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ORIGINAL RESEARCH

Unfavorable carcinoma of unknown primary with a gastrointestinal profile: a retrospective study

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Background: Carcinoma of unknown primary (CUP) with a gastrointestinal profile is categorized by the European Society of Medical Oncology (ESMO) guidelines into favorable and unfavorable subsets. Favorable CUPs benefit from site-specific chemotherapy (CT), while the optimal treatment for unfavorable CUPs is still undefined.

Materials and methods: We conducted a single-center retrospective study to describe outcomes of patients with CUP with a gastrointestinal profile referred to our center from January 2000 to August 2023. Favorable CUPs were defined as CK7−/CK20+/CDX2+ by immunohistochemistry, according to the ESMO definition; all other cases were considered unfavorable. The main endpoint was the progression-free survival (PFS) of first-line CT for advanced disease in all patients and in the unfavorable group.

Results: A total of 56 patients were included, of whom 46 (82%) had unfavorable CUPs. After a median follow-up of 43.9 months, the median overall survival (mOS) was 11.8 months [95% confidence interval (CI) 8.3-15.3 months]. At univariate analysis, the presence of peritoneal metastases and residual tumor after primary surgery were associated with a shorter OS. The median PFS (mPFS) was 6.1 months (95% CI 3.6-8.7 months). In the unfavorable CUP subgroup, the mOS was 12.6 months (95% CI 8.7-16.5 months), the mPFS was 6.1 months (95% CI 3.5-8.9 months) and none of the CT regimens used showed to portend better PFS. The most relevant altered genes included: *KRAS* (9/29; 31%), *BRAF* (1/26; 4%), *NRAS* (1/25; 4%), *TP53* (9/23; 39%).

Conclusions: CUPs with a gastrointestinal profile are characterized by poor prognosis and the absence of biomarker for treatment personalization. No CT regimen was superior in terms of PFS in patients with unfavorable CUPs.

Key words: carcinoma of unknown primary, gastrointestinal profile, unfavorable CUPs, biomarkers

INTRODUCTION

Cancer of unknown primary (CUP) is defined as a carcinoma or undifferentiated neoplasm for which a standardized diagnostic work-up fails to identify the primary tumor responsible for metastases.[1] CUPs account for 3%-5% of all cancers and are characterized by a poor prognosis due to the late tumor presentation and challenges in the diagnosis definition, and therefore in the appropriate treatment choice.[2] The reported median overall survival (mOS) in single- and multi-institutional studies is ∼9-11 months.[3] In the first-line setting, response rates with various empiric chemotherapeutic agents, often given as doublets or triplets, range between 20% and 30%. However, most responses are not sustained and have a moderate effect on median survival.[1] Beyond the first line, response rates drop to 8%-13%. Therefore, a critical need to develop novel therapies exists.[4]

The management of CUPs represents an evolving field in oncology. With the increasing availability of immunohistochemistry (IHC) stains, molecular assays and the emergence of new cytotoxic and targeted therapies, this heterogeneous group of rare tumors can be now better dissected, in order to optimize treatment choices. Furthermore, the recent development in molecular technology that allows molecular gene profiling of tumors provides an opportunity for improved diagnosis of patients with CUP and aids in treatment decisions according to the 'likely' histology of origin.[1]

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According to the European Society of Medical Oncology (ESMO) guidelines, CUPs are classified into favorable and unfavorable subsets. Favorable CUPs (20% of patients) have either clinical and pathological aspects highly suggestive of a specific site of origin or metastases amenable to localized treatment with curative intent, either being single or oligo-metastatic cancers: in this case, patients are treated with site-specific chemotherapy (CT). All the remaining cases of CUPs are defined unfavorable and are treated with empiric CT regimens. There are no data about the best CT regimen for unfavorable CUPs with a gastrointestinal profile, i.e. those CUPs that do not meet the criteria of favorable colon-like CUP (CK7−/CK20+/CDX2+) but have a morphological/immunohistochemical profile suggestive of an origin within the digestive system, according to the IHC profile. Furthermore, despite the advancement in molecular profiling, no molecular predictive biomarker has been identified.

The main aim of this study is to describe outcomes and predictive and prognostic factors of patients with CUP with a 'gastrointestinal profile', candidate to receive first-line CT for advanced disease.

MATERIALS AND METHODS

Study population

We conducted a single-center, retrospective, observational study at European Institute of Oncology (IEO), IRCCS, Milan.

Patients meeting the following criteria were included: age ≥18 years, a histologically confirmed diagnosis of CUP with a gastrointestinal profile, referred to our center from January 2000 to August 2023, eligible to receive first-line CT for advanced disease. The unknown primary was defined if esophagogastroduodenoscopy, colonoscopy and full abdomen imaging were negative for gastrointestinal primary tumors and other appropriate imaging including computed tomography scan, positron emission tomography scan or other diagnostic evaluations carried out even *post hoc*, during the therapeutic process, excluded a clear primary site.

In pathology report, the definition of gastrointestinal profile was: (i) negativity for GATA Binding Protein 3 (GATA-3), Paired box gene-8 (PAX-8), Thyroid Transcription Factor 1 (TTF-1) by IHC and (ii) presence of an abundant mucinous component and/or a signet ring cell component. According to ESMO guidelines, favorable colon-like CUPs were defined as CK7−/CK20+/CDX2+ by IHC or if metastases amenable to localized treatment with curative intent were detected (i.e. single or oligo-metastatic cancers). All other cases were considered unfavorable (i.e. CK7+/CK20−/any CDX2 or CK7−/CK20+/CDX2− or CK7−/CK20−/CDX2+). The likely origin was defined as: lower gastrointestinal tract, if CK7−/CK20+ or CK7+/CK20+/CDX2+; biliopancreatic district, if CK7+/CK20− and CK19+ or SATB-2+ or absence of signet ring cells; all other cases were considered from the upper gastrointestinal tract.

Patients were included in the CT group if they received at least one cycle of first-line CT for metastatic disease, in the biomarker group if at least a genomic alteration was tested by polymerase chain reaction (PCR) or next-generation sequencing (NGS) and in the unfavorable group if they were diagnosed with unfavorable CUP and received at least one cycle of CT.

All information was obtained through access to medical records, including somatic alteration if tested. The study was approved by the IEO institutional review board (UID4210) and was conducted in accordance with the principles stated in the Declaration of Helsinki and with the principles of good clinical practice.

Endpoints

Study endpoints included: median progression-free survival (mPFS) on first-line CT for advanced disease (calculated in the CT group and in the unfavorable group), defined as the time from the first cycle of first-line CT to disease progression or death due to any cause, whichever occurred first; mOS, calculated in all comers, biomarker group and unfavorable group, defined as the time from histological diagnosis of metastatic disease to death due to any cause; and objective response rate (ORR), calculated in the CT group, defined as the percentage of complete responses or partial responses as per RECIST v1.1 criteria in patients receiving first-line CT.

Statistical analyses

Descriptive statistics were used to analyze patients' characteristics. Clinical and biological variables were grouped in standard categories whenever reasonable. Continuous variables are expressed as the median and interquartile range. Categorical variables are expressed as numbers and proportions (%) and were compared using Fisher's exact test or chi-square test, as appropriate.

Survival was calculated using the Kaplan−Meier method and log-rank test was used in univariate analysis to assess factors associated with clinical endpoints. The Cox proportional hazards models were used to estimate the independent factors prognostic for PFS and OS in multivariable analysis, which are expressed as hazard ratio (HR) and confidence interval (CI). Median follow-up was calculated using the reverse Kaplan−Meier method.

All tests were carried out two-sided at a significance level of $\alpha = 0.05$. Statistical analyses were carried out using SPSS software (version 28.0.1.0; Chicago, IL).

RESULTS

Overall, 56 patients were included. Patient characteristics are reported in Table 1. The median age at diagnosis was 62 years (IQR 53-69 years). Fifty (89%) patients had visceral disease and 31 (55%) peritoneal metastases. According to pathology report, the suspected tumor origin was related to upper gastrointestinal, lower gastrointestinal or biliopancreatic district in 14 (25%), 20 (36%) and 22 (39%) patients, respectively. Furthermore, 46 (82%) patients presented unfavorable CUP.

Fifty-two (93%) patients received at least one cycle of first-line CT for advanced disease; among these patients (CT

Table 1. Patient characteristics

	All patients ($N = 56$)	Unfavorable group treated with CT ($N = 43$)
Male, *n* (%)	14 (25)	12 (29)
Age at diagnosis, median (IQR)	62 (53-69)	
ECOG performance status 0-1, *n* (%)	49 (87)	41 (95)
Visceral disease at baseline, *n* (%)	50 (89)	37 (86)
Peritoneal disease at baseline, *n* (%)	31 (55)	20 (46)
Cytoreductive surgery, *n* (%)	32 (57)	
No residual tumor after surgery, *n* (%)	12 (21)	
>1 metastatic site, *n* (%)	40 (71)	34 (79)
Suspected origin		
Upper GI, *n* (%)	14 (25)	10 (23)
Lower GI, *n* (%)	20 (36)	13 (43)
Biliopancreatic, *n* (%)	22 (39)	20 (56)
CDX2 status		
Positive, *n* (%)	29 (52)	17 (40)
Negative, *n* (%)	13 (23)	13 (30)
Not assessed, *n* (%)	14 (25)	13 (30)
Unfavorable CUP, *n* (%)	46 (82)	43 (100)
Receipt of 1L CT, *n* (%)	52 (93)	43 (100)
Platinum-based regimen, *n* (%)	44 (79)	36 (83)
Platinum–fluoropyrimidines, *n* (%)	24 (43)	16 (37)
Platinum–taxanes, *n* (%)	13 (23)	7 (16)
Platinum–gemcitabine, *n* (%)	7 (12)	13 (30)

1L, first line; CT, chemotherapy; CUP, carcinoma of unknown primary; GI, gastrointestinal; IQR, interquartile range.

group), 44 (79%) received a platinum-based regimen which consisted of oxaliplatin in 61% of patients (27/44). The most common platinum-free regimen was gemcitabine and nab-paclitaxel [4/8 (50%)]. No patients included in the study received immunotherapy or targeted therapy. Furthermore, 32 (57%) patients underwent cytoreductive surgery and no post-surgical residual tumor was reported in 12 (21%) patients.

After a median follow-up of 43.9 months (95% CI 6.1-81.8 months), 45 deaths were registered. The mOS was 11.8 months (95% CI 8.3-15.3 months) (Figure 1A).

At univariate analysis, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1 ($P < 0.001$), the presence of peritoneal metastases ($P < 0.001$), residual tumor after surgery ($P = 0.049$) and platinum-based CT with fluoropyrimidines or gemcitabine ($P = 0.05$) were associated with a shorter OS. When all these variables were included in the multivariable analysis, all of them lost their independent prognostic value. Interestingly, the presence of peritoneal metastases was associated with a shorter OS after adjusting for ECOG PS >1 and CT regimen (HR 3.0, 95% CI 1.3-7.1, $P = 0.01$), but not when considering also residual tumor after surgery (HR 3.6, 95% CI 16.8-17.0, $P = 0.10$).

Considering the CT group, 33 PFS events were registered. The mPFS was 6.1 months (95% CI 3.6-8.7 months) (Figure 1B). At univariate analysis, male patients ($P = 0.017$), peritoneal metastases ($P = 0.010$), residual tumor after surgery ($P = 0.037$), suspected biliopancreatic origin ($P = 0.033$) and CDX2− status ($P = 0.035$) were associated with a shorter PFS. At multivariable analysis, the presence of peritoneal metastases was independently associated with a shorter PFS, after adjusting for sex and suspected origin (HR 2.5, 95% CI 1.3-4.8, $P = 0.04$). The ORR was 30.7% (95% CI 18.7% to 45.1%); the disease control rate was 65.4% (95% CI 50.9% to 78.0%). After progression, 19/52 (36%) patients received a second line of CT.

In the subgroup of 43 patients with unfavorable CUP who received at least one cycle of CT, 33 deaths were registered and the mOS was 12.6 months (95% CI 8.7-16.5 months) (Figure 2A). Forty PFS events were registered and the mPFS was 6.1 months (95% CI 3.5-8.9 months) (Figure 2B). At univariate analysis, male gender ($P = 0.034$), peritoneal metastases ($P = 0.0282$), residual tumor after surgery ($P = 0.002$), suspected biliopancreatic origin ($P = 0.033$), ECOG PS >1 ($P < 0.001$) and CDX2− status ($P = 0.025$) were associated with a shorter PFS. No CT regimen was superior in terms of PFS at both univariate ($P = 0.282$) and multivariable analyses after adjusting for peritoneal metastases ($P = 0.041$), suspected origin ($P = 0.912$) and baseline ECOG PS ($P = 0.894$).

Twenty-nine (52%) patients were tested for at least one mutation by PCR (4/29; 14%) or NGS (25/29; 86%) and were included in the exploratory biomarker analysis. Among them 27 and 24 events of PFS and OS were registered, respectively. The most relevant genomic alterations were mutations in *KRAS* (9/29; 31%), *BRAF* (1/26; 4%), *NRAS* (1/25; 4%), *TP53* (9/23; 39%), *HER2* (1/23; 4.3%), *POLE* (2/25; 8%), *PTEN* (2/25; 8%), *PIK3CA* (1/25; 4%), *SMAD4* (2/25; 8%), *CDH1* (1/25; 4%) and *HER2* amplifications (1/3; 33%). All 20 tumors tested for microsatellite instability were stable (MSS). The presence of a pathogenic mutation of *KRAS* or *NRAS* was associated with a shorter OS at univariate analysis (mOS 9.5 versus 18.8 months, $P = 0.023$), but not when adjusting for peritoneal metastases (HR 2.1, 95% CI 0.6-7.3, $P = 0.234$).

DISCUSSION

This retrospective analysis showed that the prognosis of patients affected by CUP with a gastrointestinal profile remains poor, especially in case of unfavorable CUPs or peritoneal metastases, consistent with the current literature.[3]

Specifically, most of the patients included in this study were women, with peritoneal disease at baseline. Based on our analysis, the presence of peritoneal metastases was significantly associated with poorer outcomes. This result is in line with Hemmink et al.'s study, which involved 18 911 patients with CUP and showed that peritoneal metastases were more frequent in women and were associated with significantly poorer survival rates in both adenocarcinomas and undifferentiated tumors.[5]

Furthermore, 57% of patients included in our study underwent cytoreductive surgery and significant worse survival outcomes were found in case of residual tumor after surgery. This finding supports the curative role of peritoneal surgery in selected patients with CUPs with a gastrointestinal profile. Indeed, in clinical practice,

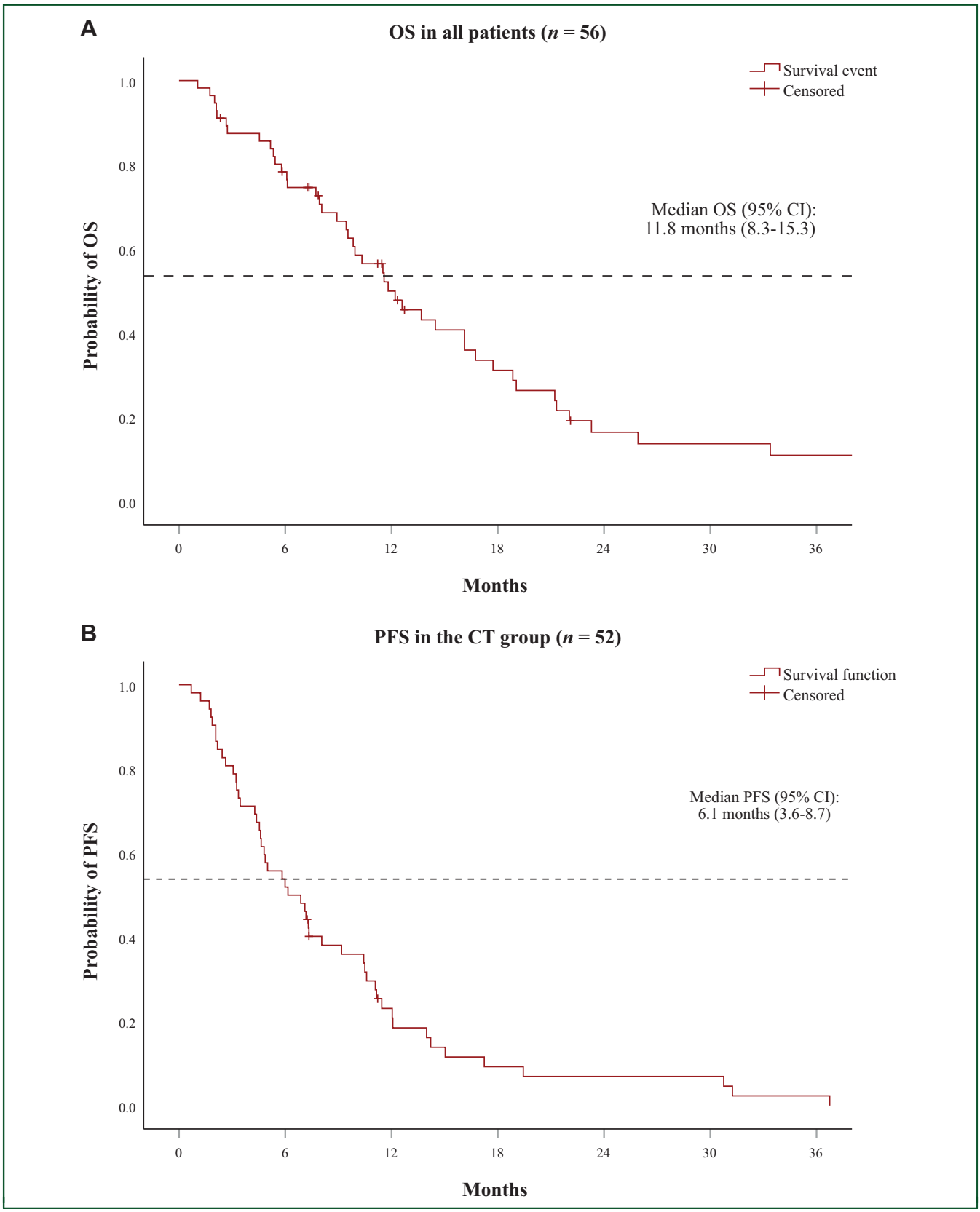

Figure 1. Kaplan–Meier analysis of OS (A) and PFS (B) among all patients.
CI, confidence interval; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.

peritoneal surgery is usually not considered apart from cases misdiagnosed for ovarian cancer, where it demonstrated to improve OS.[6]

In this regard, ESMO practice guidelines discussed the lack of data on peritonectomy in patients with 'unfavorable CUP'; indeed, only a small retrospective analysis and some

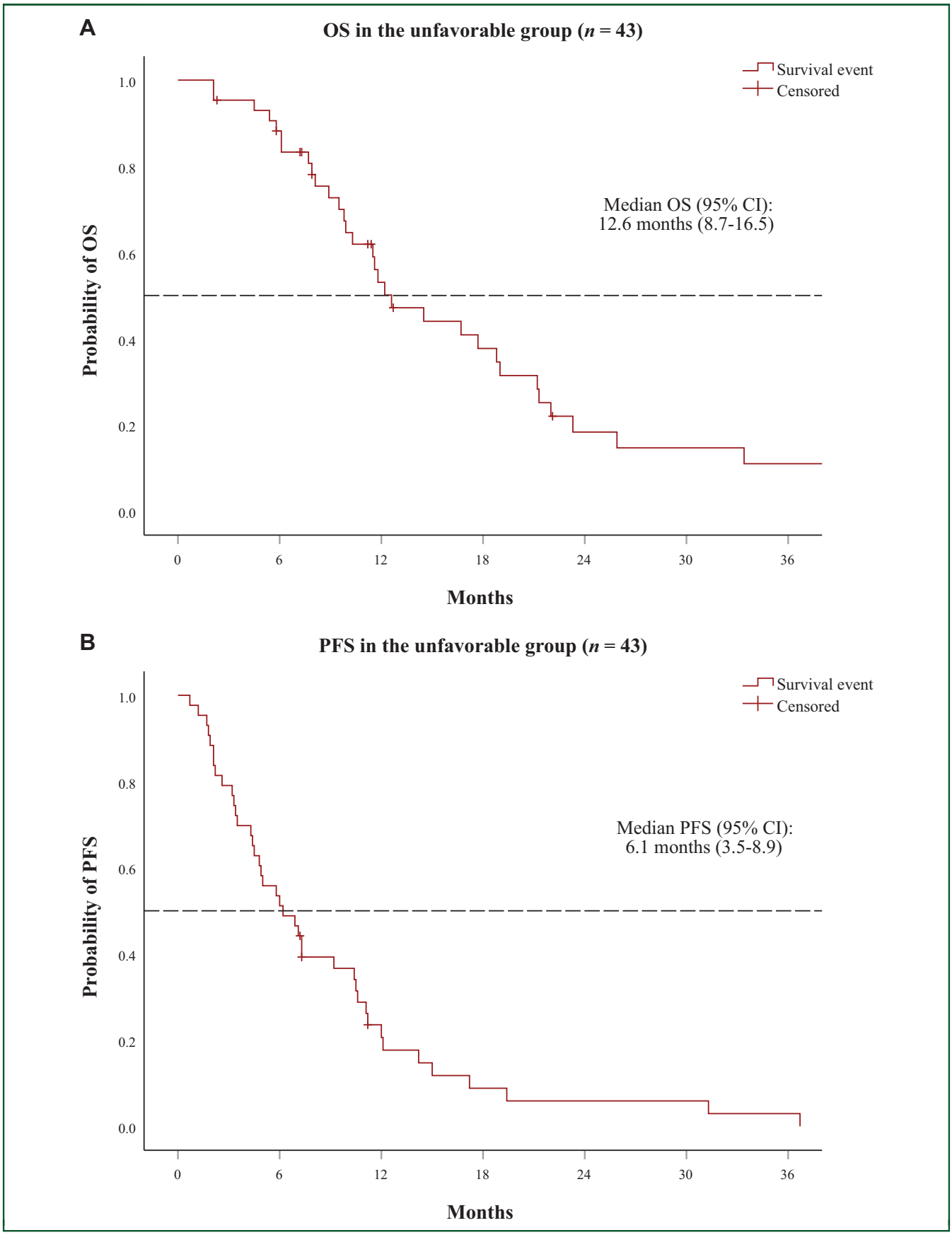

Figure 2. Kaplan–Meier analysis of OS (A) and PFS (B) among patients with unfavorable carcinoma of unknown primary with a gastrointestinal profile.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

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case reports have suggested a survival benefit after cytoreductive surgery in patients with favorable (ovary-like or colon-like) CUPs and isolated peritoneal carcinomatosis.[7-9] Therefore, ESMO guidelines indicate that patients with unfavorable CUPs can be candidate to cytoreductive surgery according to strict criteria, i.e. on the basis of PS and peritoneal cancer index and in experienced referral centers.

CDX2 positivity has emerged as a positive prognostic biomarker of lower gastrointestinal cancers and its assessment is frequently carried out in CUP diagnostic work-up. In our work, CDX2 has been assessed in 75% of patients and those with positive status (52%) had a longer PFS at univariate analysis. Consistently, many observational studies demonstrated that the lack of CDX2 is associated with poorer outcomes in patients with metastatic colorectal cancer, independently of other prognostic factors, including histological grade. It is, therefore, conceivable that CDX2− CUPs are associated with a more aggressive behavior,[10] as per prognostic significance in colorectal cancers, or displaying non-colon primary cancers.

In this regard, Varadhachary et al. paved the way for defining colon-like favorable CUPs by IHC as CK20+/CK7−/CDX2+, which reflects the definition used in our analysis.[11] This specific CUP subset should be considered as favorable and seems to benefit from site-specific treatments. Indeed, a subsequent study also conducted by MD Anderson in 2013 has provided encouraging indications about patients with CDX2+ favorable CUP with a gastrointestinal profile treated with site-specific treatments.[12] However, tumors with decreased or absent CDX2 expression were not included, unlike our study.

The treatment of patients with CDX2− and/or unfavorable CUPs with a gastrointestinal profile is unclear due to the lack of evidence. According to ESMO guidelines, platinum-based doublet CT is generally considered as standard of care in this setting. However, many randomized clinical trials including patients with all unfavorable CUPs and evaluating different CT regimens failed to demonstrate a statistically significant superiority of a specific treatment regimen. To the best of our knowledge, our study is the first to report outcomes of patients with unfavorable CUPs with a gastrointestinal profile; however, due to the small sample size, no difference among treatment regimens emerged in the unfavorable subgroup.[13-16]

Given the poor prognosis of CUPs treated by non-targeted conventional therapies, comprehensive genomic profiling should be carried out in order to identify targeted therapeutic approaches and improve outcomes. Of note, Ross et al. observed that almost all patients included in their NGS-based analysis harbored at least one clinically relevant genomic alteration, enabling a detailed and comprehensive characterization of clinical specimens.[17] Moreover, in 2018, a comprehensive survey of predictive biomarkers to immune checkpoint blockade in CUP was carried out, and predictive biomarkers to immune checkpoint blockade were found in 28% of patients.[18]

In our exploratory analysis, all 20 tumors tested for microsatellite instability resulted MSS, highlighting a potential aspect of CUP with a gastrointestinal profile; however, patients were not tested for tumor mutational burden or for programmed death-ligand 1. Additionally, *KRAS*, *NRAS* and *BRAF* were found to be the most relevant altered genes and poorer outcomes were observed in patients with *KRAS* or *NRAS* alteration; however, their prognostic significance was lost when adjusting for peritoneal metastases.

This study presents some limitations including the small sample size resulting in limited statistical power, the lack of data on the second-line treatment and the retrospective nature of the study which may have introduced selection bias. However, it is additional evidence in literature in a challenging setting, of patients diagnosed and treated in a reference cancer center, with expertise in the multidisciplinary management of gastrointestinal tumors.

CONCLUSIONS

CUPs with a gastrointestinal profile are a heterogeneous subgroup of neoplasms characterized by poor outcomes. To the best of our knowledge, this is the first retrospective analysis describing the outcomes of patients with unfavorable CUPs with a gastrointestinal profile. According to our data, in this subgroup, no CT regimen has demonstrated to be superior in terms of PFS. Peritonectomy should be considered case by case according to clinical features and tumor burden. Molecular determinants of prognosis and prediction of CT benefit are missing. Lacking prospective data from multicenter cohorts, a personalized multidisciplinary approach represents the best management of patients with these rare tumors.

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DISCLOSURE

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