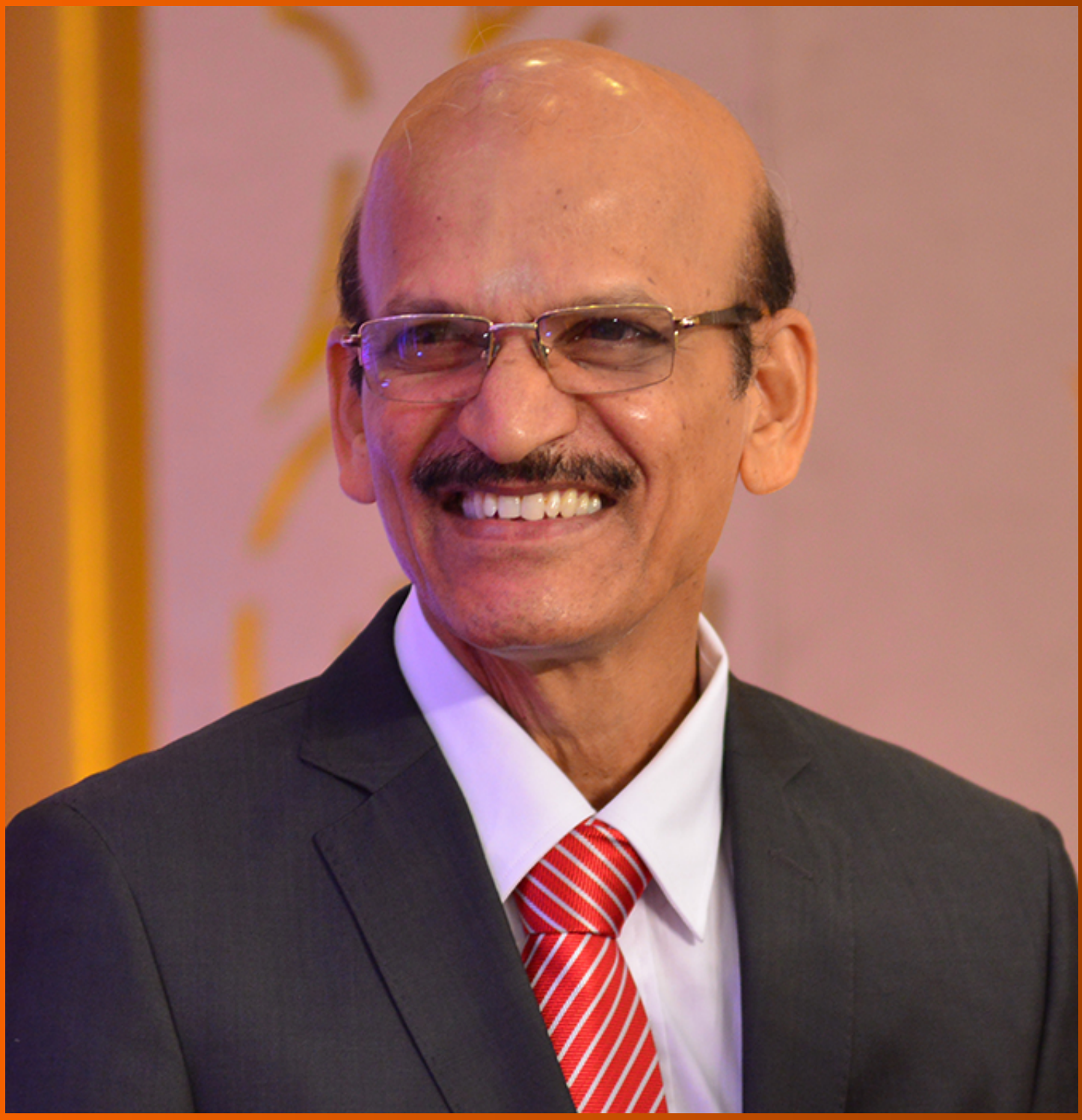
ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2024 April 27; 16(4): 974-1217



Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 16 Number 4 April 27, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 4 April 27, 2024

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 4 April 27, 2024

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 4 April 27, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Arunachalam Rathnaswami, FACS, MBBS, MS, MNAMS, MCh, Ex-Professor and Head, Department of Surgical Gastroenterology, SRM Medical College Hospital and Research Institute SRMIST, Kattankulathur, Chennai, TamilNadu 603203, India. arunarathna@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGS* as 2.0; IF without journal self cites: 1.9; 5-year IF: 2.2; Journal Citation Indicator: 0.52; Ranking: 113 among 212 journals in surgery; Quartile category: Q3; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
April 27, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2024 April 27; 16(4): 999-1007

DOI: 10.4240/wjgs.v16.i4.999

ISSN 1948-9366 (online)

EDITORIAL

Carcinoembryonic antigen in the diagnosis, treatment, and follow-up of focal liver lesions

Osman Nuri Dilek, Dilara İrem Arslan Kahraman, Gökhan Kahraman

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jankovic K, Serbia

Received: January 7, 2024
Peer-review started: January 7, 2024
First decision: January 30, 2024
Revised: February 2, 2024
Accepted: March 13, 2024
Article in press: March 13, 2024
Published online: April 27, 2024

Osman Nuri Dilek, Department of Surgery, İzmir Katip Celebi University, School of Medicine, İzmir 35150, Turkey

Dilara İrem Arslan Kahraman, Department of Patology, Merzifon KMP State Hospital, Amasya 5300, Turkey

Gökhan Kahraman, Department of Radiology, Suluova State Hospital, Amasya 5500, Turkey

Corresponding author: Osman Nuri Dilek, FACS, Professor, Department of Surgery, İzmir Katip Celebi University, School of Medicine, Basın Sitesi, İzmir 35150, Turkey.
osmannuridilek@gmail.com

Abstract

In this editorial review, we comment on the article published in the recent issue of the *World Journal of Gastrointestinal Surgery*. Carcinoembryonic antigen (CEA) is a fetal glycoprotein and can be secreted in very small amounts from healthy adults after birth. CEA is widely used not only for diagnostic tumor markers but also importantly for the management of some gastrointestinal tumors. The most common clinical use is surveillance for the monitoring of colorectal carcinoma. However, CEA can become elevated in several malign or benign characterized pathologies. Serum CEA level may vary depending on the location of the lesion, whether it metastasizes or not, and its histopathological characteristics. It has been determined that cases with high preoperative CEA have a more aggressive course and the risk of metastasis to the lymph tissue and liver increases. In this editorial review, we focused on evaluating the role of CEA in clinical practice with a holistic approach, including the diagnostic and prognostic significance of CEA in patients with focal liver lesions, the role of CEA in follow-up after definitive surgery, and also hepatic resection for metastasis, and the management of all patients with raised CEA.

Key Words: Carcinoembriyonic antigen; Liver; Focal liver lesions; Metastasis; Surgery; Prognosis; Surveillance

Core Tip: Carcinoembryonic antigen (CEA) is not normally produced in significant quantities after birth but is mainly elevated in colorectal cancer and some other pathologies. CEA is widely used not only for diagnostic tumor markers but also importantly for the management of some gastrointestinal tumors. In this study, the relationship of CEA with clinical, radiological, and histopathological evaluations in the diagnosis and treatment of focal liver lesions detected in the liver was evaluated with a holistic approach.

Citation: Dilek ON, Arslan Kahraman Dİ, Kahraman G. Carcinoembryonic antigen in the diagnosis, treatment, and follow-up of focal liver lesions. *World J Gastrointest Surg* 2024; 16(4): 999-1007
URL: https://www.wjgnet.com/1948-9366/full/v16/i4/999.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i4.999

INTRODUCTION

Carcinoembryonic antigen (CEA) consists of 36 different glycoproteins located on the cell membrane belonging to the immunoglobulin superfamily. It is a prototypical member of this family[1-3]. CEA is a structural protein of cell membranes. CEA is also a tumor-associated antigen expressed on the tumor cells originating from endoderm[4]. Its molecular weight is 180 kDa, and encodes on the long arm of chromosome 19 (19q) and consists of 29 genes.

According to the classification based on the CEA gene family, CEA is also known as CEA-related cell adhesion molecule 5 (CEACAM5)[5]. CEACAM6 is expressed in granulocytes and various epithelial cells[6,7]. CEACAM6 has also been observed to be expressed in various types of cancer[8]. During the fetal period, CEA plays a role in cellular adhesion, and its substantial production is not typical after birth[9]. Just as it is secreted in fetal life, it continues to be secreted after birth, albeit in small amounts (2-4 ng/mL), from epithelial organs, especially the digestive tract mucosa[10,11]. Normal serum CEA value is considered to be < 5 ng/mL in normal adult non-smokers and < 10 ng/mL in smokers. Serum CEA levels are < 2.5 ng/mL in 85% of adults and < 5 ng/mL in 95%. It is slightly higher in men than in women. CEA, which is high in fetal life, is measured at normal levels in pregnant women because it cannot cross the placenta[12-14].

CEA is primarily metabolized in the liver and CEA may increase more in malignant or benign pathologies that cause liver failure[15]. Serum CEA may be elevated levels causing false positives in 70% of people with chronic liver disease without focal liver lesions (FLLs) and in 50% of patients with acute liver disease[10,14].

CEA has been used as a tumor marker for approximately 6 decades. CEA was first isolated from human colorectal cancer (CRC) tissue in 1965 by Canadian scientists Gold and Freedman[16]. It is a fetal glycoprotein that circulates at high levels and is detectable in only tiny amounts in the blood of healthy adults. It is a non-specific tumor marker that can be secreted in some physiological conditions as well as in malignant or benign lesions (Table 1). It may be increased in stomach, pancreas, lung, breast, and medullary thyroid carcinomas, especially CRC. CEA levels may also increase in many non-neoplastic conditions such as ulcerative colitis, cirrhosis, pancreatitis, Crohn's disease, chronic obstructive pulmonary disease, peptic ulcer, diverticulitis, chronic renal failure, and hypothyroidism[10,14,17,18].

Here in, we aimed to evaluate the relationship of CEA with clinical, radiological, and histopathological evaluations for the management of FLLs.

CURRENT RESEARCH FOR CEA AND ITS CLINICAL APPLICATIONS

The data used in the study was obtained from websites where medical literature was searched on the internet. Reference Citation Analysis (RCA) is a unique artificial intelligence system that can be used to collect data in medical literature review and allows a wide range of data scanning. Using the RCA database, CEA-related data were accessed and analyzed from hundreds of thousands of articles, starting from 1967, through different combinations of the keywords CEA, liver, diagnosis, treatment, and follow-up. Similar searches were performed with PubMed and Medline searches, focusing on CEA and liver-related data. Articles regarding CEA published starting from 1965 were accessed[16].

CLINICAL IMPLICATIONS

It is expected that the use of tumor markers in the clinic will contribute to the diagnosis of pathology at an earlier stage and to the early recognition of relapses after treatment.

Serum CEA level may vary depending on the location of the lesion, whether it metastasizes or not, and its histopathological characteristics. It is also known that more CEA is secreted in well-differentiated tumors[7]. Preoperatively elevated CEA levels are expected to decrease postoperatively. Situations where the difference between two measurements during follow-up is more than 20% should be considered significant[14]. It may be useful in the detection and follow-up of recurrences, metastases, and lymphatic involvement, especially for CRCs[19].

Table 1 Conditions in which carcinoembryonic antigen elevation can be detected

Malign (neoplastic) pathologies	Benign (non-neoplastic) pathologies		Others
	Liver pathologies	GI tract pathologies	
CRC	Obstructive jaundice	Pancreatitis	Smoking
Cervix mucinous adenocancer	Chronic liver disease	Inflammatory bowel diseases	Fibrocystic disease of the breast
Lung cancer	Alcoholic liver disease	Diverticulitis	Renal failure
Thyroid cancer	Primary biliary cirrhosis	Peptic ulcer	COPD
HCC, CCC			Hypothyroidism
Prostate cancer			
Pancreatic cancer			
Ovarian cancer			
Breast			
Esophagus			
Tongue			

CRC: Colorectal cancer; COPD: Chronic obstructive pulmonary disease; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinomas; GI: Gastrointestinal.

Parameters whose significance increases when evaluated together with tumor markers have also begun to be used more in recent years. Preoperative evaluation of the controlling nutritional status score and CEA value may contribute to the diagnosis, determination of tumor stage, and prognosis[20-22]. There are also many clinical studies on different tumor marker combinations with CEA[23-25]. Kimchy *et al*[24]reported that checking serum alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and bilirubin values in patients with melanoma, breast, CRC, and lung tumors to determine whether there is metastasis to the liver will facilitate diagnosis much earlier than radiological imaging [24].

CEA is widely used not only for diagnostic tumor markers but also importantly for the management of some gastrointestinal tumors. Serum CEA level can be used to monitor different periods, including diagnosis, treatment, and follow-up periods after surgery/chemotherapy.

Diagnosis

CEA levels can be elevated in a variety of benign and malignant conditions[26,27]. Among the benign liver diseases reported with elevated CEA levels are alcoholic liver disease, chronic liver disease, primary biliary cirrhosis, obstructive jaundice, and hepatic abscess. Malignant liver diseases associated with elevated CEA levels include metastasis, hepatocellular carcinoma (HCC), and cholangiocarcinoma[26,28,29] (Table 1).

CEA is one of the tumor markers whose relationship with CRC has been most studied in the literature. CRC metastases are the most common cause of liver disease that raises CEA levels[4,30]. However, CEA does not have sufficient sensitivity as a screening test in detecting tumors, especially for CRCs[18,25]. Serum CEA is above the cut-off value of 2.5 ng/mL in 30% of early-stage (Duke's 1 and 2) CRCs[14,25].

It has been determined that cases with high preoperative CEA have a more aggressive course and the risk of metastasis to the lymph tissue and liver increases. The positive effect of adjuvant chemotherapy is greater in such patients[31]. In their CEACAM analysis, Blumenthal *et al*[7] found that the amount of CEACAM6 was higher in most solid and well-differentiated tumors. They also reported that CEACAM6 was found in higher amounts in metastatic lesions in the liver in CRC cases than in primary tumors. In the same study, they found that the amount of CEACAM6 in metastatic lymph nodes and primary tumors from cases with breast, colon, or lung tumors was similar[7]. Cases have also been reported in the literature stating that CEA levels may increase more in patients with left colon tumors and/or intestinal obstruction, and interestingly, cases where CEA levels may decrease in patients undergoing decompression[14].

In the field of pathology, monoclonal and polyclonal CEA immunohistochemical stains serve as diagnostic tools. Polyclonal CEA staining reveals a canalicular pattern, which is a specific indicator of HCC. It allows for the precise and confident diagnosis of HCC, distinguishing it from other types of tumors[32]. The cytoplasmic and membranous staining pattern observed in adenocarcinomas provides valuable clues for pathologists to identify and differentiate adenocarcinomas from HCCs[33]. Nevertheless, interpreting these staining patterns can be challenging due to factors such as background staining, technical variations, and overlapping patterns in different tumor types.

It has been observed that CEA is extensively expressed in numerous types of human carcinomas[7]. Due to its involvement in various stages of cancer progression, increased serum CEA levels can be observed in certain types of cancers. CEA triggers the activation of fibroblasts through the activation of the STAT3 and AKT1-mTORC1 pathways. As a result, these fibroblasts transform into cancer-related fibroblasts[34]. Furthermore, aside from its role as a proangiogenic substance, CEA enhances the viability of metastatic cells, influences the microenvironment of sinusoids, and augments the metastatic potential of colorectal carcinomas by upregulating the expression of adhesion molecules[35].

Colon cancers producing CEA persist longer in the liver compared to those not producing CEA[36]. It is believed that the CEA molecule in colon cancers stimulates Kupffer cells, leading to the release of various cytokines from these cells and an increase in ICAM-1 expression in sinusoidal endothelial cells, contributing to the development of the metastatic process[37]. CEACAM5 protects colon tumor cells from apoptotic stimuli, such as 5-fluorouracil, used in the treatment of colon carcinomas, by influencing the expression of various cell cycle and apoptosis genes[38]. In another study, it has been shown that the expression of CEACAM5 and CEACAM6 plays a role in inhibiting a type of apoptosis known as anoikis[39].

Imaging plays a crucial role not only in the differential diagnosis of liver diseases that can increase CEA levels but also in the evaluation of liver metastases. The radiological evaluation of FLLs is critical for treatment planning[40].

Contrast-enhanced magnetic resonance imaging (MRI) has been shown to detect more liver lesions than computed tomography (CT) and positron emission tomography (PET)/CT[41-44]. The use of gadoxetic acid-enhanced MRI in conjunction with diffusion-weighted imaging significantly improves diagnostic performance in detecting liver metastases. In a meta-analysis, it was found that the sensitivity of MRI performed with this combination (93.1%) is higher than the sensitivities of CT and PET/CT (82.1% and 74.1%, respectively)[42]. According to the results of another meta-analysis, it has been suggested that MRI should be preferred for the pre-treatment evaluation of liver metastasis in CRC[43].

CEA is primarily recognized as a marker for malignancies, particularly within the gastrointestinal and hepatic systems. However, its rare presentation in benign lesions like biliary duct hamartomas emphasizes the importance of considering broader clinical context and complementary diagnostic tools to avoid misinterpretations. Biliary duct hamartomas are congenital malformations defined by the presence of multifocal, microscopic to millimetric cystic dilatations of intrahepatic bile ducts, exhibiting a uniform distribution throughout the liver parenchyma. Biliary duct hamartomas can mimic cystic metastases due to their mixed solid-cystic appearance on imaging. However, their characteristic strong and uniform hyperintensity on T2-weighted MRI is often diagnostic, obviating the need for biopsy in most cases. magnetic resonance cholangiopancreatography's ability to demonstrate non-communicating cysts significantly enhances the diagnostic specificity for biliary duct hamartomas compared to other cystic liver lesions. Nevertheless, occasional cases with atypical MR features may necessitate percutaneous biopsy for definitive diagnosis[45,46].

CEA is also an independent prognostic factor for intrahepatic cholangiocarcinoma, which is a primary liver tumor[27]. While the exact mechanism remains unclear, the study provides evidence that intrahepatic cholangiocarcinomas (ICCC) with high CEA expression were more likely to involve lymph nodes compared to those with lower CEA levels[47].

Rarely, high CEA levels can be seen in hepatic epithelioid hemangioendothelioma (HEH)[48]. Due to its rarity, HEH is often misdiagnosed preoperatively, and the definitive diagnosis is confirmed pathologically. Given the relatively specific MRI features when there is suspicion of these tumors, evaluation with MRI is necessary[49].

In cases of non-small-cell lung cancer (NSCLC) where sufficient data cannot be obtained or lesions are overlooked in radiological imaging, elevated CEA levels may indicate that the disease is more advanced than initially considered. In 30% of Stage 1 NSCLC cases, lymph node metastasis is present at the time of diagnosis. Elevated levels of CEA and cytokeratin 19 fragment combination in NSCLC cases may serve as an indicator of liver metastasis and distant organ metastases[10,50,51]. In cases where radiological imaging is insufficient and CEA levels are elevated, additional imaging modalities (PET/CT, bronchoscopic ultrasound, and thoracoscopic examinations) may assist in the diagnosis.

Treatment

CEA is metabolized in the liver, and its half-life is approximately one week. In patients with CRC undergoing surgery due to liver metastases, CEA concentration returns to normal within 4-6 wk. If CEA levels do not return to normal within six weeks or if they rise, the inadequacy of treatment or the presence of new metastases should be investigated[10,14].

Efforts are underway to develop and utilize anticancer agents specifically designed to target CEA in the treatment of cancer. This targeted approach, which focuses on cancer cells expressing elevated levels of CEA, has the potential to improve treatment outcomes and minimize side effects. Due to their roles in tumor cell apoptosis and interaction with various chemotherapeutic agents, CEACAM5 and CEACAM6 molecules should be considered as potential target molecules for therapy. One of these agents includes vaccines. In a Phase I trial, significant regression was observed in the tumor formed in the syngeneic mouse model following the administration of a vaccine containing a recombinant virus expressing CEA[52]. It has been demonstrated that treatments using antibodies targeting CEA alone have minimal effects [53,54]. When combined with other agents specifically targeting T cells, CEA-targeting agents have demonstrated potent antitumor activity[55].

Another developed agent is RNA aptamers, which have been demonstrated to inhibit liver metastasis in mice with colon tumors by binding to CEA[56]. Studies employing fluorescently labeled anti-CEA antibodies in the literature have demonstrated their assistance in the detection and removal of tumors both in murine models and clinical trials. Moreover, anti-CEA fluorescent antibodies have proven successful in photoimmunotherapy, a recently developed approach in cancer treatment[57].

Recent clinical trials have demonstrated that the drug SAR408701, developed against CEACAM5, exhibits favorable safety profiles in advanced-stage solid tumors[58]. Furthermore, ongoing clinical trials involve the use of anti-CEACAM5 and anti-CEACAM6 in advanced-stage solid tumors (NCT05464030, NCT05703555, NCT03596372). In a study utilizing anti-CEACAM6 for lung adenocarcinomas, it has been observed to be effective in treatment, and its efficacy is further enhanced when used in combination with paclitaxel[59].

Surveillance (follow up)

The use of serial CEA analyses in the follow-up of patients who show no evidence of disease after primary treatment is a subject of debate. There are numerous studies suggesting that the presence of elevated CEA levels may have prognostic significance[15,20,23]. However, in some studies, it was found that postoperative CEA elevation was significant for

recurrence/metastasis in 40% of cases, while in 60% of cases, the elevation was considered false positive[14]. There are also numerous studies indicating that CEA can be a significant diagnostic and prognostic indicator in the follow-up of CRC patients and the early detection of recurrences[25,60,61]. The sensitivity and specificity of repeated CEA analyses are quite high, reaching 90%. Surgical treatment of isolated CRC metastases detected in the liver can be curative in 20%-50% of cases. The American Society of Clinical Oncology (ASCO) strongly recommends periodic CEA analysis during the postoperative period. After surgery, it is recommended to monitor CEA levels every 2-3 months for at least two years[14,62]. Monitoring with serum CEA levels can detect the presence of CRC recurrence 4-10 months earlier (average 5 months) compared to other methods[14]. Elevated serum CEA levels may be indicative of the aggressiveness of CRC. A CEA value of around 30 ng/mL may indicate a high chance of resection for metastatic lesions in the liver[63,64]. It has been determined that CEA is superior to endoscopy, CT, and US in the diagnosis of local recurrences[14].

There are studies indicating that the use of CA 15-3, a tumor marker used in the diagnosis and follow-up of breast cancer patients, along with CEA, CA 27.29, and radiological imaging, can be beneficial in monitoring metastatic lesions [65].

Although elevated CEA levels in cases of medullary thyroid carcinoma are non-specific, in patients who have undergone thyroidectomy, it may serve as an indicator of disease progression. If the CEA level remains elevated after surgery or if the CEA level is above 100 ng/mL, it may be an indicator of distant organ metastases. Measuring Calcitonin and CEA together in distant organ metastases can enable a more meaningful interpretation of imaging data.

MRI is especially useful for detecting lesions smaller than 10 mm in size[44]. Nevertheless, with recent technological developments, state-of-the-art CT devices capable of high-sensitivity detection of liver metastases are frequently used in clinical practice. ASCO suggests that patients with CRC eligible for surgery or chemotherapy should undergo CEA level measurements every three months and annual CT scans following surgery or treatment[10,62].

CEA levels increase long before clinical recurrences appear. In patients with CRC, CEA is the most sensitive test for detecting surgically treatable liver metastases[66]. Therefore, cases with a high suspicion of liver metastasis due to elevated CEA levels should be evaluated using MRI if a definitive diagnosis cannot be established with CT. There are studies suggesting that the combination of CEA analysis and CT is more beneficial in detecting metastatic FLLs[67].

While elevated CEA is a strong indicator of CRC liver metastases, its usefulness in definitively diagnosing or predicting the recurrence of HCC is limited due to its lack of specificity for this particular cancer type. Although not universally present, elevated CEA levels have been documented in some patients diagnosed with HCC, prompting further investigation into its potential etiological and clinical relevance[68-70].

While recurrence of HCC following liver transplantation can occur in various locations, pulmonary and intrahepatic metastases are the most commonly observed, posing a significant challenge to long-term patient outcomes. Therefore, the American Association for the Study of Liver Diseases recommends post-transplant surveillance to be conducted using contrast-enhanced abdominal CT or MRI and chest CT. In cases where tumor markers such as alpha-fetoprotein and CEA are high and there is no overt recurrence, re-imaging with alternative modalities (*e.g.* MRI if the first imaging is CT) or PET scan should be performed. Patients treated with locoregional therapies such as transarterial chemoembolization are recommended to undergo their initial imaging with contrast-enhanced CT or MRI 4-6 wk after treatment, followed by repeat imaging every 3 months[71].

Due to the high risk of recurrence in ICCC, postoperative imaging is crucial for the early diagnosis of recurrence. There is no specific modality recommended to evaluate the recurrence of ICCC in the postoperative period. Postoperative surveillance for ICCC recurrence necessitates a patient-centered approach, with the choice of imaging modality contingent on individual risk factors and clinical presentation. Given the limitations of individual imaging modalities, a multidisciplinary diagnostic approach is crucial for accurate interpretation and diagnosis of suspected recurrences in the post-surgical setting[72]. Ongoing research efforts aim to refine and validate radiomics and artificial intelligence-based models for early recurrence detection, potentially paving the way for personalized and optimized postoperative surveillance strategies in intrahepatic cholangiocarcinoma[73,74].

Vaccination

There are studies in the literature related to CEA vaccines. Currently, the aim is to break immunological tolerance in cancer patients and to improve clinical outcomes by reducing tumor progression and metastases in appropriate cases[75]. In the experiments conducted by Hensel *et al*[76] in mice, it was demonstrated that immunological tolerance could be broken and an anti-tumor response could be generated by using a recombinant adeno-associated virus vector encoding CEA in tumors that express CEA. However, the studies are still in the early stages.

CONCLUSION

In conclusion, while CEA is an important tumor marker, its use for screening is not recommended due to its non-specific elevation in both malignant and benign conditions. Elevated CEA levels after surgery or chemotherapy may indicate tumor aggressiveness or the presence of relapse, especially in CRC cases. Elevated CEA levels in FLL cases may indicate metastasis, prompting the use of complementary biomarkers to identify primary foci. Ongoing research, particularly on drugs that target CEA, such as SAR408701, anti-CEACAM5, and anti-CEACAM6, demonstrates a growing interest in CEA-targeted approaches to improving cancer treatment outcomes. Regardless of its significance, the rare elevation of CEA in benign lesions highlights the importance of a thorough clinical evaluation and additional diagnostic tools. In practice, elevated CEA levels during post-surgery follow-up necessitate additional investigation for metastasis or relapse, especially if lesions are missed or imaging is inadequate. The widespread expression of CEA across various carcinomas

highlights its potential as both a diagnostic and therapeutic target, supported by ongoing research on CEA-targeted agents like vaccines, antibodies, and RNA aptamers, promising advancements in tailored cancer therapies.

FOOTNOTES

Author contributions: Dilek ON designed the overall concept and outline of the manuscript; Arslan Kahraman Dİ and Kahraman G contributed the contemporary data related to pathology and radiology to the discussion; Kahraman G and Dilek ON also contributed to the writing, editing, and review of the literature.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Turkey

ORCID number: Osman Nuri Dilek 0000-0002-6313-3818; Dilara İrem Arslan Kahraman 0000-0003-0251-9597; Gökhan Kahraman 0000-0001-9902-8844.

S-Editor: Li L
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Terry WD**, Henkart PA, Coligan JE, Todd CW. Carcinoembryonic antigen: characterization and clinical applications. *Transplant Rev* 1974; **20**: 100-129 [PMID: 4846098 DOI: 10.1111/j.1600-065X.1974.tb00143.x]
2 **Paxton RJ**, Mooser G, Pande H, Lee TD, Shively JE. Sequence analysis of carcinoembryonic antigen: identification of glycosylation sites and homology with the immunoglobulin supergene family. *Proc Natl Acad Sci USA* 1987; **84**: 920-924 [PMID: 3469650 DOI: 10.1073/pnas.84.4.920]
3 **Obrink B**. CEA adhesion molecules: multifunctional proteins with signal-regulatory properties. *Curr Opin Cell Biol* 1997; **9**: 616-626 [PMID: 9330864 DOI: 10.1016/S0955-0674(97)80114-7]
4 **Hao M**, Wang K, Ding Y, Li H, Liu Y, Ding L. Which patients are prone to suffer liver metastasis? A review of risk factors of metachronous liver metastasis of colorectal cancer. *Eur J Med Res* 2022; **27**: 130 [PMID: 35879739 DOI: 10.1186/s40001-022-00759-z]
5 **Beauchemin N**, Draber P, Dveksler G, Gold P, Gray-Owen S, Grunert F, Hammarström S, Holmes KV, Karlsson A, Kuroki M, Lin SH, Lucka L, Najjar SM, Neumaier M, Obrink B, Shively JE, Skubitz KM, Stanners CP, Thomas P, Thompson JA, Virji M, von Kleist S, Wagener C, Watt S, Zimmermann W. Redefined nomenclature for members of the carcinoembryonic antigen family. *Exp Cell Res* 1999; **252**: 243-249 [PMID: 11501563 DOI: 10.1006/excr.1999.4610]
6 **Schölzel S**, Zimmermann W, Schwarzkopf G, Grunert F, Rogaczewski B, Thompson J. Carcinoembryonic antigen family members CEACAM6 and CEACAM7 are differentially expressed in normal tissues and oppositely deregulated in hyperplastic colorectal polyps and early adenomas. *Am J Pathol* 2000; **156**: 595-605 [PMID: 10666389 DOI: 10.1016/S0002-9440(10)64764-5]
7 **Blumenthal RD**, Leon E, Hansen HJ, Goldenberg DM. Expression patterns of CEACAM5 and CEACAM6 in primary and metastatic cancers. *BMC Cancer* 2007; **7**: 2 [PMID: 17201906 DOI: 10.1186/1471-2407-7-2]
8 **Kuroki M**, Matsushita H, Matsumoto H, Hirose Y, Senba T, Yamamoto T. Nonspecific cross-reacting antigen-50/90 (NCA-50/90) as a new tumor marker. *Anticancer Res* 1999; **19**: 5599-5606 [PMID: 10697625]
9 **Fletcher RH**. Carcinoembryonic antigen. *Ann Intern Med* 1986; **104**: 66-73 [PMID: 3510056 DOI: 10.7326/0003-4819-104-1-66]
10 **Kankanala VL**, Mukkamalla SKR. Carcinoembryonic Antigen. 2023 Jan 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [PMID: 35201700]
11 **Gan N**, Jia L, Zheng L. A sandwich electrochemical immunosensor using magnetic DNA nanoprobes for carcinoembryonic antigen. *Int J Mol Sci* 2011; **12**: 7410-7423 [PMID: 22174606 DOI: 10.3390/ijms12117410]
12 **Goslin R**, O'Brien MJ, Steele G, Mayer R, Wilson R, Corson JM, Zamcheck N. Correlation of Plasma CEA and CEA tissue staining in poorly differentiated colorectal cancer. *Am J Med* 1981; **71**: 246-253 [PMID: 6167166 DOI: 10.1016/0002-9343(81)90125-X]
13 **Fukuda I**, Yamakado M, Kiyose H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. *J Med Syst* 1998; **22**: 89-93 [PMID: 9571515 DOI: 10.1023/A:1022643102208]
14 **Exeter Clinical Laboratory International**. Carcinoembryonic Antigen (CEA). [cited 21 December 2023]. Available from: https://www.exeterlaboratory.com/test/carcinoembryonic-antigen-cea/
15 **Duffy MJ**. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? *Clin Chem* 2001; **47**: 624-630 [PMID: 11274010 DOI: 10.1093/clinchem/47.4.624]
16 **Thomson DM**, Krupey J, Freedman SO, Gold P. The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. *Proc Natl Acad Sci U S A* 1969; **64**: 161-167 [PMID: 5262998 DOI: 10.1073/pnas.64.1.161]
17 **Maestranzi S**, Przemioslo R, Mitchell H, Sherwood RA. The effect of benign and malignant liver disease on the tumour markers CA19-9 and CEA. *Ann Clin Biochem* 1998; **35**: 99-103 [PMID: 9463746 DOI: 10.1177/000456329803500113]

18 **Hall C**, Clarke L, Pal A, Buchwald P, Eglinton T, Wakeman C, Frizelle F. A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. *Ann Coloproctol* 2019; **35**: 294-305 [PMID: 31937069 DOI: 10.3393/ac.2019.11.13]

19 **Goldstein MJ**, Mitchell EP. Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. *Cancer Invest* 2005; **23**: 338-351 [PMID: 16100946 DOI: 10.1081/CNV-58878]

20 **Chen X**, Chen C, Huang L, Wu P. Pretreatment controlling nutritional status (CONUT) score and carcinoembryonic antigen level provide tumor progression and prognostic information in gastric cancer: A retrospective study. *Medicine (Baltimore)* 2023; **102**: e36535 [PMID: 38065858 DOI: 10.1097/MD.0000000000036535]

21 **Cheng X**, Xia J, Xu Q, Gui H. The value of color Doppler ultrasonography combined with serum tumor markers in differential diagnosis of gastric stromal tumor and gastric cancer. *Open Med (Wars)* 2023; **18**: 20230805 [PMID: 38025541 DOI: 10.1515/med-2023-0805]

22 **Huang P**, Meng L, Pang J, Huang H, Ma J, He L, Amani P. Development of a high-performance label-free electrochemical immunosensor for early cancer diagnosis using anti-CEA/Ag-MOF/GO/GCE nanocomposite. *Environ Res* 2023; **238**: 117178 [PMID: 37734580 DOI: 10.1016/j.envres.2023.117178]

23 **Boyev A**, Prakash LR, Chiang YJ, Newhook TE, Bruno ML, Arvide EM, Dewhurst WL, Kim MP, Ikoma N, Lee JE, Snyder RA, Tzeng CD, Katz MHG, Maxwell JE. Elevated CA 19-9 is associated with worse survival in patients with resected ampullary adenocarcinoma. *Surg Oncol* 2023; **51**: 101994 [PMID: 37742542 DOI: 10.1016/j.suronc.2023.101994]

24 **Kimchy AV**, Singh H, Parikh E, Rosenberg J, Sanghavi K, Lewis JH. The predictive value of liver tests for the presence of liver metastases. *Hepat Oncol* 2023; **10**: HEP48 [PMID: 37885607 DOI: 10.2217/hep-2023-0003]

25 **Lakemeyer L**, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J. Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer. *Diseases* 2021; **9** [PMID: 33802962 DOI: 10.3390/diseases9010021]

26 **Loewenstein MS**, Zamcheck N. Carcinoembryonic antigen (CEA) levels in benign gastrointestinal disease states. *Cancer* 1978; **42**: 1412-1418 [PMID: 361200 DOI: 10.1002/1097-0142(197809)42:3+<1412::AID-CNCR2820420805>3.0.CO;2-8]

27 **Go VL**. Carcinoembryonic antigen: clinical application. *Cancer* 1976; **37**: 562-566 [PMID: 1247982 DOI: 10.1002/1097-0142(197601)37:1+<562::AID-CNCR2820370721>3.0.CO;2-0]

28 **Loosen SH**, Roderburg C, Kauertz KL, Koch A, Vucur M, Schneider AT, Binnebösel M, Ulmer TF, Lurje G, Schoening W, Tacke F, Trautwein C, Longerich T, Dejong CH, Neumann UP, Luedde T. CEA but not CA19-9 is an independent prognostic factor in patients undergoing resection of cholangiocarcinoma. *Sci Rep* 2017; **7**: 16975 [PMID: 29208940 DOI: 10.1038/s41598-017-17175-7]

29 **Zhao J**, Yan T, Bi X, Zhao H, Huang Z, Zhou J, Li Z, Li C, Cai J. [Correlation of carcinoembryonic antigen with prognosis of hepatocellular carcinoma after hepatectomy]. *Zhonghua Zhong Liu Za Zhi* 2014; **36**: 430-434 [PMID: 25241784]

30 **Wu XZ**, Ma F, Wang XL. Serological diagnostic factors for liver metastasis in patients with colorectal cancer. *World J Gastroenterol* 2010; **16**: 4084-4088 [PMID: 20731024 DOI: 10.3748/wjg.v16.i32.4084]

31 **Yang KL**, Yang SH, Liang WY, Kuo YJ, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Chang SC, Chu LS, Wang LW. Carcinoembryonic antigen (CEA) level, CEA ratio, and treatment outcome of rectal cancer patients receiving pre-operative chemoradiation and surgery. *Radiat Oncol* 2013; **8**: 43 [PMID: 23452434 DOI: 10.1186/1748-717X-8-43]

32 **Di Tommaso L**, Roncalli M. Tissue Biomarkers in Hepatocellular Tumors: Which, When, and How. *Front Med (Lausanne)* 2017; **4**: 10 [PMID: 28280721 DOI: 10.3389/fmed.2017.00010]

33 **Carrozza MJ**, Calafati SA, Edmonds PR. Immunocytochemical localization of polyclonal carcinoembryonic antigen in hepatocellular carcinomas. *Acta Cytol* 1991; **35**: 221-224 [PMID: 1851357]

34 **Abdul-Wahid A**, Cydzik M, Fischer NW, Prodeus A, Shively JE, Martel A, Alminawi S, Ghorab Z, Berinstein NL, Gariépy J. Serum-derived carcinoembryonic antigen (CEA) activates fibroblasts to induce a local re-modeling of the extracellular matrix that favors the engraftment of CEA-expressing tumor cells. *Int J Cancer* 2018; **143**: 1963-1977 [PMID: 29756328 DOI: 10.1002/ijc.31586]

35 **Campos-da-Paz M**, Dórea JG, Galdino AS, Lacava ZGM, de Fatima Menezes Almeida Santos M. Carcinoembryonic Antigen (CEA) and Hepatic Metastasis in Colorectal Cancer: Update on Biomarker for Clinical and Biotechnological Approaches. *Recent Pat Biotechnol* 2018; **12**: 269-279 [PMID: 30062978 DOI: 10.2174/1872208312666180731104244]

36 **Jessup JM**, Petrick AT, Toth CA, Ford R, Meterissian S, O'Hara CJ, Steele G Jr, Thomas P. Carcinoembryonic antigen: enhancement of liver colonisation through retention of human colorectal carcinoma cells. *Br J Cancer* 1993; **67**: 464-470 [PMID: 8439497 DOI: 10.1038/bjc.1993.88]

37 **Gangopadhyay A**, Lazure DA, Thomas P. Adhesion of colorectal carcinoma cells to the endothelium is mediated by cytokines from CEA stimulated Kupffer cells. *Clin Exp Metastasis* 1998; **16**: 703-712 [PMID: 10211983 DOI: 10.1023/A:1006576627429]

38 **Soeth E**, Wirth T, List HJ, Kumbhani S, Petersen A, Neumaier M, Czubayko F, Juhl H. Controlled ribozyme targeting demonstrates an antiapoptotic effect of carcinoembryonic antigen in HT29 colon cancer cells. *Clin Cancer Res* 2001; **7**: 2022-2030 [PMID: 11448920]

39 **Ordoñez C**, Screaton RA, Ilantzis C, Stanners CP. Human carcinoembryonic antigen functions as a general inhibitor of anoikis. *Cancer Res* 2000; **60**: 3419-3424 [PMID: 10910050]

40 **Morris VK**, Kennedy EB, Baxter NN, Benson AB 3rd, Cercek A, Cho M, Ciombor KK, Cremolini C, Davis A, Deming DA, Fakih MG, Gholami S, Hong TS, Jaiyesimi I, Klute K, Lieu C, Sanoff H, Strickler JH, White S, Willis JA, Eng C. Treatment of Metastatic Colorectal Cancer: ASCO Guideline. *J Clin Oncol* 2023; **41**: 678-700 [PMID: 36252154 DOI: 10.1200/JCO.22.01690]

41 **Sahani DV**, Bajwa MA, Andrabi Y, Bajpai S, Cusack JC. Current status of imaging and emerging techniques to evaluate liver metastases from colorectal carcinoma. *Ann Surg* 2014; **259**: 861-872 [PMID: 24509207 DOI: 10.1097/SLA.0000000000000525]

42 **Choi SH**, Kim SY, Park SH, Kim KW, Lee JY, Lee SS, Lee MG. Diagnostic performance of CT, gadoxetate disodium-enhanced MRI, and PET/CT for the diagnosis of colorectal liver metastasis: Systematic review and meta-analysis. *J Magn Reson Imaging* 2018; **47**: 1237-1250 [PMID: 28901685 DOI: 10.1002/jmri.25852]

43 **Niekel MC**, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010; **257**: 674-684 [PMID: 20829538 DOI: 10.1148/radiol.10100729]

44 **Schulz A**, Viktil E, Godt JC, Johansen CK, Dormagen JB, Holtedahl JE, Labori KJ, Bach-Gansmo T, Kløw NE. Diagnostic performance of CT, MRI and PET/CT in patients with suspected colorectal liver metastases: the superiority of MRI. *Acta Radiol* 2016; **57**: 1040-1048 [PMID: 26622057 DOI: 10.1177/0284185115617349]

45 **Sheikh AAE**, Nguyen AP, Leyba K, Javed N, Shah S, Deradke A, Cormier C, Shekhar R, Sheikh AB. Biliary Duct Hamartomas: A Systematic Review. *Cureus* 2022; **14**: e25361 [PMID: 35774682 DOI: 10.7759/cureus.25361]

46 **Del Poggio P**, Buonocore M. Cystic tumors of the liver: a practical approach. *World J Gastroenterol* 2008; **14**: 3616-3620 [PMID: 18595127 DOI: 10.3748/wjg.14.3616]

47 **Qiang Z**, Zhang W, Jin S, Dai K, He Y, Tao L, Yu H. Carcinoembryonic antigen, α-fetoprotein, and Ki67 as biomarkers and prognostic factors in intrahepatic cholangiocarcinoma: A retrospective cohort study. *Ann Hepatol* 2021; **20**: 100242 [PMID: 32841741 DOI: 10.1016/j.aohep.2020.07.010]

48 **Zhao M**, Yin F. Hepatic epithelioid hemangioendothelioma: Clinical characteristics, diagnosis, treatment, and prognosis. *World J Clin Cases* 2022; **10**: 5606-5619 [PMID: 35979122 DOI: 10.12998/wjcc.v10.i17.5606]

49 **Liu X**, Yu H, Zhang Z, Si S, Huang J, Tan H, Teng F, Yang Z. MRI appearances of hepatic epithelioid hemangioendothelioma: a retrospective study of 57 patients. *Insights Imaging* 2022; **13**: 65 [PMID: 35380293 DOI: 10.1186/s13244-022-01213-8]

50 **Numata T**, Endo T, Yanai H, Ota K, Yamamoto Y, Shimizu K, Yamada H, Hayashihara K, Okauchi S, Satoh H, Yamada Y, Tamura T, Saito K, Kikuchi N, Kurishima K, Ishikawa H, Watanabe H, Shiozawa T, Hizawa N, Funayama Y, Hayashi S, Nakamura H, Yamashita T. Serum CEA and CYFRA Levels in ALK-rearranged NSCLC Patients: Correlation With Distant Metastasis. *In Vivo* 2020; **34**: 2095-2100 [PMID: 32606188 DOI: 10.21873/invivo.12013]

51 **Nasralla A**, Lee J, Dang J, Turner S. Elevated preoperative CEA is associated with subclinical nodal involvement and worse survival in stage I non-small cell lung cancer: a systematic review and meta-analysis. *J Cardiothorac Surg* 2020; **15**: 318 [PMID: 33059696 DOI: 10.1186/s13019-020-01353-2]

52 **Bilusic M**, Heery CR, Arlen PM, Rauckhorst M, Apelian D, Tsang KY, Tucker JA, Jochems C, Schlom J, Gulley JL, Madan RA. Phase I trial of a recombinant yeast-CEA vaccine (GI-6207) in adults with metastatic CEA-expressing carcinoma. *Cancer Immunol Immunother* 2014; **63**: 225-234 [PMID: 24327292 DOI: 10.1007/s00262-013-1505-8]

53 **Adams GP**, Schier R, McCall AM, Simmons HH, Horak EM, Alpaugh RK, Marks JD, Weiner LM. High affinity restricts the localization and tumor penetration of single-chain fv antibody molecules. *Cancer Res* 2001; **61**: 4750-4755 [PMID: 11406547]

54 **Graff CP**, Wittrup KD. Theoretical analysis of antibody targeting of tumor spheroids: importance of dosage for penetration, and affinity for retention. *Cancer Res* 2003; **63**: 1288-1296 [PMID: 12649189]

55 **Bacac M**, Fauti T, Sam J, Colombetti S, Weinzierl T, Ouaret D, Bodmer W, Lehmann S, Hofer T, Hosse RJ, Moessner E, Ast O, Bruenker P, Grau-Richards S, Schaller T, Seidl A, Gerdes C, Perro M, Nicolini V, Steinhoff N, Dudal S, Neumann S, von Hirschheydt T, Jaeger C, Saro J, Karanikas V, Klein C, Umaña P. A Novel Carcinoembryonic Antigen T-Cell Bispecific Antibody (CEA TCB) for the Treatment of Solid Tumors. *Clin Cancer Res* 2016; **22**: 3286-3297 [PMID: 26861458 DOI: 10.1158/1078-0432.CCR-15-1696]

56 **Lee YJ**, Han SR, Kim NY, Lee SH, Jeong JS, Lee SW. An RNA aptamer that binds carcinoembryonic antigen inhibits hepatic metastasis of colon cancer cells in mice. *Gastroenterology* 2012; **143**: 155-65.e8 [PMID: 22465431 DOI: 10.1053/j.gastro.2012.03.039]

57 **Turner MA**, Lwin TM, Amirfakhri S, Nishino H, Hoffman RM, Yazaki PJ, Bouvet M. The Use of Fluorescent Anti-CEA Antibodies to Label, Resect and Treat Cancers: A Review. *Biomolecules* 2021; **11** [PMID: 34944463 DOI: 10.3390/biom11121819]

58 **Gazzah A**, Bedard PL, Hierro C, Kang YK, Abdul Razak A, Ryu MH, Demers B, Fagniez N, Henry C, Hospitel M, Soria JC, Tabernero J. Safety, pharmacokinetics, and antitumor activity of the anti-CEACAM5-DM4 antibody-drug conjugate tusamitamab ravtansine (SAR408701) in patients with advanced solid tumors: first-in-human dose-escalation study. *Ann Oncol* 2022; **33**: 416-425 [PMID: 35026412 DOI: 10.1016/j.annonc.2021.12.012]

59 **Hong KP**, Shin MH, Yoon S, Ji GY, Moon YR, Lee OJ, Choi SY, Lee YM, Koo JH, Lee HC, Lee GK, Kim SR, Lee KH, Han HS, Choe KH, Lee KM, Hong JM, Kim SW, Yi JH, Ji HJ, Kim YB, Song HG. Therapeutic effect of anti CEACAM6 monoclonal antibody against lung adenocarcinoma by enhancing anoikis sensitivity. *Biomaterials* 2015; **67**: 32-41 [PMID: 26204223 DOI: 10.1016/j.biomaterials.2015.07.012]

60 **Sørensen CG**, Karlsson WK, Pommergaard HC, Burcharth J, Rosenberg J. The diagnostic accuracy of carcinoembryonic antigen to detect colorectal cancer recurrence - A systematic review. *Int J Surg* 2016; **25**: 134-144 [PMID: 26700203 DOI: 10.1016/j.ijsu.2015.11.065]

61 **Nozawa H**, Yokota Y, Emoto S, Yokoyama Y, Sasaki K, Murono K, Abe S, Sonoda H, Shinagawa T, Ishihara S. Unexplained increases in serum carcinoembryonic antigen levels in colorectal cancer patients during the postoperative follow-up period: an analysis of its incidence and longitudinal pattern. *Ann Med* 2023; **55**: 2246997 [PMID: 37963211 DOI: 10.1080/07853890.2023.2246997]

62 **Meyerhardt JA**, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB 3rd; American Society of Clinical Oncology. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013; **31**: 4465-4470 [PMID: 24220554 DOI: 10.1200/JCO.2013.50.7442]

63 **Bakalakos EA**, Burak WE Jr, Young DC, Martin EW Jr. Is carcino-embryonic antigen useful in the follow-up management of patients with colorectal liver metastases? *Am J Surg* 1999; **177**: 2-6 [PMID: 10037299 DOI: 10.1016/S0002-9610(98)00303-1]

64 **Ishizuka D**, Shirai Y, Sakai Y, Hatakeyama K. Colorectal carcinoma liver metastases: clinical significance of preoperative measurement of serum carcinoembryonic antigen and carbohydrate antigen 19-9 Levels. *Int J Colorectal Dis* 2001; **16**: 32-37 [PMID: 11317695 DOI: 10.1007/s003840000268]

65 **Zhao W**, Li X, Wang W, Chen B, Wang L, Zhang N, Wang Z, Yang Q. Association of Preoperative Serum Levels of CEA and CA15-3 with Molecular Subtypes of Breast Cancer. *Dis Markers* 2021; **2021**: 5529106 [PMID: 34621407 DOI: 10.1155/2021/5529106]

66 **Arnaud JP**, Koehl C, Adloff M. Carcinoembryonic antigen (CEA) in diagnosis and prognosis of colorectal carcinoma. *Dis Colon Rectum* 1980; **23**: 141-144 [PMID: 7379666 DOI: 10.1007/BF02587615]

67 **Bhattacharjya S**, Aggarwal R, Davidson BR. Intensive follow-up after liver resection for colorectal liver metastases: results of combined serial tumour marker estimations and computed tomography of the chest and abdomen - a prospective study. *Br J Cancer* 2006; **95**: 21-26 [PMID: 16804525 DOI: 10.1038/sj.bjc.6603219]

68 **Yoshikawa M**, Morine Y, Ikemoto T, Imura S, Higashijima J, Iwahashi S, Saito YU, Takasu C, Yamada S, Ishikawa D, Teraoku H, Takata A, Yoshimoto T, Shimada M. Elevated Preoperative Serum CEA Level Is Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma Through the Epithelial-Mesenchymal Transition. *Anticancer Res* 2017; **37**: 1169-1175 [PMID: 28314278 DOI: 10.21873/anticanres.11430]

69 **Qi F**, Zhou A, Yan L, Yuan X, Wang D, Chang R, Zhang Y, Shi F, Han X, Hou J, Wei L, Zhang X. The diagnostic value of PIVKA-II, AFP, AFP-L3, CEA, and their combinations in primary and metastatic hepatocellular carcinoma. *J Clin Lab Anal* 2020; **34**: e23158 [PMID: 31821607 DOI: 10.1002/jcla.23158]

70 **Hou GM**, Liu HL, Wu H, Zeng Y. Prediction of Prognosis for cHCC-CC Patients After Surgery: Comparison of Tumor Marker Score Based on AFP, CEA, CA19-9, and Other Clinical Stages. *Ann Surg Oncol* 2021; **28**: 7647-7660 [PMID: 33900502 DOI: 10.1245/s10434-021-09949-1]

71 **Singal AG**, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, Jou JH, Kulik LM, Agopian VG, Marrero JA, Mendiratta-Lala M, Brown DB, Rilling WS, Goyal L, Wei AC, Taddei TH. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023; **78**: 1922-1965 [PMID: 37199193 DOI: 10.1097/HEP.0000000000000466]

72 **Shin YM**. Surveillance method and imaging characteristics of recurrent biliary cancer after surgical resection. *Korean J Hepatobiliary Pancreat Surg* 2014; **18**: 73-76 [PMID: 26155254 DOI: 10.14701/kjhbps.2014.18.3.73]

73 **Zhu Y**, Mao Y, Chen J, Qiu Y, Guan Y, Wang Z, He J. Radiomics-based model for predicting early recurrence of intrahepatic mass-forming cholangiocarcinoma after curative tumor resection. *Sci Rep* 2021; **11**: 18347 [PMID: 34526604 DOI: 10.1038/s41598-021-97796-1]

74 **Jolissaint JS**, Wang T, Soares KC, Chou JF, Gönen M, Pak LM, Boerner T, Do RKG, Balachandran VP, D'Angelica MI, Drebin JA, Kingham TP, Wei AC, Jarnagin WR, Chakraborty J. Machine learning radiomics can predict early liver recurrence after resection of intrahepatic cholangiocarcinoma. *HPB (Oxford)* 2022; **24**: 1341-1350 [PMID: 35283010 DOI: 10.1016/j.hpb.2022.02.004]

75 **Bhagat A**, Lyerly HK, Morse MA, Hartman ZC. CEA vaccines. *Hum Vaccin Immunother* 2023; **19**: 2291857 [PMID: 38087989 DOI: 10.1080/21645515.2023.2291857]

76 **Hensel JA**, Khattar V, Ashton R, Ponnazhagan S. Recombinant AAV-CEA Tumor Vaccine in Combination with an Immune Adjuvant Breaks Tolerance and Provides Protective Immunity. *Mol Ther Oncolytics* 2019; **12**: 41-48 [PMID: 30666318 DOI: 10.1016/j.omto.2018.12.004]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com