DOI: 10.14744/ejmi.2023.86896
EJMI 2023;7(4):447–453

Research Article

Chemotherapy Timing During Visceral Crisis in Patients with Liver Metastatic Solid Carcinoma

Mustafa Buyukkor

Department of Medical Oncology, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye

Abstract

Objectives: The aim of the study is to investigate the impact of the timing of chemotherapy (CT) initiation and CT protocol on overall survival (OS) in patients with hepatic visceral crisis (HVC).

Methods: The study evaluated the timing of starting CT and the contribution of the initiated CT protocol to OS in patients with hepatic visceral crisis (HVC) who have clinical symptoms due to tumor burden characterized by liver metastasis and hyperbilirubinemia ≥1.5 times the upper limit, along with elevated at least one of ALT/AST values.

Results: Between November 2007 and July 2021, analyzed 233 patients in HVC. 60 individuals were able to receive CT and divided into two groups based on the timing of initiating CT during HVC. CT initiated patients within 7 days were observed to have longer median OS (mOS) compared to patients initiated CT after 7 days (3.88 vs 2.99 months; p=0.04). Furthermore single-agent CT exhibited a significantly mOS compared to patients unable to undergo CT (1.70 months vs 1.08 months; p=0.03) Additionally patients who received combination CT had longer mOS compared to those who received monotherapy (4.27 months vs 1.70 months; p=0.03).

Conclusion: Initiating early CT during HVC in eligible patients has a positive impact on OS.

Keywords: Chemoterapy, liver dysfunction, metastasis, survival, visceral crisis

Cite This Article: *Buyukkor M. Chemotherapy Timing During Visceral Crisis in Patients with Liver Metastatic Solid Carcinoma. EJMI 2023;7(4):447–453.*

Visceral crisis (VC), as defined most recently, refers to disease progression and serious organ dysfunction accompanied by clinical symptoms and laboratory findings. Hepatic visceral crisis (HVC) is defined by rapidly increasing bilirubin levels >1.5 × the upper limit of normal laboratory range, without Gilbert's syndrome or bile duct obstruction.[1] VC associated with malignancies can stem from widespread organ metastases or may be secondary to the primary pathophysiology of the disease and paraneoplastic causes. In cases of VC with intense metastases affecting vital organs and posing a life-threatening condition, the primary goal is to mitigate rapid clinical deterioration. For prompt symptom relief and disease control, the current approach for these patients should preferably involve combination chemotherapies.[1]

Liver metastases refer to tumors that originate from cancers in other parts of the body and spread to the liver. They are most commonly seen as secondary tumors resulting from colorectal cancer (CRC), pancreatic cancer, breast cancer, melanoma, and lung cancer.[2] Worldwide, lung cancer and CRC are the leading causes of cancer-related deaths, with stomach cancer ranking third. Stomach cancer often

Address for correspondence: Mustafa Buyukkor, MD. Abdurrahman Yurtaslan Ankara Onkoloji Egitim ve Arastirma Hastanesi, Tibbi Onkoloji Klinigi, Ankara, Türkiye
Phone: +90 312 336 09 09-5713 **E-mail:** mbuyukkor@hotmail.com

Submitted Date: August 16, 2023 **Revision Date:** September 16, 2023 **Accepted Date:** September 18, 2023 **Available Online Date:** September 20, 2023

presents in advanced stages due to its insidious course, and among the frequently metastasized sites, the liver is one of the prominent locations.[3] Malignancy-induced liver dysfunction is a rare cause of acute liver failure. The mechanism by which malignancy leads to liver dysfunction is multifactorial, with one aspect involving the direct reduction of functional healthy liver volume by the tumor.[4]

HVC due to diffuse liver metastases is defined as a condition that causes elevated bilirubin levels and hepatocellular insufficiency, resulting in impaired liver function, without extrahepatic bile duct obstruction. This condition is associated with a poor prognosis and short survival for patients. Given the unsafe nature of biopsies for these patients and the expectation that biopsy results may not influence treatment decisions, biopsies should be avoided. Instead, prompt initiation of systemic treatment is crucial for disease and symptom control.[5]

In the literature, patients with VC have been observed to have significantly lower OS compared to those without VC, and it has been observed that the survival of these patients improves with chemotherapy CT.[6,7] In this context, combination chemotherapies are preferred over single-agent (monotherapy) due to their association with higher objective response rates (ORR) and survival rates. However, guidelines do not specify which CT regimen should be preferred and generally recommend individualizing the choice of the best CT based on the patients' frailty and organ dysfunction.[7] During visceral crisis, apart from hormone receptor-positive, HER2-negative breast cancer patients,[8] there is no clear consensus on how to approach treatment for different patients.

The aim of the study is to examine the contribution of the systemic chemotherapy protocol (monotherapy and combination chemotherapy) and the timing of its administration to the survival of patients with liver metastases.

Methods

Between November 2007 and July 2021, a retrospective study was conducted at the Department of Medical Oncology of Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital. The study focused on patients aged 18 and above with solid tumors who developed hepatic visceral crisis due to liver metastases. Inclusion criteria encompassed patients with hepatocellular metastasis, rapid progression accompanied by hyperbilirubinemia ≥1.5 times the upper limit,[1] elevated at least one of ALT/AST values, and clinical symptoms due to tumor burden, who were deceased during follow-up and were able to initiate chemotherapy.

The study was prepared following the principles of the Helsinki Declaration. Patient information was collected through retrospective screening of the hospital database. Patients who did not meet the inclusion criteria, or had incomplete data were excluded from the study.

The ethical approval for the study was obtained from the Central Ethics Committee with the reference number 2022-05/1860 on June 8, 2022.

In this study, it's investigated the impact of the timing of chemotherapy initiation and its protocol (monotherapy vs. combination chemotherapy) on overall survival (OS) in 60 eligible patients with liver metastatic carcinoma who were followed due to hepatic visceral crisis. The study aimed to assess the impact of these factors on survival. Within the study, 173 patients with HVC due to liver metastasis from solid tumors were also retrospectively examined. However, these patients were not suitable for chemotherapy initiation based on their clinical and laboratory characteristics, and they were deceased during follow-up. Their clinicopathological characteristics were analyzed and compared with those of patients who could initiate treatment, specifically regarding overall survival (OS).

Furthermore, within the scope of the study, the clinicopathological characteristics of 173 patients with solid tumors and hepatic visceral crisis due to liver metastasis, who could not receive chemotherapy due to their ineligible clinical and laboratory characteristics, were examined. A comparison was conducted between ourCT ineligibl patients and those who received chemotherapy in terms of OS.

The statistical analysis of the study was conducted using SPSS version 24.0. Categorical data were expressed as numbers and percentages. Kaplan-Meier curve was employed for survival analysis, and it was compared using the log-rank test. The statistical relationship between nonparametric laboratory values tested during visceral crises in patients eligible for inclusion in the study was analyzed using the Spearman correlation test. A significance level of $p<0.05$ was considered for all statistical tests.

Results

In the study, out of the 60 patients who could undergo KT, 32 (53.3%) were male and 28 (46.7%) were female. Additionally, the median age of the patients was 57 (minimum 27-maximum 75). Among them, 34 (56.7%) were below the age of 60, while 26 (43.3%) were 60 years or older. The most frequently diagnosed disease among these patients was pancreatic cancer (Ca) with 13 individuals (21.7%), while the lowest number of patients were diagnosed with head and neck cancer, gastrointestinal neuroendocrine carcinoma, and testicular cancer (1 patient each; 1.7% for each diagnosis). The most common symptom observed during

visceral hepatic crisis in patients was fatigue (36.7%), while the number of individuals diagnosed with de novo liver metastasis was determined to be 48 (80%).

The demographic and clinical characteristics of the 60 patients eligible for CT are summarized in Table 1.

Table 1. Clinical and Pathological Characteristics of Patients Receiving CT

	Totally n=60/(%)
Sex	
Female	28 (46.7)
Male	32 (53.3)
Age median (min-max)	57 (27-75)
<60	34 (56.7)
≥60	26 (43.3)
Ecog	
1	16 (26.7)
2	44 (73.3)
Diagnoses	
Pancreas Ca	13 (21.7)
Breast Ca	11 (18.3)
Gastric Ca	7 (11.7)
Colon Ca	7 (11.7)
Primary Unknown Ca	7 (11.7)
Lung Ca	6 (10)
Neuroendocrine Tumor	3 (5)
Biliary tract Ca	2 (3.3)
Ovarian Ca	1 (1.7)
Head and Neck Ca	1 (1.7)
Gastrointestinal NEC	1 (1.7)
Testicular Ca	1 (1.7)
Symptoms During HVC	
Fatigue	22 (36.7)
Jaundice	6 (10)
Ascites	1 (1.7)
Jaundice+Fatigue	13 (21.7)
Ascites+Fatigue	4 (6.7)
Ascites+Jaundice	2 (3.3)
Ascites+Jaundice+Fatigue	12 (20)
Denovo Liver metastasis	
Present	48 (80)
Absent	12 (20)
Number of metastatic sites during HVC	
<2	23 (38.3)
≥2	37 (61.7)
Percutan Biliary Drainage	
Present	19 (31.7)
Absent	41 (68.3
CT protocol during HVC	
Monotherapy (Single-agent)	22 (36.7)
Combination therapy	38 (63.3)

*Ecog: Eastern Cooperative Oncology Group; CT: Chemotherapy; Ca: Cancer; NEC: Neuroendocine carcinoma; HVC: Hepatic visceral crisis.

During HVC, CT eligible patients were categorized into two groups based on the time of initiating CT; those who started CT within 7 days or less, and those who started CT after 7 days. Patients who initiated CT within 7 days were observed to have a statistically significant approximately 1-month longer median overall survival (mOS) compared to those who initiated CT after 7 days following VC (3.87 months vs. 2.99 months; p=0.04) (Fig. 1).

The summary of demographic and clinical characteristics of 173 patients ineligible for CT is presented in Table 2.

In this study, an analysis was conducted between patients who did not receive any treatment during HVC due to liver metastasis and those who received single-agent chemotherapy. It was observed that patients who received single-agent chemotherapy had statistically significantly longer mOS compared to those who received no treatment (1.70 months vs. 1.08 months; p=0.03, Fig. 2a). Another analysis revealed that patients who received combination chemotherapy during HVC had a significantly approximately 2.5 times longer median OS compared to those who received monotherapy (4.27 months vs. 1.70 months; p=0.03, Fig. 2b).

In addition, in this study, a Spearman correlation test was conducted using nonparametric variables among the monitored blood parameters of patients who could undergo CT during hepatic visceral crisis. A positive and statistically significant correlation was found between total bilirubin and albumin (r=0.315, p=0.014) total bilirubin and ALT (r=0.288, p=0.026), ALT and albumin (r=0.330, p=0.01), ALT and AST (r=0.477, p<0.01), lymphocyte and albumin (r=0.321, p=0.012) (Table 3).

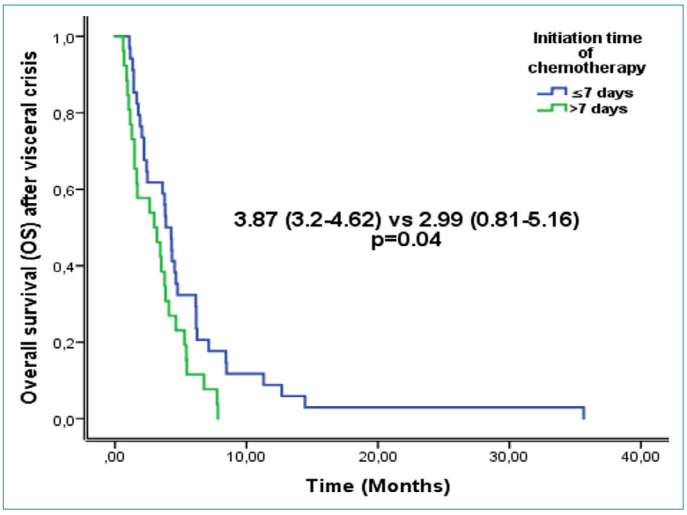

Figure 1. The impact of CT timing on OS during HVC.

Table 2. Clinical and Pathological Characteristics of Patients unable to receive CT

	Totally n=173/(%)
Sex	
Female	79 (45.7)
Male	94 (54.3)
Age median (min-max)	57 (27-75)
<60	97 (56.1)
≥ 60	76 (43.9)
Ecog	
2	43 (24.9)
3	117 (67.6)
4	13 (7.5)
Diagnoses	
Colorectal Ca	43 (24.9)
Breast Ca	31 (17.9)
Gastric Ca	25 (14.5)
Pancreas Ca	25 (14.5)
Primer Unknown Ca	13 (7.5)
Lung Ca	9 (5.2)
Biliary Tract Ca	7 (4.0)
Ovarian Ca	6 (3.5)
Esophageal Ca	2 (1.2)
Endometrial Ca	2 (1.2)
Melanoma	2 (1.2)
Prostate Ca	2 (1.2)
Bladder Ca	2 (1.2)
Head and Neck Ca	1 (0.6)
Cervical Ca	1 (0.6)
Neuroendocrine Tumor	1 (0.6)
Soft Tissue Sarcoma	1 (0.6)
Denovo Liver metastasis	
Present	105 (60.7)
Absent	68 (39.3)
Percutan Biliary Drainage	
Present	45 (26)
Absent	128 (74)
Number of metastatic sites during HVC	
<2	70 (40.5)
≥2	103 (59.5)

*Ecog: Eastern Cooperative Oncology Group; Ca: Cancer; HVC: Hepatic visceral crisis.

Discussion

Visceral crisis (VC) is a challenging clinical condition that can rapidly lead to a life-threatening situation, requiring urgent and effective intervention. From a clinical practice perspective, the lack of well-defined criteria for VC has left clinicians with a significant area of interpretation.[7] Consequently, clinicians primarily assess patients in a state of VC for organ-specific local treatments (eg. percutaneous biliary drainage, thoracentesis) followed by systemic treatments based on treatment tolerabilities.[8] The incidence of VC and the affected visceral region due to insufficiency vary according to the primary tumor site and characteristics. Among the conducted studies, hepatic VC secondary to breast cancer is the most common presentation, while clinical manifestations of VC related to lung, bone marrow, and carcinomatous meningitis can also be observed.[5,6,9] In the study by Yang et al., among patients with breast cancer, the best survival was seen in cases of bone marrow VC, whereas patients with hepatic VC had the worst survival.[9]

Delays in treatment can increase mortality in cancer patients.[10] Therefore, the early identification of factors influencing survival, the initiation of treatment with optimal timing, or early interventions for treatment in cancer-related hepatic dysfunction patients, especially in cases where survival is measured in mere weeks, can extend survival periods. The gold standard for assessing liver damage is liver biopsy. However, due to the need for prompt treatment initiation, delays in diagnosis, complications during the procedure, and the requirement for rapid treatment initiation, the evaluation of clinical and laboratory findings in conjunction has become more crucial for defining hepatic visceral crisis.[11]

Furthermore, cancer-induced liver dysfunction is multifactorial and can be attributed to a direct reduction in the healthy volume of the liver due to metastases or obstruction of the bile ducts.[12] In this study, the definition of patients with HVC was based on having liver metastases, rapid progression of hyperbilirubinemia (≥1.5x laboratory cut-off) in laboratory values, elevation of either ALT or AST values, and the presence of clinical symptoms due to tumor burden. A total of 60 patients who could undergo CT during HVC were included in the study, and the impact of initiating combined or single systemic treatment within an optimal time frame on overall survival was investigated. Additionally, these 60 patients with CT-initiated hepatic visceral crisis were compared in terms of the contribution of treatment to survival with 173 patients who had solid tumors in hepatic visceral crisis but were not able to undergo CT.

Current guidelines for VC still recommend combination chemotherapy regimens that are effective in achieving rapid disease control.[1,13,14] In other words, due to the aggressive nature of visceral crises and the imperative for rapid treatment initiation, the molecular characterization poses a significant challenge in acquiring metastatic tissue and identifying targets for potentially more successful treatments. Consequently, these patients are often excluded from clinical trials that test new therapeutic agents or

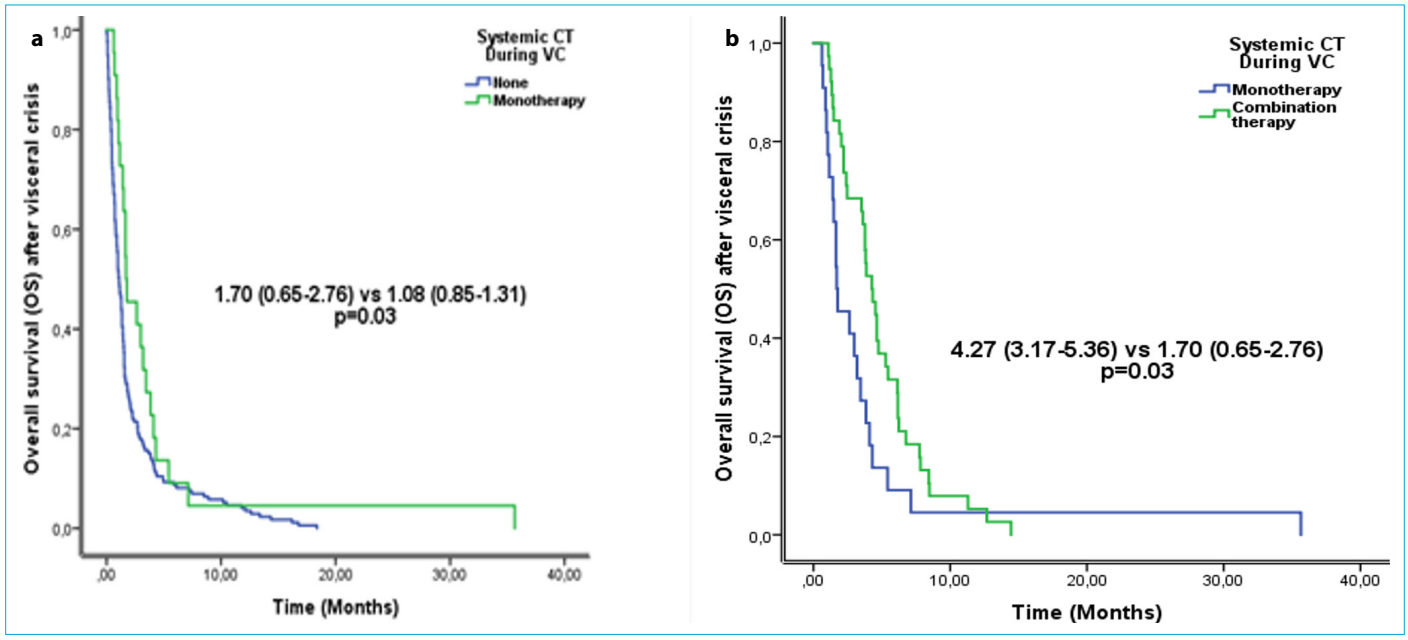

Figure 2. (a) The impact of Single agent CT vs CT free on OS during HVC. **(b)** The impact of Single agent CT vs Combination CT on OS during HVC.

Table 3. Correlation analysis of non-parametric laboratory tests in patients during HVC

	1	2	3	4	5	6	7	8
1-Total Bilirubin								
r	1							
p	.							
2-Albumin								
r	.315*	1						
p	0.014	.						
3-AST								
r	0.048	0.048	1					
p	0.714	0.714	.					
4-INR								
r	0.113	-0.078	-0.203	1				
p	0.392	0.556	0.119	.				
5-BUN								
r	0.029	-0.037	-0.038	0.063	1			
p	0.829	0.78	0.771	0.63	.			
6-ALT								
r	.288*	.330**	.477**	-0.009	-0.037	1		
p	0.026	0.01	0	0.947	0.78	.		
7-Lymphocyte								
r	0.008	.321*	0.011	0.197	-0.152	0.017	1	
p	0.949	0.012	0.935	0.132	0.246	0.898	.	
8-Platelet								
r	0.199	-0.026	0.001	0.077	-0.087	0.158	0.055	1
p	0.127	0.846	0.991	0.561	0.51	0.229	0.674	.

* Spearman Correlation test; ALT: alanine transaminase; AST: aspartate aminotransferase; INR: International normalized ratio; BUN: blood urea nitrogen.

combinations that might yield better outcomes than chemotherapy. Moreover, data comparing polychemotherapy regimens in these patients are quite limited.[6] Therefore, the selection of the most effective and least side-effect inducing treatment tailored to the individual patient by the clinician is of utmost importance.

Sbitti et al. reported a median overall survival mOS of only 4.7 weeks in 35 patients with advanced stage hormone receptor +/human epidermal growth factor 2 (HER2) negative breast cancer who met the criteria for VC. Among these patients, 35% were not eligible for chemotherapy (CT) and were directed towards the best supportive care, while the remaining 65% received different CT regimens. Despite the fact that all these patients had a very poor prognosis, CT did not provide any significant survival benefit compared to the best supportive care (5.8 and 6.2 weeks, respectively, p=0.23).[5] A retrospective cohort study spanning 11 years, involving 441 patients treated with a platinum-based combination CT regimen for advanced stage breast cancer, included 261 patients diagnosed with VC. In this study, VC patients who received CT had statistically lower overall survival compared to those who did not experience a VC (8.6 months vs. 3.7 months, p<0.001).[6] Mogrovejo et al. reported a 1-week survival period in breast cancer patients with diffuse liver metastasis-associated VC.[15] A pilot study by Sharma et al. demonstrated that the combination of vinorelbine with cisplatin for diffuse liver metastasis could extend mOS up to 6.5 months.[16] Furthermore, in a study among advanced pancreatic cancer patients, those who received CT during hepatic VC had a significant difference in post-VC mOS compared to those who did not receive CT

(3.45 months vs. 1.11 months; p=0.003).[17] In this study, 233 patients with solid tumors diagnosed with HVC due to liver metastasis were included. Among them, 60 (25.8%) eligible patients received single or combined systemic CT during HVC, based on clinical and laboratory findings. When comparing those who started treatment within 7 days or less of the VC diagnosis to those who started treatment after 7 days, there was a statistically significant difference in post-VC mOS in favor of the early treatment group (3.87 months vs. 2.99 months; p=0.04 Fig. 1). Moreover, a comparison between patients who never received any systemic treatment during HVC and those who received single chemotherapy showed a significant OS contribution in favor of the CT-treated group (1.70 months vs. 1.08 months; p=0.03, Fig. 2a).

Additionally, in this study, among patients who received CT in HVC, those who received combination therapy showed a positive impact on mOS compared to those who received single CT protocols (4.27 months vs. 1.70 months; p=0.03, Fig. 2b). Reviewing the literature data, limited studies focused on VC, especially involving advanced breast cancer patients, have indicated that patients benefit from combination systemic therapies but without a contribution to OS. This study is a retrospective basket study conducted specifically in the context of hepatic VC. Similar to the literature, it demonstrates that mOS durations are short across all patient groups and the greatest benefit is observed in appropriate patients who receive combined CT treatment during VC.

In a study in the field of breast cancer, starting combination CT during VC demonstrated benefits in terms of progression-free survival and objective response rate but did not show a contribution to OS.[18,19] The heterogeneity of patient diagnoses in this study, categorizations based on treatment initiation times, and the inclusion of only patients with visceral crisis due to liver metastases can explain why both combination therapy and single systemic therapies provide significant OS contributions compared to those who did not receive treatment.

The limitations of this study include its single-center nature, the presence of patients with different cancer diagnoses, the heterogeneity of administered chemotherapy protocols and the absence of information regarding viral hepatitis, alcohol use, and non-alcoholic fatty liver conditions, which can negatively impact hepatic reserve in patients.

Looking at the overall population of advanced cancer patients, prognostic markers are perceived as an unmet need in clinical practice. In this context, new prognostic markers are being derived based on clinical and laboratory findings. Tay et al. has suggested that calculating MELD (The model for end-stage liver disease) scores and SII (systemic immune-inflammatory index) values in patients with solid tumor-related hepatic visceral crisis can be used in clinical follow-ups for prognosis prediction.[20] In this study, which included patients with solid tumors who could undergo CT during hepatic VC, spearman correlation tests were conducted using nonparametric variables with laboratory markers used for calculating MELD scores and SII values. Significant and positive correlations were found between total bilirubin and albumin (r=0.315, p=0.014) , total bilirubin and ALT (r=0.288, p=0.026), ALT and albumin (r=0.330, p=0.01), ALT and AST (r=0.477, p<0.01), lymphocyte and albumin (r=0.321, p=0.012) (Table 3.)

Conclusion

VC remains a clinical challenge for oncologists, presenting numerous unresolved questions. A consensus regarding the definition of visceral crisis is only established in breast cancer, with a substantial portion of studies in this field focusing on breast cancer patients. Consequently, indications for treatment in VC still rely on outdated indirect comparisons and are currently based on outdated and insufficient regimens.

The scarcity of studies conducted in this field, the retrospective nature of this study, and the statistically significant findings regarding the chosen chemotherapy protocol and timing of treatment initiation are highly valuable. Although this study is limited by its single-center and retrospective design, it underscores the need for more comprehensive and multicenter research to incorporate this information into clinical practice.

Disclosures

Ethics Committee Approval: The ethical approval for the study was obtained from the Central Ethics Committee with the reference number 2022-05/1860 on June 8, 2022.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Cardoso, F., Paluch-Shimon, S., Senkus, E., Curigliano, G., Aapro, M. S., André, F., et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Annals of Oncology 2020;31(12):1623-1649.
2. Tsilimigras, D. I., Brodt, P., Clavien, P. A., Muschel, R. J., D'Angelica, M. I., Endo, I. et al Liver metastases. Nature reviews Disease primers 2021;7(1):27.
3. Büyükkör, M., Tay, F., & Özakyol Harmancı, A. Gastric cancer patient characteristics in a city in the Central Anatolian Region of Turkey: a single-center descriptive study. Journal of Current

Hematology & Oncology Research 2023;36-40.
4. Faugeras, L., Dili, A., Druez, A., Krug, B., Decoster, C., & D'Hondt, L. Treatment options for metastatic colorectal cancer in patients with liver dysfunction due to malignancy. Critical reviews in oncology/hematology 2017;115:59-66.
5. Sbitti, Yassir, et al. "Visceral crisis means short survival among patients with luminal A metastatic breast cancer: a retrospective cohort study." World journal of oncology 2017;8(4):105.
6. Franzoi, M. A., Saúde-Conde, R., Ferreira, S. C., Eiger, D., Awada, A., & de Azambuja, E. Clinical outcomes of platinum-based chemotherapy in patients with advanced breast cancer: An 11-year single institutional experience. The Breast 2021;57:86-94.
7. Benvenuti, C., Gaudio, M., Jacobs, F., Saltalamacchia, G., De Sanctis, R., Torrisi, R., et al. Clinical Review on the Management of Breast Cancer Visceral Crisis. Biomedicines 2023;11(4):1083.
8. NCCN guidelines insights: Breast cancer ,version 4.2023 .Journal of the National Comprehensive Cancer Network, March 23, 2023.
9. Yang, R., Lu, G., Lv, Z., Jia, L., & Cui, J. Different treatment regimens in breast cancer visceral crisis: A retrospective cohort study. Frontiers in Oncology 2022;12:1048781.
10. Buyukkor, M., Tay, F., & Ates, O. Experiences of the combined use of Favipiravir in patients using Lorlatinib and Brigatinib. Journal of Oncology Pharmacy Practice 2022;28(8):1906-1909.
11. Tay, F., Büyükkör, M., & Duran, A. O. Factors contributing to survival in hepatic dysfunction due to colorectal cancer. Srpski arhiv za celokupno lekarstvo 2022;150(11-12):685-689.
12. Field, K. M., Dow, C., & Michael, M. Part I: Liver function in oncology: biochemistry and beyond. The lancet oncology 2008;9(11):1092-1101.
13. RUGO, Hope S., et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. Journal of Clinical Oncology 2016;34:25:3069-3103.
14. Giordano, S. H., Temin, S., Chandarlapaty, S., Crews, J. R., Esteva, F. J., Kirshner, J. J., et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2–positive breast cancer: ASCO clinical practice guideline update. Journal of Clinical Oncology 2018:36(26):2736-2740.
15. Mogrovejo, E., Manickam, P., Amin, M., & Cappell, M. S. Characterization of the syndrome of acute liver failure caused by metastases from breast carcinoma. Digestive diseases and sciences 2014;59:724-736.
16. Sharma, R. A., Decatris, M. P., Santhanam, S., Roy, R., Osman, A. E., Clarke, C. B.,et al. Reversibility of liver failure secondary to metastatic breast cancer by vinorelbine and cisplatin chemotherapy. Cancer chemotherapy and pharmacology 2003;52:367-370.
17. Buyukkor, M., Tay, F., Karacin, C., & Duran, A. O. Prognostic Markers after Hepatic Function Impairment in Patients with Pancreatic Adenocarcinoma. Age 2023;55(27):47-4.
18. Sledge, G. W., Neuberg, D., Bernardo, P., Ingle, J. N., Martino, S., Rowinsky, E. K.,et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as frontline chemotherapy for metastatic breast cancer: an intergroup trial (E1193). Journal of clinical oncology 2003;21(4):588-592.
19. O'Shaughnessy, J., Miles, D., Vukelja, S., Moiseyenko, V., Ayoub, J. P., Cervantes, G., et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. Journal of clinical oncology 2002;20(12):2812-2823.
20. Tay, F., Buyukkor, M., & Duran, A. O. Prognostic Importance of Combined Use of MELD Scores and SII in Hepatic Visceral Crisis in Patients with Solid Tumours. Age 2023;50(82):27-8.