International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	CLINICAL UTILITY OF CYFRA 21-1 IN ONCOLOGY: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE AND FUTURE DIRECTIONS
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4207
RECEIVED	19 September 2025
ACCEPTED	14 December 2025
PUBLISHED	30 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

CLINICAL UTILITY OF CYFRA 21-1 IN ONCOLOGY: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE AND FUTURE DIRECTIONS

Paweł Jurczak *(Corresponding Author, Email: pawel.jurczak99@gmail.com)*
Hospital of the Order of Brothers Hospitallers of St. John Grande, Trynitarska 11, 31-061 Kraków, Poland
ORCID ID: 0009-0004-0083-6876

Dominik Małek
The Regional Specialist Hospital in Olsztyn, Żołnierska 18, 10-561 Olsztyn, Poland
ORCID ID: 0009-0001-3499-5929

Paweł Puczel
St. Adalbert's Hospital, Copernicus PL, al. Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0003-1352-4911

Marta Siwek
St. Adalbert's Hospital, Copernicus PL, al. Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0005-2665-9449

Klaudia Sztaba
Hospital of the Order of Brothers Hospitallers of St. John Grande, Trynitarska 11, 31-061 Kraków, Poland
ORCID ID: 0009-0004-7800-8034

ABSTRACT

CYFRA 21-1, a soluble fragment of cytokeratin-19 released during epithelial cell apoptosis and necrosis, has emerged as a promising serum biomarker across a wide range of epithelial malignancies. This review synthesizes current evidence regarding its diagnostic, prognostic, and predictive roles in oncology, with emphasis on its clinical applicability, limitations, and future perspectives. Elevated baseline concentrations of CYFRA 21-1 consistently correlate with greater tumor burden, advanced stage, and poorer survival in cancers such as non–small cell lung cancer, head and neck squamous carcinoma, esophageal, colorectal, breast, thyroid, and urothelial tumors. Serial measurement provides additional clinical insight, as reductions during treatment reflect therapeutic response, whereas rising levels may precede radiologic or clinical relapse. Despite these strengths, limited sensitivity in early-stage disease, biological heterogeneity, and lack of assay standardization currently restrict universal application. Integrative approaches combining CYFRA 21-1 with complementary tumor markers, inflammatory indices, or molecular assays show improved diagnostic and prognostic performance, underscoring its potential as part of multimarker algorithms rather than a stand-alone test. Ongoing efforts to harmonize assays, define reference intervals, and evaluate kinetic behavior in prospective cohorts are essential for translation into practice. Ultimately, CYFRA 21-1 represents a biologically grounded, minimally invasive biomarker capable of enhancing personalized oncology by refining risk stratification, guiding therapeutic decisions, and enabling earlier detection of relapse. Continued validation and clinical integration may establish CYFRA 21-1 as a key component in the evolving landscape of evidence-based cancer management.

KEYWORDS

Cyfra 21-1, Oncology, Lung Cancer, Head and Neck Cancers, Esophageal Cancer, Colorectal Cancer, Breast Cancer, Thyroid Cancer, Bladder Cancer

CITATION

Paweł Jurczak, Dominik Małek, Paweł Puczel, Marta Siwek, Klaudia Sztaba. (2025) Clinical Utility of CYFRA 21-1 in Oncology: A Comprehensive Review of Current Evidence and Future Directions. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4207

1. Introduction

Cytokeratins, particularly CK19, are intermediate filament proteins abundantly expressed in simple epithelial cells and serve as key molecular markers in oncology. Specific soluble fragments, such as CYFRA 21-1, are released during apoptosis or normal cell turnover, providing an accurate reflection of tumor cell activity. Routine measurement of these fragments in body fluids offers a minimally invasive approach to monitoring disease progression and assessing treatment efficacy in epithelial malignancies [1]. CYFRA 21-1 represents a soluble fragment of cytokeratin 19, generated through proteolytic cleavage of the parent protein during epithelial cell apoptosis. This process is strictly dependent on caspase activation, which mediates the degradation of cytoskeletal components during the terminal stages of programmed cell death. Elevated serum levels of CYFRA 21-1 reflect increased tumor cell turnover and may serve as an indirect biomarker of apoptotic activity within malignant tissues [2]. CK19 itself is a low-molecular-weight cytoskeletal protein widely expressed across various malignancies, including lung, colorectal, and breast cancers. Strong CK19 expression is observed in most non-small cell lung carcinomas, whereas its presence is lower in small cell lung cancers and variable in metastatic intrathoracic tumors. Although CK19 demonstrates high sensitivity for non-small cell lung cancers, its diffuse expression pattern limits its prognostic utility when based solely on staining intensity [3]. The role of CK19 and its fragments in treatment monitoring is particularly significant, encompassing the assessment of surgical efficacy, evaluation of chemotherapy response, and early identification of disease recurrence. Beyond its monitoring function, CYFRA 21-1 also serves as an independent prognostic indicator, offering valuable insights into disease progression. While clinical decision-making currently depends largely on population-based reference ranges, the high consistency of commercial assays and the potential for international standardization underscore the importance of incorporating this marker into external quality assurance schemes to ensure reliable application in clinical practice [4]. Serum CYFRA 21-1 levels may fluctuate over time, with some individuals exhibiting transient elevations that normalize in subsequent measurements. Factors such as advanced age, heavy smoking, and weight loss have been associated with an increased likelihood of elevated CYFRA 21-1 levels, emphasizing the need to consider these variables when interpreting results. These findings suggest that a single measurement may be insufficient for reliable clinical assessment, particularly in the context of lung cancer screening [5]. Beyond its oncological relevance, recent evidence suggests that CYFRA 21-1 may also reflect systemic pathological processes, including cardiovascular risk, highlighting its potential as a broader prognostic biomarker. These findings underscore the marker's dual clinical significance and support further investigation of its diagnostic and prognostic applications [6]. CYFRA 21-1 has emerged as a pivotal biomarker for the early detection and monitoring of cancer, offering promising opportunities to improve patient outcomes. Various biosensors are already employed in clinical and research settings to detect this marker, and ongoing technological advancements continue to enhance their sensitivity, multiplexing capacity, and real-time monitoring capabilities, paving the way for next-generation diagnostic strategies and personalized oncology care [7].

Materials and methods: As a narrative review, we conducted a comprehensive literature search to evaluate the diagnostic, prognostic, and therapeutic significance of CYFRA 21-1 across various malignancies. Bibliographic research was performed in October 2025. Articles were selected through PubMed and open-access databases using keywords related to CYFRA 21-1 in oncology. A total of 70 publications were included in the analysis, encompassing clinical studies, meta-analyses, and reviews addressing the clinical utility of CYFRA 21-1 in different cancer types.

2. Clinical Utility of CYFRA 21-1 in Oncology.

2.1 Lung cancer

CYFRA 21-1 levels are consistently higher in patients with non-small cell lung cancer (NSCLC), particularly in squamous cell carcinoma. Measuring CYFRA 21-1 alongside carcinoembryonic antigen (CEA) enhances the ability to distinguish malignant from benign pulmonary conditions. The combined use of these markers improves early detection and supports clinical decision-making [8]. Compared to other tumor markers such as CEA, CA 19-9, and neuron-specific enolase (NSE), CYFRA 21-1 demonstrates particular strength in detecting squamous cell carcinoma. Incorporating it into a multimarker panel increases diagnostic precision, allowing for better patient stratification and more informed treatment planning [9]. CYFRA 21-1 levels naturally increase with age, a factor that should be considered during interpretation. Age-specific reference ranges help reduce the risk of false-positive results, and adjusting diagnostic thresholds based on patient age can enhance the reliability of this biomarker in clinical practice [10]. When combined with other tumor markers such as CEA, NSE, pro-gastrin-releasing peptide (ProGRP), and squamous cell carcinoma antigen (SCC), CYFRA 21-1 improves the sensitivity of early lung cancer detection. This approach is particularly valuable for identifying peripheral squamous and adenocarcinomas. Multimarker panels may facilitate earlier intervention and improved patient outcomes [11]. CYFRA 21-1 concentrations are significantly higher in malignant pulmonary diseases compared to benign conditions. Diagnostic cutoff values may require adjustment depending on specific clinical scenarios, such as the presence of cavitary lesions. Tailoring these thresholds to clinical context enhances diagnostic accuracy [12]. Higher CYFRA 21-1 levels correlate with more advanced tumor stages and reduced overall survival in patients with NSCLC. Elevated concentrations indicate a poorer prognosis and help identify high-risk individuals. Incorporating CYFRA 21-1 into prognostic models may aid in guiding personalized treatment strategies [13]. In patients undergoing immunotherapy, elevated CYFRA 21-1 levels have been associated with shorter overall survival, suggesting a link to treatment resistance. Regular monitoring of CYFRA 21-1 during immunotherapy may provide insights into therapeutic response and allow for timely treatment adjustments [14]. CYFRA 21-1 levels typically decrease in patients responding to chemotherapy, whereas non-responders exhibit little or no change. This makes CYFRA 21-1 a valuable biomarker for evaluating treatment efficacy. Serial measurements enable clinicians to better assess therapeutic response and modify strategies as needed [15]. Monitoring dynamic changes in CYFRA 21-1 levels during chemotherapy provides critical information regarding patient outcomes. Sequential measurements reflect treatment effectiveness and support more personalized clinical decision-making [16]. Combining CYFRA 21-1 with additional markers such as CEA, NSE, SCC-Ag, and ProGRP enhances diagnostic accuracy for lung cancer. This multimarker approach allows for more precise differentiation between tumor types and stages, improving patient management and enabling tailored therapeutic plans [17]. Preoperative CYFRA 21-1 levels have been identified as independent prognostic factors for survival and tumor recurrence in patients with resected NSCLC. Elevated preoperative concentrations are associated with a decreased likelihood of survival or recurrence-free status 15 months or more after surgery. These findings suggest that CYFRA 21-1 is a valuable tool for identifying patients at high risk of treatment failure [18]. CYFRA 21-1 also serves as a prognostic marker in patients with advanced NSCLC undergoing chemotherapy. Higher baseline levels are associated with shorter progression-free and overall survival. Monitoring serum CYFRA 21-1 during treatment can guide clinical decisions and identify patients who may benefit from more intensive therapy [19]. In patients with extensive-stage small cell lung cancer (ED-SCLC) receiving first-line platinum-doublet chemotherapy, elevated pretreatment serum CYFRA 21-1 levels (≥7.0 ng/mL) were associated with significantly shorter progression-free survival (118 days vs. 125 days) and overall survival (213 days vs. 295 days) compared to patients with lower levels. Increased CYFRA 21-1 concentrations also correlated with a higher incidence of refractory relapse, supporting its potential as a prognostic biomarker in ED-SCLC [20]. In a prospective observational study of 121 patients with advanced NSCLC treated with combined chemoimmunotherapy, serum CYFRA 21-1 levels above 3.0 ng/mL were significantly associated with improved progression-free survival (PFS) in both discovery and validation cohorts. In contrast, carcinoembryonic antigen (CEA) levels did not show a significant correlation with PFS. These findings highlight the potential of CYFRA 21-1 as a predictive biomarker for treatment efficacy in NSCLC patients receiving combined chemoimmunotherapy [21]. A pilot study investigating serum biomarkers for lung cancer risk among individuals exposed to residential radon demonstrated that the combination of interleukin-6 (IL-6) and CYFRA 21-1 significantly improved diagnostic accuracy. While IL-6 alone exhibited high specificity but moderate sensitivity, the combined measurement of IL-6 and CYFRA 21-1 yielded the highest area under the receiver operating characteristic curve (AUC), sensitivity, and specificity for distinguishing lung cancer patients from high-risk individuals. These results suggest that IL-6 and CYFRA 21-1 co-assessment could enhance early detection strategies in radon-exposed populations [22].

2.2 Head and neck cancers

CYFRA 21-1 exhibits moderate diagnostic sensitivity but remarkably high specificity in head and neck squamous cell carcinoma (HNSCC). Elevated serum levels are strongly associated with poorer overall and disease-free survival, indicating that this cytokeratin-19 fragment not only reflects tumor burden but also mirrors biological aggressiveness. Its measurement can refine clinical assessment and complement conventional diagnostic methods such as imaging and histopathology [23]. Although CYFRA 21-1 alone may not be sufficiently sensitive for early detection, its reliability and specificity make it a valuable adjunct in oncologic diagnostics. When interpreted alongside other serum markers or radiological findings, it enables more precise differentiation between malignant and benign lesions in the head and neck region, supporting its role as a complementary rather than stand-alone biomarker in clinical evaluation [24]. Higher pretreatment CYFRA 21-1 concentrations are frequently observed in patients with advanced disease and correlate with unfavorable therapeutic outcomes. Elevated levels prior to chemoradiotherapy are associated with an increased risk of locoregional recurrence and distant metastasis, underscoring the potential value of CYFRA 21-1 in pretreatment risk stratification. Regular monitoring of CYFRA 21-1 dynamics may help identify patients who could benefit from intensified follow-up or adjuvant therapy [25]. In laryngeal carcinoma, increased CYFRA 21-1 levels closely correspond with tumor presence and stage, reinforcing its significance as a biochemical marker of disease activity. Although the optimal diagnostic cutoff remains under debate, this marker provides practical value when interpreted in conjunction with endoscopic and imaging findings. Incorporating CYFRA 21-1 into standard diagnostic panels can therefore enhance the accuracy of clinical staging [26]. In certain subtypes, such as cutaneous squamous cell carcinoma of the head and neck, serum CYFRA 21-1 levels may offer additional insight into tumor size, invasiveness, and biological behavior. These observations suggest its potential as a complementary indicator for disease monitoring, particularly in aggressive or metastatic cases [27]. Baseline serum CYFRA 21-1 concentrations appear to reflect overall tumor load and pathological aggressiveness, providing supplementary information for prognosis and treatment planning. When combined with traditional staging parameters, this biomarker can improve individualized therapeutic decision-making and strengthen risk prediction [28]. Although CYFRA 21-1 lacks sufficient sensitivity to detect all cases of minimal residual disease following radiotherapy, sequential measurement may reveal early recurrence patterns. Integrating serial CYFRA 21-1 testing into post-treatment monitoring protocols could therefore provide an earlier indication of disease reactivation or progression [29]. Progressive increases in CYFRA 21-1 levels have been shown to precede the clinical or radiological detection of distant metastases by several weeks, suggesting that dynamic monitoring rather than single measurements may be crucial for early relapse identification at potentially more treatable stages [30]. Combining CYFRA 21-1 with additional tumor markers such as CEA, SCC-Ag, or tissue polypeptide-specific antigen (TPS) substantially improves both diagnostic sensitivity and prognostic performance. Multimarker strategies capture a broader spectrum of tumor activity, providing a more comprehensive and reliable assessment of disease status compared to single-marker evaluation [31]. Persistent elevation of CYFRA 21-1 is frequently linked to increased metastatic potential and reduced overall survival. Tracking its trajectory over time can help differentiate between active disease and remission, thereby supporting more individualized follow-up strategies [32]. Continuous post-treatment increases in CYFRA 21-1 concentrations often signal early recurrence and poorer prognosis. Regular measurement of this marker as part of follow-up protocols may enhance early relapse detection and enable timely therapeutic intervention, ultimately improving long-term outcomes for patients with HNSCC [33].

2.3 Esophageal cancer

CYFRA 21-1 has been extensively investigated as both a diagnostic and prognostic biomarker in squamous cell carcinoma of the esophagus. Preoperative serum concentrations exceeding 3.5 ng/mL were observed in approximately 20% of patients and were associated with larger tumor size (≥40 mm), deeper invasion (T2–T4), and lymph node metastasis. Following radical resection, CYFRA 21-1 levels significantly declined, and elevated preoperative values were identified as independent predictors of overall survival [34]. When combined with squamous cell carcinoma antigen (SCC-Ag) to form the Tumor Marker Index (TMI), CYFRA 21-1 enables a more refined prognostic assessment. Patients with a high TMI demonstrated significantly poorer survival compared to those with a low TMI, while the addition of postoperative adjuvant chemotherapy improved outcomes in the high-TMI group [35]. CYFRA 21-1 also serves as a valuable marker for monitoring treatment response, as reductions in serum levels following radiotherapy or chemoradiotherapy correlate with favorable clinical outcomes and a lower risk of disease recurrence [36]. Furthermore, integrating CYFRA 21-1 with inflammatory parameters such as the platelet-to-lymphocyte ratio (PLR) or lymphocyte-to-

monocyte ratio (LMR) enhances its prognostic utility. Elevated PLR × CYFRA 21-1 values or the combination of high CYFRA 21-1 with low LMR are associated with poorer prognosis, increased risk of relapse, and a reduced likelihood of achieving a complete therapeutic response [37,38]. Pre-treatment assessment of CYFRA 21-1 may also help predict tumor sensitivity to chemoradiotherapy. Li et al. reported that patients with low pre-treatment CYFRA 21-1 levels (<3.4 ng/mL) achieved higher overall response rates (CR + PR: 96.3%) compared to those with elevated levels (60%) [39]. However, CYFRA 21-1 alone does not consistently correlate with clinicopathological parameters. Sugase et al. found that elevated serum CYFRA 21-1 was not associated with age, sex, TNM stage, tumor location, histological differentiation, or Ki-67 expression, underscoring the need to combine this marker with others for a more accurate prognostic evaluation [40]. Wu et al. demonstrated that CYFRA 21-1 is more suitable for monitoring treatment efficacy than for early diagnosis. Its diagnostic sensitivity was 33.9%, surpassing that of SCC-Ag, CEA, and CA19-9, and serum levels correlated with TNM stage and lymph node metastasis following resection [41]. In conclusion, CYFRA 21-1 represents a valuable biomarker for diagnosis, therapeutic response evaluation, and prognostication in esophageal squamous cell carcinoma. Integrating this marker with other tumor-associated biomarkers and systemic inflammatory indicators markedly enhances prognostic accuracy [42].

2.4 Colorectal cancer

CYFRA 21-1 has demonstrated significant clinical utility in identifying primary colorectal malignancies, particularly in distinguishing malignant from benign lesions. In a study by Lee et al., a serum threshold of ≥1.13 ng/mL yielded a diagnostic sensitivity of 47%, surpassing that of CEA (37%) and CA 19-9 (32.6%), with an area under the ROC curve of 0.81 ± 0.03, underscoring its superior diagnostic accuracy for colorectal cancer detection. Its strong performance in detecting recurrent disease further highlights its clinical relevance [43]. Measurement of CYFRA 21-1 is also valuable for evaluating therapeutic response. Lee et al. observed that postoperative or post-chemotherapy declines in serum levels were indicative of favorable treatment outcomes, whereas rising concentrations frequently preceded clinical recurrence, confirming its role in longitudinal patient monitoring [43]. Beyond established malignancies, CYFRA 21-1 may assist in detecting advanced precancerous colorectal lesions. Lim et al. reported that serum CYFRA 21-1 effectively differentiated individuals with advanced adenomas from healthy controls, achieving an AUC of 0.732 (95% CI 0.656–0.809, $P < 0.001$) and demonstrating higher sensitivity than other tumor markers, suggesting its potential role in early detection and preventive screening strategies [44]. Serum CYFRA 21-1 concentrations also correlate with disease progression and metastatic burden, particularly hepatic metastases. Shimada et al. found that elevated serum levels were associated with more advanced Dukes stages (C and D), supporting its utility in assessing tumor spread and disease severity [45]. When compared with established tumor markers such as CEA and CA 19-9, CYFRA 21-1 demonstrates enhanced sensitivity for detecting both early metastases and recurrent disease. The combination of CYFRA 21-1 with other biomarkers has been shown to improve diagnostic accuracy and strengthen the monitoring of therapeutic response and disease dynamics [45]. High pre-treatment CYFRA 21-1 concentrations have been linked to poorer prognosis and an increased risk of disease recurrence. Huang et al. reported that patients with elevated baseline levels exhibited shorter overall survival, suggesting that CYFRA 21-1 can serve as a complementary prognostic indicator alongside traditional clinical parameters [46]. Preoperative evaluation of CYFRA 21-1 provides additional prognostic insight, as elevated levels have been associated with increased recurrence risk and reduced survival duration, enabling clinicians to better identify high-risk patients and optimize perioperative management strategies [47]. Emerging evidence also suggests a potential role for CYFRA 21-1 in identifying serrated colorectal lesions. Ye et al. reported significant associations between serum CYFRA 21-1 concentrations and sessile serrated lesions or traditional serrated adenomas, while a diagnostic scoring model integrating thermal imaging with CYFRA 21-1 levels improved lesion detection and surveillance accuracy [48].

2.5 Breast cancer

Measurement of CYFRA 21-1 in fine-needle aspiration rinses of axillary lymph nodes has been shown to improve the sensitivity of detecting metastatic involvement compared to cytology alone, enhancing preoperative diagnostic accuracy and supporting more informed decisions regarding sentinel lymph node procedures [49]. Quantification of CYFRA 21-1 directly in fine-needle aspirates or their rinses represents an innovative adjunct to cytological assessment for detecting axillary lymph node metastases, aiding in identifying tumor involvement even when cytological findings are inconclusive and refining surgical planning [50]. When compared with traditional tumor markers such as CA 15-3 and CEA, serum CYFRA 21-1 levels

correlate with disease stage and tumor burden in breast cancer patients. Although its prognostic value is comparable to that of CA 15-3, current evidence does not support its use as a standalone diagnostic marker due to limited sensitivity and specificity in early-stage disease [51]. Serum CYFRA 21-1 has also been investigated for treatment monitoring and early relapse detection, with decreasing concentrations following therapy associated with response and increasing levels often preceding clinical or radiological signs of progression, suggesting its potential utility in follow-up protocols for metastatic breast cancer [52]. The detection of cytokeratin 19 (CK19) fragments, including CYFRA 21-1, in bone marrow samples is associated with poor prognosis and may indicate micrometastatic disease, as the presence of CK19-positive cells correlates with reduced survival, highlighting the relevance of cytokeratin-based assays for risk stratification [53]. Combining CYFRA 21-1 with other circulating biomarkers such as CA 15-3, CEA, HER2 shed antigen, LDH, or CRP improves the sensitivity of relapse detection compared to single-marker assessment. Such multimarker panels may enhance clinical monitoring in patients with high recurrence risk, although their predictive value should be interpreted cautiously [54]. Perioperative assessment of CYFRA 21-1 in patients undergoing hepatic resection for metastatic breast cancer provides additional prognostic information, with elevated pre- and postoperative levels linked to poorer outcomes, underscoring the marker's value in therapeutic decision-making and postoperative surveillance [55]. In patients with leptomeningeal carcinomatosis secondary to breast cancer, CYFRA 21-1 concentrations in cerebrospinal fluid may reflect treatment efficacy, as changes in CSF levels parallel clinical course, indicating that CYFRA 21-1 could serve as a minimally invasive biomarker for monitoring disease in this rare complication [56]. Studies in Asian populations have demonstrated that CYFRA 21-1 correlates not only with tumor stage but also with inflammatory cytokine profiles such as IL-6, IL-8, and IL-10, suggesting that CYFRA 21-1 reflects both tumor activity and systemic inflammatory response and reinforcing its potential role in integrated prognostic models [57]. Cytological washings obtained postoperatively from axillary regions have shown that CYFRA 21-1 can facilitate the detection of regional recurrence after surgery, complementing imaging and cytology and offering a sensitive approach for local recurrence surveillance [58]. In differentiating pulmonary lesions in patients with a history of breast cancer, elevated CYFRA 21-1 levels combined with higher primary tumor stage are indicative of metastatic rather than primary pulmonary carcinoma, supporting its use as an adjunct marker to distinguish pulmonary metastases from new primary lung cancers in complex diagnostic scenarios [59].

2.6 Thyroid cancer

CYFRA 21.1, a soluble fragment derived from cytokeratin 19, has been identified as an indicator of dedifferentiation in advanced thyroid cancers, with increased serum levels often associated with a more aggressive clinical course. Evaluating CYFRA 21.1 may provide additional insight into the differentiation status of thyroid tumors [60]. Research indicates that serum CYFRA 21.1 concentrations are elevated in patients with thyroid malignancies compared to those with benign nodular disease, suggesting its potential utility in distinguishing malignant from non-malignant thyroid lesions, although its specificity is limited since elevated levels may also occur in other clinical conditions [61]. Serum CYFRA 21.1 levels show a positive correlation with disease activity in patients with metastatic thyroid carcinoma, and an upward trend may indicate advancing disease. Continuous monitoring of CYFRA 21.1 can therefore provide useful information regarding therapeutic effectiveness and disease dynamics [62]. Assessing CYFRA 21.1 in lymph node aspirates ("washout" fluid) can enhance the detection of metastatic involvement in thyroid carcinoma, as elevated levels in nodal aspirates suggest metastatic infiltration; however, additional studies are warranted to establish its routine clinical application [63]. Serum CYFRA 21.1 may also serve as a tool to evaluate response to therapy in thyroid cancer patients, with higher levels linked to an increased likelihood of recurrence. Serial measurements can thus contribute to patient risk stratification and prognostic assessment [64]. Moreover, elevated CYFRA 21.1 concentrations may reflect resistance to radioiodine therapy in individuals with thyroid carcinoma, potentially identifying patients less likely to benefit from standard radioiodine treatment, although further investigation is needed to validate its clinical applicability [65].

2.7 Bladder cancer

CYFRA 21.1, a soluble fragment of cytokeratin 19, has been identified as a circulating biomarker in bladder cancer, with higher serum concentrations associated with advanced tumor stage and aggressive clinical features. Its measurement can provide insight into disease burden and the biological behavior of the tumor. Integrating CYFRA 21.1 with additional biomarkers such as ERCC1, p53, FGFR3, or TATI may improve prognostic and diagnostic accuracy, as multi-marker panels allow better patient stratification based on risk and guide personalized treatment strategies, although further validation is needed before widespread clinical adoption [66]. Elevated serum CYFRA 21.1 levels have been linked to worse survival outcomes in patients with bladder carcinoma, with higher concentrations often corresponding to advanced tumor grade and stage. Incorporating this marker into prognostic assessment can therefore support treatment decision-making [67]. Dynamic changes in serum CYFRA 21.1 during chemotherapy reflect therapeutic efficacy, as decreasing levels generally indicate a favorable response, whereas rising concentrations may signal disease progression, providing a minimally invasive method for monitoring patient response over time. Serum CYFRA 21.1 levels also correlate with disease extent in invasive bladder cancer, with higher concentrations frequently observed in patients with metastatic involvement or large tumor volume, thus offering indirect information regarding disease severity [68]. CYFRA 21.1 has been evaluated as part of multi-marker urine panels for bladder cancer detection, and when combined with markers such as VEGF, IL-8, MMP-9, and survivin, it can enhance diagnostic accuracy and sensitivity, supporting the development of non-invasive, rapid screening strategies [69]. However, urinary CYFRA 21.1 alone demonstrates limited reliability for detecting bladder cancer recurrence, as sensitivity and specificity remain suboptimal even with optimized detection thresholds, restricting its use as a standalone surveillance tool [70].

3. Discussion

The collective body of evidence reviewed in this article highlights the considerable but still only partially realized potential of CYFRA 21-1 as a biomarker across a variety of epithelial malignancies. The principal clinical applications of CYFRA 21-1 across major epithelial malignancies, including its diagnostic, prognostic, and monitoring value, are summarized in Table 1. The biological basis of this marker—originating from the caspase-mediated cleavage of cytokeratin-19 during apoptosis or epithelial turnover—provides a compelling rationale for its release into circulation and for its association with tumor dynamics. In principle, CYFRA 21-1 reflects the biological activity of malignant epithelium, acting as a measurable proxy for the cellular disintegration that accompanies tumor progression. Translating this mechanistic insight into robust clinical utility, however, has proven more complex than initially anticipated.

Across different tumor types, a coherent pattern emerges. High serum CYFRA 21-1 levels consistently correlate with larger tumor burden, more advanced disease, and inferior survival. A reduction in concentration during treatment usually mirrors therapeutic efficacy, whereas rising levels often precede or accompany relapse. These associations are particularly strong in non–small cell lung cancer, where CYFRA 21-1 has shown prognostic and monitoring value in numerous independent studies. Comparable though somewhat less pronounced trends have been observed in head and neck squamous cell carcinoma, esophageal and colorectal cancers, and in metastatic breast, thyroid, and urothelial tumors. Taken together, these findings suggest that CYFRA 21-1 captures a shared biological phenomenon—epithelial cell disruption—rather than a signal specific to one organ or histologic subtype. In that sense, it functions as a broad indicator of tumor burden and cell turnover, bridging the gap between histopathological activity and clinical manifestation.

A further strength of this biomarker lies in its practicality. CYFRA 21-1 measurement is minimally invasive, requiring only a simple blood draw, which allows for serial assessment over the course of therapy. In an era defined by precision oncology, when real-time feedback is critical for therapeutic adjustment, the ability to track disease activity through serum-based monitoring is extremely valuable. Several commercial assays have already achieved acceptable analytical performance, and progress toward assay harmonization and external quality control continues. Although standardization remains incomplete, CYFRA 21-1 already stands out for its feasibility and clinical accessibility, particularly when integrated alongside imaging and established tumor markers.

Despite these advantages, several limitations temper enthusiasm for routine clinical adoption. Sensitivity remains the principal obstacle. Although specificity is generally adequate, the ability of CYFRA 21-1 to detect early-stage disease is modest in many cancer types, which restricts its value as a screening tool. Its greatest utility currently lies in prognostication and monitoring rather than primary diagnosis. Moreover, biological and analytical variability complicate interpretation. Serum concentrations can be influenced by factors such as

age, smoking, weight loss, or benign epithelial injury. These confounders may yield false-positive results if not properly contextualized. Expression of cytokeratin-19 also varies between tumors, contributing to heterogeneity in release kinetics. As a result, no single universal threshold can be applied confidently across all malignancies.

Analytical inconsistency among studies remains another challenge. Investigators have employed a range of cut-off values—often between 3.0 ng/mL and 3.5 ng/mL—but without consensus regarding reference intervals or adjustment for demographic variables. This heterogeneity makes cross-study comparison difficult and limits meta-analytic synthesis. Establishing standardized cut-offs, validated through large multicenter cohorts, would significantly strengthen the evidence base and facilitate translation into practice.

The temporal dimension of CYFRA 21-1 monitoring also deserves greater attention. The kinetics of change during therapy and follow-up appear clinically meaningful, but the optimal sampling interval and timing of measurements remain undefined. In advanced disease, CYFRA 21-1 often decreases with effective treatment and rises again at progression, but less is known about its dynamics in early-stage or minimal residual disease settings. Determining the marker's lead time—that is, how far in advance an elevation predicts relapse—will be essential for its incorporation into modern surveillance strategies.

When viewed through a clinical lens, several patterns of use for CYFRA 21-1 become apparent. Elevated baseline concentrations can serve as a marker of aggressive disease biology and identify patients who may benefit from closer monitoring or intensified systemic therapy. During active treatment, serial measurement can provide early insight into therapeutic response, complementing imaging findings and potentially guiding timely changes in regimen. In the post-treatment setting, a renewed rise in CYFRA 21-1 can serve as an early signal of relapse, allowing clinicians to intervene before overt clinical deterioration occurs. Importantly, CYFRA 21-1 appears most effective when interpreted in combination with other biomarkers or clinical variables. Integrative models that combine CYFRA 21-1 with markers such as CEA, SCC-Ag, or inflammatory indices have achieved better discrimination and prognostic accuracy than any single marker alone. This multidimensional approach aligns with current trends toward composite biomarker panels that capture different facets of tumor biology.

The role of CYFRA 21-1 in newer therapeutic contexts is also gaining attention. As immunotherapy, targeted therapy, and combined chemo-immunotherapy become standard of care in many malignancies, dynamic serum markers that reflect early biological response are increasingly valuable. Recent reports in non–small cell lung cancer suggest that CYFRA 21-1 may retain prognostic and predictive relevance even in patients treated with immune checkpoint inhibitors, pointing to its broader applicability in modern oncologic paradigms. Similarly, preliminary data from less common tumor types, such as penile carcinoma, hint at wider relevance beyond traditional epithelial sites. These findings encourage continued exploration in both common and rare malignancies.

Future progress will depend on several research priorities. Prospective studies must validate CYFRA 21-1 across diverse cancer populations, with consistent methodology and predefined thresholds. Harmonization of assays and establishment of universally accepted reference ranges are essential for reproducibility. Longitudinal investigations should characterize the marker's kinetic behavior—how rapidly it changes with therapy, how soon it signals progression, and how these dynamics compare with imaging or molecular markers such as circulating tumor DNA. Integrative research combining CYFRA 21-1 with genomic, radiomic, or immunologic parameters could yield composite signatures that more accurately mirror tumor biology and therapeutic response. Finally, health-economic analyses should quantify whether serial CYFRA 21-1 monitoring improves outcomes or reduces cost by enabling earlier intervention and more efficient use of resources.

The existing literature, while promising, is not without its limitations. Many studies are retrospective, involve small and heterogeneous cohorts, and lack standardized methodologies. Follow-up durations are often short, and potential confounders such as comorbid pulmonary disease or chronic inflammation are not always controlled. These issues may inflate effect estimates or obscure the true scope of the marker's utility. Consequently, although CYFRA 21-1 has demonstrated clear associations with clinical outcomes, its precise role in guiding management decisions remains to be fully defined. Careful interpretation within the clinical context is therefore imperative.

Despite these caveats, CYFRA 21-1 has gradually earned a place among the more credible circulating biomarkers in oncology. Its mechanistic plausibility, reproducible correlations with tumor activity, and ease of measurement make it a valuable adjunct to established modalities. While it is unlikely to replace imaging or tissue-based diagnostics, it can enhance them by providing a biochemical dimension to disease monitoring—

one that reflects real-time biological behavior rather than static morphology. In the broader pursuit of personalized cancer management, such dynamic indicators are indispensable.

Table 1. Clinical significance of CYFRA 21-1 across major cancer types.

Cancer type	Diagnostic Utility	Prognostic Value	Monitoring / Predictive Role	Key Remarks
Non-small cell lung cancer (NSCLC)	Elevated particularly in squamous subtype; improves differential diagnosis when combined with CEA or SCC-Ag.	High baseline levels predict advanced stage, poor survival, and shorter PFS/OS.	Serial decline reflects treatment response; early rise may signal relapse or resistance.	Most validated malignancy for CYFRA 21-1; integral to multimarker panels.
Small cell lung cancer (SCLC)	Limited diagnostic sensitivity.	High pretreatment levels associated with refractory relapse and inferior survival.	Useful for monitoring chemotherapy response.	Supplementary rather than primary biomarker.
Head and neck squamous cell carcinoma (HNSCC)	Moderate sensitivity but high specificity; aids differentiation from benign lesions.	Elevated baseline levels linked to aggressive phenotype and poor prognosis.	Dynamic changes indicate recurrence or metastasis; supports follow-up surveillance.	Valuable adjunct to imaging and histopathology.
Esophageal squamous cell carcinoma	Elevated in ~20% of cases; correlates with tumor size and nodal spread.	Independent predictor of overall survival; high values indicate poor outcome.	Post-therapy decline correlates with favorable response.	Prognostic accuracy enhanced when combined with SCC-Ag or inflammatory ratios.
Colorectal cancer	Differentiates malignant from benign or precancerous lesions; higher sensitivity than CEA or CA 19-9.	Elevated pre- and postoperative levels predict recurrence and shorter survival.	Decrease after surgery or chemotherapy indicates effective treatment.	Promising tool for detecting recurrence and advanced adenomas.
Breast cancer	Detectable in fine-needle aspirates of axillary nodes; improves detection of metastasis.	High serum or bone marrow levels associate with worse prognosis and tumor burden.	Changes in serum levels track therapeutic response and relapse.	Useful in multimarker panels (CA 15-3, CEA, HER2, CRP).
Thyroid cancer	Elevated in poorly differentiated or metastatic disease.	High serum levels correlate with aggressive biology and dedifferentiation.	Rising levels may reflect radioiodine resistance or recurrence.	Potential marker for treatment monitoring; requires further validation.
Bladder cancer	Increased serum concentrations in invasive or metastatic stages.	High levels predict poor survival and advanced disease.	Decreasing levels suggest treatment response; rising levels signal progression.	Limited reliability in urine; best used with additional markers (VEGF, IL-8, MMP-9).

Abbreviations: CEA – carcinoembryonic antigen; SCC-Ag – squamous cell carcinoma antigen; PFS – progression-free survival; OS – overall survival.

4. Conclusions

In summary, CYFRA 21-1 exemplifies how a single molecular fragment, when properly understood and applied, can illuminate the underlying biology of cancer and refine patient care. Although challenges remain regarding sensitivity, specificity, and standardization, the accumulating evidence positions CYFRA 21-1 as an emerging component of evidence-based oncology. With continued refinement, validation, and integration into multiparametric models, it could become a practical tool for risk assessment, treatment monitoring, and relapse detection across diverse tumor types. Ultimately, the successful translation of CYFRA 21-1 from research to routine care would not only deepen our biological understanding of epithelial malignancies but also bring tangible benefits to patients— enabling more responsive, individualized, and effective cancer management.

REFERENCES

1. Barak, V., Goike, H., Panaretakis, K. W., & Einarsson, R. (2004). Clinical utility of cytokeratins as tumor markers. Clinical biochemistry, 37(7), 529–540. https://doi.org/10.1016/j.clinbiochem.2004.05.009
2. Sheard, M. A., Vojtesek, B., Simickova, M., & Valik, D. (2002). Release of cytokeratin-18 and -19 fragments (TPS and CYFRA 21-1) into the extracellular space during apoptosis. Journal of cellular biochemistry, 85(4), 670–677. https://doi.org/10.1002/jcb.10173
3. Verma, V., & Rao, R. N. (2022). Cytokeratin 19 expression in intrathoracic neoplasms: First study utilizing cellblocks, evaluating the role of a rarely used cytokeratin for lung cancers. Diagnostic cytopathology, 50(3), 105–111. https://doi.org/10.1002/dc.24927
4. Ebert, W., Bodenmüller, H., & Hölzel, W. (1995). CYFRA 21-1--clinical applications and analytical requirements. Scandinavian journal of clinical and laboratory investigation. Supplementum, 221, 72–80. https://doi.org/10.3109/00365519509090568
5. Minamibata, A., Kono, Y., Arimoto, T., Marunaka, Y., & Takayama, K. (2023). Variability of serum CYFRA 21 - 1 and its susceptibility to clinical characteristics in individuals without cancer: a 4-year retrospective analysis. BMC pulmonary medicine, 23(1), 344. https://doi.org/10.1186/s12890-023-02650-x
6. Bracun, V., Suthahar, N., Shi, C., de Wit, S., Meijers, W. C., Klip, I. T., de Boer, R. A., & Aboumsallem, J. P. (2021). Established Tumour Biomarkers Predict Cardiovascular Events and Mortality in the General Population. *Frontiers in cardiovascular medicine*, *8*, 753885. https://doi.org/10.3389/fcvm.2021.753885
7. Ashour, A. A., Tayeb, F. J., Felemban, M. F., & Shafie, A. (2025). Nanomaterial-based biosensors for cancer diagnosis: trends and innovations (2022-2025). *Mikrochimica acta*, *192*(7), 404. https://doi.org/10.1007/s00604-025-07276-w
8. Okamura, K., Takayama, K., Izumi, M., Harada, T., Furuyama, K., & Nakanishi, Y. (2013). Diagnostic value of CEA and CYFRA 21-1 tumor markers in primary lung cancer. *Lung cancer (Amsterdam, Netherlands)*, *80*(1), 45–49. https://doi.org/10.1016/j.lungcan.2013.01.002
9. Bréchot, J. M., Chevret, S., Nataf, J., Le Gall, C., Frétault, J., Rochemaure, J., & Chastang, C. (1997). Diagnostic and prognostic value of Cyfra 21-1 compared with other tumour markers in patients with non-small cell lung cancer: a prospective study of 116 patients. *European journal of cancer (Oxford, England : 1990)*, *33*(3), 385–391.
10. Yoon, S., Lim, Y. K., Kim, H. R., Lee, M. K., & Kweon, O. J. (2023). Establishment of Reference Intervals of Cytokeratin 19 Fragment Antigen 21-1 in Korean Adults. *Annals of laboratory medicine*, *43*(1), 82–85. https://doi.org/10.3343/alm.2023.43.1.82
11. Schneider J. (2010). Early detection of lung cancers - Comparison of computed tomography, cytology and fuzzy-based tumor markers panels. *Cancer biomarkers : section A of Disease markers*, *6*(3-4), 149–162. https://doi.org/10.3233/CBM-2009-0126
12. Kim, Y. C., Lim, S. C., Bom, H. S., Park, K. O., Na, K. J., Park, H. K., & Hwang, J. H. (2000). Different cutoff values of Cyfra 21-1 for cavitary and noncavitary lung cancers. *Lung cancer (Amsterdam, Netherlands)*, *30*(3), 187–192. https://doi.org/10.1016/s0169-5002(00)00134-3
13. Yu, Z., Zhang, G., Yang, M., Zhang, S., Zhao, B., Shen, G., & Chai, Y. (2017). Systematic review of CYFRA 21-1 as a prognostic indicator and its predictive correlation with clinicopathological features in Non-small Cell Lung Cancer: A meta-analysis. *Oncotarget*, *8*(3), 4043–4050. https://doi.org/10.18632/oncotarget.14022
14. Miyadera, K., Kakuto, S., Sugai, M., Tsugitomi, R., Amino, Y., Uchibori, K., Yanagitani, N., Sugiura, H., Seike, M., Nishio, M., & Ariyasu, R. (2024). Serum CYFRA 21-1 as a Prognostic Marker in Non-Small-Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors. *Cancers*, *16*(21), 3712. https://doi.org/10.3390/cancers16213712
15. Takei, Y., Minato, K., Tsuchiya, S., Takise, A., Nakano, H., Ezawa, K., Fueki, N., Hoshino, H., Naruse, I., Nomoto, T., Makimoto, T., Ishihara, S., Saito, R., & Mori, M. (1997). CYFRA 21-1: an indicator of survival and therapeutic effect in lung cancer. *Oncology*, *54*(1), 43–47. https://doi.org/10.1159/000227660
16. Yoshimura, A., Uchino, J., Hasegawa, K., Tsuji, T., Shiotsu, S., Yuba, T., Takumi, C., Yamada, T., Takayama, K., & Hiraoka, N. (2019). Carcinoembryonic antigen and CYFRA 21-1 responses as prognostic factors in advanced non-small cell lung cancer. *Translational lung cancer research*, *8*(3), 227–234. https://doi.org/10.21037/tlcr.2019.06.08

17. Bi, H., Yin, L., Fang, W., Song, S., Wu, S., & Shen, J. (2023). Association of CEA, NSE, CYFRA 21-1, SCC-Ag, and ProGRP with Clinicopathological Characteristics and Chemotherapeutic Outcomes of Lung Cancer. *Laboratory medicine*, *54*(4), 372–379. https://doi.org/10.1093/labmed/lmac122
18. Niklinski, J., Burzykowski, T., Niklinska, W., Laudanski, J., Chyczewski, L., Rapellino, M., & Furman, M. (1998). Preoperative CYFRA 21-1 level as a prognostic indicator in resected nonsmall cell lung cancer. *The European respiratory journal*, *12*(6), 1424–1428. https://doi.org/10.1183/09031936.98.12061424
19. Cabrera-Alarcon, J. L., Carrillo-Vico, A., Santotoribio, J. D., Leon-Justel, A., Sanchez-Gil, R., Gonzalez-Castro, A., & Guerrero, J. M. (2011). CYFRA 21-1 as a tool for distant metastasis detection in lung cancer. *Clinical laboratory*, *57*(11-12), 1011–1014.
20. Nakao, M., Kinoshita, R., Kuriyama, M., Kiyotoshi, H., Sugihara, M., Takeda, N., Ohtakara, K., & Muramatsu, H. (2024). Serum CYFRA 21-1 Level as a Prognostic Marker for Extensive Disease Small Cell Lung Cancer. *Anticancer research*, *44*(2), 845–851. https://doi.org/10.21873/anticanres.16877
21. Kataoka, N., Katayama, Y., Yamada, T., Morimoto, K., Takeda, T., Okada, A., Shiotsu, S., Chihara, Y., Hiranuma, O., Yamada, T., Ota, T., Harada, T., Hasegawa, I., Nishioka, N., Iwasaku, M., Tokuda, S., & Takayama, K. (2024). CYFRA 21-1 predicts efficacy of combined chemoimmunotherapy in patients with advanced non-small cell lung cancer: a prospective observational study. *Translational lung cancer research*, *13*(8), 1929–1937. https://doi.org/10.21037/tlcr-24-190
22. Autsavapromporn, N., Duangya, A., Klunklin, P., Chitapanarux, I., Kranrod, C., Jaikang, C., Monum, T., & Tokonami, S. (2025). Combined Serum IL-6 and CYFRA 21-1 as Potential Biomarkers for Radon-Associated Lung Cancer Risk: A Pilot Study. *Biomedicines*, *13*(9), 2145. https://doi.org/10.3390/biomedicines13092145
23. Liu, L., Xie, W., Xue, P., Wei, Z., Liang, X., & Chen, N. (2019). Diagnostic accuracy and prognostic applications of CYFRA 21-1 in head and neck cancer: A systematic review and meta-analysis. *PloS one*, *14*(5), e0216561. https://doi.org/10.1371/journal.pone.0216561
24. Wang, Y. X., Hu, D., & Yan, X. (2013). Diagnostic accuracy of Cyfra 21-1 for head and neck squamous cell carcinoma: a meta-analysis. *European review for medical and pharmacological sciences*, *17*(17), 2383–2389.
25. Rudhart, S. A., Langen, P., Thangavelu, K., Gehrt, F., Stankovic, P., Wilhelm, T., Stuck, B. A., & Hoch, S. (2022). Clinical Impact of CYFRA 21-1 a Marker for Treatment Failure in Patients With Oropharyngeal Cancer Treated by Radio(chemo)therapy. *Anticancer research*, *42*(1), 137–146. https://doi.org/10.21873/anticanres.15467
26. Tokic, L., Hasukic, S., Brkic, F., Umihanic, S., Hukic, F., & Mustafic, S. (2025). The Diagnostic Significance of the Tumor Marker CYFRA 21-1 in Patients with Laryngeal Carcinoma. *Materia socio-medica*, *37*(2), 131–135. https://doi.org/10.5455/msm.2025.37.131-135
27. Rudhart, S. A., Schultz, J. D., Gehrt, F., Pavel, F. L., Birk, R., Hoch, M., Stuck, B. A., & Hoch, S. (2019). CYFRA 21-1: a suitable tumor marker in patients with head and neck cutaneous squamous cell carcinoma?. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *276*(12), 3467–3475. https://doi.org/10.1007/s00405-019-05614-2
28. Kalfert, D., Ludvik, J., Kucera, R., Topolcan, O., Celakovsky, P., Pesta, M., Kholova, I., Plzak, J., & Ludvikova, M. (2019). Pretreatment Serum Levels of Soluble Cytokeratin Fragments (Cyfra 21-1, TPS, MonoTotal) in Relation to Clinical and Pathobiological Aspects of Head and Neck Squamous Cell Carcinomas. *Anticancer research*, *39*(9), 5171–5177. https://doi.org/10.21873/anticanres.13713
29. Pradier, O., Hille, A., Schmiberger, H., & Hess, C. F. (2002). Monitoring of therapy in head and neck patients during the radiotherapy by measurement of Cyfra 21-1. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique*, *6*(1), 15–21. https://doi.org/10.1016/s1278-3218(01)00110-x
30. Kuropkat, C., Lippert, B. M., & Werner, J. A. (2002). Follow-up with serum Cyfra 21-1 in patients with squamous cell carcinomas of the head and neck. *Oncology*, *63*(3), 280–285. https://doi.org/10.1159/000065476
31. Barak, V., Meirovitz, A., Leibovici, V., Rachmut, J., Peretz, T., Eliashar, R., & Gross, M. (2015). The Diagnostic and Prognostic Value of Tumor Markers (CEA, SCC, CYFRA 21-1, TPS) in Head and Neck Cancer Patients. *Anticancer research*, *35*(10), 5519–5524.
32. Maass, J. D., Hoffmann-Fazel, A., Goeroegh, T., Hoffmann, M., Meyer, J. E., Gottschlich, S., Rudert, H., & Maune, S. (2000). Cyfra 21-1: a serological help for detection of distant metastases in head and neck cancer. *Anticancer research*, *20*(3B), 2241–2243.
33. Doweck, I., Barak, M., Uri, N., & Greenberg, E. (2000). The prognostic value of the tumour marker Cyfra 21-1 in carcinoma of head and neck and its role in early detection of recurrent disease. *British journal of cancer*, *83*(12), 1696–1701. https://doi.org/10.1054/bjoc.2000.1502
34. Shimada, H., Nabeya, Y., Okazumi, S., Matsubara, H., Miyazawa, Y., Shiratori, T., Hayashi, H., Gunji, Y., & Ochiai, T. (2003). Prognostic significance of CYFRA 21-1 in patients with esophageal squamous cell carcinoma. *Journal of the American College of Surgeons*, *196*(4), 573–578. https://doi.org/10.1016/s1072-7515(02)01905-1
35. Qiao, Y., Chen, C., Yue, J., & Yu, Z. (2019). Tumor marker index based on preoperative SCC and CYFRA 21-1 is a significant prognostic factor for patients with resectable esophageal squamous cell carcinoma. *Cancer biomarkers : section A of Disease markers*, *25*(3), 243–250. https://doi.org/10.3233/CBM-190058

36. Wakatsuki, M., Suzuki, Y., Nakamoto, S., Ohno, T., Ishikawa, H., Kiyohara, H., Kiyozuka, M., Shirai, K., Nakayama, Y., & Nakano, T. (2007). Clinical usefulness of CYFRA 21-1 for esophageal squamous cell carcinoma in radiation therapy. *Journal of gastroenterology and hepatology*, *22*(5), 715–719. https://doi.org/10.1111/j.1440-1746.2006.04498.x
37. Shishido, Y., Matsunaga, T., Sawata, S., Makinoya, M., Miyauchi, W., Miyatani, K., Uejima, C., Morimoto, M., Murakami, Y., Hanaki, T., Kihara, K., Yamamoto, M., Tokuyasu, N., Takano, S., Sakamoto, T., Saito, H., Hasegawa, T., & Fujiwara, Y. (2021). Platelet-to-Lymphocyte Ratio Multiplied by the Cytokeratin-19 Fragment Level as a Predictor of Pathological Response to Neoadjuvant Chemotherapy in Esophageal Squamous Cell Carcinoma. *Yonago acta medica*, *64*(3), 249–259. https://doi.org/10.33160/yam.2021.08.003
38. Yang, Y., Liu, Z., Jiang, C., Pan, J., Yu, B., Zhu, K., Xu, Y., & Li, Z. (2023). Prognostic Value of Combination of Lymphocyte-to-Monocyte-Ratio and CYFRA 21-1 in Esophageal Squamous Cell Carcinoma. *World journal of surgery*, *47*(12), 3240–3249. https://doi.org/10.1007/s00268-023-07190-3
39. Yi, Y., Li, B., Wang, Z., Sun, H., Gong, H., & Zhang, Z. (2009). CYFRA21-1 and CEA are useful markers for predicting the sensitivity to chemoradiotherapy of esophageal squamous cell carcinoma. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals*, *14*(7), 480–485. https://doi.org/10.3109/13547500903180265
40. Sunpaweravong, S., Puttawibul, P., Sunpaweravong, P., Nitiruangjaras, A., Boonyaphiphat, P., & Kemapanmanus, M. (2016). Correlation between Serum SCCA and CYFRA 2 1-1, Tissue Ki-67, and Clinicopathological Factors in Patients with Esophageal Squamous Cell Carcinoma. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*, *99*(3), 331–337.
41. Nakamura, T., Ide, H., Eguchi, R., Hayashi, K., Takasaki, K., & Watanabe, S. (2017). CYFRA 21-1 as a tumor marker for squamous cell carcinoma of the esophagus. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus*, *11*(1), 35–39. https://doi.org/10.1093/dote/11.1.35
42. Yin, N., & Liu, W. (2020). Clinical Value of Tumor Marker Index Based on Preoperative CYFRA 21-1 and SCC-Ag in the Evaluation of Prognosis and Treatment Effectiveness in Patients with Esophageal Squamous Cell Carcinoma. *OncoTargets and therapy*, *13*, 4135–4143. https://doi.org/10.2147/OTT.S243038
43. Lee J. H. (2013). Clinical Usefulness of Serum CYFRA 21-1 in Patients with Colorectal Cancer. *Nuclear medicine and molecular imaging*, *47*(3), 181–187. https://doi.org/10.1007/s13139-013-0218-4
44. Lim, D. H., Lee, J. H., & Kim, J. W. (2018). Feasibility of CYFRA 21-1 as a serum biomarker for the detection of colorectal adenoma and advanced colorectal adenoma in people over the age of 45. *Journal of clinical laboratory analysis*, *32*(1), e22163. https://doi.org/10.1002/jcla.22163
45. Holdenrieder, S., Stieber, P., Liska, V., Treska, V., Topolcan, O., Dreslerova, J., Matejka, V. M., Finek, J., & Holubec, L. (2012). Cytokeratin serum biomarkers in patients with colorectal cancer. *Anticancer research*, *32*(5), 1971–1976.
46. Li, S., Wei, W., Feng, Z., Bian, Y., Pan, J., Mai, J., Ning, S., Huang, J., Gao, X., & Zhang, L. (2023). Role of Serum CYFRA 21-1 in Diagnosis and Prognostic in Colorectal Liver Metastases. *Cancer management and research*, *15*, 601–614. https://doi.org/10.2147/CMAR.S410477
47. Hu, W. Q., Cong, H., Fang, R. H., Yuan, W. T., Mao, C. Y., Wang, J. R., Wang, Y., & Shi, X. Y. (2023). *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]*, *57*(10), 1613–1619. https://doi.org/10.3760/cma.j.cn112150-20230611-00457
48. Ye, F., Qian, Y., Liu, J., Li, J., Zhang, Y., Li, H., Bei, S., Zhang, X., & Feng, L. (2025). Potential utility of CYFRA 21-1 and neuron-specific enolase molecular structures for the recognition and surveillance of sessile serrated lesions and traditional serrated adenomas. *International journal of biological macromolecules*, *310*(Pt 3), 143476. https://doi.org/10.1016/j.ijbiomac.2025.143476
49. Liscia, D. S., Detoma, P., Zanchetta, M., Anrò, P., Molinar, D., Favettini, E., & Paduos, A. (2017). The Use of CYFRA 21-1 for the Detection of Breast Cancer Axillary Lymph Node Metastases in Needle Washouts of Fine-Needle Aspiration Biopsies. *Applied immunohistochemistry & molecular morphology : AIMM*, *25*(3), 190–195. https://doi.org/10.1097/PAI.0000000000000287
50. Choi, J. S., Han, K. H., Kim, E. K., Moon, H. J., Yoon, J. H., & Kim, M. J. (2015). Fine-needle aspirate CYFRA 21-1, an innovative new marker for diagnosis of axillary lymph node metastasis in breast cancer patients. *Medicine*, *94*(19), e811. https://doi.org/10.1097/MD.0000000000000811
51. Giovanella, L., Ceriani, L., Giardina, G., Bardelli, D., Tanzi, F., & Garancini, S. (2002). Serum cytokeratin fragment 21.1 (CYFRA 21.1) as tumour marker for breast cancer: comparison with carbohydrate antigen 15.3 (CA 15.3) and carcinoembryonic antigen (CEA). *Clinical chemistry and laboratory medicine*, *40*(3), 298–303. https://doi.org/10.1515/CCLM.2002.047
52. Nakata, B., Takashima, T., Ogawa, Y., Ishikawa, T., & Hirakawa, K. (2004). Serum CYFRA 21-1 (cytokeratin-19 fragments) is a useful tumour marker for detecting disease relapse and assessing treatment efficacy in breast cancer. *British journal of cancer*, *91*(5), 873–878. https://doi.org/10.1038/sj.bjc.6602074
53. Pierga, J. Y., Deneux, L., Bonneton, C., Vincent-Salomon, A., Nos, C., Anract, P., Magdelénat, H., Pouillart, P., & Thiery, J. P. (2004). Prognostic value of cytokeratin 19 fragment (CYFRA 21-1) and cytokeratin-positive cells in bone marrow samples of breast cancer patients. *The International journal of biological markers*, *19*(1), 23–31. https://doi.org/10.5301/jbm.2008.649

54. Di Gioia, D., Blankenburg, I., Nagel, D., Heinemann, V., & Stieber, P. (2016). Tumor markers in the early detection of tumor recurrence in breast cancer patients: CA 125, CYFRA 21-1, HER2 shed antigen, LDH and CRP in combination with CEA and CA 15-3. *Clinica chimica acta; international journal of clinical chemistry*, *461*, 1–7. https://doi.org/10.1016/j.cca.2016.07.014
55. Treska, V., Topolcan, O., Zoubkova, V., Treskova, I., Narsanska, A., & Kucera, R. (2018). Perioperative Tumour Marker Levels as Prognostic Factors for Surgical Treatment of Breast Cancer Liver Metastases. *Anticancer research*, *38*(6), 3647–3652. https://doi.org/10.21873/anticanres.12640
56. Hyun, J. W., Shin, H. S., Kim, S. H., Kong, S. Y., Yoo, H., Gwak, H. S., & Kim, H. J. (2020). CYFRA 21-1 levels in cerebrospinal fluid as a putative therapeutic monitoring biomarker for patients with leptomeningeal carcinomatosis: A pilot study. *Cancer biomarkers : section A of Disease markers*, *28*(1), 81–89. https://doi.org/10.3233/CBM-190187
57. Wang, H., & Yang, X. (2017). Association between serum cytokines and progression of breast cancer in Chinese population. *Medicine*, *96*(49), e8840. https://doi.org/10.1097/MD.0000000000008840
58. Won, S. Y., Kim, E. K., Moon, H. J., Yoon, J. H., Park, V. Y., & Kim, M. J. (2020). Diagnostic Value of CYFRA 21-1 Measurement in Fine-Needle Aspiration Washouts for Detection of Axillary Recurrence in Postoperative Breast Cancer Patients]. *Taehan Yongsang Uihakhoe chi*, *81*(1), 147–156. https://doi.org/10.3348/jksr.2020.81.1.147
59. Mai, S., Liu, H., Zeng, H., Cheng, Z., Huang, J., Shi, G., Li, Y., & Wu, Z. (2024). Diagnostic challenge and survival analysis of pulmonary oligometastases and primary lung cancer in breast cancer patients. *Thoracic cancer*, *15*(12), 1017–1028. https://doi.org/10.1111/1759-7714.15285
60. Giovanella, L., Treglia, G., Verburg, F. A., Salvatori, M., & Ceriani, L. (2012). Serum cytokeratin 19 fragments: a dedifferentiation marker in advanced thyroid cancer. *European journal of endocrinology*, *167*(6), 793–797. https://doi.org/10.1530/EJE-12-0660
61. Giovanella, L., Ceriani, L., Ghelfo, A., & Maffioli, M. (2008). Circulating cytokeratin 19 fragments in patients with benign nodules and carcinomas of the thyroid gland. *The International journal of biological markers*, *23*(1), 54–57. https://doi.org/10.1177/172460080802300109
62. Jeong, C., Lee, J., Yoon, H., Ha, J., Kim, M. H., Bae, J. S., Jung, C. K., Kim, J. S., Kang, M. I., & Lim, D. J. (2021). Serum CYFRA 21.1 Level Predicts Disease Course in Thyroid Cancer with Distant Metastasis. *Cancers*, *13*(4), 811. https://doi.org/10.3390/cancers13040811
63. Lee, J., Shin, Y., Kwak, J., Park, H. L., Lee, S., Kim, M. K., Bae, J. S., Jung, C. K., Jung, S. L., Lee, J. M., Chang, S. A., & Lim, D. J. (2025). Validation of Diagnostic Utility of Washout CYFRA 21-1 in Lymph Node Metastasis of Thyroid Cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *31*(10), 1922–1930. https://doi.org/10.1158/1078-0432.CCR-24-3562
64. Giovanella, L., Imperiali, M., & Trimboli, P. (2017). Role of serum cytokeratin 19 fragment (Cyfra 21.1) as a prognostic biomarker in patients with differentiated thyroid cancer. *Scientific reports*, *7*(1), 7359. https://doi.org/10.1038/s41598-017-07915-0
65. Malapure, S. S., Patel, C. D., Lakshmy, R., & Bal, C. (2020). Evaluation of CYFRA 21.1 as a Dedifferentiation Marker of Advanced Thyroid Cancer. *Indian journal of nuclear medicine : IJNM : the official journal of the Society of Nuclear Medicine, India*, *35*(2), 116–121. https://doi.org/10.4103/ijnm.IJNM_148_19
66. Matuszczak, M., & Salagierski, M. (2020). Diagnostic and Prognostic Potential of Biomarkers CYFRA 21.1, ERCC1, p53, FGFR3 and TATI in Bladder Cancers. *International journal of molecular sciences*, *21*(9), 3360. https://doi.org/10.3390/ijms21093360
67. Satyam, A., Singh, P., Sharma, M., Seth, A., & Sharma, A. (2011). CYFRA 21-1: a potential molecular marker for noninvasive differential diagnosis of urothelial carcinoma of bladder. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals*, *16*(5), 413–421. https://doi.org/10.3109/1354750X.2011.582152
68. Andreadis, C., Touloupidis, S., Galaktidou, G., Kortsaris, A. H., Boutis, A., & Mouratidou, D. (2005). Serum CYFRA 21-1 in patients with invasive bladder cancer and its relevance as a tumor marker during chemotherapy. *The Journal of urology*, *174*(5), 1771–1776. https://doi.org/10.1097/01.ju.0000176742.53556.25
69. Nisman, B., Barak, V., Shapiro, A., Golijanin, D., Peretz, T., & Pode, D. (2002). Evaluation of urine CYFRA 21-1 for the detection of primary and recurrent bladder carcinoma. *Cancer*, *94*(11), 2914–2922. https://doi.org/10.1002/cncr.10565
70. Fernandez-Gomez, J., Rodríguez-Martínez, J. J., Barmadah, S. E., García Rodríguez, J., Allende, D. M., Jalon, A., Gonzalez, R., & Alvarez-Múgica, M. (2007). Urinary CYFRA 21.1 is not a useful marker for the detection of recurrences in the follow-up of superficial bladder cancer. *European urology*, *51*(5), 1267–1274. https://doi.org/10.1016/j.eururo.2006.12.019