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Review Article

Clinical Relevance of Tumor Markers in Gastrointestinal Cancers: A Critical Analysis and Literature Review

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Abstract

Objective: The objective of this article is to offer current and evidence-based recommendations for the application of the most prominent tumor markers in various gastrointestinal cancers, especially Colorectal Carcinoma (CRC), pancreatic cancer and Hepatocellular Carcinoma (HCC). We focused on the most used tumor markers being used for diagnostic and therapeutic purposes for intestinal malignomas being Carcino Embryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA 19-9) and Alpha-FetoProtein (AFP) . We will describe their constraints and explain the usage in clinical practice and their significance in primary diagnosis, therapy monitoring and the early detection of recurrences, to enhance the quality of multidisciplinary care of cancer patients.

Conclusion: Tumor markers have a clear role in clinical practice. In situations where imaging results are inconclusive, tumor markers offer additional confirmation of recurrence and prove valuable in postoperative surveillance and assessing the response to various therapeutic modalties. Due to their limited positive predictive value, specificity and sensitivity, they are not suitable for screening purposes. Knowledge of this markers is crucial to enhance the multidisciplinary care and treatment coordination for cancer patients. Therefore they should be included into future guidelines, surveillance-algorythms and staging-programmes for certain tumor-stages.

ABBREVATIONS

AFP: Alpha-Fetoprotein; AJCC: American Joint Comitee on Cancer; ASCO: American Society of Clinical Oncology; Au: Gold; CA 125: Cancer Antigen 125; CA 72-4: Cáncer Antigen 72-4; CA19-9: Carbohydrate Antigen 19-9; CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; CT: Computed Tomography; ESMO: European Society of Clinical Oncology; Fe_3O_4: Iron (III) Oxide; GI: Gastrointestinal; HCC: Hepatocellular Carcinoma; IARC: International Agency for Research on Cancer; LDH: Lactate Dehydrogenase; NCCN: National Co0.mprehensive Cancer Network; NSE: Neuron-Specific Enolase; PET: Positron Emisson Tomography; SEER: The Surveillance Epidemiology and End Results; TNM: Tumor Nodes Metastases

INTRODUCTION

When taking a look at numbers of new cases and deaths, gastrointestinal cancers represent highest numbers in both categories. Colorectal Cancer (CRC) is still the most dominant of them, with approximately 1.9 million new cancer diagnoses in 2020, making it the third most prevalent cancer after lung and breast cancer. In the same year The International Agency for Research on Cancer (IARC) reported 1.1 million new cases of gastric cancer, 900 000 new cases of liver cancer, 600 000 new cases of esophageal cancer and 500 000 new cases of pancreatic cancer globally [1].

In the era of personalized medicine and individualized therapy options in oncology, predictive markers measuring presence or absence of response to specific treatment or interventions are widely used in practice today [2]. Currently, there are several serum-based tumor markers available for diagnosis, prognosis and monitoring of GI cancer, including CarcinoEmbryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA19-9) and Alpha-Fetoprotein (AFP) being the most researched, as well as a huge number of other markers like Cancer-Antigen 72-4 (CA 72-4), Cancer Antigen 125 (CA 125), Chromogranin A, Neuron-Specific Enolase (NSE) and Lactate Dehydrogenase (LDH) [3-5]. With CEA, CA 19-9 and AFP being the most researched, most used in clinical practice and best available tumor markers, this article focused its research and literature review on those markers [5,6].

Traditionally, they have been deployed in clinical practice, for

monitoring disease response. This involves evaluating treatment effectiveness by observing decrease of a marker, which was previously elevated in primary diagnosis [7]. Several research studies have highlighted the clinical importance of each tumor marker [8-10]. However with limited sensitivity and specificity, especially adding low positive predictive values for applying markers in asymptomatic patients, the use of those markers for screening purposes is still limited and does not correspond to the original objective [11,12].

In this article we will review serum tumor markers used in the most common gastrointestinal tumors, being colorectal carcinoma, pancreatic cancer and hepatocellular carcinoma, according to their normal and pathological values, sensitivity and specificity in their relevance as supplementary information to imaging diagnostics and their ability for serving as screening tools. Additionally, their significance in monitoring treatment success and anticipating recurrences will be discussed and backed up by current literature. Special focus was given to reviews including the few relevant systematic reviews, large studies and clinical guidelines published by expert panels.

TUMOR MARKERS IN GI CANCERS

Definition and function of tumor markers

Traditionally, the term tumor marker is used to describe substances, which are found in the blood as well as other body fluids such as urine, pleural fluid or peritoneal fluid, that are either produced by tumor cells themselves or by other cells in the body as an expression of the presence of a malignancy [13]. Key qualities characterizing an ideal tumor marker are exhibition of high specificity for a particular type of tumor, allowing early detection before clinical diagnosis and demonstrating high sensitivity to minimize false positive results. Furthermore, it should have a short half-life, have reliable correlation with tumor size and be cheap enough for screening in targeted populations [14]. Table 1 gives an overview of common markers and their associated gastrointestinal malignancies [5,15,16].

Carcino Embryonic Antigen (CEA)

CEA is released from the apical surface of mature columnar cells into the gut lumen and has restricted expression in normal adult tissue. Due to loss of polarity and absence of basal lamina, CEA is spread out around the cell surface and accumulates at high levels in the blood [17].

Table 1: Common tumormarkers and their associated malagnacies.

Marker	Associated Cancers	Normal Value
CEA	Colorectal cancer Pancreatic cancer	< 2.5 ng/ml in non-smokers <5 ng/ml in smokers
CA 19-9	Pancreatic adenocarcinoma Cholangiocarcinoma Colorectal cancer	0-37 U/ml
CA 125	Pancreatic ductal adenoma	0-35 U/ml
AFP	Hepatocellular carcinoma	0-10 ng/ml
CA 72-4	Gastric cancer	< 6 U/ml

Being a high glycosylated cell surface glycoprotein, it consist of amino-terminal domain with a processed leader sequence, three internal domains, as well as a short 27 amino acid hydrophobic carboxy terminal-domain. CEA's amino acid sequence shows notable similarity to proteins in the immunoglobulin superfamily, which includes molecules involved in intercellular recognition process, such as immunoglobulins, T cell receptors, growth factor receptors and intercellular adhesion molecules like N-Cam [18]. Studies propose, that CEA and its family member CEACAM6 are upregulated in cells retaining division potential and can result in a gradual decline of cellular polarization, distortion of tissue architecture as well as inhibition of differentiation [19].

To determine situations in which tumor markers have proven clinical validity, clinical practice guidelines should be taken for scientific evidence [13]. Comparing guidelines, elevated preoperative CEA levels do not fall within the clinicopathological factors that categorize stage II colon cancer as 'high risk', according to American Society of Clinical Oncology (ASCO) [20] and the National Comprehensive Cancer Network (NCCN) [21]. Despite not being updated since 2006, ASCO published recommendations for the use of tumor markers in gastrointestinal cancers. Guidelines recommend ordering CEA preoperatively for patients if it can aid in determining extend of the cancer and assist in planning surgical treatments [22]. Guidelines published by the European Group on Tumor Markers in 2014 follow a similar approach recommending measuring preoperative CEA levels in newly diagnosed CRC patients. Guidelines published by the European Society of Clinical Oncology (ESMO) follow a different approach in considering high preoperative CEA levels as a minor prognostic parameter for stage II disease. Nevertheless all Guidelines suggest CEA levels should be evaluated before surgery and examined regularly during the post-operative period to help early detection of metastatic disease. However, due to low specificity and sensitivity the level of serum-CEA are not sufficient for colon cancer diagnosis in absence of a confirmatory tumor biopsy [23].

Comparing concrete preoperative serum levels, several studies show numbers >5.0 ng/mL to negatively affect survival outcomes regardless of the tumor's stage [24-28]. For example a study published by Wiratkapun et al. showed significantly higher percentages of patients developing metastasis having CEA levels above 5 ng/ml in comparison to patients with lower numbers. This study also indicated numbers higher than 15 ng/ml to be a significant prognostic indicator for disease-free survival [29]. Several studies showed similar effects for patients with stage II disease [30-32]. Another study by Thirunavukarasu analyzed 17 910 colon cancer patients at any stage, which were reported to SEER database in 2004. Those patients with elevated preoperative CEA level had significantly higher risk of overall mortality (HR for death 1.60, 95% CI 1.46-1.76) [27]. The largest study to date examining correlation between elevated CEA levels and overall survival in CRC patients in 2016 included 137 381

patients and was published by Adan Z. et al. This study showed an increase hazard of death by 62% for patients showing elevated preoperative CEA levels in comparison to patients with normal CEA levels [33].

With data indicating high levels of preoperative CEA having prognostic significance, some experts suggest integrating preoperative CEA levels into the traditional TNM staging system for colon cancer [34]. The 2017 revision of the system does not directly use serum CEA levels for assigning stages but suggest gathering data for its prognostic value and for postoperative monitoring to detect recurrences [35,36].

With 50% of patients presenting with nonmetastatic disease and manifesting metastatic disease, as well as approximately 35% of patients presenting with metastatic disease at diagnosis, studies show benefit in early detection of metastases as metastasectomy improves patient's survival [5,37] With liver being the most prominent organ for metastasis, overexpression of CEA can be used as a tumor marker after cancer therapy or surgery in cancer patients [38]. As recommended by NCNN, postoperative CEA levels should be measured every 3 to 6 months for at least 2 years, then every 6 months for a total of 5 years for tumors higher than stage II. Patients showing serial CEA elevation should get workup-treatment consisting of physical examination, colonoscopy and even chest/abdominal/pelvic CT with contrast [39].

Guidelines published by ASCO prior to 2018 follow similar approaches for stage II and III disease [22,40]. ESMO guidelines recommend determination of CEA levels every 3-6 months for 3 years, as well as every 6-12 months at years 4 and 5 after surgery combined with CT scan of chest and abdomen with colonoscopy A systematic review published in 2017 by Shinkins et al. recommended testing frequency should be increased to monthly for 3 months and then every 2 months with threshold for investigating being 10 µg/l after the second CEA test [41]. However, a Cochrane Database systematic review published in 2015 concluded CEA being insufficiently sensitive used alone, therefore it is crucial to impliment CEA monitoring together with another diagnostic method to avoid missed cases [42]. Despite checking CEA levels, periodical clinical visits as well as CT and endoscopy should be used for surveillance for CRC [16,43]. On the other hand, there are studies showing little or no minimal benefit using CEA for surveillance [44,45], as well as claiming, that only 30% of all CRC release CEA in early states [46].

Another clinical advantage measuring CEA levels consists in the prediction of response to chemotherapy and in monitoring progression under treatment of advanced CRC patients undergoing chemotherapy [5]. International guidelines also recommend following this strategy in advanced tumor stages, recommending measurement of CEA at the start of treatment for metastatic disease and every 1 to 3 months during active treatment [22,40]. A study published by de Haas et al. compared correlation between tumor marker response and radiological response in form of computed tomography. Patients with isolated liver metastasis showed accordance in >90% of cases, patients with stable diseases in 94% of cases and patients showing radiological evidence of disease progression showed correlation in 95% of cases [40,47].

It is necessary to mention, that rises in CEA levels may occur in some assays, being falsely elevated in the context of cigarette smoking or adjuvant 5-Fluouracil (FU) treatment during the first 4 to 6 weeks [22,46].

Carbohydrate antigen 19-9

As a mucinous marker, glycoprotein CA 19-9, also termed Sialyl Lewis [48], is produced by various normal cells in the pancreas, bile ducts, stomach and saliva glands and presented in small amounts in the bloodstream. Because of alteration in processes that regulate the passage of CA 19-9 into the bloodstream, levels tend to increase during cancer development as well as certain inflammatory conditions like pancreatitis and a number of other pancreato-biliary conditions [49].

Being a tetrasaccharid, carbohydrate Antigen 19-9 is synthazised by glucosyltransferases which sequentially bind the monosaccharide precursors onto both N-linked and O-linked glykans. The Lewis blood group system consist of a set of fucosylated glycosphingolipids synthesized by exocrine epithelial cells. These are subsequently adsorbed onto the surface of erythrocytes defining their Lewis phonotype and circulating as red blood cells in body fluids [49].

It has been widely recognized, that glycan structures on the cell surface undergo significant alterations during malignant transformation. These changes are attributed to a process referred to as 'incomplete synthesis' of complex carbohydrate determinants, leading to the expression of structurally less complex carbohydrate molecules [49].

Clinical guidelines published by ESMO in 2015 state that CA 19-9 is not effective as a primary diagnostic marker for pancreatic cancer, despite an elevation of the marker can be seen in 80% of patients with advanced disease [50]. Data indicate measuring preoperative CA 19-9 levels correlate with staging by American Joint Comitee on Cancer (AJCC) and resectability. Therfore, recent guidelines published by NCCN recommend the use of CA 19-9 as a diagnostic marker, adding insights to the staging process [51].

In order to represent an accurate baseline, CA 19-9 levels should be best performed after biliary decompression is completed by anymeans and bilirubin is normal or back to baseline. Hence, Guidelines suggest measuring CA 19-9 levels after neoadjuvant therapy, pre-surgery, post-surgery before starting adjuvant treatment and during surveillance [51].

Using serum CA 19-9 as a screening tool was observed in two large studies [52,53], concluding, that screening in asymptomatic individuals using CA 19-9 as a marker for malignant disease showed no efficiency, due to its low positive predictive value [54]. In a large study involving more than 70 000 asymptomatic

individuals, serum CA 19-9 level >37 U/L had a Positive Predicative Value (PPV) of only 0.9 percent [55]. Even when using elevated CA 19-9 for screening symptomatic patients, sensitivity and specificity are approximately 79-81% and 82-80% [56]. A metanalysis published by Zhang et al in 2015 comparing diagnostic power of CA 19-9 to other markers such as CA 242 and CEA showed CA 19-9 to have the highest sensitivity and CA 242 to have highest specificity, indicating that combination of both markers in one test pattern could increase sensitivity without impairing specificity in diagnosis of pancreatic cancer [57].

As a prognostic factor, CA 19-9 has notable importance as well as an indicator to assess the progression of disease and potentially influence treatment choices. Several studies show that the extent of CA 19-9 elevation both at the initial diagnosis and after surgery is linked to long-term survival [58-60]. ESMO-guidelines recommend taking preoperative serum levels of CA 19-9 >500 IU/ml as indication of poor prognosis after surgery [50]. Furthermore studies suggest that normalization or decrease in postoperative CA 19-9 levels by >20% to 50% from baseline after surgery or chemotherapy correlate with prolonged survival [61]. A study published by Ferrone et al. stated decrease in CA 19-9 as well as CA 19-9 value less than 200 IU/ml as significant predictors in survival for patients with pancreatic adenocarcinoma even after adjusting for stage [62]. Taking a look at the chronological relationship between CA 19-9 elevation and radiographic recurrence, data show that CA 19-9 disappointingly provides only poor positive predictive value (average 35%) but high negative predictive value (average 92%) for recurrence at 6-months intervals. However, data also shows CA 19-9 being able to predict prognosis at each survival interval and precede both clinical and radiological signs [16,63].

A study reviewing 491 patients undergoing staging laparoscopy for radiographically resectable pancreatic adenocarcinoma assessed association between preoperative CA 19-9 levels with presence of subradiographic unresectable disease. Results showed that values greater than 130 U/ml was a predictor of tumor unresectability and indicated preoperative CA 19-9 levels to allow surgeons to better select patients for staging laparoscopy [64].

In accordings with these findings, monitoring CA 19-9 levels can also be used to predict prognosis and incidence of recurrence after neoadjuvant therapy [16]. A multicenter case-control study by Aoki et al. revealed CA 19-9 level ≤ 103 IU/ml to be a significant predictor of overall survival with better prognosis and lower hepatic recurrence after surgery for patients receiving neoadjuvant therapy [65]. For adjuvant chemotherapy measuring serum CA 19-9 levels could also have potential clinical utility in predicting outcome and response [66].

It is important to mention, that 10% of the population lack the enzyme needed for epitope production of Sialyl Lewis antigen called 1,4-fucosyl transferase. Due to the fact, that these patients are unable to produce CA 19-9, measurement of this marker will provide falsely negative results [56].

Alpha-fetoprotein

Deriving from embryonic endoderm tissue cells, AFP is released into fetal bloodstream, with mature hepatocytes being unable to release this glycoprotein. Through malignant transformation liver cancer cells are able to produce AFP again making it the most commonly used tumor marker for Hepatocellular Carcinoma (HCC) [67,68].

The AFP gene is part of the albumin gene family forming a multigene cluster distinguished by their affinity for the lectin Lens culinaris agglutinin: AFP-L1, AFP-L2, and AFP-L3. The regulation of AFP expression primarily occurs at the transcriptional level with the gene having an upstream region, including a tissue-specific promoter, three idependent enhancers and two silencer regions. According to preclinical studies, it seems, that in adult cells, the expression of AFP is inhibited at the promoter and two enhancers through the involvement of corepressors and methylated histones [69].

AFP is mainly snythosized during embryonic development by fetal liver, visceral endoderm of the yolk sac and reaches its maximal value in human fetal blood at 12-16 week of gestitation. In typical circumstances, the concentration of AFP in the blood of adult humans is approximately 5 to 10 ng/ml [70].

Using a threshold value of 20ng/ml in patients with cirrhosis sensitivity and specificity for detecting HCC vary from 41-65% and 80-94% respectively [71]. Due to its low positive predictive value and the fact that AFP levels are normal in about 30 to 40% of patients with HCC, AFP alone is not recommended as a screening tool, nor as surveillance for patients with risk for developing HCC [72]. Due to its weakness as a screening tool, clinical practice guidelines recommend using ultrasound with or without AFP measurement for patients at risk [73-75].

Several studies highlight the importance of using alpha-fetoprotein as a diagnostic tool for monitoring prognosis and survival in patients with a proven HCC diagnosis [76,77]. Data shows significantly lower survival rate for patients showing AFP levels of ≥400 IU/ml in comparison to patients with lower levels [78], with one study showing patients with tumor sizes >5cm and AFP levels >1000 to have an 82% incidence of vascular invasion [79]. Furthermore studies showed that HCC patients with higher AFP levels are likely to have greater tumor size, bilobar involvement and portal vein thrombosis [80].

Another important indication is that AFP can be used for surveillance in patients after receiving liver transplantation [72]. Data indicate AFP progression of more than 15µg/l per month to be a major predictive factor for tumor recurrence, as well as for poor survival after transplantation [81]. A comparative study by Merani et al. showed that among patients who had initial AFP levels >400ng/ml at time of listing, those who achieved reduction in AFP to 400 or lower experienced significantly better overall survival than patients who did not succeed to this reduction [82]. Data also prove AFP levels to predict recurrence after transplantation, with AFP levels >200ng/ml being associated

with higher relapse rates in patients after liver transplantation, showing other risk factors such as presence of vascular invasion or satellite nodules. Therefore, including measurement of AFP levels has been suggested to be included when selecting patients for inclusion on liver transplant lists, as well as a surrogate marker of poor pathological conditions after transplantation [72,83].

Predicting radiological response and survival of patients undergoing systemic chemotherapy, data indicate that AFP response after receiving systemic therapy correlates with better survival rates and tend to identify patients with stable disease more likely. Furthermore AFP-response is clearly associated with radiographic response and qualifies as a prognostic factor for progression-free survival and overall survival [84,85]. Besides chemotherapy, measurement of AFP levels also provides prognostic value for surveillance of antiangiogenic drugs like bevacizumab [86], sorafenib [87] or ramucirumab [88], as well as tyrosine kinase-inhibitors such as cabozantinib [89].

Improving diagnostic accuracy

Despite several markers showing benefits when using in multimodal diagnostic approaches, combination of multiple biomarkers is necessary to improve the accuracy of diagnostic tests [90]. Due to the fact, that relying on a single biomarker for diagnosis may lack sufficient accuracy, it is increasingly prevalent in medical research and practice to conduct multiple biomarker tests on individuals and combine corresponding measurements into a unified score [91,92]. Using more diagnostic markers simultaneously increases the chance of one marker showing higher sisnsitivity [93]. In recent years the addition of nanomaterials for detection of biomarkers correlating with cellular alterations has attracted tremendous attention. There have been ongoing developments of nanomaterials including carbon nanotubes, graphene, Au, and Fe_3O_4-based biosensors being used in early disease detection and diagnostics of lung, prostate, breast and colon cancer [94]. Despite having a higher diagnostic accuracy, imaging methods such as MRI, CT and PET-CT are usally very expensive and are often times inefficient for early stage cancer detection as these methods depend on phenotypic charcteristics of the tumor [95,96]. Including biosensors alongside tumor markers into the diagnostic process could be a more cost-effective and non-invasive methode, with a fast response due to the ability of direct assement of the physiological fluids [97]. Furthermore protein and microRNA based biomarkers and corresponding biosensors are becoming a promising tool forearly diagnosis of GI cancers and propose another diagnostic paramaeter to add to improve diagnostic accuracy [97,98].

CONCLUSIONS

Tumor markers play an important role in today's multimodal therapeutic process in modern oncology, which is mainly driven by precision medicine and innovative treatment strategies. This review aimed to give an overview of three most studied and used tumor markers in clinical practice being CEA, CA 19-9 and AFP. Although some issues related to their importance have not been fully evaluated, the significance of the markers described in this review is of clear use in everyday clinical practice in specific situations.

Clinical guidelines recommend preoperative CEA measurement to better understand disease progression and support treatment planning. Studies show, that elevated preoperative CEA levels, especially above 5.0 ng/ml are associated with poor prognosis and reduced survival rates. Therefore, measurement of CEA levels should be a part of future recommendations by clinical practice guidelines, as well as including high levels into high-risk features for stage II colon cancer. It is important to mention, that high CEA levels alone do not provide definitive diagnosis due to its low sensitivity and specificity, and complementary diagnostic methods are necessary. However, testing CEA levels regularly in the years following surgery can be useful in postoperative monitoring. CEA plays also a role in assessing response rates to chemotherapy and monitoring treatment process.

While using CA 19-9 as a diagnostic marker for primary diagnostics is not recommended due to its limited specificity and sensitivity, it holds significant prognostic significance and can serve as an indicator to assess disease severity and potentially influence treatment. Attempts of using CA 19-9 as a tool for screening in asymptomatic induvials have yielded into negative results, due to its low positive predictive value. Even in symptomatic individuals its sensitivity and specificity are suboptimal. As a prognostic factor elevated levels of CA 19-9 at diagnosis and post-treatment are associated with poor long-term survival, while a decrease in CA 19-9 levels after surgery correlates with improved outcome. Studies showed that CA 19-9 can also predict recurrence and prognosis at various intervals, even preceding clinical and radiological signs. Furthermore, CA 19-9 can aid in patient selection for staging laparoscopy and has potential utility predicting outcomes and responses to neoadjuvant and adjuvant therapy.

While AFP alone is not recommended for a screening tool, due to its low positive predictive value and the fact that a significant portion of HCC patients remain undetected, it holds immense value in various clinical aspects of HCC management. Elevated AFP levels are associated with larger tumor size, bilobar involvement, specific tumor types, as well as vascular invasion, all of which are critical factors influencing patient's outcome. Furthermore, AFP proves value in post-liver transplantation setting, with progressive AFP elevation correlating with poor survival and as predictive factor for tumor recurrence. Data indicate that patients achieving lower AFP levels after transplantation tend to experience better overall survival. In HCC-Patients AFP offers insight into response to chemotherapy and antiangiogenic drugs, correlating with radiographic response, Progression-Free Survival (PFS) and even Overall Survival (OS) in patients undergoing systemic therapy.

A remarkable study done in 2021 analyzing diagnostic and prognostic value of CEA and CA 19-9 in CRC showed 69% of patients with CEA and 66% with CA 19-9 levels greater than 200 had significantly shorter 5-year overall survival, as well as patients with both tumormarkers increased, showed remarkably shorter 5-year survival rate of 23% [99]. Furthermore, patients with both markers elevated had shortest recurrence-free survival rates of 44% and also shorter rates when only one marker was elevated (65%) in comparison to patients showing no elevation (79%) [99]. This emphasizes the importance of including measurement of these tumor markers from the onset of diagnosis, as well as throughout the treatment process.

Overviewing current and past data published on tumor markers, it can be concluded, that due to their low positive predictive value, as well as specificity and sensitivity, they should not be used for screening purposes. However, data indicate their role in clinical practice clearly. Tumor markers may provide additive confirmation for recurrence in doubtful situations, where imaging is not absolutely conclusive. Furthermore they are a valuable add- on- information in the situation of postoperative surveillance and in the assesemant of the response to neo-adjuvant, adjuvant and palliative treatment of all available therapy modalities, such as classical chemotherapy, targeted treatments, immune- therapy, radiation therapy or a combination of all the mentioned options.

Therefore, future clinical guidelines should consequently and strictly evidence- based include tumor markers into the surveillance- algorithms, consider them as prognostic parameters to estimate survival, include them into the TNM staging in defined stages and recommend the optimal times for the repeated determination, in order to characterize the further course of the disease as well as to estimate the individual prognosis of the patient more precisely.

Conflicts of Interest: There was no conflict of interest.

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