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RESEARCH

EFFICACY AND TOLERABILITY OF CHEMOTHERAPY IN ELDERLY PATIENTS WITH METASTATIC GASTRIC CANCER

ABSTRACT

Introduction: Elderly patients are under-represented in the clinical trials of patients with metastatic gastric cancer (GC); therefore, the efficacy and tolerability of palliative chemotherapy are unclear in these patients. We aimed to assess the efficacy and tolerability of first-line palliative chemotherapy in elderly patients (age ≥70 years) with metastatic GC.

Materials and Method: From 2005 to 2014, 89 patients with metastatic GC who were 70 years and older and were treated with at least two cycles of systemic chemotherapy as first-line treatment were included retrospectively. Disease and patient characteristics, prognostic factors, treatment response, grade 3–4 toxicity related to treatment, progression free survival (PFS), and overall survival (OS) were evaluated.

Results: Of the 89 patients, 65 (73%) were males; median age was 74 (70–84) years. The median follow-up period was 7 months (min–max: 2–57 months), median PFS was 5 months (95% CI: 3.7–6.3), and median OS was 7 months (95 % CI: 5.2–8.9). The disease was controlled in 43.8% patients, whereas progression was observed in 56.2% patients. Univariate analysis showed that the Eastern Cooperative Oncology Group (ECOG) performance status, number of chemotherapy cycles, and response to the first line chemotherapy had a significant effect on PFS and OS; liver metastasis had an effect only on PFS; lung metastasis had an effect only on OS.

Conclusion: Fewer chemotherapy cycles, lung metastasis, liver metastasis, and poor ECOG performance scores were found to be poor prognostic factors.

Key Words: Stomach Neoplasms; Neoplasm Metastasis; Aged; Drug Therapy.

ARAŞTIRMA

METASTATİK MİDE KANSERLİ YAŞLI HASTALARDA KEMOTERAPİNİN ETKİNLİĞİ VE TOLERABİLİTESİ

ÖZ

Giriş: Yaşlı hastalar klinik çalışmalara alınmadığından metastatik mide kanseri (MK) olan hastalarda kemoterapinin etkinliği ve tolerabilitesi konusunda bilgiler yetersizdir. Bu çalışmada 70 yaş ve üstü metastatik MK hastalarında ilk seride verilen palyatif kemoterapinin etkinliğini ve tolerabilitesini araştırmayı amaçladık.

Gereç ve Yöntem: 2005-2014 yılları arasında, ≥70 yaş, ilk seride en az iki kür kemoterapi alan 89 hasta retrospektif incelendi. Hasta özellikleri, prognostik faktörler, tedavi cevabı, grad 3-4 toksisite, progresyonsuz-sağkalım (PSK) ve genel-sağkalım (GS) değerlendirildi.

Bulgular: 89 hastanın 65 (%73)'i erkekti ve medyan yaş 74 (70-84)'dü. Medyan takip süresi 7 ay (min–max:2–57ay), PSK 5 ay (%95GA:3,7–6,3) ve GS 7 ay (%95GA:5,2–8,9)'dı. Hastalık kontrolü %43,8'inde sağlanmasına rağmen %52,2'sinde progresyon görüldü. Tek değişkenli analizde Eastern Cooperative Oncology Group (ECOG) performans skoru, kemoterapi siklusu ve alınan cevap etkindi. Karaciğer metastazı PSK'da, akciğer metastazı ise GS'da etkindi.

Sonuç: Düşük kemoterapi siklusu, akciğer veya karaciğer metastazı ve kötü performans skoru olumsuz prognostik faktörlerdi.

Anahtar Sözcükler: Mide kanseri; Metastaz; Yaşlı; Kemoterapi.

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Introduction

Gastric cancer (GC) is the second leading cause of cancer-related death worldwide and is usually diagnosed at advanced stages. The number of patients aged 65 years and above diagnosed with GC is increasing, although the total incidence of GC is decreasing (1-3). The expected survival time with best supportive care (BSC) is limited to 4–5 months in advanced gastric cancer (AGC). Many combination chemotherapy regimens have been studied in randomized trials and a prolonged survival period up to 7–10 months has been reported for AGC (4-6).

Elderly patients have usually been excluded from or underrepresented in clinical trials; therefore, the efficacy and tolerability of palliative chemotherapy are unclear in these patients (7-9). While deciding the chemotherapy protocol in elderly patients, performance status, mental status, co-morbidity, medical fitness, basic activities of daily living, instrumental activities of daily life, concept of quality of life, home conditions, social support, nutrition, polypharmacy, and cognitive/psychosocial health should be evaluated (10). In planning medical treatment, the chronologic age of a patient does not reflect the physiological age. The assessment of the physiological age involves patient's tolerance to the planned treatment and the estimated life expectancy (11).

No gold standard combination regimen has yet been defined in patients with AGC. The superiority of combination treatments against single agent treatments in AGC patients is well- known (8). A study in 2003 reported that weekly cisplatin, leucoverin, and 5-FU (PLF) chemotherapy was safe and effective in elderly patients with AGC (12). Hematologic toxicities with combination chemotherapies (such as, docetaxel, cisplatin, and 5-FU regimen) are more frequent. In elderly patients, chemotherapy tolerance and safety is not similar to that of the patients under the age of 65; therefore, administration of full-dose combined chemotherapies is more difficult.

Here, we aimed to assess the efficacy and tolerability of first-line palliative chemotherapy in elderly patients (age ≥70 years) with AGC.

Materials and Method

Patients

A total of 89 patients received at least two cycles of systemic chemotherapy as first-line therapy at the Ataturk University Hospital, Erzurum, Turkey between 2005 and 2014 and were retrospectively evaluated.

Inclusion criteria consisted of patients diagnosed with pathologically proven metastatic GC, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, disease measurable by imaging, age 70 years and above, and at least two cycles of systemic chemotherapy received as first-line treatment.

Disease and patient characteristics, prognostic factors, treatment response, grade 3–4 toxicity related to treatment, progression free survival (PFS) and overall survival (OS) were evaluated.

Patients were categorized as per the ECOG performance status criteria. Chemotherapy regimens and dosages were adjusted according to the ECOG performance status, clinical findings, laboratory findings, and co-morbidities. All tumor measurements and treatment response evaluations were done after every two or three cycles of chemotherapy using imaging methods and other tests that were initially used to stage the tumor. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Toxicity was assessed according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0 toxicity scale.

We obtained a local ethics committee permission dated 16.10.2015 and number 16 for our study.

Chemotherapy Regimens

The chemotherapy regimens used in our study were weekly DCF (docetaxel 25 mg/m^2 i.v. on days 1, 8, and 15 + cisplatin 25 mg/m^2 i.v. on days 1, 8, and 15 + 5-FU 750 mg/m^2 i.v. on days 1, 8, 15, and every 21 days), modified DCF [docetaxel 40 mg/m^2 i.v. on day 1 + folinic acid (FA) 400 mg/m^2 i.v. on day 1 + 5-FU 400 mg/m^2 i.v. bolus followed by 2000 mg/m^2 46 hours infusion, cisplatin 40 mg/m^2 i.v. on day 3 and every 14 days], ECF (epirubicin 50 mg/m^2 i.v. on day 1 + cisplatin 60 mg/m^2 i.v. on day 1 + 5-FU l,200 mg/m^2 per day i.v. daily continuous infusion, every 21 days), capecitabine–cisplatin (capecitabine 625 mg/m^2 orally twice daily, day1-day21 (D1-D21) + cisplatin 75 mg/m^2 i.v. on day 1, every 21 days), FOLFIRI (irinotecan 180 mg/m^2 i.v. on day 1 + FA 400 mg/m^2 i.v. on day 1 + 5-FU 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 over 46 hours infusion, every 14 days), mFOLFOX-6 (oxaliplatin 85 mg/m^2 i.v. on day 1, FA 400 mg/m^2 i.v. on day 1 + 5-FU 400 mg/m^2 i.v. bolus followed by 2400 mg/m^2 over 46 hours infusion, every 14 days), XELOX (oxaliplatin 130 mg/m^2 i.v. on day 1 + capecitabine 1000 mg/m^2 oral twice daily, D1–D14, every 21 days), trastuzumab combination chemotherapy (trastuzumab 8 mg/kg

Table 1— Chemotherapy Regimens Used in the Study

	No. of Patients (%)	PFS (months)	95% CI	OS (months)	95% CI
wDCF and mDCF	30 (33.7)	4	1.8-6.1	7	5.9-8.1
DOF	16 (18)	3	0.1-5.8	5	0-12.8
Cisplatin+Capecitabine	8 (9)	4	1.5-6.5	6	4.6-7.3
XELOX	8 (9)	3	1.6-4.3	6	3.3-26
mFOLFOX-6	4 (4.5)	6	1.5-6.5	16	1-30.9
Cisplatin+5-FU	7 (7.9)	5	2.4-7.6	11	0-26
ECF	7 (7.9)			5	2.4-7.6
Trastuzumab combination chemotherapy	4 (4.5)	7	3-11	9	
Capecitabine	4 (4.5)	4	0-15	11	0-28.5
FOLFIRI	1 (1.1)	8		10	

wDCF: weekly Docetaxel, cisplatin, Fluorouracil; mDCF: modified DCF; XELOX: Capecitabine, oxaliplatine; FOLFOX: Oxaliplatine, folinic acide, fluorouracil; ECF: Epirubicine, cisplatine, fluorouracil; FOLFIRI: Irinotecan, folinic acide, fluorouracil.

loading dose and 6 mg/kg maintenance dose with cisplatin 80 mg/m^2 on day 1, plus capecitabine 1000 mg/m^2 orally twice daily, D1–D14, every 21 days or with 5-FU 800 mg/m^2 on D1-D5, every 21 days) (Table 1)

Statistical Analysis

Descriptive statistics were used to describe the demographical and clinical characteristics of the patients, treatment outcome, and incidence of toxicity. χ^2 test was used to determine the relation between categorical variables. PFS was defined as the time from the date of the first administration of chemotherapy to the date of progressive disease or death from any cause. OS was defined as the time from the date of diagnosis to the date of death from any cause. PFS and OS analyses were all estimated using the Kaplan–Meier method. Survival difference was analyzed using the log-rank test.

Multivariate analyses using the Cox proportional hazard regression model were performed to assess the impact of the following variables on PFS and OS: ECOG performance status, metastatic site, and number of chemotherapy cycles. The statistical data were obtained using an SPSS software package (SPSS 22.0 Inc., Chicago, IL, USA) and p values of <0.05 were accepted as significant.

Results

Of the 89 patients, 65 (73%) were males. The median age was 74 (70–84) years. Three patients (3.4%) had diabetes mellitus and 24 (27%) had hypertension. The last date of follow-up was May 1, 2015; till this date, 77 patients (86.5%) had died and 12 patients (13.5%) were still alive. Demographical and clinical characteristics of the patients are shown in Table 2.

Four patients (4.5%) received single drug therapy, 24 patients (27%) received two-drug combination therapy, and 61 patients (68.5%) received three-drug combination therapy as first-line chemotherapy. Chemotherapy regimens are shown in Table 2. The most administered combination was docetaxel, cisplatin, and 5-FU (33.7%).

The median follow-up period was 7 months (min–max: 2–57 months), median time to progression was 5 months (95% CI: 3.7–6.3) and median OS time was 7 months (95% CI: 5.2–8.9). Complete response was observed in one patient (1.1%); partial response and stabilization were observed in 31.5% and 11.2% patients, respectively. The disease was controlled in 43.8%, whereas progression was observed in 56.2% of the patients. In patients with ECOG performance status 0, chemotherapy was more effective compared to those with ECOG performance status 1 and 2, in terms of PFS and OS ($p = 0.001$ and $p = 0.001$, respectively). There was no significant difference between the chemotherapy regimens in terms of PFS and OS ($p = 0.74$ and $p = 0.59$, respectively), hematological toxicities ($p > 0.05$ for all), and response rates ($p = 0.88$). Furthermore, there was no significant difference between dublets and triplet drugs in terms of hematological toxicities ($p > 0.05$ for all) and response rates ($p = 0.93$).

In univariate analysis, ECOG performance status, number of chemotherapy cycles, and response to the first-line chemot-

Table 2— Demographical and Clinical Characteristics of the Patients

	No. of patients (n=89)	%
Gender		
Male	65	73
Female	24	27
ECOG		
0	7	7.9
1	48	53.9
2	34	38.2
Age		
70-74	52	58.4
74-79	23	25.8
≥80	14	15.7
Location		
Cardia	52	58.4
Corpus	11	12.4
Antrum	16	18.0
Diffuse	10	11.2
History of operation		
Yes	12	13.5
No	77	86.5
History of adjuvant chemotherapy		
Yes	6	6.7
No	83	93.3
Metastasis		
Liver	59	66.3
Lung	18	20.2
Bone	8	9.0
Peritoneal	29	32.6
Brain	1	1.1
Metastatic lesions		
1	66	74.2
2	20	22.5
3	3	3.4
Chemotherapy cycles		
2-3	35	39.3
4-6	48	53.9
<6	6	6.7
Chemotherapy regimen		
One drug	4	4.5
Two drugs	24	27
Three drugs	61	68.5
Response to chemotherapy		
Complete response	1	1.1
Partial response	28	31.5
Stable disease	10	11.2
Progressive disease	50	56.2
Last status		
Dead	77	86.5
Alive	12	13.5

herapy had an effect on PFS and OS, whereas liver metastasis effected only on PFS and lung metastasis effected only on OS (Table 3).

Multivariate analysis revealed that PFS and OS were not significantly associated with ECOG performance status (p=0.122 and p=0.747, respectively). Decreased PFS was significantly associated only with decreased number of chemotherapy cycles (p < 0.001), whereas decreased OS was significantly associated with lung metastasis and decreased number of chemotherapy cycles (p=0.003 and p<0.001, respectively) (Table 4).

Among patients with grade 3–4 toxicity; 19.1% had neutropenia; 12.4% had anemia; and 4.5% had thrombocytopenia and non-hematologic toxicities, including renal toxicity (2.2%), neuropathy (2.2%), cardiotoxicity (2.2%), and allergic reactions (1.1%) (Table 5).

Discussion

Gastric cancer is usually diagnosed at advanced stages and 60% of the patients are above 65 years of age (13). The elderly population has been increasing in recent years, and treatment responses are not well-known, particularly in patients aged 70 years and above who have metastatic GC. Randomized trials have shown that combined systemic chemotherapy is superior to BSC in patients with metastatic GC (4-6). However, these studies included patients younger than 65 years of age.

The prevalence and the incidence of adenocarcinoma of the lower esophagus and of the stomach increase with age. The biology of these tumors may not change with age, but due to an increased risk of treatment-related complications and a reduced life expectancy, the benefits of chemotherapy may decline. It was recommended that the treatment of patients aged ≥70 years with these malignancies be personalized based on the risk of complications and life expectancy (14).

In our study, median age of patients was 74 (70-84) years. Age groups were not associated with PFS and OS, which was similar to the literature findings of Z. Lu et al. (15) on patients with advanced or metastatic GC among the elderly population.

In our study, palliative chemotherapy was at least as effective as to those in the medical literature in patients less than 65 years old; OS was 1–2 months shorter, but PFS was similar. OS was longer than that of patients who received BSC as reported in literature findings (4, 16). Toxicity was generally mild in all the study patients.

Table 3— Univariate Analysis of Clinicopathological Factors and Treatments in Elderly Patients with Metastatic Gastric Cancer (PFS and OS)

PFS (months)		95% CI	p	OS (months)	95% CI	p	
Gender							
	Male	5	3.8-6.2	0.36	7	5.9-8.1	0.38
	Female	6	2.6-9.4		8	2.1-14	
ECOG							
	0	13	0-31.5	**0.001**	24	8-40	**0.001**
	1	6	4.2-7.8		10	7.1-13	
	2	3	2.3-3.7		6	4.4-7.6	
Age							
	70-74	5	2.7-7.3	0.51	9	4.9-13	0.21
	74-79	4	1.8-6.2		6	4.6-7.4	
	≤80	2	0.5-3.5		4	0-8.9	
Location							
	Cardia	4	2.7-5.3	0.6	7	4.9-9.1	0.99
	Corpus	7	2.7-11		7	0-14.9	
	Antrum	3	0-8.9		6	0-15.8	
	Diffuse	3	0.8-5.9		8	0.3-16	
History of operation							
	Yes	3	0-6.4	0.74	4	0.6-7.4	0.13
	No	5	3.7-6.3		8	5.1-7.4	
History of adjuvant chemotherapy							
	Yes	3	0-9	0.54	4	0-10	0.44
	No	5	3.8-6.2		7	4.3-9.7	
Metastasis							
	Liver	4	2.9-5.1	**0.036**	7	5.1-8.7	0.48
	Lung	4	1.5-6.5	0.62	5	2.2-7.8	**0.01**
	Bone	7	3.4-11	0.49	8	2.1-14	0.73
	Peritoneal	6	2.7-9.3	0.13	12	5.9-18	0.27
	Brain	3	3	0.38	6	6	0.52
Metastatic lesions							
	1	5	3.5-6.5	0.52	8	5.5-11	0.37
	2	3	0-6.1		5	2.1-7.9	
	3	2	0.4-3.6		2		
Chemotherapy cycles							
	2-3	2	1.5-2.5	**<0.0001**	4	3.3-4.7	**<0.0001**
	4-6	8	6.7-9.3		12	9.9-14	
	<6	8	1.3-15		16	8.5-23	
Chemotherapy regimen							
	One drug	4	0-15.7	0.38	7	0-28	0.19
	Two drugs	4	2.2-5.8		6	4.8-7.2	
	Three drugs	5	3-7		8	5.6-10	
Response of chemotherapy							
	Complete response	26	26	**<0.0001**	57	57	**<0.0001**
	Partial response	13	10-16		13	1.4-10	
	Stable disease	6	0.8-11		14	9.8-18	
	Progressive disease	3	2.3-.37		5	3.8-6.2	

Table 4— Multivariate Analysis of Clinicopathological Factors and Treatments in Elderly Patients with Metastatic Gastric Cancer (PFS and OS)

	PFS		OS	
	HR (95% CI)	p	HR (95% CI)	p
ECOG				
0	1 (reference)	0.122	1 (reference)	0.747
1	2.008 (0.697-5.783)		1.104 (0.423-2.884)	
2	2.903 (0.947-8.899)		1.329 (0.476-3.714)	
Metastasis				
Liver	1.198 (0.716-2.005)	0.49		**0.003**
Lung			2.387 (1.332-4.281)	
Chemotherapy cycles				
2-3	1 (reference)	<0.001	1 (reference)	**<0.001**
4-6	0.138 (0.070-0.269)		0.216 (0.121-0.386)	
6<	0.112 (0.038-0.325)		0.152 (0.044-0.528)	

Table 5— Grade 3-4 Hematologic and Non-hematologic Toxicities (National Cancer Institute Common Toxicity Criteria, Version 3.0)

	No. of patients (%)
Hematologic toxicities	
Neutropenia	17 (19.1)
Anemia	11 (12.4)
Thrombocytopenia	4 (4.5)
Febrile neutropenia	1 (1.1)
Non-hematologic toxicities	
Renal toxicity	2 (2.2)
Neuropathy	2 (2.2)
Cardiotoxicity	2 (2.2)
Allergic reactions	1 (1.1)

Various chemotherapy agents (single or combination) have been studied in patients with AGC since 1970; however, the median survival still remains between 6 and 9 months (17). In a study performed by Choi IS et al. (18) in 2007, oxaliplatin 100 mg/m^2, FA 100 mg/m^2 and 5-FU 2400 mg/m^2 (46 hours infusion) every 2 weeks regimen in elderly patients with AGC showed an overall response rate of 41.2%, a PFS of 5.7 months (95% CI: 4.2–6.3 months), and an OS of 9.8 months (95% CI: 4.4–12 months). Also grade 3–4 neutropenia was observed in 8.1% of the patients. They suggested that oxaliplatin/5-FU/FA had good efficacy and acceptable toxicity profile in this group.

Similarly, Zhao et al. (19) showed that the modified FOLFOX regimen is well-tolerated for elderly patients older than 65 years as first-line chemotherapy for AGC. The overall response rate was 45.6% (95% CI: 31–61%), median time to progression was 6.2 months (95% CI: 4.6–7.8), and median OS was 9.8 months (95% CI: 8.2–11.4). Grade 3 toxicity included neutropenia (8.7%), vomiting (4.3%), nausea (4.3%), and diarrhea (2.2%). In a phase II study by Santini et al. (20) comprising 42 chemotherapy-naïve patients aged 70 years or above who had locally advanced and metastatic GC, a regimen of weekly oxaliplatin 40 mg/m^2, 5-FU 500 mg/m^2, and FA 250 mg/m^2 was used. The response rate was 45.2%, the median time to disease progression was 5.0 months, and the median survival time was 9.0 months. Grade 3–4 neutropenia was 4.8% and the regimen was well-tolerated. In addition, Liu et al. (21) showed similar results with modified FOLFOX-4 regimen, and they declared that this was a well-tolerated and an active combination for elderly patients with AGC who were ≥65 years old.

In a study by Dong et al. (22), it was shown that XELOX was active and well-tolerated by elderly patients. Thus, it may be a good therapeutic option as first-line chemotherapy in AGC because of its easy administration. Median follow-up period was 9.5 months, median time to progression was 5.6 months (95% CI: 4.6–6.6), and OS was 9.8 months (95% CI: 7.4–12.2). Grades 3–4 adverse events included neutropenia (13.6%), thrombocytopenia (11.4%), anemia (2.3%), diarrhea (13.6%), hand-foot syndrome (9.1%), nausea, and vomiting (4.5%).

The phase III V325 trial comparing cisplatin and 5-FU with DCF as a first-line therapy showed that DCF should be reserved only for fit elderly patients because of a higher incidence of toxicity in AGC (23). In our study, the toxicity profile was found to be similar to that of other chemotherapy regimens because none of the patients had received standard DCF.

Elderly patients' have specific clinicopathological characteristics. Lu et al. (24) reported that body mass index, Karnofsky performance score, number of metastatic lesions, ascites, tumor differentiation grade, lactate dehydrogenase (LDH) activity, chemotherapy, and local treatment were independent prognostic factors. Serum LDH activity was superior to the serum carcinoembryonic antigen level for the prognosis of advanced or metastatic GC in elderly patients. Body mass index, Karnofsky performance score, and a well-differentiated histopathology were the factors favoring longer survival, whereas a greater number of metastatic lesions and elevated serum LDH activity were associated with poor prognosis among the studied elderly patients.

Univariate analysis of our study showed that ECOG performance status, number of chemotherapy cycles, and response to first-line chemotherapy had an effect on PFS and OS. We found that in patients with ECOG performance status 0, OS was longer than the patients with ECOG status 1 and 2. Moreover, liver metastasis was associated with poorer PFS, whereas having lung metastasis was associated with poorer OS. Multivariate analysis showed that decreased PFS was significantly associated with decreased number of chemotherapy cycles only, whereas decreased OS was significantly associated with both lung metastasis and decreased number of chemotherapy cycles.

While deciding chemotherapy administration in patients with metastatic GC who are ≥70 years old, parameters of physiological age, such as ECOG performance status, should be considered rather than the chronological age. It is reported that combined chemotherapy regimens are superior to single agents in patients younger than 65 years old. However, in our study, we found that preferred treatment regimen, drug numbers, and dose reduction had no effect on OS. This might be due to the low number of patients in the chemotherapy groups. While planning chemotherapy in patients aged ≥70 years, physiological age and co-morbidities of the patient should be considered. The treatment should be personalized based on the risk of complications and life expectancy. Possible minimally toxic single or combined regimens can be administered with dose reductions if necessary.

Main limitations of our study are its retrospective origin, low number of patients in the chemotherapy groups, and having no comparative control groups.

Conclusion

We found that PFS time and tolerability in our geriatric population was similar to those reported in the previous studies conducted among populations less than 70 years of age. Having fewer cycles of chemotherapy, lung metastasis, liver metastasis, and ECOG performance status 1 and 2 were found to be poor prognostic factors. We believe that physiological rather than the chronological age of the patient is the main factor to be considered during treatment planning in a geriatric population. In future, large phase III clinical trials should be designed for elderly patients taking into account their various physiological profiles.

Compliance With Ethical Standards

Disclosure of Potential Conflicts of Interest: The authors declare that they have no conflict of interests.

Ethical Approval: All procedures performed in this study 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. We have obtained a local ethics committee permission dated 16.10.2015 and number 16 for our study.

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