survival.

Patients and methods

This retrospective study was conducted on patients diagnosed with BCR-ABL positive CML in the hematology department of Diskapi Yildirim Beyazit Training and Research Hospital between 2010 and 2020. The diagnosis and classification of CML were made according to the WHO diagnostic criteria of myeloid neoplasms [14]. At the time of diagnosis, hematological, biochemical parameters and BCR-ABL IS levels were recorded. Demographic and disease characteristics of the patients, treatment management, complications, evaluation of the effect of planned treatment, distribution of first, second and next line treatment characteristics of patients, mutation analysis and follow-up periods were recorded for all patients.

Statistical analyses were performed using SPSS software (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used in the interpretation of the findings. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and / or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Approval for this study was given by the Local Ethics Committee (No: 107/2 Date: 22.03.2021).

Results

Evaluation was made of a total of 59 patients, comprising 30 (50.8%) females and 29 (49.2%) males with the mean age of 55.59 ±

Table 2. Distribution of findings regarding disease characteristics

(N=59)	
Splenomegaly	
No	24 (%40,7)
Yes	35 (%59,3)
Bone marrow blast at diagnosis (n=31)	
<%5	22 (%66,7)
%5-10	7 (%21,2)
>%10	4 (%12,1)
Eutos score Median [Min-Max]	12,0 [0,0-131,0]
Sokal score Median [Min-Max]	1,0 [0,6-20,0]
ELTSeutos score Median [Min-Max]	1,7 [0,7-3,2]
In diagnosis BCR-ABL IS (%) Median [Min-Max]	61,5 [0,0-291,4]
Total follow-up time (months) Median [Min-Max]	33,9 [0,2-172,0]
Final status	
Survivor	54 (%91,5)
Exitus	5 (%8,5)
Total follow-up time (months) Median [Min-Max]	33,9 [0,2-191,9]

Table 3. Distribution of patients' IMATINIB treatment characteristics

(N=59)	n (%)
BCR-ABL IS at 3rd month (n=42)	
≤10	28 (%66,7)
>10	14 (%33,3)
BCR-ABL IS at 6th month (n=39)	
≤1	27 (%69,2)
>1	12 (%30,8)
BCR-ABL IS at 12th month (n=30)	
≤0,1	16 (%53,3)
>0,1	14 (%46,7)
Adverse effects (n=8)	
Allergic rx-skin rash	2 (%18,2)
Nausea, vomiting, peripheral edema	1 (%9,1)
Drug eruption	1 (%9,1)
Leukopenia-skin rashes	1 (%9,1)
Pancytopenia	3 (%27,2)
Peripheral edema	2 (%18,2)
Cytopenia	1 (%9,1)
Total treatment duration Median [Min-Max], months	11,6 [0,0-87,7]

Table 4. Distribution of second and next line treatment characteristics of patients

(N=59)	n (%)
Reason for discontinuation of Imatinib (n=31)	
Inadequate response	19 (%61,3)
Adverse effect	10 (%32,3)
Discontinuation trial	2 (%6,4)
2nd line treatment type (n=29)	
Dasatinib	14 (%48,3)
Nilotinib	15 (%51,7)
BCR-ABL IS at 3rd months after 2nd line TKI (n=19)	
≤10	18 (%94,7)
>10	1 (%5,3)
BCR-ABL IS at 6th months after 2nd line TKI (n=17)	
≤1	15 (%88,2)
>1	2 (%11,8)
BCR-ABL IS at 12th months after 2nd line TKI (n=18)	
≤0,1	14 (%77,8)
>0,1	4 (%22,2)
Reason for discontinuation of 2nd line TKI (n=8)	
Inadequate response	4 (%50)
Adverse effect	4 (%50)
3rd line treatment type (n=8)	
Dasatinib	3 (%37,5)
Nilotinib	3 (%37,5)
Bosutinib	2 (%25)
Reason for discontinuation of 3rd line TKI (n=3)	
Inadequate response	3 (%100)
Adverse effect	-
4th line treatment type (n=3)	
Dasatinib	-
Nilotinib	-
Bosutinib	3 (%100)

14.48 years. At least one comorbidity was present in 23 (39.0%) patients. The distribution of demographic characteristics, hematological and biochemical parameters of the patients is shown in Table 1. The median total follow-up duration was 33.9 [0.2-172.0] months. At the last follow-up, 54 (91.5%) patients were survivors, and five (8.5%) patients were non-survivors. The median Sokal score was 1.0 [0.6-20.0]. Median BCR-ABL IS (%) at diagnosis was found to be 61.5 [0.0-291.4]. The distribution of findings related to disease characteristics is shown in Table 2.

All patients were given imatinib as the first-line treatment. Pancytopenia was seen as the most common side-effect leading to cessation of imatinib (n = 3, 27.2%). At 12 months after imatinib treatment, 16 patients achieved major molecular response (BCR ABL <0.1). The distribution of the first-line imatinib treatment characteristics of the patients is given in Table 3. During the follow-up, imatinib was discontinued in 19 patients due to insufficient response and in 10 patients for other reasons, and second generation TKIs were started. Two patients were included in the imatinib cessation trial at another center. Among the second generation TKIs, dasatinib was preferred in 14 (46.7%) patients and nilotinib in 15 patients (50%). Although MMR was obtained under imatinib treatment in one patient, unexpected ALL conversion was detected. Also transformation to blastic phase

(AML) was detected in two patients. The distribution of the second and next line treatment characteristics of the patients is shown in Table 4.

Discussion

With the development of TKIs, treatment options for CML patients have changed significantly. As imatinib and other next generation TKIs have become widely used, survival rates have also recently increased, to even reach similar levels to those of healthy subjects [15-17]. Due to the prolongation of survival, the management of side effects as well as optimal response to treatment has become increasingly important.

The main purpose of this study was to examine not only the clinical and demographic characteristics of the patients, but also their treatment preferences and responses, and to compare these with findings in the literature. In a previous real-life study conducted in Turkey for CML, median age was reported to be 46.1 ± 14.8 years [18]. In the current study, the median age at diagnosis of CML was 55.59 ± 14.48 years. However, this wide difference in the median age parameter has been demonstrated in many countries and studies [19]. Similar to national real data, there was no difference between male and female patient rates as 50.8% of the patients were female and 49.2% male [18]. In the current study, the median follow-up time was 33.9 months, and 39% of the patients had documented comorbidities, which was similar to CML Study IV [20]. There are findings stating that the presence of comorbidity negatively affects the prognosis of CML. In the CML STUDY IV where the median age was 56 years, at least one comorbidity was found in 55.5% of the patients diagnosed with CML in Europe, and in the current study, the average age was found to be similar and patients had at least one comorbid disease. Splenomegaly, which is known to be a common physical examination finding in CML patients has been detected in approximately 50% of cases in previous studies, and in the current study this rate was 59.3% [3].

All the current study CML patients received imatinib as the first treatment due to the national health insurance protocol. However, if it is possible, second generation TKIs can be used as the first choice in high-risk patients, and those who are young or need early deep response results [3].

The Grade 3-4 adverse events of neutropenia (17%), thrombocytopenia (9%) and anemia (4%) have been reported in many studies, and in the current study, pancytopenia (27.2%) was observed [21]. In CML long-term treatment, imatinib intolerance is considered an important treatment problem.

The IRIS study showed that approximately 30% of 553 imatinib-treated patients with CML-CP discontinued imatinib after 4.5 years of follow-up due to insufficient response and adverse events [22]. Studies have compared TKI treatments in respect of achieving complete cytogenetic response (CCyR, Ph-positive meta-phases 0%; BCR-ABL1 transcripts [IS] ≤ 1% at 12 months or later) and significant survival benefit has been associated with CCyR for up to 12 months. Therefore, the primary endpoint of TKI therapy used in CML patients should be to achieve CCyR. In addition, achieving Major Molecular response (MMR) by reaching the target of [IS] 0.1% during treatment increases incident-free survival rates and provides longer CCyR times. In patients with loss of response during treatment, BCR-ABL [IS] >10% after 6 months of treatment or not reaching the CCyR target in 12 months, switching the TKI therapy should be considered [23-25]. In the current study, at 12 months after imatinib treatment, 16 patients

achieved major molecular response (BCR ABL <0.1).

Imatinib was discontinued in 19 patients because of insufficient response to TKI treatment during follow-up and in 10 patients for other reasons, and second generation treatments were then started. Similar to the literature, in 49% of patients first-line TKI treatment was terminated at the end of 12 months and second generation TKI treatment was started [26]. It was observed that dasatinib was preferred in 14 (46.7%) patients and nilotinib was preferred in 15 patients (50%) as a 2nd generation TKI. Bosutinib was not widely used as 2nd generation TKI because of national health insurance protocol issues. Most patients are followed in the CP (85% to 95%) if they are followed-up appropriately and in a timely manner, but if poorly controlled, CML can transform into accelerated or blastic phases very quickly [27]. CML-BP patients have a poor prognosis. It is considered to be the most resistant acute leukemia and objective responses are seen in 20% of patients, with a median survival of 2–5 months [28]. In the current study, despite the use of three different TKIs and strict BCR-ABL [IS] control, 2 patients transformed to blastic phase (AML) and died in less than 1 year.

Nevertheless, TKI discontinuation trials are ongoing worldwide and promising results have started to emerge. Of the current study patients, two were included in the imatinib cessation trial at another center in Turkey. One of these patients remains in treatment-free follow up after 3 years. The other patient had molecular relapse after 1 year without imatinib, and so it was re-started. The patient achieved MMR again and is still being followed up without any complications.

Limitations of this study were the retrospective design and the relatively small study group. With a longer total follow-up period for CML, survival rates after TKI treatment may have been seen to be similar to those of the normal population. There is a need for larger prospective studies to make more detailed analyses.

In conclusion, as imatinib and other next generation TKIs have become widely used in CML patients, survival rates have recently increased, and even become similar to those of healthy subjects. The results of the current study showed that the treatment options, response rates and side-effects were all comparable to the results of other real-world studies. Clinicians should focus on how to obtain the optimal response to drugs and the management of side-effects. Larger patient-based studies are needed to cover the course of the disease and to better manage these patients.

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Original Article

Standart Prophylactic Granulocyte Colony Stimulating Factor Usage as a Part of Autologous Stem Cell Transplantation Procedure

Otolog Kök Hücre Naklinin Bir Parçası Olarak Standart Profilaktik G-CSF Uygulanması

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ABSTRACT

Introduction: One of the major causes of morbidity and mortality of autologous hematopoietic stem cell transplantation (ASCT) is infections during prolonged neutropenia. In this study, we aimed to investigate the effect of prophylactic G-CSF use in ASCT patient on the frequency of infection, duration of neutrophil engraftment and neutropenia, length of hospital stay and transplant-related morbidity and mortality.

Methods: G-CSF has been routinely used after autologous stem cell transplantation in our unit for 3 years since February 2014. In this study, three years before and after the application consecutive auto-HSCT data were collected retrospectively. In addition to routine antimicrobial prophylaxis, In the group receiving G-CSF, 5mcg/kg/day G-CSF sc was started from fifth day and application was continued until neutrophil engraftment.

Results: A total of 226 patients (129 males, 97 females) were included in the study. In patients receiving prophylactic G-CSF, neutrophil engraftment was earlier [13 (9-23) and 12 (10-22) days], and the duration of neutropenia [11 (5-23) and 8 (5-19) days] was shorter ($p < 0.001$). In the ASCT series prophylactic use of G-CSF showed that reduced the duration of neutropenia and decreased in neutropenic fever frequency.

Discussion and Conclusion: Transplant-related mortality (TRM) and infection-related mortality analyzes were not very significant due to the low level of event ($p > 0.05$).

Keywords: Auto-SCT, prophylactic G-CSF, SCT complications

ÖZET

Giriş ve Amaç: Otolog hematopoietik kök hücre transplantasyonunun (ASCT) morbidite ve mortalitesinin başlıca nedenlerinden biri, uzun süreli nötropeni sırasındaki enfeksiyonlardır. Bu çalışmada ASCT hastalarında profilaktik G-CSF kullanımının enfeksiyon sıklığı, nötrofil engraftmanı ve nötropeni süresi, hastanede kalış süresi ve nakille ilişkili morbidite ve mortalite üzerine etkisini araştırmayı amaçladık.

Yöntem ve Gereçler: G-CSF, birimimizde Şubat 2014'ten itibaren 3 yıldır otolog kök hücre nakli sonrası rutin olarak kullanılmaktadır. Bu çalışmada, uygulamadan üç yıl önce ve sonra ardışık oto-HSCT verileri geriye dönük olarak toplanmıştır. Rutin antimikrobiyal profilaksiye ek olarak, G-CSF alan grupta beşinci günden itibaren 5 mcg/kg/gün G-CSF sc başlandı ve nötrofil engraftrasyonuna kadar uygulamaya devam edildi.

Bulgular: Çalışmaya toplam 226 hasta (129 erkek, 97 kadın) dahil edildi. Profilaktik G-CSF alan hastalarda nötrofil engraftmanı daha erkendi [13 (9-23) ve 12 (10-22) gün] ve nötropeni süresi [11 (5-23) ve 8 (5-19) gün] daha kısaydı ($p < 0.001$). ASCT serisinde profilaktik olarak G-CSF kullanımının nötropeni süresini azalttığını ve nötropenik ateş sıklığını azalttığını göstermiştir.

Tartışma ve Sonuç: Organ nakline bağlı ölüm oranı (TİM) ve enfeksiyona bağlı ölüm oranı analizleri, olay seviyesinin düşük olması nedeniyle çok anlamlı değildi ($p > 0.05$).

Anahtar Kelimeler: OKHN, profilaktik g-CSF, OKHN komplikasyonları

Introduction

Autologous stem cell transplantation (ASCT) is widely used in many benign and malignant hematologic diseases [1]. Infections are common complications in patients undergoing ASCT due to prolonged neutropenia,

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immunosuppressive treatments and catheter applications [1,2,3,4,5]. The quality and quantity of stem cell product, myeloid growth factor uses such as granulocyte colony stimulating factor (G-CSF) and patient-specific factors are effective in neutrophil engraftment [1,6,7]. Hematopoietic growth factors are multifunctional: they have a critical role for proliferation, survival and differentiation of hematopoietic stem cells [8,9]. In many centres, G-CSF is used to shorten the duration of engraftment after autologous SCT and allo-HSCT. However, there is no consensus on the standard use of G-CSF after transplantation. Infection-related morbidity and mortality can be reduced by adding to ASCT procedure prophylactic hematopoietic growth factors [8].

We aimed to investigate the effect of prophylactic G-CSF usage on autologous stem cell transplantation on the frequency of infection, neutrophil engraftment and neutropenia, length of hospital stay, transplant-related morbidity and mortality.

Materials and Methods

The approval was obtained from the Gazi Univercity Clinical Research Ethics Committee with the number 77082166-302.08.01 dated 10.02.2017. This study was conducted in accordance with the Declaration of Helsinki.

Patients received ASCT with or without G-CSF prophylaxis were included this study between 2011 and 2016. In our center, prophylactic G-CSF application in ASCT started routinely in February 2014. Tree years before and 3 years after this date were determined and the patients who underwent ASCT between these dates were included consecutively in the study. Patients who did not receive prophylactic G-CSF were used as the historical control group. Patients with haematological malignancies who had autologous peripheral stem cell trans-plantation were included in the study. Patients who died before prophylactic G-CSF administration (+5th day), and patients received G-CSF before +5th due to the other causes such as severe infection were excluded.

G-CSF was used in 99 patients and 127 patients did not use hematopoietic growth factor. G-CSF-related side effects and neutrophil engraftments were recorded as the first day of absolute neutrophil numbers (ANC)> 500/mm^3 for 3 consecutive days. The duration of neutropenia was taken as the number of days from the onset of neutropenia after the first day of conditioning regimen to neutrophil engraftment. In the G-CSF group, patients were treated prophylactically with filgastrim 5mcg/kg/day subcutaneously until neutrophil engraftment was achieved. Both group patients received fluconazole, levofloxacin, and acyclovir as standard antimicrobial prophylaxis.

Statistical analysis

Categorical variables were compared with chi-square test. Student-t and Mann Whitney U tests were used to compare continuous parameters. Pearson correlation test was used to investigate relationship between parameters. Survival analyses were performed by Kaplan Meier analysis and log rank test. Statistical analysis was performed using SPSS 22. All statistical tests were performed 2-sided and P value 0.05 was considered as statistically significant.

Results

A total of 226 patients (129 males, 97 females) were included in the study. 121 patients had multiple myeloma and other plasma cell diseases, 62 had non-Hodgkin's lymphoma, 23 had Hodgkin's lymphoma and 20 had acute myeloblastic leukaemia. 99 (43.8%) of the patients included in the analysis used median 9 (4-16) days of prophylactic G-CSF and 127 (56.2%) of them did not use G-CSF.

Table 1. Comparison of demographic, diagnostic and treatment characteristics of patients

	Prophylactic G-CSF		
	Absent (n=127)	Present (n=99)	P
Age (year)	54 (18-69)	55(18-70)	N.S.
Gender n(%) (Male/female)	71/56 (55.9/44.1)	58/41 (58.5/41.5)	N.S.
Diagnosis n(%)			
MM	68 (53.5)	53(53.6)	
Lymphoma	47 (37.1)	38 (38.3)	N.S.
AML	12 (9.4)	8 (8.1)	
Conditioning regimen			
Melphalan±bortezomib	68(53.5)	53(53.6)	
BEAM	39 (30.8)	22 (22.2)	N.S.
TEAM	8(6.3)	16(16.1)	
CyBu	12(9.4)	8(8.1)	
Product $CD34^+$/kg	4.8(2.5-6.9)	4.5(2.4-6.3)	N.S.

MM: Multipl myeloma
AML: Acute myeloblastic leukemia
BEAM: Karmustin,Etoposid, , Sitarabin, Melfalan
TEAM: Thiotepa, Etoposid, Sitarabin, Melfalan
CyBu: Siklofosfamid, Busulfan
N.S: No significant

Table 2. Comparison of both groups in terms of endpoints

	Prophylactic G-CSF		
	Absent (n=127)	Present (n=99)	P
Neutrophil engraftment (day)	13(9-23)	12(10-22)	<0.001
Neuthrophil>1000/mm^3 (day)	16(9-36)	12(10-22)	<0.001
Neutropenia duration (day)	11(5-23)	8 (5-19)	<0.001
Platelet engraftment (day)	13(7-27)	15(10-56)	<0.001
Duration of hospitalization (day)	18(8-54)	17(13-35)	N.S.
Neutropenic fever n(%)	109 (85.8)	69 (69.6)	<0.001
Catheter infection n(%)	35(27.5)	18(18.1)	<0.05
Pneumonia n(%)	14(11.0)	12(12.1)	N.S.

Comparison of two groups according to demographic, diagnostic and treatment characteristics of patients were shown in Table 1. Median age and infused CD34+ cells/kg of patients, distributions of gender and diagnosis were similar between two groups (p>0.05).

G-CSF related severe side effect was not documented. Neutrophil engraftment was earlier [12 (10-22 vs 13 (9-23) days] and the duration of neutropenia were shorter [8 (5-19) vs 11(5-23) days] in patients received prophylactic G-CSF (p <0.001). There was no difference neutrophil engraftment time between males and females (13.0±2.7 days vs 13.1±2.7 days, p>0.05); also between lymphoma and myeloma patients (12.9±2.8 days vs 13.2±2.7 days, p>0.05). Neutrophil engraftment day was similar between patients with and without febrile neutropenia (12.9±2.7 days vs 13.1±2.7 days, p>0.05). A negative correlation was found between the number of infused CD34 cells and the time to neutrophil engraftment (r=-0.0135, p=0.04). The frequencies of neutropenic fever attack (69.6% vs 85.8%, p<0.001) and catheter infection (18.1% vs 27.5%, p <0.05) were significantly lower in patients received G-CSF. The diagnosis of pneumonia was found with a similar frequency (p>0.05). Platelet engraftment time was earlier in patients received prophylactic G-CSF [13(7-27) vs 15(10-56), p<0.001]. Duration of hospitalization time was similar in both two groups. Transplantation related mortality (2.0% vs 3.2%, p>0.05) and overall survival (2.6% vs 3.6%, p>0.05) within first 100 days was similar statistically in patients received ASCT with and without prophylactic G-CSF.

Discussion

G-CSF reduces the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute leukaemia [10,11,12]. G-CSF is well tolerated. The most common side effects are transient fever and bone pain that responds to analgesics. Other side effects include inflammation at the injection site, elevation of LDH and ALP. Splenomegaly and splenic infarction may be seen in long-term use. [9,13,14]. In ASCT area, studies pointed that prophylactic G-CSF reduces the duration of neutropenia and febrile neutropenia frequency [1,15,16,17,18]. The recommended dose of G-CSF is 5 mcg/kg/day [9,19]. Optimal starting time of prophylactic G-CSF adapted ASCT procedure is controversial [15-20]. Few data are available regarding the ability of G-CSF to accelerate engraftment further in patients who receive adult PBSC following high-dose therapy [15,16,22-25]. Despite of the all-favourable effects, prophylactic usage of G-CSF retained controversial because of the high treatment cost [8].

In our study, we retrospectively searched the ASCT database; we composed two groups. First group-enclosed patients received prophylactic G-CSF started at day 5, and second group patients did not received prophylactic G-CSF (historical control). We documented earlier neutrophil and thrombo-cyte engraftment, shorter neutropenia duration, lower febrile neutropenia and catheter infection frequency in patients received prophylactic G-CSF. However duration of hospitalization, TRM and OS in first 100 days were statistically similar. The statistical significance level could not be reached due to the fact that the “event” was very low in the TRM and infection related mortality analyses.

Khwaja A et al. [22] G-CSF started on day + 8 after auto-HSCT and patients received G-CSF for an average of 10 days. They showed that the duration of neutrophil engraftment with G-CSF was significantly shortened. Linch et al. [23] had undertaken a prospective randomized study in 90 patients with relapsed or resistant lymphomas to assess the value of G-CSF in the acceleration of myeloid

recovery after ASCT. This was associated with shorter duration of time in hospital post ASCT. Median days to platelet independence, platelet transfusions, and incidence of infection and red cell transfusion were the same in both arms. Gisselbrecht et al. [24] administered 163 patients G-CSF daily infusion and 152 patients received placebo daily for 28 days or until neutrophil recovery. In G-CSF treated group, time to neutrophil recovery was faster; patients had fewer infection, antibiotic usage and hospital stay. Survival was the same on days 100 and 365. Transplantation teams treat to patient's infections through modern approaches; also decreasing neutropenia and its complications are safety. Brice at all [25] reported that the average cost of autologous BMT was lower in patients receiving G-CSF. Results were largely attributable to decreased expenditure on hospitalisation and antimicrobial therapy in the G-CSF treated group. G-CSF is increasingly used to accelerate neutrophil engraftment after bone marrow transplantation [26]. Current data recommend the use of G-CSF when the risk of febrile neutropenia is greater than 20% [9].

The major limitation of this study is its retrospective character and have historical control group. However, in our study show that prophylactic G-CSF administration adapted to autologous stem cell transplantation procedure was led to shorter neutrophil engraftment, and decreased neutropenic fever frequency. G-CSF prophylaxis might be adapted to ASCT procedure as a standard, thus infection-related morbidities can further decrease.

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Original Article

Value of ADC Thresholds to Diagnose Head and Neck Lesions: Can ADC Values Replace Biopsy?

Baş-Boyun Lezyonlarının Teşhisinde ADC Eşik Değerlerinin Kullanımı: ADC Değeri Biyopsinin Yerini Alabilir mi?

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ABSTRACT

Introduction: We aimed in this study to evaluate the usefulness of DWI in tissue characterization of head and neck lesions, to investigate the difference in ADC values for distinguishing malignant and benign head and neck lesions (group A), lymphoma and carcinoma (group B), malignant and benign lymph nodes (group C) and to determine threshold values for these distinctions.
Methods: We included 95 lesions in 88 patients. 84 lesions were histopathologically confirmed. DWI using single-shot echo-planar imaging with b factors of 0, 400 and 800 sec/mm^2 were performed on 1.5TMR unit. Groups were compared using Kruskal-Wallis test.
Results: Statistically significant difference was found in group A, group B and group C. When an ADC value of 1.13×10^{-3} mm^2/s was used for predicting malignancy in group A, the sensitivity, specificity and accuracy were 85.7%, 71.7%, 78.9%, respectively. If 0.85×10^{-3} mm^2/s was used as a threshold value for differentiating in group B the best results were obtained with an accuracy of 83.7%, sensitivity of 92.9% and specificity of 78.3%. When 0.95×10^{-3} mm^2/s was used as a threshold value for differentiating in group C the highest accuracy of 82.8%, with 90.5% sensitivity and 71.4% specificity was obtained.
Discussion and Conclusion: DWI can be used to characterize head and neck lesions based on ADC values, but cannot replace biopsy.

Keywords: Diffusion-weighted imaging, head and neck masses, ADC threshold, ADC measurement.

ÖZET

Giriş ve Amaç: Bu çalışmada, baş boyun lezyonlarının doku karakterizasyonunda difüzyon ağırlıklı görüntülemenin kullanımını değerlendirmek adına, malign ve benign baş boyun lezyonları (grup A), lenfoma ve karsinom (grup B), malign ve benign lenf nodları (grup C) ayrımını yapabilmek için ADC değerleri arasındaki farklılıkları araştırdık ve bu ayrımlar için eşik değerler belirlemeyi amaçladık.
Yöntem ve Gereçler: Çalışmaya 88 hastadaki 95 lezyonu dahil ettik. 84 lezyon histopatolojik olarak doğrulandı. 1.5T MR ünitesinde 0, 400 ve 800 sn/mm^2 b değerleri ile difüzyon ağırlıklı görüntüleme yapıldı. Gruplar Kruskal-Wallis testi kullanılarak karşılaştırıldı.
Bulgular: Grup A, grup B ve grup C'de istatistiksel olarak anlamlı fark bulundu. Grup A'da maligniteyi öngörmek için 1.13×10^{-3} mm^2/s'lik bir ADC değeri kullanıldığında, duyarlılık, özgüllük ve doğruluk sırasıyla %85.7, %71.7 ve %78.9 idi. Grup B'de ayrım yapmak için eşik değer olarak 0.85×10^{-3} mm^2/s kullanıldığında en iyi sonuçlar %83,7 doğruluk, %92.9 duyarlılık ve %78,3 özgüllük ile elde edildi. Grup C'de ayrım yapmak için eşik değer olarak 0.95×10^{-3} mm^2/s kullanıldığında en yüksek doğruluk %82.8, duyarlılık%90.5 ve özgüllük %71.4 ile elde edildi.
Tartışma ve Sonuç: Difüzyon ağırlıklı görüntüleme ADC değerleri kullanılarak baş ve boyun lezyonlarını karakterize etmek için kullanılabilir, ancak biyopsinin yerini alamaz.

Anahtar Kelimeler: Difüzyon ağırlıklı görüntüleme, baş ve boyun kitleleri, ADC eşik değeri, ADC ölçümü.

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Introduction

Head and neck masses represent a wide array of pathologies. Different routine sequences of magnetic resonance imaging (MRI) may not accurately exclude malignancy. Diffusion-weighted imaging (DWI) has been used as an aid for imaging these masses [1, 2].

In diffusion-weighted MRI, image contrast depends on the motion of water molecules [3]. The extent of translational diffusion of molecules measured in the human body is referred to as the apparent diffusion coefficient (ADC). ADCs are expected to vary according to the microstructures of tissues or pathophysiologic states that are intrinsic to different tissues.

DWI with calculation of ADC values has been investigated in the past to distinguish benign and malignant head and neck lesions [4]. In literature, it is indicated that malignant head and neck masses show restricted diffusion, whereas in benign lesions this restriction decreases as the lesion progresses to a cystic inner structure, yet more, elevated diffusion is observed. Therefore, low ADC values are obtained in malignant lesions [5].

The purpose of our study is to evaluate the usefulness of DWI in tissue characterization of head and neck lesions.

Material and Methods

Subjects

Our study involved 95 head and neck lesions in 88 patients (49 men, 39 women, age range: 3 months to 86 years, mean age 52 years) over a 2-year period, retrospectively. Patients who underwent head and neck MRI including DWI, for lumps prediagnosed by clinican, were enrolled to the study. This study was approved by Başkent University Medicine and Health Sciences Research Ethics Committee (project number: KA12/67).

Of the histopathologically confirmed 84 lesions, 41 were diagnosed by biopsy and 43 were surgically removed. The rest 11 lesions, such as hemangioma, lymphangioma, thyro-glossal duct cyst and glomus caroticum tumor, were diagnosed by typical radiological findings based on MRI or angiography. In patients with multipl similar masses, the biggest lesion was chosen to work on. Patients who had taken chemotherapy or radiotherapy, or biopsied before MRI were excluded. All cases were divided into five groups (Table 1).

MRI Acquisition

MRI examinations were performed on 1,5-T (Siemens Avanto) using head coil. In axial and coronal planes T1W, in axial plane T2 turbo spin echo and fat suppressed T2, after contrast administration (gadoversetamide, 0.2mmol/kg) in axial, coronal and sagittal planes fat suppressed T1 images were obtained with a slice thickness of 4 mm.

DWI was performed before contrast administration, obtaining images in axial plane using echo-planar spin-echo T2 (factor b of 0, 400 and 800 s/mm²). The scanning parameters were as follows: Field of view, 250 x250 mm; NEX, 3; matrix size, 104x160; slice thickness, 4 mm; bandwidth, 1250 Hz/pixel. The acquisition time for DWI was 2min 36s. ADC maps were automatically generated. DWI images were collected on a single workstation (Leonardo, Software version syngo MR B17; Siemens, Germany) to calculate ADC values.

Image Analysis

The radiological evaluation was made by a neuroradiologist with 12 years of experience, blinded to the pathologies. In order to achieve best results, three different ROIs were placed on ADC maps in concordance with T1 or T2 images. If it enhances, the most contrast-enhancing area of the lesion was chosen on T1 images. If cystic or necrotic content is present, ROI was placed to comprise only the solid component, avoiding the cystic-necrotic part by taking advantage of T2-weighted images

Table 1. The ADC[1] values of the subtypes and subgroups of head and neck masses

Subtypes	Pathology	Number	ADC value (10^{-3} mm^2/s)		
			Mean±SD	Minimum	Maximum
1.Lymphoma		14	0.64±0.16	0.30	0.93
2.Carcinoma		23	1.09±0.36	0.63	1.40
	2.1. Squamous cell carcinoma	14	1.11±0.29	0.78	1.75
	2.2. Carcinoma metastasis	7	0.93±0.36	0.63	1.70
	2.3. Other carcinomas (Adenoid cystic carcinoma, adenocarcinoma)	2	1	0.80	1.20
			2.03	1.90	2.20
3.Malignant lesions other than lymphoma and carcinoma	(Fibrosarcoma, non-skeletal Ewing sarcoma, PNET[2], plasmocytoma)	5	1.03±0.49	0.43	1.80
4.Benign solid lesions		46	1.50±0.48	0.70	1.66
	4.1. Pleomorphic adenoma	4	1.59±0.22	1.30	1.83
	4.2. Warthin tumor	10	1.32±0.43	0.80	2.10
	4.3. Vascular lesions (Hemangioma, glomus caroticum tumor, arteriovenous malformation)	7	1.98±0.24	1.76	2.36
	4.4. Inflammatory lesions (Benign lymph nodes, necrotizing lymphadenitis, chronic inflammatory lymph nodes, abscess)	14	1.19±0.45	0.70	2.16
	4.5. Other benign solid lesions (Papillomatous squamous lesion, enchondroma, vagal nerve schwannoma, ameloblastoma, Castleman disease, granuloma, inverted papilloma, nasal polyp, vocal cord polyp)	11	1.72±0.42	1.10	2.30
5.Benign cystic lesions	(Lymphangioma, thyroglossal duct cyst, Thornwaldt cyst, parathyroid cyst)	7	2.64±0.59	1.90	3.76
Total		95			

[1] ADC: Apparent Diffusion Coefficient, [2] PNET: Primitive Neuroectodermal Tumors

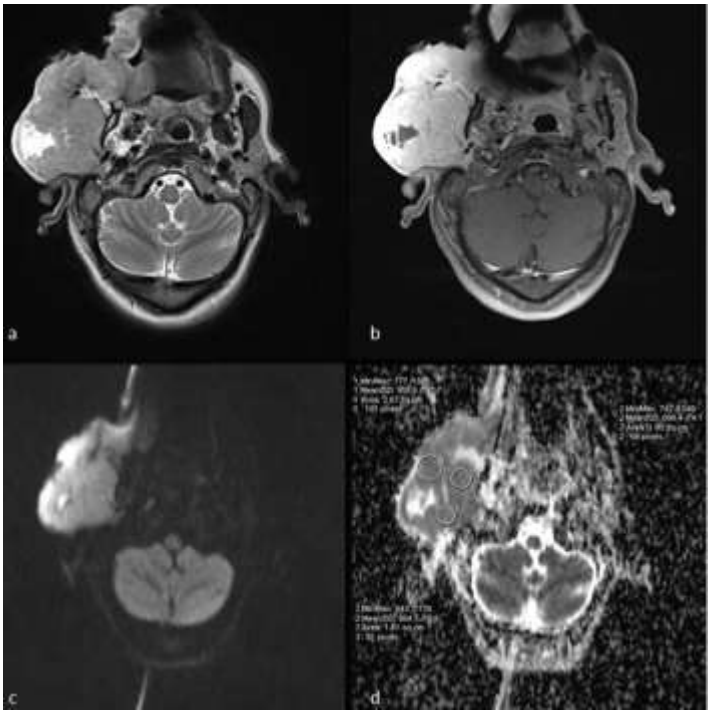

Figure 1 Excluding the cystic/necrotic portions from ROI in a case of epidermoid carcinoma. a. Axial T2-weighted image b. Axial contast fat suppressed T1-weighted image c. DWI d. ADC map (0.95×10^{-3} mm2/s, 0.89×10^{-3} mm^2/s and 0.96×10^{-3} mm^2/s)

(Figure 1). The mean ADC value was calculated afterwards.

Statistical Analysis

The statistical analysis was made using SPSS 15.0 (Statistical Package for Social Sciences, 15.0) and MedCalc programs. Shapiro-Wilk test was used to interpret normality and the data was not normally distributed according to the test. Continuous variables were presented as mean ± standard deviation and median (minimum-maximum). "Kruskal-Wallis Test" was used to evaluate ADC values of the groups. and $p<0.05$ was regarded statistically significant. In order to compare groups in pairs, Mann-Whitney U test was used for post-hoc analysis with Bonferroni correction, where "p" value less than 0.01 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to evaluate diagnostic efficiency of the ADC values to differentiate in between certain groups, and threshold ADC values with highest accuracy were determined.

Results

Out of 95 lesions, 42 were malignant and 53 were benign. We established five groups including lymphoma (group 1), carcinoma (group 2), malignant lesions other than lymphoma and carcinoma (group 3), benign solid lesions (group 4) and benign cystic lesions (group 5). Additionally, carcinoma and benign solid lesions were divided into two and five subgroups, respectively (Table 1). Statistically significant difference was found between all pairs of five groups ($p<0.05$) except between group 2 and group 3. Additionally, the ADC values of pleomorphic adenoma and Warthin tumor subgroups were compared, but there was no statistically significant difference ($p=0.148$).

Group 1 mostly consisted of diffuse large B cell lymphoma. Benign solid lesions, was the

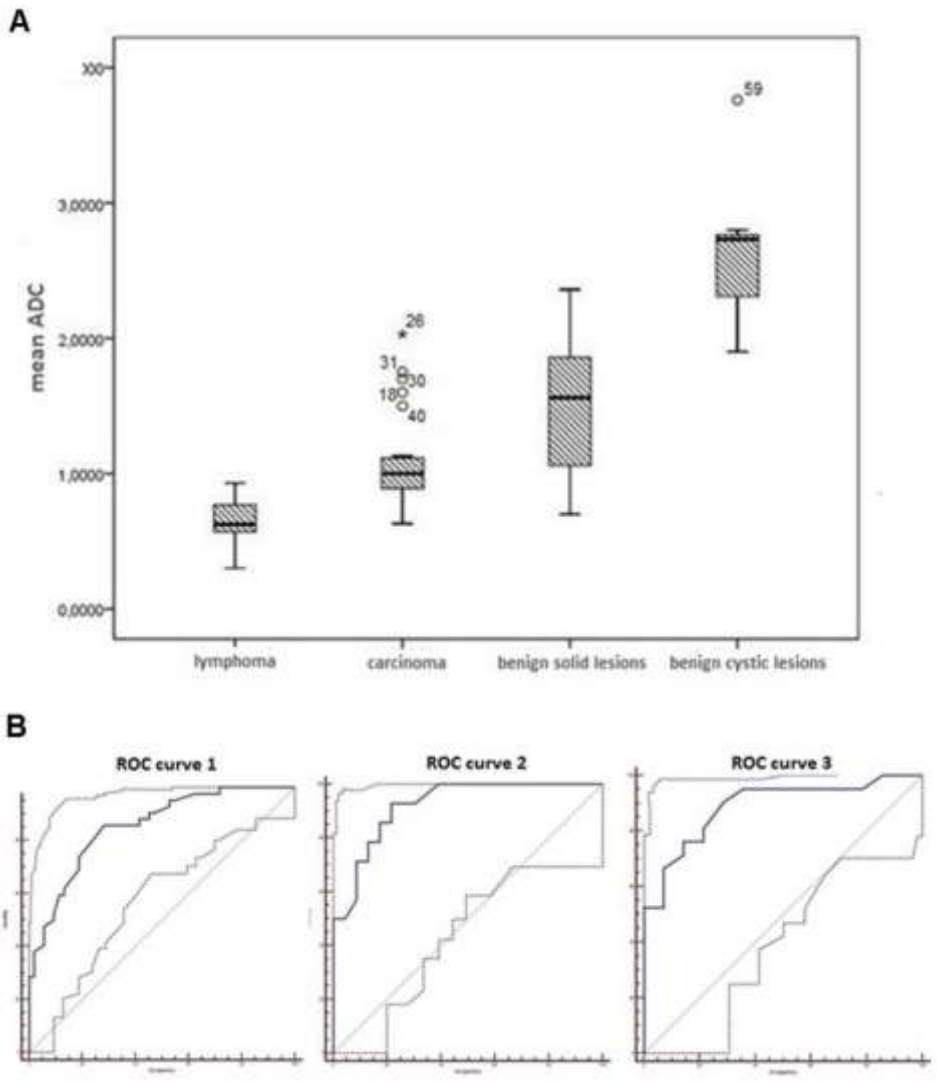

Figure 2 a. Box and whisker plot of the ADC values of 95 head and neck lesions b. ROC curves of the ADC values. In order to distinguish in between group A we used ROC curve 1 (cut off ADC value: 1.13×10^{-3} mm^2/s), in group B we used ROC curve 2 (cut off ADC value:0.85×10^{-3} mm^2/s) and in group C we used ROC curve 3 (cut off ADC value: 0.95×10^{-3} mm^2/s)

largest group in number. Group 1 and carcinoma metastasis subgroup together comprised malignant lymph nodes (n=21), whereas inflammatory lesions subgroup alone comprised benign lymph nodes (n=14). The ADC values of head and neck lesions and the relationship between four main groups are shown on box and whisker plot graphic in Figure 2.

The group with lowest mean ADC value of malignant lesions was lymphoma, while the highest was squamous cell carcinoma (SCC). Among benign lesions, inflammatory lesions and Warthin tumor had the lowest mean ADC values, whereas the highest mean ADC value belonged to cystic lesions.

The ROC curves were used to differentiate malignancy from benign lesions, lymphomas from carcinomas and malignant lymph nodes from benign lymph nodes (Figure. 2). When an ADC value of 1.13×10^{-3} mm^2/s or lower was used for predicting malignancy (group A), the sensitivity, specificity, and accuracy

Table 2. The threshold ADC[1] values used for differentiating in between group A, group B, group C and the statistical data for diagnostic use

Groups compared	ADC threshold value ($\times10^{-3}$ mm^2/s)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy Rate (%)
Group A (Malignant-Benign)	1.13	85.7	71.7	70.6	86.4	78.9
Group B (Lymphoma-Carcinoma)	0.85	92.9	78.3	72.2	94.7	83.7
Group C (Malignant lymph node - Benign lymph node)	0.95	90.5	71.4	82.6	83.3	82.8

[1] ADC: Apparent Diffusion Coefficient

Table 3. Comparative literature threshold ADC[1] values for differentiating in group A, group B and group C

	Authors of the study	Tesla of the MRI system	Number of lesions	Threshold ADC value ($\times10^{-3}$ mm^2/s)
Group A	Wang et al.	1.5	81	1.22
	Abdel Razel et al.	1.5	76	1.25
	Srinivasan et al.	3	33	1.3
	Chang et al.	1.5	114	1.22
	Our study	1.5	95	1.13
Group B	Wang et al.	1.5	81	0.84
	Maeda et al.	1.5	39	0.76
	Our study	1.5	95	0.85
Group C	Abdel Razek et al.	1.5	85	1.38
	Our study	1.5	95	0.95

[1] ADC: Apparent Diffusion Coefficient

were 85.7%, 71.7% and 78.9%, respectively (Table 2). If an ADC value of 0.85×10^{-3} mm^2/s was used as a threshold value for differentiating lymphoma from carcinoma (group B) the best results were obtained with an accuracy of 83.7%, sensitivity of 92.9% and specificity of 78.3%. When an ADC value of 0.95×10^{-3} mm^2/s was used as a threshold value for differentiating malignant lymph nodes from benign lymph nodes (group C), the highest accuracy of 82.8%, with 90.5% sensitivity and 71.4% specificity was obtained.

Discussion

It is not uncommon to encounter lesions that have indeterminate findings on ultrasound, computed tomography and conventional MRI and necessitate further investigation4. Tissue contrast attained by DWI is different from that of conventional MRI. ADCs are expected to vary according to the microstructures of tissues or pathophysiologic states that are intrinsic to different tissues. Generally, malignant tumors have enlarged nuclei, hyperchromatism, and angulation of nuclear contour, and they show hypercellularity. These histopathologic characteristics reduce the extracellular matrix and the diffusion space of water protons in the extracellular and intracellular dimensions, with a resultant decrease in the ADCs [5].

Several studies have been published to evaluate head and neck lesions by using DWI to predict malignancy (Table 3). In this study, we observed that diffusion restriction incre-

Table 4. Comparative mean ADC[1] values of Warthin tumor, pleomorphic adenoma and benign cystic lesions in different studies

	Authors of the study	Tesla of the MRI system	Number of lesions	Threshold ADC value ($\times 10^{-3}$ mm^2/s)
Warthin tumor	Habermann et al.	…	45	0.85±0.10
	Yerli et al.	1.5	30	0.97±0.16
	Our study	1.5	95	1.32±0.43
Pleomorphic adenoma	Habermann et al.	…	45	2.14±0.11
	Yerli et al.	1.5	30	1.74±0.37
	Our study	1.5	95	1.59±0.22
Benign cystic lesions	Sakamoto et al.	1.5	67	2.41±0.48
	Wang et al.	1.5	81	2.05±0.62
	Abdel Razek et al.	1.5	76	2.01±0.21
	Our study	1.5	95	2.64±0.59

[1] ADC: Apparent Diffusion Coefficient

ased along with the malignancy level, prominently in the lymphoma group, whereas elevated diffusion was seen in the cystic component. When such strong diffusion restriction is detected, we can diagnose malignancy without biopsy, especially in lymph nodes. However, when the values we measure are close to the cut-off, some conflicts start to appear. In such cases, we can still use DWI as a guidance to biopsy, as in sampling the areas with lowest ADCs as possible.

In our study, considering the threshold value for predicting malignancy, five malignant tumors were falsely diagnosed as benign lesions. Four of these were primary or metastatic SCC and the remaining one was thyroid papillary adenocarcinoma. According to the pathology results, the four SCCs contained foci of micronecrosis, which may have caused high ADCs. MRI visible necrosis is possible to exclude while placing the ROI in solid components. However, avoiding micronecrotic areas is not possible and that's an unintentional limitation apparently. The small foci of necrosis confirmed only by pathological findings might be the major reason of high ADCs of malignant tumors in our study, because SCC and SCC metastasizing to the lymph node are likely to develop necrosis [5]. Besides, the intense mucin areas determined in one of the lymph nodes of a metastasizing SCC might be another reason for explaining high ADC values, as well as extracellular fluid found abundantly in follicular parts in thyroid adenocarcinoma.

In literature, ADC values in lymphomas were found lower than that of SCCs [5,6]. In our study, we achieved the similar result. Considering the threshold value to differentiate lymphoma from carcinoma, five carcinoma cases showed low ADCs mimicking lymphoma. Three of these were carcinoma metastasis and the rest two were larynx SCC. Poorly differentiated carcinomas have more cellularity, larger and more angulated nuclei with more abundant macro-molecular proteins, and less extracellular space [5]. In our study, the two larynx SCCs mimicking lymphoma were reported as poorly differentiated SCCs in pathologic evaluation. There were two more lesions showing poor differentiation and they both had ADCs very close to the cut-off value. The rest SCCs were all either well differentiated or moderately differentiated. There are common aspects of carcinoma metastasis and lymphoma

histologically and cytologically as well. Carcinoma metastases are high stage malignancies, that would have histologically poor differentiation. The deterministic factor for SCC is squamous differentiation, which is characterized by keratin formation1. It is known that keratin impairs water movement, therefore, the presence of keratin may intensify the ADC decrease in metastatic lymph nodes [7].

Among benign lesions, cystic lesions and vascular lesions had the highest mean ADC values while the group with the lowest ADCs was inflammatory lesions. Benign vascular lesions, as hemangiomas and venous mal-formations, show higher ADCs than that of the other benign solid tumors such as granuloma and pleomorphic adenoma, due to excess extracellular spaces with free diffusion within the vascular lesions [2]. Thirteen of 53 benign lesions showed lower ADCs than the threshold value. These false positive 13 lesions included four Warthin tumors, four reactive lymph nodes, one necrotizing lymphadenitis, one abscess, one granuloma and two chronic inflammation. The hyper-cellular structure of some benign lesions, such as granuloma and abscess, might be responsible for low ADCs in benign category. A proliferation of the epithelial component and intense lymphoid accumulation in the stroma may have limited the motion of the water protons in the extracellular space of the Warthin tumor [5]. For these reasons, DWI remains insufficient to differentiate certain inflammatory lesions from malignant tumors [8].

Although we found significant difference between the ADC values of benign and malignant lesions, in literature, ADCs show diversity among each group. For instance, the mean ADC value of Warthin tumor is reported as (0.85±0.10) $\times10^{-3}$ mm^2/s by Habermann et al. [9] and (0.97±0.16) $\times10^{-3}$ mm^2/s by Yerli et al. [10], where we found (1.32±0.43) $\times10^{-3}$ mm^2/s in our study (Table 4). In both studies statistically significant difference is found between Warthin tumor and pleomorphic adenoma, unlike our study (p=0.148). Ikeda and colleagues suggested that the lower ADC value of Warthin tumors could be explained by the higher protein content in the cystic portions [11]. Those tumors have the highest microvessel count of all parotid gland tumors, and they also exhibit high cellularity. These variable ADCs in Warthin tumor may overlap carcinomas, particularly salivary duct carcinomas [10]. In our study the Warthin tumor group, which consists of 10 cases, has a range of ADCs between 0.80×10^{-3} mm^2/s and 2.10×10^{-3} mm^2/s. The case with the lowest ADC value revealed intense lymphoid cell accumulation in its pathological examination, whereas one of the Warthin tumor cases with high ADCs contained cystic component together with marked mucinous metaplasia on pathology studies. Intense mucinous content and cystic component might explain high ADCs in this subgroup.

The mean ADC value of pleomorphic adenoma was reported as (2.14±0.11) $\times10^{-3}$ mm^2/s and (1.74±0.37) $\times10^{-3}$ mm^2/s in the studies by Habermann et al. [9] and Yerli et al. [10], respectively. In our study we obtained a mean value of (1.59±0.22) $\times10^{-3}$ mm^2/s. Histopathologically, pleomorphic adenomas have a biphasic appearance that reflects the admixture of epithelium and stroma. Most of the epithelial component is of a glandular nature. It could be that water protons move relatively freely in the areas of pleomorphic adenomas that are glandular or contain fluid, and that a high ADC value may indicate a pleomorphic adenoma [10]. The reason of low ADCs in our study might be the stromal component predominating and that there are only a few number of cases of pleomorphic adenoma present. We think that for all these reasons we could not find statistically significant difference between Warthin tumor and pleomorphic adenoma.

The mean ADC for cystic lesions reported in some previous studies were $(2.41\pm0.48)\times10^{-3}$ mm^2/s, $(2.05\pm0.62)\times10^{-3}$ mm^2/s and $(2.01\pm0.21)\times10^{-3}$ mm^2/s [2, 5, 12], whereas we obtained a value of $(2.64\pm0.59)\times10^{-3}$ in our series. The ADC value of a cystic lesion varies depending on its content such as fat, protein, and septa. In case of a prior infection, an increasing protein concentration would be considered to have decreased the water protons movement [5, 12].

The mean ADCs of both lymphoma and metastasizing lymph nodes were significantly lower than that of benign lymph nodes in our study ($p<0.05$), however an overlap was observed occasionally. There were two malignant lymph nodes above and four benign lymph nodes below the threshold value. Both the malignant lymph nodes were metastasizing of which one had a primary of colon adenocarcinoma and the other revealed intense mucinous areas in its pathology report. Another factor that elevates the ADCs in malignant lymph nodes is the foci of necrosis which is seen frequently in carcinoma metastasis. Therefore, the mucinous content, the glandular structure of the colon adeno-carcinoma and the foci of necrosis may explain the elevation in ADC values. In our study, the ADCs of all the lymphomas were below the threshold value. The contributions of different components, such as fibrous scar tissue and granulation tissue, may alter the ADC value by restricting diffusion [13]. This might explain the diversity of ADCs measured in benign lymph nodes and the relatively low ADC values in our study.

The potential contribution of echo-planar DWI in the head and neck is still limited by technical problems regarding susceptibility artifacts, spatial resolution and motion artifact due to swallowing, respiration or blood flow [13].

The categories of patients we evaluated in this study are heterogenous by age which consists of mostly young adults and adults. Pediatric patients remain limited. Further researches are needed to be studied with larger series of pediatric patients on different magnetic strengths. Another restriction of our study is the lack of comparing DWI with positron emission tomography-computed tomography (PET-CT), which is being used for lymphoma patients preferentially. Comparison between these two imaging methods needs to be accomplished, since both of the techniques are based on histopathology and are sensitive to lymph node evaluation [14]. We also realized that ADC measurements of head and neck lesions differ among various studies, yielding to a conflict on cut-off values. That is why we strictly place the ROI in the solid component of the mass with lowest ADC area on the map and make more than one measurements. But still, we think larger populated studies or meta analysis would enlighten this conflict in the future, while our study is a contribute to literature with this broad variety of head and neck masses.

Conclusions

In conclusion, DWI is a fast and sensitive MRI sequence that can be used to characterize head and neck lesions by ADC mapping according to the histopathological variety that reflects their inner structure. Additionally, DWI still cannot replace biopsy, especially in cases with ADCs very close to the cut-off values, but it is a non-invasive diagnostic technique which can prevent certain biopsies or can provide useful additional information about the masses that are scheduled for biopsy or surgery.

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Case Report

Palbociclib Associated Deep Vein Thrombosis: A Case Report

Palbociclib Ilişkili Derin Ven Trombozu: Olgu Sunumu

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ABSTRACT

Cyclin-D-cyclin dependent kinase 4/6 (CDK 4/6) inhibitors started a new era in metastatic hormone receptor positive breast cancer. Ribociclib, palbociclib and abemaciclib (CDK 4/6 inhibitors) are used in combination with endocrine therapy and they provide a significant benefit in progression free and overall survival. Fatigue, neutropenia, anemia, and diarrhea are commonly seen side effects which are easily manageable with dose modifications. Herein, we presented a case of deep vein thrombosis developed twice under palbociclib treatment which is a rarely reported side effect causing cessation of the treatment.

Keywords: CDK4/6 inhibitors, metastasis, thrombosis

ÖZET

Siklin-D-sikline bağımlı kinaz 4/6 (CDK 4/6) inhibitörleri metastatik hormon reseptörü pozitif meme kanserinde yeni bir dönem başlatmıştır. Ribociclib, palbociclib ve abemaciclib (CDK 4/6 inhibitörleri) endokrin tedavisi ile kombinasyon halinde kullanılır ve progresyonsuz ve genel sağkalımda önemli bir fayda sağlamıştır. Yorgunluk, nötropeni, anemi ve diyare yaygın görülen ve doz modifikasyonları ile kolaylıkla kontrol edilebilen yan etkilerdir. Burada, palbosiklib tedavisi altında gelişen, tekrarlayıcı ve tedavinin kesilmesi ile sonuçlanan nadir bir yan etki olan derin ven trombozu olgusunu sunduk.

Anahtar Kelimeler: CDK 4/6 inhibitörleri, metastaz, tromboz

Introduction

Cyclin proteins constitute the control step of the mitosis in the cell cycle. It is known that cyclin-D-cyclin dependent kinase 4/6 (CDK 4/6), one of these proteins, is responsible for the resistance to hormonal therapies in hormone receptor positive breast cancer and can cause excessive proliferation in cancer cells as a result of increased activity. CDK4/6 inhibitors (CDKIs) act by suppressing this protein. The estrogen pathway in breast cancer also escapes from the CDK4/6 control step and causes tumor growth[1]. Therefore, it has been suggested that inhibition of the estrogen and CDK4/6 pathways together may be an effective treatment method in terms of both preventing the development of hormonotherapy resistance and delaying tumor growth. Today, the use of CDKIs in the first step with hormonotherapy in hormone receptor positive metastatic breast cancer, is a standard care of treatment. The most common side effects of CDKIs are fatigue, alopecia, nausea, diarrhea, neutropenia and anemia[2]. Herein, we presented a breast cancer case who developed thromboembolism under palbociclib treatment which is a rarely reported side effect causing discontinuation of the treatment in the literature.

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Case report

A 73-year-old female patient referred to our oncology clinic in May 2020, after diagnosed with breast cancer. She noticed a lump in her right breast 4 months ago. The mammogram and breast ultrasonography revealed 32x29x38mm mass lesion with micro-calcifications in her right breast causing distortion (BIRADS 5) and 14mm pathological right axillary lymph node. A positron emission tomography (PET) scan done with preliminary diagnosis of breast cancer showed 18-F FDG uptake at the right breast upper quadrant (3x2.5cm) and axillary lymph node (18mm). The lesions in right lung, liver and on 2nd rib were interpreted as metastases. Cranial magnetic resonance imaging did not reveal any pathology. She underwent a tru-cut breast biopsy. The pathological examination of the biopsy specimen showed invasive breast carcinoma. The immunohistochemical examination findings were as followed; estrogen receptor (ER) 100%, progesterone receptor (PR) 30%, Ki67 15%, c-erb-B2 score 0. Patient's medical history revealed hyperthyroidism and hypertension. On physical examination, patient's Eastern Cooperative Oncology Group (ECOG) Performance Status score was 1 and 3x4cm ulcerated breast mass was present on the right side. Patient had stage IV breast cancer. Since her hemotological and biochemical labarotory parameters were in normal ranges, palbociclib 125mg and letrozole 2.5mg were administered. The patient's neutrophil count was $4.85x10^3$/L on her 15th day control. One month later, the laboratory results were as followed; white blood cell: $4.41x10^3$/L, neutrophil: $1.48x10^3$/L, hemoglobin: 12.7g/dL, platelet: $134x10^3$/L. Although the neutropenia was grade 2, taking the patient's age into consideration as well as grade 3 fatigue, dose modification was planned to 100mg before second cycle. In the third month of treatment, the patient complained of right leg pain. The venous ultrasound showed deep vein thrombosis so low molecular weight heparin and rivoraxaban were prescribed. Her neutrophil level was $8.36x10^3$/L. We continued palbociclib and letrozol. After one month, while on anticoagulation treatment, blood clots developed in the left leg. She had operation and endovascular stent was placed. She was consulted with hematology. Since she had cancer, does not have a history of thromboembolic event as well as family history, hematology department found it inappropriate to test for genetic thrombophilia. After her second thrombosis, we decided to stop palbociclib treatment and continue with letrozole. The patient is under hormone replacement and anticoagulant treatment for 6 months without new thromboembolic event.

Discussion

Breast cancer is the most common type of cancer in women worldwide, and 60-75% of the cases are ER+[3]. In recent years, CDKIs have been shown to play a role in mediating the resistance to endocrine therapy. Abemaciclib, ribociclib and palbociclib are CDKIs that are approved by Food and Drug Agency (FDA).

PALOMA-2 trial demonstrated improved progression free survival (PFS) in palbociclib and letrozole arm compared with letrozole and placebo[4]. After a median follow-up of approximately 38 months, median PFS was 27.6 months. Although the efficacy is proven, the risk of venous thromboembolism (VTE) with this treatment, which is one of the major mortality and morbidity reasons in breast cancer patients, had never been reported. Thein et al. undertook a systematic review and meta-analysis of randomized controlled trials to determine the risk of VTE with abemaciclib based regimens versus other CDKI containing regimens[5]. No significant increase in the risk of VTE was noted with palbociclib in this meta-analysis. On the other hand, Gervaso et al. conducted a retrospective cohort study of

consecutive metastatic breast cancer patients who received any of CDKIs[6]. They included 424 patients where palbociclib was the most commonly used CDKI (91.8%). Venous thromboembolism occurred in 38 patients (6.3%) at 1 year, where deep vein thrombosis (DVT) was seen in 52.6%. But, they didn't differentiate the patients who were on palbociclib and had DVT. Watson et al., however, found the VTE rate around 11% in 66 patients receiving palbociclib[7]. In a recent analysis including 266 patients with 89% using palbociclib, the 1-year incidence of thrombosis was 10.9% for palbociclib, 8.3% for ribociclib and 4.8% for abemaciclib [8]. DVT was the most frequent thrombotic event.

VTE is seen in 1 to 2 out of 100 women as a side effect of aromatase inhibitors and they are even the preferred hormonotherapy agents when the patient has a history of inherited thrombotic disorder[8,9]. In our case, since the patient is elderly and does not have a history of tromboembolic event, we excluded the probability of genetic disorders. Palbociclib was the reason of thrombosis in our case. The fact that the patient had a second attack, especially on anticoagulation therapy, and stabilized after discontinuation of the drug is another entity that points palbociclib as the responsible factor.

Although the regulatory agencies such as the FDA and European Medicines Agency do not currently provide any warning for thromboembolic complications during palbociclib therapy, considering the meta analysis and case reports, physicians should be alert for the development of venous thromboembolism during the treatment with CDKIs. However, more studies are needed including larger number of breast cancer patients receiving CDKIs.

Consent: Informed consent is given by the patient.

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Case Report

Hodgkin Lymphoma Identified After Non-Hodgkin Lymphoma: Two Case Reports

Non Hodgkin Lenfoma Sonrası Tanımlanan Hodgkin Lenfoma: İki Olgu Sunumu

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ABSTRACT

The coexistence of different malignant diseases in the same patient is an entity that can rarely be encountered clinically. This can be observed as the presentation of two distinct types of cancer in the same patient simultaneously or at different times. The genetic structure of the individual, environmental factors and chemotherapeutic agents and radiotherapy used in the treatment of primary disease may play a role in this process. Hodgkin lymphoma is hardly ever observed after non-Hodgkin lymphoma treatment. In this report, we aimed to share two cases that were diagnosed with classical Hodgkin lymphoma in their follow-up after non-Hodgkin lymphoma diagnosis and treatment in our clinic.

Keywords: Non-Hodgkin lymphoma, Hodgkin lymphoma, secondary malignancy, relapse

ÖZET

Aynı hastada farklı malign hastalıkların bir arada bulunması klinik olarak nadiren karşılaşılabilen bir durumdur. Bu, aynı hastada aynı anda veya farklı zamanlarda iki farklı kanser türünün ortaya çıkması olarak gözlemlenebilir. Bireyin genetik yapısı, çevresel faktörler, kemoterapötik ajanlar ve birincil hastalığın tedavisinde kullanılan radyoterapi bu süreçte rol oynayabilir. Hodgkin lenfoma, Hodgkin dışı lenfoma tedavisinden sonra neredeyse çok nadir görülür. Bu yazıda, kliniğimizde Hodgkin dışı lenfoma tanı ve tedavisi sonrası klasik Hodgkin lenfoma tanısı alan iki olguyu paylaşmayı amaçladık.

Anahtar Kelimeler: Non-Hodgkin lenfoma, Hodgkin lenfoma, sekonder malignite, relaps

Introduction

The coexistence of different malignant diseases in the same individual is not uncommon in oncology-hematology practice. In the treatment of non-Hodgkin lymphoma (NHL), the risk of secondary malignancy was found to be high in patients who received both radiotherapy and chemotherapy combined therapy [1]. It was observed that NHL before Hodgkin lymphoma(HL) diagnosis were mostly of B-cell origin. While NHL development can be observed after the diagnosis and treatment of HL, the development of HL after NHL diagnosis and treatment is an extremely rare condition. In this report, we discussed two patients who were diagnosed and treated for NHL and later developed HL lymphoma in our clinic. The pathological diagnoses of the patients were

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Table 1. Immunohistochemistry of the biopsies case#1

Markers	NHL Pathology (Initial diagnosis)	HL Pathology
BCL1	Negative	Negative
BCL2	Positive	Negative
BCL6	Positive	Negative
BOB1	Not available	Positive
CD3	Negative	Not available
CD5	Negative	Not available
CD10	Positive	Not available
CD15	Not available	Positive
CD20	Positive	Negative
CD23	Negative	Not available
CD30	Positive	Positive
C-myc	Negative	Positive(weak/dim)
Ki-67	95%	High
LCA	Positive	Negative
MUM1	Positive	Positive
OCT2	Not available	Positive
Pancytokeratine	Negative	Not available
PAX5	Not available	Positive(weak/dim)

BCL: B-Cell Lymphoma, BOB1: B Cell Specific Octamer Binding Protein1, CD: Cluster of Differentiation, LCA: Leukocyte Common Antigen,HL: Hodgkin Lymphoma,MUM1: Multiple Myeloma Oncogene 1, NHL: Non-Hodgkin's Lymphoma, OCT2: Octamer Binding Transcription Factor 2 PAX-5: Paired Box Protein 5.

reconfirmed by re-evaluating the samples. An informed consent form was obtained for both cases.

Case #1

A thirty-eight-year-old male patient applied to the clinic with abdominal pain in January 2018. As a result of the examinations, in the right lung, a mass of 5x5cm in the upper lobe and a mass of 4x5cm in the superior side of the lower lobe was detected on computerized tomography (CT). A 17mm hypodense lesion in the posterior segment of the right liver lobe and thickening of the stomach antrum wall were observed. Upper GIS (gastrointestinal system) endoscopy was performed, malignant ulcer surrounding the lumen infiltrating the pylorus was detected in the distal of the antrum, and the biopsy revealed germinal center diffuse large B-cell lymphoma (DLBCL), the immunophenotype of the biopsy were given in Table 1. Lung biopsy was non-specific and bone marrow biopsy revealed no involvement. The patient was evaluated as Ann Arbor stage 4B DLBCL and R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) treatment was initiated. After completion of the four-cycle, treatment response was evaluated, the volume of lung masses decreased by 70%, and regarded as (partial remission) PR response. After the treatment was completed with six cycles R-CHOP +2R, control PET-CT was performed. Control PET-CT was compatible as pathological lymph node which size 15x14mm, and SUVmax:13 in the right supra-clavicular region. Prompt biopsy was performed and reported as classical HL. Salvage GDP (gemcitabine, dexamethasone, and cisplatin) treatment was started after the diagnosis of HL. PET-CT was taken to evaluate the response after three cycles of GDP and evaluated as (complete remission)

Table 2. Immunohistochemistry of the biopsies case#2

Markers	NHL Pathology (Initial diagnosis)	HL Pathology
BCL1	Positive (weak/dim)	Negative
BCL 2	Positive	Positive (weak/dim)-rare cells
BCL 6	Positive	Negative
CD3	Negative	Negative
CD5	Negative	Not available
CD10	Negative	Negative
CD15	Not available	Positive
CD20	Positive	Negative
CD23	Positive	Negative
CD30	Negative	Positive
C-myc	Negative	Not available
EBER	Negative	Not available
K.İ.67	99%	High
LCA	Not available	Negative
MUM1	Positive	Positive (weak/dim)- rare cells
PAX5	Not available	Positive (weak/dim)- rare cells

BCL: B-Cell Lymphoma, CD: Cluster of Differentiation, EBER: Epstein Barr Virus Encoded Small RNAs, HL: Hodgkin Lymphoma,LCA:Leukocyte Common Antigen, MUM1: Multiple Myeloma Oncogene 1, NHL:Non-Hodgkin's Lymphoma, PAX-5: Paired Box Protein 5.

CR. After four cycles of GDP, the patient underwent autologous stem cell transplantation (ASCT) with BEAM (BCNU (carmustine), Etoposide, Ara-C (cytarabine), Melphalan) protocol. Brentuximab vedotin (BV) treatment was initiated as maintenance treatment due to the high relapse risk. After the ASCT, the patient under BV treatment was taken PET-CT to evaluate the response at 3rd month and was evaluated as CR.

Case # 2

An eighteen-year-old female patient admitted with shortness of breath, 10 kg weight loss in two months, and night sweats. As a result of the examinations, a 6 cm mass in the anterior mediastinum was detected in thorax CT. Biopsy performed by bronchoscopy was evaluated as a non-germinal center diffuse large B-cell lymphoma, immunophenotype of the biopsy were given in Table 2. The patient was regarded as Ann Arbor stage IV and six cycles R-EPOCH (Rituximab +Etoposide + Prednisone + Vincristine + Cyclo-phosphamide + Doxorubicin) and additional two cycles of rituximab were given. Treatment response evaluation was done after the completion of treatment. Cervical LAP with 4,68 SUVmax (Deauville score:3) was detected and the patient was regarded as refractory. Salvage R-GDP therapy was initiated for two cycles and reevaluation of treatment by the PET-CT response was compatible with CR.The patient underwent ASCT with BEAM protocol in August 2019. In her follow-up, 33x15mm LAP developed in the right supraclavicular region in June 2020. A prompt biopsy was done and reported as classical HL. The pathological diagnoses of the patients were reconfirmed by re-evaluating the same samples. Bendamustine and brentuximab treatment was initiated and now the treatment is ongoing.

Discussion

In this article, two patients who were recently diagnosed HL with after being diagnosed and treated as NHL in our clinic are discussed.

Due to the development of diagnosis and treatment modalities, surveillance after NHL is prolonged and the rate of secondary malignancy increases [2]. Development of HL can be seen in the follow-ups after NHL treatment, though; it is a very rare condition [3-4].

Our first case was thirty-eight years old, and our second case was diagnosed with DLBCL at the age of eighteen. The median age of diagnosis of DLBCL is seventy, both patients are in the AYA age group, and in this age group, NHL is uncommon [5-6]. In our first case, the diagnosis period between DLBCL and HL a was eight months. In our second case, this period is twenty months. Studies have shown that the rate of secondary malignancy increases as the time after diagnosis increases [4].

Patients diagnosed with non-Hodgkin lymphoma have an increased risk of not only Hodgkin lymphoma but also all cancers [4,7-9]. The frequency of non-Hodgkin lymphoma after Hodgkin lymphoma varies between 1-6% [10]. In patients with NHL, the risk of developing HL has increased three times compared to the normal population and the prognosis was found to be worse than de novo HL patients. According to a retrospective study, HL was reported in 14 of 29153 NHL patients [11]. In conclusion, inadequate immune surveillance, exposure to chemo-radiotherapy during treatment, and genetic structure are effective in increasing the risk of lymphoma development and poor prognosis. More clinical studies are needed to fully elucidate this issue.

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