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The role of CEA in the diagnosis, treatment, and follow-up of focal liver lesions

Relationship between focal liver lesions and CEA

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Abstract

In this editorial review, we comment on the article titled “Prognostic role of serum carcinoembryonic antigen (CEA) in patients receiving liver resection for colorectal cancer liver metastasis: A meta-analysis” by Fang T *et al* published in the recent issue of the World Journal of Gastrointestinal Surgery 2023 Dec. 27;15(12):2890-2906.

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: Carcinoembryonic antigen (CEA); liver; focal liver lesions; metastasis; surgery; prognosis; surveillance

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Core Tip: ¹ 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.

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). It's 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 carcinoembryonic antigen gene family, CEA is also known as 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 colorectal cancers. CEA levels may also increase in many non-neoplastic conditions such as ulcerative colitis, cirrhosis, pancreatitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), 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).

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 (CONUT) 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* reported that checking serum ALP, AST, ALT, 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, 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. Colorectal cancer 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 carcinoembryonic antigen-related cell adhesion molecule (CEACAM) analysis, Blumenthal *et al* 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 hepatocellular carcinoma (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 MRI has been shown to detect more liver lesions than CT and PET-CT (41-44). The use of gadoteric 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 colorectal cancers (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. MRCP'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 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, hepatic epithelioid hemangioendothelioma (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 (CYFRA) 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 (Colorectal Cancer) 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. ¹ 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 colorectal cancer 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 colorectal cancer, 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 colorectal cancer liver metastases, its usefulness in definitively diagnosing or predicting the recurrence of hepatocellular carcinoma (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 AFP 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 intrahepatic cholangiocarcinomas (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* 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 (rAAV-CEA) in tumors that express CEA (76). However, the studies are still in the early stages.

CONCLUSION

CEA is a non-specific tumor marker, as its levels can elevate in numerous malignant and benign pathological conditions. The use of CEA for screening purposes is not recommended.

CEA can be an indicator of tumor aggressiveness, especially in CRCs. Elevated CEA levels after surgery or chemotherapy may indicate the presence of relapse or overlooked metastasis.

Elevated CEA levels in FLL cases may indicate that the lesion is metastatic. Combinations of CEA and other biomarkers can provide **more** information about the primary foci of metastatic FLLs. Additionally, ongoing research explores the potential of CEA as an independent prognostic factor in intrahepatic cholangiocarcinoma.

Studies involving drugs such as SAR408701, anti-CEACAM5, and anti-CEACAM6 indicate a growing interest in using CEA-targeted approaches to improve treatment outcomes in cancer patients.

While CEA is a valuable marker for malignancies, its rare elevation in benign lesions like biliary duct hamartomas underscores the importance of considering a broader clinical context and utilizing complementary diagnostic tools to avoid misinterpretations.

In cases of elevated CEA levels detected during follow-up after surgery, in situations where lesions are overlooked or imaging is inadequate, the possibility of metastasis or relapse should be investigated through additional methods.

The extensive expression of CEA in various human carcinomas highlights its potential as a diagnostic and therapeutic target in cancer treatment.

Ongoing research on CEA-targeted agents, including vaccines, antibodies, and RNA aptamers, demonstrates promising advancements in developing targeted therapies for cancers expressing elevated CEA levels.

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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 colorectal cancer 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 colorectal cancer, 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 colorectal cancer liver metastases, its usefulness in definitively diagnosing or predicting the recurrence of hepatocellular carcinoma (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 AFP 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 intrahepatic cholangiocarcinomas (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* 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 (rAAV-CEA) in tumors that express CEA (76). However, the studies are still in the early stages.

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