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Preprocedural Platelet-To-Lymphocyte and Platelet-To-Neutrophile Ratios As The Predictors of Local Recurrence Following Ultrasound-Guided Microwave Ablation For Colorectal Cancer Liver Metastases

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ABSTRACT

The aim of the present study was to demonstrate the role of blood parameters as a potential prognostic factor for local recurrence (LR) after ultrasound (US)-guided percutaneous microwave ablation (MWA) of colorectal liver metastases (CRLM).

Between February 2016 and February 2020, 76 patients with US-guided percutaneous MWA of the CRLM were analysed. The patients with LR were included in first or study group (15 patients) and the patients with no evidence of LR were included in second or control group (20 patients). The following blood parameters obtained from the blood sampling at the day before the MWA treatment were also recorded: Haemoglobin (gr/dl), neutrophile (uL), lymphocyte (uL) and platelet (10^3/uL) counts, platelet distribution width (PDW) (fL) and red cell distribution width (RDW) (%) values. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and platelet-to-neutrophile ratio (PNR) were calculated.

The mean PLR was 129.9 (97.6-197.7) and 92.1 (83.7-117.7) in the study and the control group respectively and we found statistically significant association between the groups (p=0.036). The mean PNR was 61.4 (49.5-68.5) and 44.35 (38-55.3) in study and control group respectively A statistically significant association were also seen between these two groups (p=0.003)

In conclusion, this study suggests that CRLM patients with elevated preprocedural PLR and PNR values are more inclined to local recurrence after US-guided MWA. This simple and costless way can be easily used in order to predict the local response of the thermal ablative treatments in routine clinical practice.

Key Words: Platelet-to-lymphocyte ratio, Platelet-to-neutrophile ratio, Microwave ablation, Ultrasound, Local recurrence

Introduction

Since the liver is the quite often site for the distant metastasis of the primary tumors, especially for colorectal cancer metastases (CRCM), apart from the primary site, the treatment strategies also focus on the liver in order to have good long-term outcomes (1,2). Although surgical resection is already the gold standart therapy for liver metastasis, other local and regional treatment options have been a good alternative especially for the patients with technically unresectable metastases (3,4). Being minimal invasive procedures and their hepatocyte sparing features are some advantages of locoregional treatment options over surgery (5). Nevertheless, the main disadvantage is their inferior local tumor control rates resulting recurrence (6).

There are many procedural, technical and lesion-based risk factors for local recurrence (LR) such as tumor size, histopathologic type, ablation zone, segmental distributions, presence of an adjacent vessel, ablation method used, described and analysed in previous studies (7). In addition to this, some blood parameters such as C-reactive Protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) were defined as a prognostic factors in metastatic liver disease (8,9).

The aim of the present study was to demonstrate the role of blood parameters as a potential prognostic factor for LR after ultrasound (US)-

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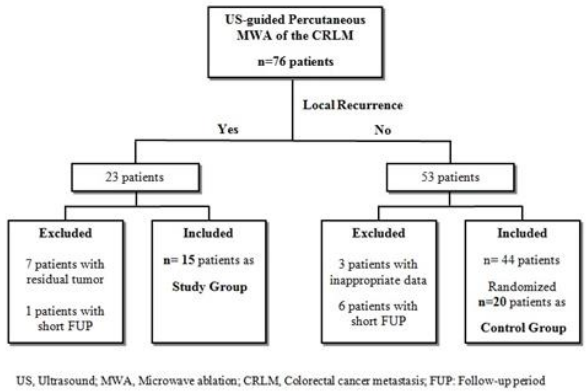

Fig. 1. Study Flow Chart

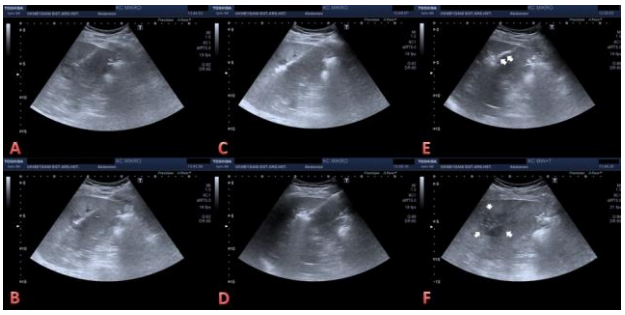

Fig. 2. Percutaneous ultrasound (US)-guided microwave ablation (MWA) procedures (A-F). Advancing ablation probe towards to the center of the targeted lesion (A). After centralisation of the lesion with a correct position (B) the MWA was begun. Early (C) and the late (D) phases of the ablation procedure. Tract ablation through the adjacent liver parenchyma towards to the liver capsule soon after the ablation period was accomplished (arrows in E). Sonographic appereance of the ablation zone (arrows) in the contol US imaging of the patient at following day (F)

guided percutaneous microwave ablation (MWA) of colorectal liver metastases (CRLM).

Materials and Methods

This retrospective study was approved by local ethics committee (06.07.2020, Prof. Dr. Cemil TAŞCIOĞLU State Hospital Ref.No:48670771). Informed consent has been obtained from all patients. It is confirmed by the author that the study is appropriate for Declaration of Helskinki Standards.

Patient Population: Between February 2016 and February 2020, 76 patients with US-guided percutaneous MWA of the CRLM were analysed with both their patient files including the whole follow–up informations and all radiological images on local Picture Archiving and Communication System (PACS). The patients were categorised as two groups. The patients with LR were included in first or study group (23/76) and the patients with

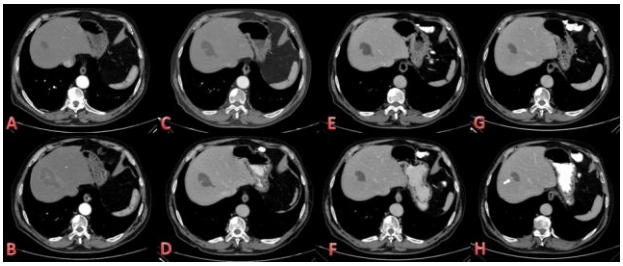

Fig. 3. Intravenous contrast enhanced Computed Tomography (CECT) images of a patient with no evidence of local recurrence of colorectal liver metastasis (A-H). Axial CECT images of before the ablation (A), the following day of ablation (B), postprocedural 1st month (C), 4th month (D), 7th month (E), 12th month (F), 16th month (G) and the 20th month (H). Note that the ablated lesion showing reduction in size over time and the segmental portal vein branch adjacent to the ablation zone was intact (arrow in H)

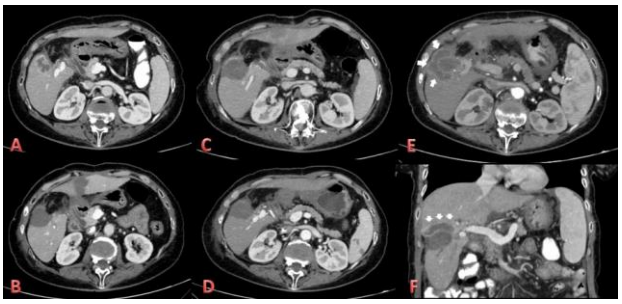

Fig. 4. Intravenous contrast enhanced Computed Tomography (CECT) images of a patient with local recurrence of colorectal liver metastasis (A-F). Preprocedural axial CECT image of the metastatic lesion which was showing contrast enhancement peripherally (A). Axial CECT of the metastatic lesion obtained at the following day of ablation showed the ablation zone without any pathologic contrast enhancement (B). Axial CECT images showed no residual tumor and the evidence of any local recurrence on site in postprocedural 1st (C) and the 4th (D) month controls. However a gross local recurrence with a peripheral contrast enhancement (arrows) was demonstrated on axial (E) and coronal (F) CECT images on 7th month control

no evidence of LR were included in second or control group (53/76). Seven patients with residual tumor rather than LR and one patient with a short follow-up period (< 3 moths after MWA) due to non-follow up or death are excluded from the study population. Of 53 patients in control group, 3 patients having inappropriate data in their patient follow-up form or radiological images, 6 patients with a short follow-up period (< 3 moths after MWA) due to non-follow up or death are excluded from the control group. Then the rest control group population had been randomized in order to form the final control group. Finally fifteen patients in

study group and twenty patients in control group were enrolled into study (Figure 1).

Pre-procedural Evaluations: All thermal ablation treatment decisions of the liver tumors are taken by the multidisciplinary local tumor board formed by the specialist in medical oncology, hepatopancreatobiliary surgery, nuclear medicine, radiation oncology, radiology and interventional radiology. The patients who were referred to interventional radiology service for further evaluation were underwent ultrasound and doppler ultrasound evaluation in order to plan the ablation and the procedures accompanied by the findings of contrast-enhanced (CE) triphasic liver computed tomography (CT) or dynamic CE liver magnetic resonance (MR) scans which were obtained within 1 month before the TA procedure. Every single patient decided as eligible for MWA ablation treatment was given detailed information of the procedure and the follow-up period. Then they were directed to anesthesia service for the convenience of anesthesia and they were planned to give some blood samples including whole blood count, bleeding and coagulation parameters the day before the MWA treatment.

Thermal Ablation Procedure: All thermal ablation procedures were performed with percutaneous MWA using only US guidance under general anesthesia. MWA systems were 15-gauge electrodes with 2.45 GHz Solero and Acculis MWA generators (Angiodynamics, New York, USA) in all ablation procedures. Aplio 500 ultrasound system (Toshiba Medical Systems Corporation, Tochigi, Japan) had been used with 3-6 Mhz convex or 4-9.2 Mhz linear array transducers for ablation guidance. After a local and subcapsular anesthesia and a skin puncture, the ablation probe was advanced towards to the center of the targeted lesion. Once the probe tip was positioned at the targeted ablation zone, two interventional radiologists checked whether the lesion had been centralized or not from different plans by US probe maneuvers. After ensuring the correct position, MWA process was begun with general anesthesia. The ablation energy and duration were selected according to the targeted tumor ablation size and location using standard algorithms by aiming at least for 5 mm of each margin around the tumor. Soon after the ablation period was accomplished, the procedure was completed by performing tract ablation through the adjacent liver parenchyma towards to the liver capsule (Figure 2).

Patient Follow-up: All patients were underwent triphasic liver CT scans or dynamic CE MR imaging performed at first day after ablation, quarterly in the first 2 years, and biannually thereafter for follow up (Figure 3 and 4). In addition, US and Doppler US imaging were performed at the time of each follow-up admisions and patient files were examined in detail. In case of suspicious imaging findings for LR, diffusion-weighted (DW) MR and Positron Emission Tomography (PET) scans were also applied.

Definitions and Data Obtaining: Age and gender of the patients were recorded. The following blood parameters obtained from the blood sampling at the day before the MWA treatment were also recorded: Haemoglobin (gr/dl), neutrophile (uL), lymphocyte (uL) and platelet (10^3/uL) counts, platelet distribution width (PDW) (fL) and red cell distribution width (RDW) (%) values. NLR was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. PLR was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes. Lastly, platelet-to-neutrophile ratio (PNR) was calculated by dividing the absolute number of platelets by the absolute number of neutrophils. All ablated lesions in both study and the control groups were assessed with multiplanar reconstructed (MPR) CT or axial and coronal MR images in order to evaluate the ablation success and the LR.

Statistical Analysis: Contious variables and categorical variables were presented median (IQR) and number (%). Man-Whitney U test, Chi-square test or Fisher's extact test were used to compare the differences between groups. An overall p-value of less than 0.05 was considered to show a statisfically significant result. Statistical analysis was performed with Statistical Package of the Social Sciences (SPSS) version 22.0 (IBM Corp.).

Results

The median age was 57 (53-70) years in study group and 62 (55-68) years in control group. Of 15 patients in study group, 11 patients were male 412and the 4 patients were women. The control group was consist of 14 male and 6 female patients. The mean PLR was 129.9 (97.6-197.7) and 92.1 (83.7-117.7) in the study and the control group respectively and we found statistically significant association between the groups (p=0.036). The mean PNR was 61.4 (49.5-68.5)

Table 1. Patient Characteristics and the Associations Between the Variables

Variables		Total	Local Recurrence		P value
		(n=35)	Yes (n=15)	No (n=20)	
Age	years	60 (54-69)	57 (53-70)	62 (55-68)	0.236
Gender	male	25 (71.4%)	11 (73.3%)	14 (70%)	1.000
Hgb	gr/dl	12.8 (12.0-13.7)	12.6 (11.7-13.9)	13.0 (12.0-14.3)	0.359
Neut	uL	4250 (3480-5650)	4080 (2540-5680)	4390 (3810-5267.5)	0.294
Lymp	uL	1900 (1530-2470)	1710 (1530-2300)	2160 (1500-2722.5)	0.342
Plt	10^3/uL	212 (170-275)	268 (179-306)	211 (168.5-249)	0.193
PDW	fL	15.7 (12.8-16.2)	15.6 (12.8-16)	15.8 (13.6-16.3)	0.229
RDW	%	14.9 (13.9-16.7)	15.5 (14.4-19.2)	14.7 (13.7-16.1)	0.101
NLR		2.29 (1.66-2.93)	2.41 (1.37-2.93)	2.19 (1.67-3.03)	0.994
PLR		106.3(83.8-147.2)	129.9 (97.6-197.7)	92.1 (83.7-117.7)	0.036
PNR		52.8 (40.4-61.4)	61.4 (49.5-68.5)	44.35 (38-55.3)	0.003

Hgb: Haemoglobine, Neut: Neutrophile, Lymp: Lymphocyte, Plt: platelet, PDW: Platelet distribution width, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PNR: Platelet-to-neutrophile ratio. Fisher's exact test used for "gender", Man-Whitney U test used for the other variables

and 44.35 (38-55.3) in study and control group respectively A statistically significant associations were also seen between these two groups (p=0.003). The associations of haemoglobin, neutrophile, lymphocyte, platelet, PDW, RDW and NLR values between the study and the control groups were not statistically significant (Table 1).

Discussion

We demonstrated in the present study that the patients with LR following US-guided MWA treatment were found to have elevated PLR and PNR when compared to patients who had no evidence of LR. Besides this, we concluded that these ratios were also important to predict local tumor control as well as the systemic response. To the best of our knowledge, present study is to first study about the effect of blood parameters on local recurrence occurrence in patients with CRLM treated by US-guided MWA.

The relationship between the carcinogenesis and the inflammation have been investigated for many years (10-12). On the other hand the researchers also have focused on the effects of inflammatory markers on treatment response of tumor (13,14). Due to the frequent use of local treatment options in recent years, studies in this area have been taking place in current literature (15). Since it is simple, easy and cheap to measure, peripheral blood parameters had became popular for several studies in this manner (16).

Several studies have shown that platelets might play a pivotal role in the development and progression as well as metastasis of cancer and increased platelet counts, and patients with thrombocytosis usually presented poorer prognosis (17,18). On the other hand Lymphocytes are considered as a surrogate marker for the immune status of cancer patients and a prognostic factor for recurrence and survival (19). As a result, elevation of PLR could be considered as a negative impact on prognosis. Neofytou et al. reported that preoperative PLR is an adverse prognostic factor in patients who undergo liver resection for liver-only colorectal metastases (20). PLR was mentioned as an independent risk factor for rerecurrence in recurrent hepatocellular carcinoma patients following thermal ablation in the study of Li et al. (19). Similarly, we showed that elevated PLR is a risk factor for local rerecurrence in patients with CRLM treated by US-guided MWA.

Considering the critical role of lymphocytes in inflammation related to treatment response which was mentioned above, it is expected to see an elevated ratio of it when compared to the other peripheral blood cells. In other words, the decreased number of lymphocytes would have a negative effect on immune mechanisms in cancer treatment. Giakoustidis et all reported that the elevated NLR in patients who undergo hepatectomy following neoadjuvant chemotherapy for CRLM, increases the risk of extrahepatic/multifocal recurrence (14). In another study about the effects of NLR on recurrence following thermal ablation for recurrent hepatocellular carcinoma by Li et al, it is demonstrated that patients with high preoperative

NLR have poorer recurrence-free survival following thermal ablation (15). Unlike the literature, our results for NLR didn't expouse the being an independent prognostic factor in predicting the local recurrence of the patients with CRLM treated by US-guided MWA.

Current literature showed us that the PNR is not a commonly used prognostic parameter in cancer treatment. However Jin et all. found that the PNR is a prognostic marker for 90-days outcome in acute ischemic stroke (21). PNR value was found to be elevated in the study group with local recurrence in our study. Although we think that this was the results of the elevated absolute number of platelets, its validity would be evaluated with the new study designs in future.

High RDW values have been associated with poor prognosis in many disease including cancers as a result of anisocytosis caused by inflammation (22). Sakin et al. indicated that the decreased PDW appear to be unfavorable prognostic factors in early colorectal carcinoma (23). In our study we couldn't obtain any statistical data for both RDW and PDW which could support the literature datas.

The main limitation of our study is its retrospective design because of the possibility of bias in patient selection. Small sample size is the other important limitation which could effect the reliability of the results. Although the thermal ablation treatment was performed with single MWA system under the guidance of single US system, the possible effect of the performer of the thermal ablation in the occurence of LR was not discussed.

In conclusion, this study suggests that CRLM patients with elevated preprocedural PLR and PNR values are more inclined to local recurrence after US-guided MWA. This simple and costless way can be easily used in order to predict the local response of the thermal ablative treatments in routine clinical practice.

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