ORIGINAL RESEARCH

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Clinicopathological Features and Clinical Outcomes of Metastatic Adenocarcinoma of Unknown Primary: A Single Center Experience

Fatih GÜRLER[a], Ayşegül İLHAN GÜLEŞEN[a], Berna ÖKSÜZOĞLU[a]

[a]Clinic of Medical Oncology, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Türkiye

ABSTRACT Objective: This study aimed to investigate the clinical outcomes of site-specific therapy (SST) in patients with metastatic adenocarcinoma of unknown primary (MACUP). **Material and Methods:** A retrospective observational study was conducted, including patients diagnosed with MACUP. Clinicopathological features and clinical outcomes of SST were evaluated. **Results:** Sixty patients were included in the study. The median age was 61.5 (minimum-maximum: 31.1-76.1) years, and 40.0% of the patients (n=24) were 65 years or older. The progression-free survival (mPFS) was 4.7 months [95% confidence interval (CI): 3.7-5.7] with the first-line treatment in the whole group. The mPFS was 4.1 months (95% CI: 2.9-5.2), 4.7 months (95% CI: 3.0-6.3), and 9.3 months (95% CI: 6.1-12.6) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively. The overall survival (mOS) was 14.1 months (95% CI: 9.2-18.8) in the whole group. The mOS was 9.2 months (95% CI: 3.3-14.3), 8.5 months (95% CI: 3.8-13.2), and 15.5 months (95% CI: 9.3-18.8) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively. **Conclusion:** Patients with colorectal-derived cancers of our cohort, considered as a "more sensitive" type, seemed to benefit more from immunohistochemistry-based (IHC-based) SST. However, SST determination using genomic profiling is a gold standard, and IHC also offered valuable information.

Keywords: Metastatic adenocarcinoma of unknown origin; site-specific therapy; tailored therapy; empirical therapy

Cancer of unknown primary (CUP) is metastatic cancer with a broad histopathology spectrum, where the primary tumor localization cannot be determined at the time of diagnosis using conventional diagnostic approaches.[1] CUP constitutes approximately 1-2% of all cancers, and its incidence decreases with developing technology and diagnostic approaches.[2] Different hypotheses exist regarding the carcinogenesis of CUP; however, these are inconsistent with clinical implications.[3] Approximately 70-80% of CUP is metastatic adenocarcinoma of unknown primary (MACUP).[4,5] No standard chemotherapy regimen is recommended in patients with CUP. The most commonly used empirical therapy (ET) is the platinum and taxane combinations, while site-specific therapy (SST) has been used progressively. Immunohistochemistry (IHC) is an old but useful method to estimate the origin site in CUP. Furthermore, gene expression profiling is a novel way to predict tumor origin. Bioinformatics assists in resembling CUP to known primary tumors to treat more precisely.[3] In general, patients with CUP were divided into 2 subgroups. The first subgroup constitutes approximately 15-20% of CUP and has a favorable prognosis in which the tumor resembles a specific origin.[4] In contrast, the second subgroup constitutes the rest of CUP and has a poor prognosis with ET.[6] Historical studies were not designed according to the SST approach, and different studies had controversial clinical outcomes.[7-9] Therefore, we aimed to investigate the clinical outcomes of IHC-based SST in MACUP.

MATERIAL AND METHODS

PATIENTS

An observational retrospective single-center study was conducted screening patients diagnosed with MACUP in Dr. Abdurrahman Yurtaslan Ankara Oncology Teaching and Research Hospital between January 2016 and December 2021. The inclusion criteria

Correspondence: Fatih GÜRLER
Clinic of Medical Oncology, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Türkiye
E-mail: fatih_gurler@yahoo.com

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were adenocarcinoma histopathology, age≥18 years, and treatment with at least one cycle of chemotherapy. The exclusion criteria were a second malignancy or histopathology other than adenocarcinoma. The patients' records were reviewed. The definition of progression-free survival (PFS) was the time between the beginning of therapy to progression or death (in months). RECIST (version 1.1) criteria were used to define progression. The definition of overall survival (OS) was the time between the beginning of therapy to death (in months).

Formalin-fixed paraffin-embedded tissue samples were stained as a part of a routine procedure in IHC. Conventional and organ-specific IHC markers were used to define the origins of adenocarcinoma. Lung adenocarcinoma-like (non-small cell lung cancer) staining was defined as CK7 (+), CK20 (-), NapsinA (+), and TTF-1 (+). Epithelial ovarian cancer-like staining was defined as CK7 (+), CK20 (-), PAX8 (+), and WT (+). Colorectal adenocarcinoma-like staining was defined as CK7 (+)/(-), CK20 (+), and CDX2 (+). Pancreaticobiliary adenocarcinoma-like staining was defined as CK 7 (+), CK 20 (+)/(-), CK 19 (+), and CDX2 (+)/(-).[10]

CHEMOTHERAPEUTIC AGENTS

Treatment choices were conducted with IHC based on SST. In IHC, the patients whose tumor was stained as a lung adenocarcinoma or an epithelial ovarian cancer were treated with carboplatin plus paclitaxel. Modified FOLFOX-6 regimen was administered to the patients whose tumors stained like a colorectal adenocarcinoma in IHC. On the other hand, the patients who had tumors stained as pancreaticobiliary adenocarcinoma in IHC were treated with gemcitabine plus cisplatin (Appendix 1).

STATISTICAL ANALYSIS

SPSS®, v22.0 Chicago, IL, USA software was utilized for statistical analysis. The homogeneity and distribution of the variables were shown with descriptive analysis. Non-categorical variables were reported using median (range). Pearson's chi-squared test or Fisher's exact test was used in reporting categorical variables. The Kaplan-Meier curve was used to create survival curves. Univariate and multivariate analyses were performed to estimate the effects of variables on progression and death. The tests were bidirectional, and $p<0.05$ was considered significant.

The study was conducted according to the Declaration of Helsinki. The ethics committee approval was obtained from The Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Teaching and Research Hospital (date: April 6, 2022, no: 2022-03/1727).

RESULTS

There were 60 patients included in the study with a median age of 61.5 years (minimum-maximum: 31.1-76.1). Moreover, 40.0% of the patients (n=24) were 65 years or older. In total, 56.7% of the patients (n=34) were male, and 85.0% (n=51) had an Eastern Cooperative Oncology Group performance status of 1 or higher. Lymph node metastasis was the most common (93.3%, n=56), while the liver was the second most common (56.7%, n=34) metastatic region. Three or more metastatic regions were noted in 23.3% (n=14) patients. Patients were treated with 3 chemotherapeutic regimens: gemcitabine plus cisplatin (48.3%, n=29), carboplatin plus paclitaxel (28.8%, n=17) and modified FOLFOX-6 regimen (23.3%, n=14) (Table 1).

APPENDIX 1: Treatment regimens.

Regimen	Schedule
Gemcitabine plus cisplatin	Gemcitabine 1,250 mg/m^2 (IV) on days 1 and 8 plus cisplatin 100 mg/m^2 (IV) on day 1, repeated in every 3 weeks.
Carboplatin plus paclitaxel	Carboplatin (AUC 5-6) (IV) on day 1 and paclitaxel 175-200 mg/m^2 on day 1, repeated in every three weeks.
Modified FOLFOX-6	Oxaliplatin 85 mg/m^2 (IV) plus folinic acid 400 mg/m^2 (IV) plus 5-fluorouracil 400 mg/m^2 (IV bolus) on day 1, and followed by 5-fluorouracil 2,400 mg/m^2 (IV 46-h infusion), repeated in every 2 weeks.

IV: Intravenous; AUC: Area under the curve.

TABLE 1: Patient characteristics.

Variable	Value
No. of patients, n (%)	60 (100)
Median age at diagnosis, years (minimum-maximum)	61.5 (31.1-76.1)
Elderly, n (%)	
<65 year-old	36 (60.0)
≥65 year-old	24 (40.0)
Sex, n (%)	
Female	26 (43.3)
Male	34 (56.7)
ECOG PS, n (%)	
0	9 (15.0)
≥1	51 (85.0)
Metastatic regions, n (%)	
Lymph node	56 (93.3)
Liver	34 (56.7)
Bone	20 (33.3)
Lung	16 (26.7)
Brain	1 (1.7)
Others	54 (90.0)
No. of metastatic regions, n (%)	
≤3	46 (76.7)
>3	14 (23.3)
First-line chemotherapy	
Gemcitabine plus cisplatin	29 (48.3)
Carboplatin plus paclitaxel	17 (28.8)
Modified FOLFOX-6	14 (23.3)

ECOG PS: Eastern Cooperative Oncology Group performance status.

The median duration of follow-up was 15.1 months [95% confidence interval (CI) 8.3-19.3], and the median duration of first-line treatment was 3.9 months (95% CI 3.1-5.6). The median cycles of first-line treatment were 4 (minimum-maximum: 1-16) in the gemcitabine plus cisplatin group, 4 (minimum-maximum: 1-9) in the carboplatin plus paclitaxel group, and 6 (minimum-maximum: 2-10) in the mFOLFOX-6 group.

The mPFS was 4.7 months (95% CI 3.7-5.7) with first-line treatment in the whole group (Figure 1A). When it was analyzed according to first-line treatment regimens, the mPFS was 4.1 months (95% CI 2.9-5.2), 4.7 months (95% CI 3.0-6.3), and 9.3 months (95% CI 6.1-12.6) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively (Figure 1B). In the univariate analyses to investigate the effect of variables on PFS, it was found that liver metastasis [hazard ratio (HR) 2.01, 95% CI 1.04-3.86, p=0.037] and lung metastasis (HR 2.53, 95% CI 1.18-5.42, p=0.017) variables increased the progression. Additionally, it was observed that the first-line chemotherapy variable did not affect the progression. Using these variables, a multivariate analysis was conducted that increased the progression and first-line

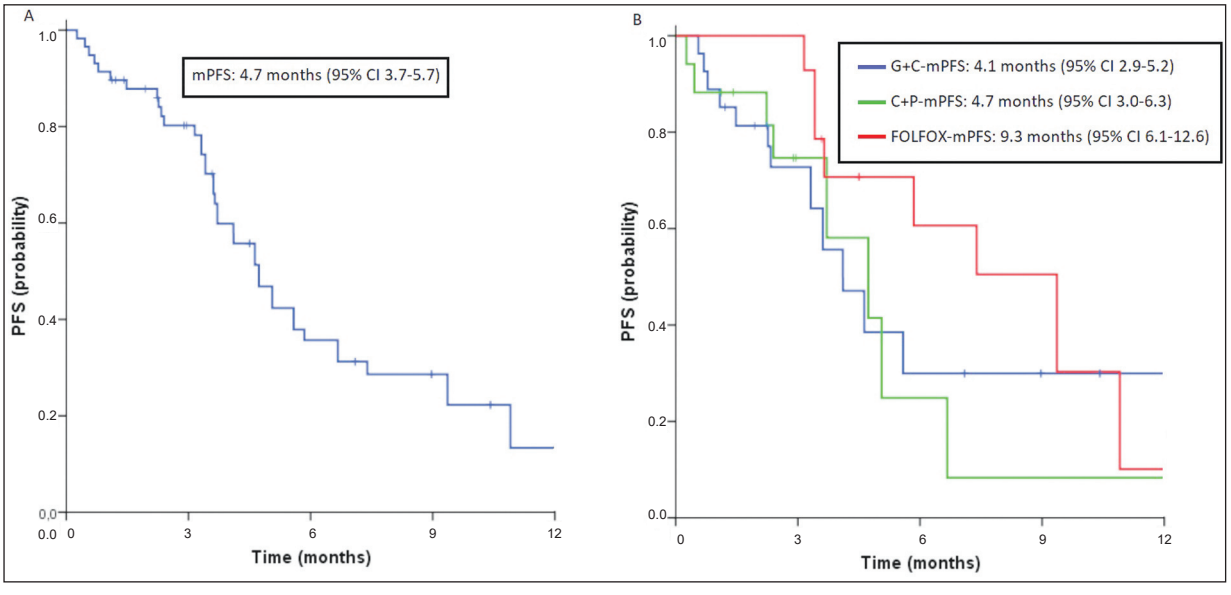

FIGURE 1: Kaplan-Meier curves of PFS with the first-line treatment in the whole group **(A)**, and according to treatment regimens **(B)** (G+C: gemcitabine plus cisplatin, C+P: carboplatin plus paclitaxel, FOLFOX: modified FOLFOX-6 regimen).
PFS: Progression-free survival; CI: Confidence interval.

chemotherapy variable, which was clinically significant. It was found that liver (HR 2.71, 95% CI 1.27-5.77, p=0.010) and lung metastasis (HR 4.02, 95% CI 1.51-10.76, p=0.005) variables increased the progression, and first-line chemotherapy variable did not affect the progression (Table 2).

The mOS was 14.1 months (95% CI 9.2-18.8) in the whole group (Figure 2A). The mOS was 9.2 months (95% CI 3.3-14.3), 8.5 months (95% CI 3.8-13.2), and 15.5 months (95% CI 9.3-18.8) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively (Figure 2B). In the univariate analyses to investigate the effect of variables on OS, liver (HR 2.42, 95% CI 1.01-4.83, p=0.047) and lung metastasis (HR 3.14, 95% CI 1.34-7.36, p=0.011) variables were observed to increase death. In contrast, the first-line chemotherapy variable did not affect death. A multivariate analysis was conducted with these variables that increased the death and first-line chemotherapy variable, which was clinically significant. It was found that the lung metastasis variable (HR 3.35, 95% CI 1.24-9.08, p=0.017) increased death. Additionally, liver metastasis and first-line chemotherapy variables did not affect death (Table 3).

DISCUSSION

It was aimed to investigate the clinical outcomes of IHC-based SST in MACUP retrospectively. It was revealed that the mPFS was 4.1 months (95% CI 2.9-5.2), 4.7 months (95% CI 3.0-6.3), and 9.3 months (95% CI 6.1-12.6) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively. Additionally, the mOS was 9.2 months (95% CI 3.3-14.3), 8.5 months (95% CI 3.8-13.2), and 15.5 months (95% CI 9.3-18.8) in the gemcitabine plus cisplatin, carboplatin plus paclitaxel, and mFOLFOX-6 groups, respectively.

TABLE 2: Univariate and multivariate Cox regression models to estimate progression.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**CI (95%)**	**p value**	**HR**	**CI (95%)**	**p value**
Elderly						
<65 year-old	Ref					
≥65 year-old	1.76	0.90-3.44	0.098	1.67	0.75-3.69	0.205
Sex						
Female	Ref					
Male	1.37	0.72-2.62	0.328	-	-	-
ECOG PS						
0	Ref					
≥1	1.51	0.62-3.65	0.356	-	-	-
Metastatic regions						
Lymph node	1.49	0.33-6.60	0.594	-	-	-
Liver	2.01	1.04-3.86	0.037	2.71	1.27-5.77	0.010
Bone	0.90	0.44-1.83	0.776	-	-	-
Lung	2.53	1.18-5.42	0.017	4.02	1.51-10.76	0.005
Others	0.39	0.15-1.02	0.055	-	-	-
No. of metastatic regions						
≤3	Ref					
>3	0.95	0.37-2.46	0.927	-	-	-
First-line chemotherapy						
Gemcitabine plus cisplatin	Ref					
Carboplatin plus paclitaxel	1.27	0.61-2.66	0.512	1.32	0.57-3.04	0.513
Modified FOLFOX-6	0.67	0.30-1.49	0.336	0.98	0.36-2.64	0.979

HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status.

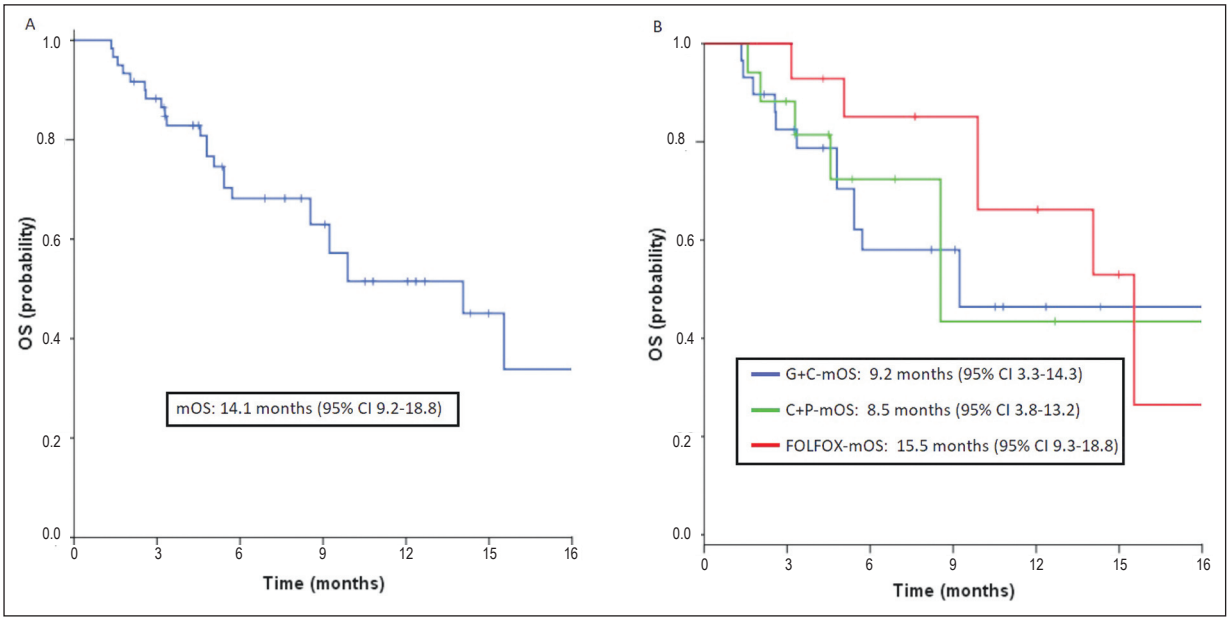

FIGURE 2: Kaplan-Meier curves of OS with the first-line treatment in the whole group **(A)**, and according to treatment regimens **(B)** (G+C: gemcitabine plus cisplatin, C+P: carboplatin plus paclitaxel, FOLFOX: modified FOLFOX-6 regimen).
OS: Overall survival; CI: Confidence interval.

TABLE 3: Univariate and multivariate Cox regression models to estimate death.

		Univariate analysis			Multivariate analysis	
Variable	**HR**	**CI (95%)**	**p value**	**HR**	**CI (95%)**	**p value**
Elderly						
<65 year-old	Ref					
≥65 year-old	1.77	0.80-3.91	0.153	1.13	0.46-2.80	0.780
Sex						
Female	Ref					
Male	1.21	0.54-2.72	0.633	-	-	-
ECOG PS						
0	Ref					
≥1	1.83	0.54-6.16	0.326	-	-	-
Metastatic regions						
Lymph node	0.85	0.19-3.69	0.831	-	-	-
Liver	2.42	1.01-4.83	0.047	2.53	0.94-6.83	0.066
Bone	1.23	0.53-2.83	0.624	-	-	-
Lung	3.14	1.34-7.36	0.011	3.35	1.24-9.08	0.017
Others	0.32	0.11-1.07	0.057	-	-	-
No. of metastatic regions						
≤3	Ref					
>3	1.63	0.68-3.94	0.267	-	-	-
First-line chemotherapy						
Gemcitabine plus cisplatin	Ref					
Carboplatin plus paclitaxel	0.92	0.35-2.45	0.878	1.08	0.30-3.01	0.876
Modified FOLFOX-6	0.60	0.22-1.62	0.323	1.09	0.35-3.40	0.878

HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status.

In a Phase II Japanese trial, patients with CUP were randomized to SST and ET (carboplatin and paclitaxel). Gene expression profiling was used in this Phase II trial, and approximately half of the tumors were adenocarcinoma in both groups. Pancreatic (21%) and gastric cancer-derived tumors (21%) are the most common types of cancers. The mOS was 9.8 months (95% CI 5.7-13.8) and 12.5 months (95% CI 8.9-16.1) with SST and ET (p=0.896), respectively. The mPFS was 5.1 months (95% CI 1.9-8.3) with SST and 4.8 months (95% CI 3.3-6.5) with ET (p=0.550).[9] This trial revealed that defining the origin of cancer might help in estimating the prognosis, especially in more responsive tumors. However, this advantage did not turn into a survival benefit. In the Phase III GEFCAPI 04 trial, patients were randomized to ET (gemcitabine and cisplatin), and SST defined with molecular tests. The most common one was pancreaticobiliary cancer (19%). The mPFS was 5.3 months and 4.6 months with ET and SST, respectively (HR 0.95, 95% CI 0.72-1.25, p=0.700). The mOS was 10.0 months and 10.7 months with ET and SST, respectively (HR 0.92, 95% CI 0.69-1.23). The GEFCAPI 04 trial also failed to improve the clinical outcomes of patients with SST.[11]

SST and ET were compared in patients with CUP in a meta-analysis conducted with 5 clinical trials. It also included non-adenocarcinoma histopathology. The mPFSs varied between 4.2 to 5.3 months, and the mOSs varied between 6.0 to 12.5 months with ET. The mPFS's varied between 4.6 to 5.1 months, and the mOSs varied between 9.8 to 20.3 months. In this meta-analysis, it was revealed that SST did not improve OS (HR 0.75, 95% CI 0.55-1.03, p=0.069) and PFS (HR 0.93, 95% CI 0.74-1.17, p=0.534) significantly. In contrast, this meta-analysis divided CUP into 2 subgroups, similar to other studies. The first subgroup comprised more responsive tumors (resembling colorectal, breast, ovarian, and lung cancers), and the second subgroup consisted of less responsive tumors (resembling biliary, gastroesophageal, and pancreas cancers). According to this subgroup analysis, an improved OS was observed in more responsive tumors with SST (HR 0.67, 95% CI 0.46-0.97, p=0.037).[12] In another meta-analysis comparing SST and ET conducted with 4 clinical trials, it was shown that neither OS (HR 0.70, 95% CI 0.52-1.02, p=0.06) nor PFS (HR 0.93, 95% CI 0.74-1.17, p=0.77) was significantly improved with SST. In this meta-analysis, there was significant heterogeneity between 4 trials.[13]

Clinicopathological features and clinical outcomes of 1,011 patients with MACUP were reviewed in a retrospective SEER database analysis. Digestive system (32.1%) and respiratory system-derived cancers (29.6%) were the 2 most common sites in MACUP. The mOS was 6 and 9 months in digestive and respiratory system cancers, respectively. Furthermore, it was revealed that digestive (HR 0.41, 95% CI 0.32-0.53, p<0.001) and respiratory system-derived cancers (HR 0.27, 95% CI 0.11-0.66, p<0.001) benefited from chemotherapy.[14] In a retrospective study comparing SST and ET in patients with CUP with standard IHC and molecular tests in 122 patients, it was observed that patients with SST had improved OS over ET. However, this retrospective study had more heterogeneous types of cancers than our cohort.[15] Furthermore, the mOS was 19.8 months in the colon cancer group. Our study was consistent with this result in terms of more benefited colorectal adenocarcinoma-derived IHC-based SST.

Our study did not have a control group with a defined origin with IHC and was treated with empirical gemcitabine plus cisplatin or carboplatin plus paclitaxel. Only IHC-based SST was applied. Although our study included only adenocarcinomas, unlike other studies, pancreaticobiliary-derived adenocarcinomas were the most common type of cancer in two previous studies.[11,16] The mOS was 9.2 months (95% CI 3.3-14.3), and the mPFS was 4.1 months (95% CI 2.9-5.2) in this "less sensitive" subgroup of our study with site-specific gemcitabine plus cisplatin therapy. These outcomes are consistent with the aforementioned 2 studies. In the colorectal-derived adenocarcinomas subgroup of our study, which is also called "more sensitive", it was obtained that the mOS was 15.5 months (95% CI 9.3-18.8) and the mPFS was 9.3 months (95% CI 6.1-12.6) with site-specific mFOLFOX-6 therapy. These results were consistent with the more sensitive group treated with SST in the previous Phase III trial.[11] It is inappropriate to compare our study and previous studies directly; however, these improved outcome trends toward SST

might highlight some points. One of them is that approximately 20% of patients with CUP have a more sensitive nature and benefit from chemotherapy. Additionally, in this particular, more sensitive group, IHC-based SST seemed to improve outcomes not statistically but clinically. In contrast, these improved outcomes might be a consequence of the nature of this origin which already has a better prognosis like colorectal adenocarcinomas. The site-specific approach is important to distinguish the group with a good prognosis. Our study had more liver and lung metastasis than the retrospective SEER database analysis; however, this study aforementioned also included female breast and prostate cancers, which differed the population from our study. Lung metastasis increased death, and lung and liver metastasis increased progression in multivariate analyses in our study. This was also consistent with the previous studies.[14]

There are some limitations in our study. First, it was an observational retrospective study with limited patients. Secondly, the SST approach was not tailored with molecular tests or gene expression profiling, and it was just defined with IHC, which might cause possible underestimation with a lesser sensitivity. Thirdly, adverse events, treatment compliance, and treatments beyond first-line therapy must be added to the study design. Lastly, our study did not have a control group. There was only an SST group comprising lesser and more sensitive subgroups.

CONCLUSION

Although direct comparisons could not be made in the present study owing to the study design, it was observed that mPFS and mOS in patients with MACUP treated with mFOLFOX-6 regimen were numerically higher than that in those treated with gemcitabine plus cisplatin and carboplatin plus paclitaxel regimens. Patients with colorectal-derived cancers in our cohort, which is considered a "more sensitive" type, seemed to benefit more from IHC-based SST. However, determining the SST with genomic profiling is a gold standard, IHC also offered valuable information. Further prospective randomized controlled clinical trials with more detailed gene expression profiling and molecular tests are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Fatih Gürler;* ***Design:*** *Fatih Gürler;* ***Control/Supervision:*** *Berna Öksüzoğlu;* ***Data Collection and/or Processing:*** *Fatih Gürler, Ayşegül İlhan Güleşen;* ***Analysis and/or Interpretation:*** *Fatih Gürler;* ***Literature Review:*** *Fatih Gürler;* ***Writing the Article:*** *Fatih Gürler;* ***Critical Review:*** *Berna Öksüzoğlu;* ***References and Fundings:*** *Ayşegül İlhan Güleşen;* ***Materials:*** *Ayşegül İlhan Güleşen.*

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