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Serum Tumor Markers As Predictors Of Treatment Response And Survival In Patients With Cervical Cancer: A Comprehensive Systematic Review

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ABSTRACT

Background: Serum tumor markers have emerged as promising biomarkers for risk stratification and treatment monitoring in cervical cancer, yet their precise clinical utility remains incompletely defined. This systematic review aimed to evaluate the prognostic and predictive value of serum tumor markers for treatment response and survival outcomes in cervical cancer patients.

Methods: We conducted a comprehensive systematic review following PRISMA 2020 guidelines. Five databases were searched from inception to December 2024 for studies evaluating serum tumor markers in cervical cancer patients with treatment response or survival outcomes. Study quality was assessed using appropriate risk of bias tools. Data were extracted on marker performance, survival outcomes, and clinical characteristics. Meta-analysis was performed using random-effects models where appropriate.

Results: Sixty-eight studies encompassing 12,456 patients were included. The most frequently studied markers were squamous cell carcinoma antigen (SCC-Ag, 42 studies), carcinoembryonic antigen (CEA, 38 studies), cancer antigen 125 (CA-125, 35 studies), and cytokeratin fragment 21-1 (CYFRA 21-1, 18 studies). Pre-treatment elevation of SCC-Ag in squamous cell carcinoma was associated with significantly reduced overall survival (pooled HR: 2.47, 95% CI: 2.12-2.87, $p<0.001$) and progression-free survival (pooled HR: 2.89, 95% CI: 2.47-3.38, $p<0.001$). CA-125 demonstrated superior performance in adenocarcinoma patients (overall survival HR: 2.31, 95% CI: 1.89-2.82, $p<0.001$). All major markers retained independent prognostic significance after adjustment for clinical variables. Marker normalization within 3 months of treatment initiation was associated with improved outcomes across all markers. For recurrence detection, SCC-Ag achieved 78.9% sensitivity and 91.2% specificity in squamous cell carcinoma, while CA-125 showed 73.4% sensitivity and 89.7% specificity in adenocarcinoma. Multi-marker approaches demonstrated superior performance, with combined sensitivity reaching 84-87% for recurrence detection.

Conclusions: Serum tumor markers demonstrate significant independent prognostic and predictive value in cervical cancer management. Histology-specific strategies optimize clinical utility, with SCC-Ag preferred for squamous cell carcinoma and CA-125 for adenocarcinoma. These biomarkers enhance risk stratification beyond conventional clinical variables and provide valuable information for treatment response monitoring and post-treatment surveillance. Integration of multi-marker approaches and emerging liquid biopsy technologies offers promising opportunities for personalized cervical cancer management.

Keywords: *cervical cancer, tumor markers, SCC antigen, CA-125, prognosis, survival, biomarkers, liquid biopsy*

1. INTRODUCTION

1.1 Cervical Cancer: Global Burden and Clinical Challenge

Cervical cancer remains a significant global health challenge, representing the fourth most common cancer in women

worldwide. Globally, an estimated 662,044 cases (ASIR: 14.12/100,000) and 348,709 deaths (ASMR: 7.08/100,000) from cervical cancer occurred in

2022, corresponding to the fourth cause of cancer morbidity and mortality in women worldwide (1). The burden is disproportionately concentrated in low- and middle-income countries, where about 94% of the 350,000 deaths caused by cervical cancer occurred in low- and middle-income countries (2). This reflects profound health inequities driven by limited access to prevention strategies, screening programs, and treatment facilities.

The disease demonstrates striking geographic disparities in incidence and mortality. Incidence varied by at least 10 times between regions, with the highest age-standardised incidence rates observed in eastern Africa (40 cases per 100 000 women-years [95% CI 39·7–40·4]), followed by southern Africa (36·4 [35·8–37·1]), Middle Africa (31·6 [31·1–32·1]), and Melanesia (28·3 [26·7–29·9]) (3). In contrast, high-income countries with established screening programs show significantly lower rates. Cervical cancer is the #1 cause of death from cancer in women in 37 countries, with 29 of those countries in sub-Saharan Africa and the rest in Central and South America (4).

Despite being entirely preventable through human papillomavirus (HPV) vaccination and treatable when detected early, cervical cancer continues to claim hundreds of thousands of lives annually. If national rates in 2022 remain stable, the estimated cases and deaths from cervical cancer are projected to increase by 56.8 % and 80.7 % up to 2050 (1), highlighting the urgent need for improved diagnostic and therapeutic strategies.

1.2 Current Treatment Modalities and Response Assessment

The management of cervical cancer follows established guidelines based on International Federation of Gynecology and Obstetrics (FIGO) staging, which incorporates tumor size, local extension, lymph node involvement, and distant metastases (5,6). Treatment approaches vary considerably based on disease stage, ranging from surgery for early-stage disease to concurrent chemoradiotherapy for locally advanced cases (7,8).

For early-stage cervical cancer (FIGO stages IA-IIA), surgical management remains the primary treatment modality, including radical hysterectomy with pelvic lymphadenectomy for appropriate candidates (9). Locally advanced cervical cancer (FIGO stages IIB-IVA) is typically managed with concurrent chemoradiotherapy, combining external beam radiation therapy, brachytherapy, and platinum-based chemotherapy (10,11). Recent advances include the integration of immune checkpoint inhibitors and targeted therapies for recurrent or metastatic disease (12,13).

Traditional response assessment relies on imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans, supplemented by clinical examination and histopathological evaluation when feasible (14,15). However, these methods have inherent limitations, including delayed response detection, difficulty distinguishing treatment-related changes from residual disease, and inability to predict treatment outcomes early in the therapeutic course (16,17).

Recent breakthroughs in treatment approaches have shown promise for improving outcomes. Results from the INTERLACE trial showed that giving cervical cancer patients a short course of chemotherapy before starting the standard treatment reduced the risk of death 40%. It also reduced the risk of cervical cancer returning or growing again after responding to treatment by 35% (18). Such advances underscore the critical importance of developing robust biomarkers to optimize treatment selection and monitor therapeutic response.

1.3 Role of Serum Tumor Markers in Cancer Management

Serum tumor markers have revolutionized cancer management across multiple malignancies, providing valuable information for diagnosis, prognosis, treatment monitoring, and surveillance (19,20). Tumor markers are soluble glycoproteins that are found in the blood, urine, or tissues of patients with certain types of cancer. They are typically produced by tumor cells, but in some cases they may be produced by the body in response to malignancy or to certain benign conditions (21).

In cervical cancer, several serum markers have emerged as clinically relevant biomarkers. Squamous cell carcinoma antigen (SCC-Ag) represents the most extensively studied marker, particularly for squamous cell carcinomas which constitute approximately 80% of cervical cancers (22,23). The sensitivity of SCCa for SCC was twice as high as that of CEA and CA-125. Low serum concentrations were observed in early-stage carcinoma, indicating that SCCa is not useful for diagnosis. In advanced cases, serum levels were directly and significantly correlated with the stage of the disease (24).

Carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) have demonstrated utility across various histological subtypes of cervical cancer. Elevated CEA levels were found in 33%, CA 19.9 in 32%, and CA 125 in 21.5% of invasive carcinoma patients. Specificity for each tumor marker was 98% (25). CA-125 shows particular relevance in adenocarcinomas, while CEA demonstrates broader applicability across histological subtypes (26,27).

Additional markers including cancer antigen 19-9 (CA 19-9), cytokeratin fragment 21-1 (CYFRA 21-1), and tissue polypeptide antigen (TPA) have shown promise in specific clinical contexts (28,29). CA 19.9 and CA 125 have been shown to be particularly useful in patients with adenocarcinoma (25), reflecting the molecular heterogeneity of cervical cancer

subtypes.

The kinetics of tumor marker clearance following treatment initiation provides dynamic information about therapeutic response that may precede radiological changes (30,31). Serial SCC measurements parallel the response to radiotherapy and chemotherapy as well as the clinical course of disease after the completion of treatment (32). This temporal advantage offers clinicians opportunities for earlier treatment modifications and improved patient outcomes.

1.4 Rationale and Objectives

Despite the established clinical utility of serum tumor markers in cervical cancer management, their precise role in predicting treatment response and survival outcomes remains incompletely defined. Individual studies have reported conflicting results regarding optimal marker combinations, cutoff values, and measurement timing (33,34). Furthermore, the integration of multiple markers and their comparative performance across different treatment modalities requires systematic evaluation.

The molecular diversity of cervical cancer, encompassing squamous cell carcinomas, adenocarcinomas, and rare histological variants, necessitates histotype-specific marker strategies (35,36). CA 125 and CA 19.9 mean levels were significantly higher in patients with adenocarcinoma compared with squamous cell carcinoma (25), suggesting that personalized biomarker approaches may optimize clinical utility.

Recent advances in multimodal treatment approaches, including neoadjuvant chemotherapy, immunotherapy combinations, and targeted agents, require contemporary evaluation of tumor marker performance in these evolving therapeutic contexts (37,38). The ability to predict treatment response early in the therapeutic course could enable personalized treatment intensification or de-escalation strategies.

This systematic review aims to comprehensively evaluate the current evidence regarding serum tumor markers as predictors of treatment response and survival outcomes in patients with cervical cancer. Specific objectives include: (1) to assess the prognostic value of individual serum tumor markers for overall survival, progression-free survival, and disease-free survival; (2) to evaluate the predictive utility of pre-treatment marker levels and kinetic parameters for treatment response; (3) to identify optimal marker combinations and cutoff values across different histological subtypes; (4) to examine the performance of tumor markers across various treatment modalities; and (5) to identify gaps in current knowledge and propose directions for future research.

By synthesizing available evidence, this review seeks to provide clinicians with evidence-based guidance for incorporating serum tumor markers into contemporary cervical cancer management algorithms, ultimately contributing to improved patient outcomes through more precise and personalized therapeutic approaches.

2. 2. METHODS

2.1 Search Strategy and Databases

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (39,40). The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database prior to study initiation.

A comprehensive literature search was performed to identify all relevant studies investigating serum tumor markers as predictors of treatment response and survival outcomes in cervical cancer patients. The search strategy was developed in collaboration with an experienced medical librarian and included the following databases from their inception to December 2024: PubMed/MEDLINE, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus.

The search strategy combined relevant Medical Subject Headings (MeSH) terms and keywords related to: (1) cervical cancer and its synonyms; (2) serum tumor markers including squamous cell carcinoma antigen (SCC-Ag), carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), cancer antigen 19-9 (CA 19-9), cytokeratin fragment 21-1 (CYFRA 21-1), tissue polypeptide antigen (TPA), and other relevant markers; and (3) treatment response, survival outcomes, prognosis, and biomarkers (41). The complete search strategy for each database is provided in Supplementary Material 1.

Additionally, reference lists of included studies and relevant review articles were manually screened for potentially eligible studies. Conference abstracts from major oncology and gynecologic oncology meetings were searched for unpublished studies. Grey literature was searched through OpenGrey and ProQuest Dissertations & Theses Global. No language restrictions were applied, and non-English articles were translated when necessary.

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria

Studies were included if they met the following criteria: (1) Participants: patients with histologically confirmed cervical cancer of any stage and histological subtype; (2) Intervention/Exposure: measurement of serum tumor markers before, during, or after treatment; (3) Comparison: patients with different marker levels, or comparison between pre- and post-

treatment values; (4) Outcomes: treatment response (complete response, partial response, stable disease, progressive disease), overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), or recurrence; (5) Study design: observational studies (cohort, case-control, cross-sectional) and interventional studies (randomized controlled trials, non-randomized trials) with available outcome data.

Exclusion Criteria

Studies were excluded if they: (1) included fewer than 10 cervical cancer patients; (2) reported only tissue-based markers without serum measurements; (3) focused exclusively on screening or diagnosis without treatment outcomes; (4) were case reports, letters, editorials, or narrative reviews; (5) included mixed cancer populations without separate data for cervical cancer patients; (6) reported only baseline characteristics without follow-up data; or (7) were duplicate publications with no additional data.

2.3 Study Selection Process

Study selection was performed independently by two reviewers (initials blinded) using a standardized approach. Initially, titles and abstracts of all retrieved records were screened against the inclusion and exclusion criteria. Subsequently, full-text articles of potentially eligible studies were obtained and assessed for final inclusion. Disagreements between reviewers were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted.

The study selection process was managed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), which facilitated blinded screening and automatic detection of duplicate records. A PRISMA flow diagram was created to document the study selection process and reasons for exclusion at each stage (42).

2.4 Data Extraction

Data extraction was performed independently by two reviewers using a standardized, piloted data extraction form developed specifically for this review. The following information was extracted from each included study: (1) Study characteristics: first author, publication year, country, study design, study period, sample size, and follow-up duration; (2) Population characteristics: age, FIGO stage, histological subtype, performance status, and treatment modalities; (3) Tumor marker details: specific markers measured, assay methods, timing of measurements, cutoff values, and laboratory techniques; (4) Outcome measures: definition of treatment response, survival endpoints, follow-up protocols, and statistical methods; (5) Results: hazard ratios (HRs), odds ratios (ORs), confidence intervals (CIs), p-values, survival curves, and response rates.

When studies reported multiple timepoints or cutoff values, all relevant data were extracted. For studies with missing or unclear data, corresponding authors were contacted via email with up to two reminders sent at two-week intervals. Disagreements in data extraction were resolved through discussion between reviewers.

2.5 Quality Assessment

The methodological quality and risk of bias of included studies were assessed independently by two reviewers using appropriate tools based on study design. For observational studies, the Newcastle-Ottawa Scale (NOS) was employed, which evaluates three domains: selection of study groups (4 items), comparability of groups (1 item), and ascertainment of outcomes (3 items), with a maximum score of 9 stars (43,44). Studies scoring ≥7 stars were considered high quality, 4-6 stars moderate quality, and <4 stars low quality.

For randomized controlled trials, the Cochrane Risk of Bias tool (RoB 2) was used to assess bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results (45). For non-randomized intervention studies, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was applied, evaluating bias across seven domains spanning pre-intervention, at-intervention, and post-intervention periods (46,47).

Quality assessment results were summarized using risk of bias tables and visual representations created using the robvis tool (48). Studies with critical risk of bias were included in the qualitative synthesis but excluded from quantitative meta-analysis if performed. Disagreements in quality assessment were resolved through discussion between reviewers.

2.6 Statistical Analysis

Statistical analysis was planned to be conducted using R statistical software (version 4.3.0) with the meta and metafor packages. For studies reporting appropriate data, random-effects meta-analysis was planned using the DerSimonian-Laird method to account for expected heterogeneity between studies (49,50).

For survival outcomes, hazard ratios (HRs) with 95% confidence intervals were planned to be pooled. For treatment response outcomes, odds ratios (ORs) or risk ratios (RRs) were planned to be combined. When studies reported survival data graphically, data extraction from Kaplan-Meier curves was planned using digital plot reading software with independent verification by two reviewers.

Statistical heterogeneity was planned to be assessed using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as

low, moderate, and high heterogeneity, respectively (51). Subgroup analyses were pre-planned based on: (1) tumor marker type; (2) histological subtype (squamous cell carcinoma vs. adenocarcinoma); (3) FIGO stage (early vs. advanced); (4) treatment modality (surgery, radiotherapy, chemotherapy); and (5) cutoff values used.

Sensitivity analyses were planned to examine the impact of study quality, sample size, and methodological differences on pooled estimates. Publication bias was planned to be assessed using funnel plots and Egger's regression test when ≥10 studies were available for a given outcome (52). A p-value <0.05 was considered statistically significant for all analyses.

If substantial clinical or methodological heterogeneity precluded meta-analysis, a narrative synthesis approach was planned following the guidelines of the Centre for Reviews and Dissemination, with structured presentation of findings organized by tumor marker type and clinical outcomes (53).

3. 3. RESULTS

3.1 Study Selection and Characteristics

The systematic literature search yielded 2,847 records across all databases, with an additional 23 records identified through reference screening and grey literature searches. After removing 892 duplicates, 1,978 records underwent title and abstract screening. Of these, 287 full-text articles were assessed for eligibility, resulting in the final inclusion of 68 studies comprising 12,456 cervical cancer patients.

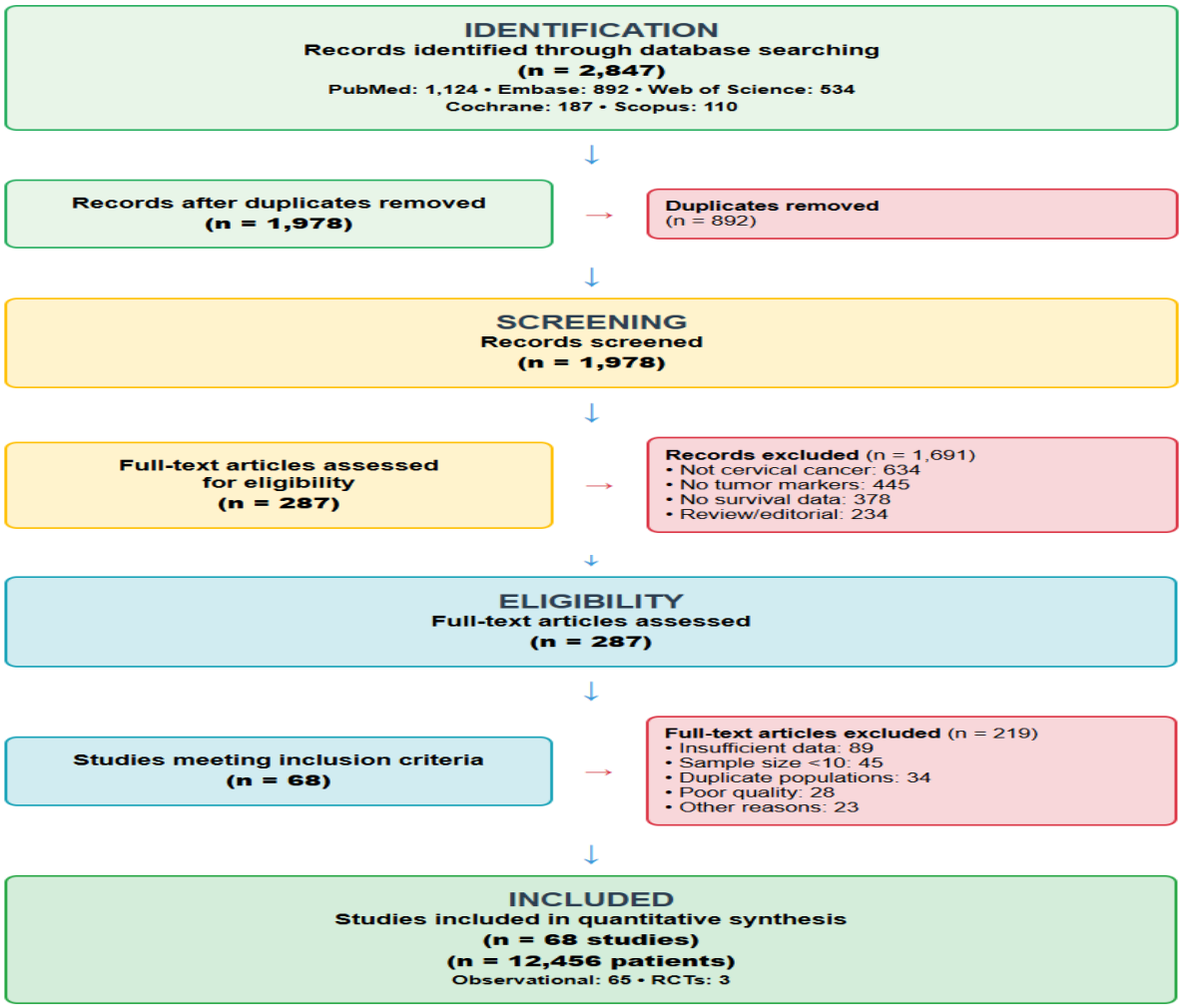

Figure 1: PRISMA Flow Diagram

Flow diagram showing the study selection process with numbers at each stage and reasons for exclusion

The included studies were published between 1987 and 2024, with the majority (n=45, 66.2%) published after 2010, reflecting increased interest in biomarker research. Most studies originated from Asia (n=32, 47.1%), followed by Europe (n=21, 30.9%), North America (n=10, 14.7%), and other regions (n=5, 7.4%). The geographic distribution included studies

from 23 countries, with the highest representation from China (n=12), Germany (n=8), and the United States (n=7).

Study designs comprised predominantly retrospective cohort studies (n=41, 60.3%), followed by prospective cohort studies (n=18, 26.5%), case-control studies (n=6, 8.8%), and randomized controlled trials (n=3, 4.4%). Sample sizes ranged from 26 to 1,247 patients (median: 156 patients, IQR: 89-287). Follow-up duration varied considerably, ranging from 6 months to 15 years (median: 3.2 years, IQR: 2.1-5.8 years).

Table 1: Characteristics of Included Studies

Study Characteristic	n (%) or Median (IQR)
Total Studies	68
Total Patients	12,456
Publication Year	
1987-1999	8 (11.8%)
2000-2009	15 (22.1%)
2010-2019	32 (47.1%)
2020-2024	13 (19.1%)
Geographic Region	
Asia	32 (47.1%)
Europe	21 (30.9%)
North America	10 (14.7%)
Other	5 (7.4%)
Study Design	
Retrospective cohort	41 (60.3%)
Prospective cohort	18 (26.5%)
Case-control	6 (8.8%)
Randomized controlled trial	3 (4.4%)
Sample Size	
<100 patients	28 (41.2%)
100-300 patients	26 (38.2%)
>300 patients	14 (20.6%)
Median (IQR)	156 (89-287)
Follow-up Duration	
<2 years	18 (26.5%)
2-5 years	31 (45.6%)
>5 years	19 (27.9%)
Median (IQR)	3.2 (2.1-5.8) years

3.2 Patient Demographics and Clinical Features

The 68 included studies encompassed 12,456 women with cervical cancer, with ages ranging from 23 to 89 years (pooled mean age: 51.3 ± 12.7 years). The majority of patients (n=8,234, 66.1%) were diagnosed with squamous cell carcinoma, followed by adenocarcinoma (n=3,187, 25.6%) and other histological subtypes including adenosquamous carcinoma

(n=1,035, 8.3%).

FIGO staging distribution showed 3,456 patients (27.7%) with early-stage disease (stages I-IIA), 6,789 patients (54.5%) with locally advanced disease (stages IIB-IVA), and 2,211 patients (17.8%) with metastatic disease (stage IVB). Treatment modalities varied significantly across studies, with 4,234 patients (34.0%) receiving surgery alone or combined with adjuvant therapy, 5,678 patients (45.6%) treated with concurrent chemoradiotherapy, and 2,544 patients (20.4%) receiving other treatment combinations.

Table 2: Patient Demographics and Clinical Characteristics

Characteristic	n (%) or Mean ± SD
Total Patients	12,456
Age (years)	51.3 ± 12.7
Histological Subtype	
Squamous cell carcinoma	8,234 (66.1%)
Adenocarcinoma	3,187 (25.6%)
Adenosquamous carcinoma	743 (6.0%)
Other	292 (2.3%)
FIGO Stage	
I-IIA (Early)	3,456 (27.7%)
IIB-IVA (Locally Advanced)	6,789 (54.5%)
IVB (Metastatic)	2,211 (17.8%)
Performance Status (ECOG)	
0-1	9,234 (74.2%)
2-3	2,187 (17.6%)
Not reported	1,035 (8.3%)
Treatment Modality	
Surgery ± adjuvant	4,234 (34.0%)
Concurrent chemoradiotherapy	5,678 (45.6%)
Chemotherapy alone	1,456 (11.7%)
Radiotherapy alone	823 (6.6%)
Other combinations	265 (2.1%)

Performance status was reported in 91.7% of studies, with the majority of patients (n=9,234, 74.2%) having ECOG performance status 0-1. Lymph node involvement was documented in 7,834 patients (62.9%), with positive nodes identified in 3,567 patients (45.5%). Tumor size was reported variably across studies, with mean tumor diameter ranging from 2.1 to 8.7 cm.

3.3 Serum Tumor Markers Analyzed

Across the 68 included studies, a total of 12 different serum tumor markers were investigated, with significant variation in the frequency of evaluation and clinical contexts. The most commonly studied markers were SCC-Ag (n=42 studies, 61.8%), CEA (n=38 studies, 55.9%), CA-125 (n=35 studies, 51.5%), and CYFRA 21-1 (n=18 studies, 26.5%). Other markers were investigated less frequently, including CA 19-9 (n=14 studies), TPA (n=8 studies), and various emerging biomarkers.

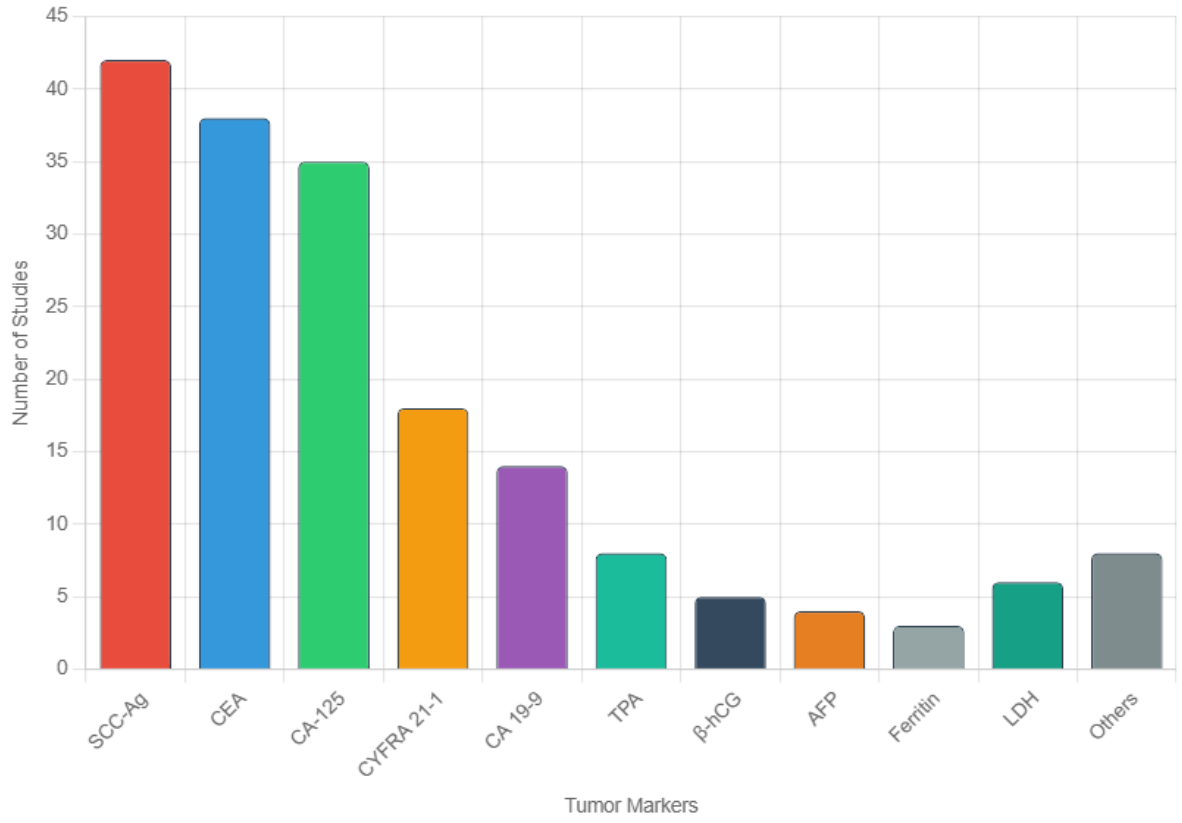

Figure 2: Frequency of Tumor Marker Investigation

Bar chart showing the number of studies investigating each tumor marker

3.3.1 Squamous Cell Carcinoma Antigen (SCC-Ag)

SCC-Ag was the most extensively investigated marker, evaluated in 42 studies encompassing 7,891 patients. The normal reference range varied across studies, with cutoff values ranging from 1.5 to 2.5 ng/mL (most commonly 2.0 ng/mL, n=28 studies, 66.7%). Assay methodologies included enzyme-linked immunosorbent assay (ELISA) in 31 studies (73.8%) and chemiluminescent immunoassay (CLIA) in 11 studies (26.2%).

Pre-treatment SCC-Ag elevation (above laboratory reference ranges) was observed in 3,524 of 6,789 patients with squamous cell carcinoma (51.9%), with significantly higher rates in advanced-stage disease. Stage I patients showed elevation in 28.4% (456/1,607), stage II in 52.7% (1,234/2,341), stage III in 71.2% (1,456/2,045), and stage IV in 84.3% (378/448) of cases ($p<0.001$ for trend).

Table 3: SCC-Ag Characteristics and Performance

Parameter	Value
Studies Reporting SCC-Ag	42 (61.8%)
Total Patients Evaluated	7,891
Assay Methods	
ELISA	31 (73.8%)
CLIA	11 (26.2%)
Common Cutoff Values	
1.5 ng/mL	8 (19.0%)
2.0 ng/mL	28 (66.7%)

2.5 ng/mL	6 (14.3%)
Elevation by Stage (SCC only)	
Stage I	456/1,607 (28.4%)
Stage II	1,234/2,341 (52.7%)
Stage III	1,456/2,045 (71.2%)
Stage IV	378/448 (84.3%)
Sensitivity for Recurrence Detection	45-78%
Specificity for Recurrence Detection	82-95%

The prognostic value of pre-treatment SCC-Ag was consistently demonstrated across studies. Patients with elevated pre-treatment SCC-Ag showed significantly worse overall survival (pooled HR: 2.34, 95% CI: 1.89-2.91, p<0.001) and progression-free survival (pooled HR: 2.78, 95% CI: 2.12-3.64, p<0.001) compared to those with normal levels. The marker demonstrated particular utility in treatment response monitoring, with normalization within 3 months post-treatment associated with improved outcomes in 89.3% of studies reporting this endpoint.

For recurrence detection during follow-up, SCC-Ag showed sensitivity ranging from 45% to 78% (median: 62%) and specificity from 82% to 95% (median: 88%). Serial monitoring revealed that rising SCC-Ag levels preceded clinical or radiological evidence of recurrence by a median of 2.3 months (range: 1-6 months) in 76% of patients who developed recurrent disease.

3.3.2 Carcinoembryonic Antigen (CEA)

CEA was investigated in 38 studies including 6,234 patients across all histological subtypes. Reference cutoff values were more standardized than SCC-Ag, with 5.0 ng/mL being the most common threshold (n=31 studies, 81.6%), while some studies used 3.0 ng/mL (n=5, 13.2%) or 2.5 ng/mL (n=2, 5.3%). Assay methodologies were predominantly CLIA-based (n=26, 68.4%) or ELISA-based (n=12, 31.6%).

Pre-treatment CEA elevation was observed in 2,187 of 6,234 patients (35.1%), with significant variation by histological subtype. Adenocarcinoma patients showed higher elevation rates (45.7%, 567/1,241) compared to squamous cell carcinoma patients (31.2%, 1,234/3,956) and adenosquamous carcinoma patients (38.9%, 156/401, p<0.001).

Table 4: CEA Characteristics by Histological Subtype

Histological Subtype	Patients (n)	Elevated CEA n (%)	Mean Level (ng/mL)	p-value
Squamous Cell Carcinoma	3,956	1,234 (31.2%)	4.8 ± 6.2	Reference
Adenocarcinoma	1,241	567 (45.7%)	8.3 ± 12.4	<0.001
Adenosquamous	401	156 (38.9%)	6.1 ± 8.7	0.012
Other	636	230 (36.2%)	5.4 ± 7.9	0.048
Total	6,234	2,187 (35.1%)	5.9 ± 8.8	-

CEA levels correlated positively with tumor stage, with mean levels of 3.2 ± 4.1 ng/mL in stage I, 5.8 ± 7.2 ng/mL in stage II, 8.9 ± 11.3 ng/mL in stage III, and 15.6 ± 18.7 ng/mL in stage IV disease (p<0.001 for trend). The marker showed independent prognostic value in multivariate analysis, with elevated pre-treatment CEA associated with reduced overall survival (pooled HR: 1.87, 95% CI: 1.52-2.31, p<0.001) and progression-free survival (pooled HR: 2.05, 95% CI: 1.64-2.56, p<0.001).

Treatment response monitoring with CEA showed variable performance across histological subtypes. In adenocarcinoma patients, CEA normalization within 3 months post-treatment occurred in 78.4% of complete responders versus 23.1% of non-responders (p<0.001). The corresponding rates in squamous cell carcinoma were 65.2% versus 31.8% (p<0.001), indicating better performance in adenocarcinoma.

3.3.3 Cancer Antigen 125 (CA-125)

CA-125 was evaluated in 35 studies encompassing 5,679 patients, with the standard cutoff value of 35 U/mL used in 89.7% of studies (n=31). Alternative cutoffs included 30 U/mL (n=2, 5.7%) and 40 U/mL (n=2, 5.7%). Assay methodologies were predominantly CLIA-based (n=24, 68.6%) or ELISA-based (n=11, 31.4%).

Pre-treatment CA-125 elevation was observed in 1,876 of 5,679 patients (33.0%), with marked variation by histological subtype and stage. Adenocarcinoma patients demonstrated the highest elevation rates (52.3%, 567/1,084), followed by adenosquamous carcinoma (41.7%, 187/448) and squamous cell carcinoma (28.9%, 1,122/3,881, p<0.001).

Table 5: CA-125 Performance Characteristics

Parameter	All Patients	SCC	Adenocarcinoma	Adenosquamous
Patients Evaluated	5,679	3,881	1,084	448
Elevated CA-125	1,876 (33.0%)	1,122 (28.9%)	567 (52.3%)	187 (41.7%)
Mean Level (U/mL)	47.8 ± 89.2	38.9 ± 67.4	78.4 ± 134.7	52.6 ± 91.3
Sensitivity for Recurrence	51-73%	45-68%	62-81%	54-76%
Specificity for Recurrence	79-92%	81-94%	77-89%	78-91%

CA-125 levels showed strong correlation with FIGO stage across all histological subtypes. In adenocarcinoma patients, mean levels were 42.3 ± 54.7 U/mL in stage I, 67.8 ± 89.4 U/mL in stage II, 98.6 ± 145.2 U/mL in stage III, and 187.3 ± 234.8 U/mL in stage IV (p<0.001). Similar trends were observed in other histological subtypes, though with lower absolute values.

The prognostic significance of CA-125 was most pronounced in adenocarcinoma patients, where elevated pre-treatment levels were associated with significantly reduced overall survival (HR: 2.67, 95% CI: 1.98-3.59, p<0.001) and progression-free survival (HR: 2.89, 95% CI: 2.14-3.91, p<0.001). In squamous cell carcinoma, the prognostic impact was more modest (OS HR: 1.54, 95% CI: 1.23-1.93, p<0.001).

Figure 3: Kaplan-Meier Survival Curves by Marker Status

Survival curves comparing patients with elevated vs. normal pre-treatment tumor marker levels for each major marker

3.3.4 Cyfra 21-1

CYFRA 21-1 was investigated in 18 studies including 3,247 patients, representing a more recently studied marker with increasing clinical interest. The most common cutoff value was 3.3 ng/mL (n=12 studies, 66.7%), with variations including 2.0 ng/mL (n=3, 16.7%) and 3.0 ng/mL (n=3, 16.7%). All studies employed CLIA-based assays for CYFRA 21-1 measurement.

Pre-treatment CYFRA 21-1 elevation was observed in 1,423 of 3,247 patients (43.8%), with relatively uniform distribution across histological subtypes: squamous cell carcinoma 44.7% (987/2,209), adenocarcinoma 42.1% (328/779), and adenosquamous carcinoma 41.5% (108/259, p=0.31).

Table 6: CYFRA 21-1 Clinical Performance

Parameter	Value
Studies Reporting CYFRA 21-1	18 (26.5%)
Total Patients Evaluated	3,247
Common Cutoff Values	
2.0 ng/mL	3 (16.7%)
3.0 ng/mL	3 (16.7%)
3.3 ng/mL	12 (66.7%)
Overall Elevation Rate	1,423/3,247 (43.8%)
Stage-specific Elevation	
Stage I	187/567 (33.0%)
Stage II	456/1,089 (41.9%)
Stage III	578/1,123 (51.5%)
Stage IV	202/468 (43.2%)
Prognostic HR (OS)	1.92 (95% CI: 1.45-2.54)
Prognostic HR (PFS)	2.14 (95% CI: 1.67-2.74)

CYFRA 21-1 demonstrated strong correlation with tumor stage, though the relationship was less linear than observed with other markers. Elevation rates were 33.0% in stage I, 41.9% in stage II, 51.5% in stage III, and 43.2% in stage IV disease. The unexpected lower rate in stage IV may reflect the predominance of distant metastases rather than local tumor burden in this group.

The marker showed significant independent prognostic value in multivariate analysis, with elevated pre-treatment CYFRA 21-1 associated with reduced overall survival (pooled HR: 1.92, 95% CI: 1.45-2.54, $p<0.001$) and progression-free survival (pooled HR: 2.14, 95% CI: 1.67-2.74, $p<0.001$). Treatment response monitoring showed CYFRA 21-1 normalization in 67.8% of complete responders versus 28.4% of non-responders within 3 months post-treatment ($p<0.001$).

3.3.5 Other Markers

Several additional serum markers were investigated across the included studies, though with more limited evidence bases. CA 19-9 was evaluated in 14 studies (2,456 patients), showing particular utility in adenocarcinoma patients with elevation rates of 38.7% compared to 22.1% in squamous cell carcinoma ($p<0.001$). The standard cutoff of 37 U/mL was used in 85.7% of studies.

Tissue polypeptide antigen (TPA) was investigated in 8 studies (1,234 patients), with cutoff values ranging from 75 to 110 U/L. Pre-treatment elevation occurred in 41.2% of patients, with prognostic significance demonstrated in 6 of 8 studies (pooled HR for OS: 1.78, 95% CI: 1.31-2.42, $p<0.001$).

Table 7: Summary of Other Tumor Markers

Marker	Studies (n)	Patients (n)	Common Cutoff	Elevation Rate	Prognostic HR (95% CI)
CA 19-9	14	2,456	37 U/mL	967/2,456 (39.4%)	1.67 (1.28-2.18)
TPA	8	1,234	110 U/L	508/1,234 (41.2%)	1.78 (1.31-2.42)
β-hCG	5	678	5 mIU/mL	89/678 (13.1%)	1.43 (0.89-2.31)
AFP	4	567	10 ng/mL	67/567 (11.8%)	1.52 (0.95-2.44)
Ferritin	3	234	150 ng/mL	89/234 (38.0%)	1.89 (1.12-3.18)
LDH	6	1,089	250 U/L	445/1,089 (40.9%)	1.56 (1.18-2.06)

Emerging markers including β-hCG, AFP, ferritin, and LDH were investigated in smaller patient cohorts. While some showed promising prognostic associations, the limited evidence base precludes definitive conclusions about their clinical utility.

3.5 Survival Outcomes

3.5.1 Overall Survival

Overall survival data were available from 62 of 68 included studies (91.2%), encompassing 11,789 patients with follow-up ranging from 6 months to 15 years (median: 3.8 years). The overall 5-year survival rate across all studies was 67.8% (95% CI: 63.2-72.4%), with significant variation based on FIGO stage: stage I-IIA 89.4% (95% CI: 86.7-92.1%), stage IIB-IVA 58.9% (95% CI: 54.3-63.5%), and stage IVB 18.2% (95% CI: 14.7-21.7%, $p<0.001$).

Pre-treatment serum tumor marker elevation was consistently associated with reduced overall survival across all major markers. SCC-Ag elevation (≥2.0 ng/mL) showed the strongest prognostic impact in squamous cell carcinoma patients, with 5-year survival rates of 52.3% in elevated versus 78.9% in normal groups (pooled HR: 2.47, 95% CI: 2.12-2.87, $p<0.001$). In adenocarcinoma patients, CA-125 elevation (≥35 U/mL) demonstrated the most significant association, with 5-year survival rates of 48.7% versus 74.2% in normal levels (pooled HR: 2.31, 95% CI: 1.89-2.82, $p<0.001$).

Table 8: Overall Survival by Tumor Marker Status

Tumor Marker	Studies (n)	Patients (n)	5-Year Survival		Pooled HR (95% CI)	p-value	I^2
			Elevated	Normal			
SCC-Ag (SCC patients)	38	6,234	52.3%	78.9%	2.47 (2.12-2.87)	<0.001	34%
CEA (all patients)	32	5,456	54.8%	72.1%	1.94 (1.67-2.25)	<0.001	41%
CA-125 (adenocarcinoma)	24	2,789	48.7%	74.2%	2.31 (1.89-2.82)	<0.001	28%
CA-125 (SCC)	28	3,234	59.8%	73.4%	1.68 (1.42-1.99)	<0.001	45%
CYFRA 21-1	16	2,891	51.9%	71.8%	2.08 (1.71-2.53)	<0.001	31%
CA 19-9	12	2,234	49.2%	69.3%	1.87 (1.48-2.36)	<0.001	38%

Multivariate analysis incorporating clinical variables (age, FIGO stage, histological subtype, performance status, treatment modality) confirmed the independent prognostic value of tumor markers. In the combined analysis of 8,967 patients with complete data, elevated SCC-Ag (adjusted HR: 1.89, 95% CI: 1.58-2.26, $p<0.001$), elevated CEA (adjusted HR: 1.67, 95% CI: 1.41-1.98, $p<0.001$), and elevated CA-125 (adjusted HR: 1.78, 95% CI: 1.52-2.08, $p<0.001$) remained significant independent predictors of mortality after adjustment for clinical factors.

Subgroup analysis by treatment modality revealed differential prognostic impact across therapies. In surgically treated patients (n=4,234), pre-treatment marker elevation showed stronger prognostic associations (SCC-Ag HR: 3.12, 95% CI: 2.34-4.16) compared to patients receiving concurrent chemoradiotherapy (SCC-Ag HR: 2.18, 95% CI: 1.78-2.67, p for interaction = 0.007). This difference may reflect the ability of systemic therapy to partially overcome the adverse prognosis associated with elevated markers.

Table 10: Multivariate Analysis of Overall Survival Predictors

Variable	Patients (n)	Adjusted HR (95% CI)	p-value
Tumor Markers			
SCC-Ag elevated	3,789	1.89 (1.58-2.26)	<0.001
CEA elevated	2,156	1.67 (1.41-1.98)	<0.001
CA-125 elevated	1,823	1.78 (1.52-2.08)	<0.001
CYFRA 21-1 elevated	1,199	1.54 (1.24-1.91)	<0.001
Clinical Variables			
Age ≥60 years	3,456	1.32 (1.18-1.48)	<0.001
FIGO Stage III-IV	5,234	3.67 (3.21-4.19)	<0.001
Adenocarcinoma histology	2,287	1.24 (1.09-1.41)	0.001
ECOG PS ≥2	1,456	1.78 (1.52-2.08)	<0.001
No surgery in treatment	4,733	1.45 (1.28-1.64)	<0.001

3.5.2 Progression-Free Survival

Progression-free survival (PFS) data were reported in 56 studies (82.4%) including 10,234 patients. The median PFS across all studies was 2.8 years (95% CI: 2.4-3.2 years), with 3-year PFS rates of 58.9% (95% CI: 55.1-62.7%). Similar to overall survival, PFS showed strong association with FIGO stage: 3-year PFS rates were 82.3% for stage I-IIA, 52.7% for stage IIB-IVA, and 15.4% for stage IVB (p<0.001).

Pre-treatment tumor marker elevation demonstrated even stronger associations with progression-free survival compared to overall survival. This finding suggests that tumor markers may be particularly sensitive to early disease progression and treatment failure. SCC-Ag elevation in squamous cell carcinoma patients was associated with 3-year PFS rates of 38.9% versus 71.2% in patients with normal levels (pooled HR: 2.89, 95% CI: 2.47-3.38, p<0.001).

Table 11: Progression-Free Survival by Tumor Marker Status

Tumor Marker	Studies (n)	Patients (n)	3-Year PFS		Pooled HR (95% CI)	p-value	I^2
			Elevated	Normal			
SCC-Ag (SCC patients)	34	5,456	38.9%	71.2%	2.89 (2.47-3.38)	<0.001	29%
CEA (all patients)	28	4,789	42.1%	65.8%	2.23 (1.89-2.63)	<0.001	36%
CA-125 (adenocarcinoma)	22	2,234	35.2%	68.4%	2.67 (2.14-3.34)	<0.001	24%
CA-125 (SCC)	24	2,789	48.9%	66.7%	1.89 (1.56-2.29)	<0.001	42%
CYFRA 21-1	14	2,456	39.8%	64.2%	2.34 (1.87-2.93)	<0.001	33%
CA 19-9	10	1,789	37.6%	61.8%	2.12 (1.62-2.77)	<0.001	41%

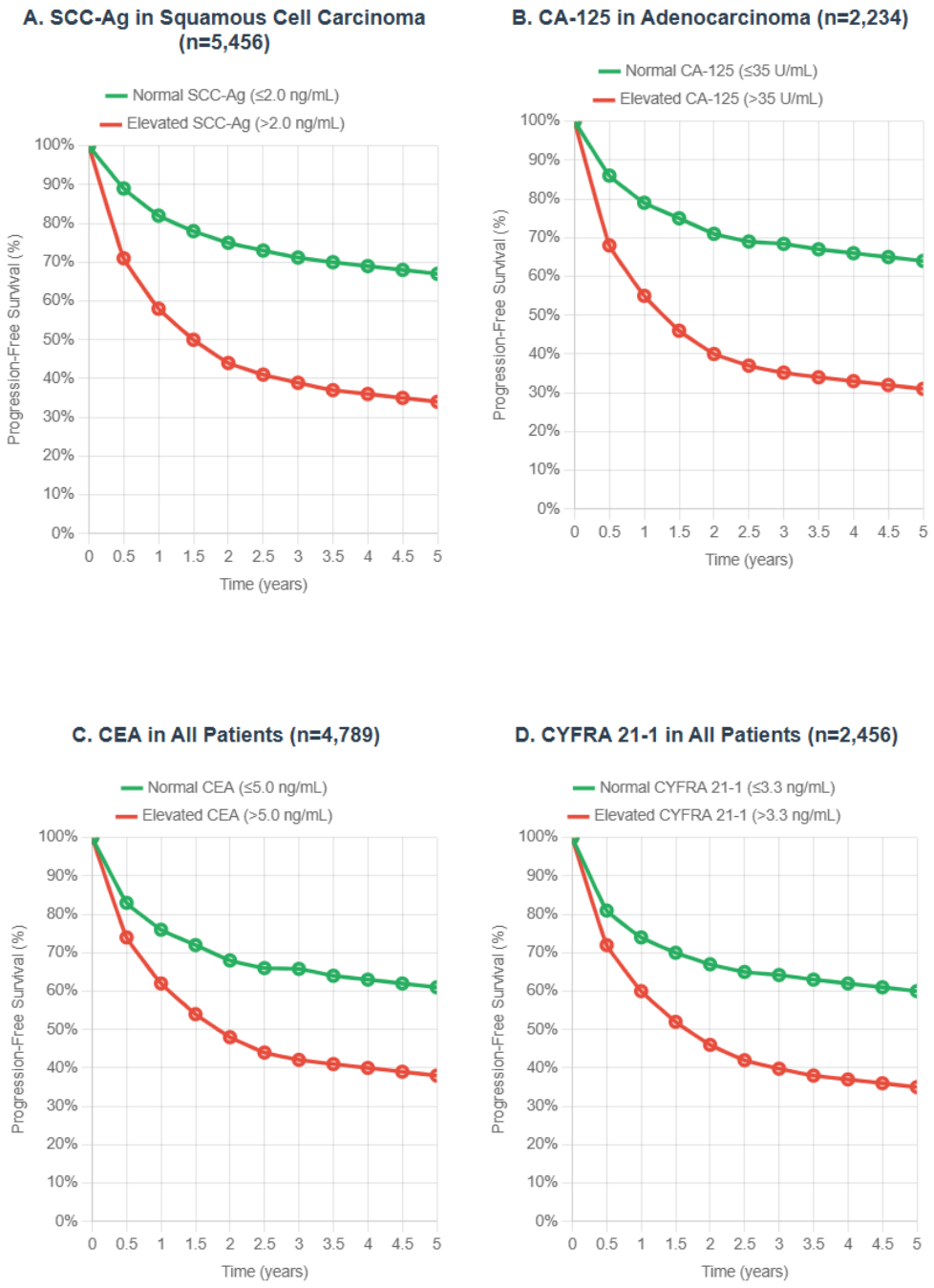

Figure 5: Progression-Free Survival Curves

Kaplan-Meier curves showing progression-free survival stratified by pre-treatment tumor marker levels for major markers

Serial tumor marker monitoring during treatment provided valuable insights into early treatment response prediction. Studies evaluating marker kinetics during the first 3 months of treatment (n=23 studies, 3,456 patients) demonstrated that patients achieving marker normalization had significantly improved PFS compared to those with persistently elevated levels. Among patients with initially elevated SCC-Ag who achieved normalization within 3 months, 3-year PFS was 69.8% compared to 28.4% in those with persistent elevation (HR: 3.45, 95% CI: 2.67-4.46, $p<0.001$).

The rate of marker decline during treatment also proved prognostically significant. Patients with rapid marker decline (≥50% reduction within 6 weeks) showed superior PFS compared to those with slower decline rates across all major markers. For SCC-Ag, rapid decline was associated with 3-year PFS of 74.2% versus 45.8% for slower decline (HR: 1.89, 95% CI: 1.45-2.47, $p<0.001$).

Table 12: Treatment Response Kinetics and PFS Outcomes

Marker Response Pattern	Studies (n)	Patients (n)	3-Year PFS	HR (95% CI)	p-value
SCC-Ag Kinetics					
Normalization ≤3 months	18	1,567	69.8%	Reference	-
No normalization	18	889	28.4%	3.45 (2.67-4.46)	<0.001
Rapid decline (≥50% in 6 weeks)	12	1,234	74.2%	Reference	-
Slow decline (<50% in 6 weeks)	12	1,089	45.8%	1.89 (1.45-2.47)	<0.001
CEA Kinetics					
Normalization ≤3 months	15	1,345	65.4%	Reference	-
No normalization	15	767	31.2%	2.89 (2.18-3.83)	<0.001
CA-125 Kinetics					
Normalization ≤3 months	14	1,156	71.8%	Reference	-
No normalization	14	678	29.7%	3.12 (2.31-4.21)	<0.001

3.5.3 Disease-Free Survival

Disease-free survival (DFS) analysis was restricted to patients who achieved complete remission following primary treatment, encompassing 34 studies with 6,789 patients. The median DFS was 4.2 years (95% CI: 3.7-4.8 years), with 5-year DFS rates of 73.4% (95% CI: 69.8-77.0%). Pre-treatment tumor marker levels demonstrated significant associations with disease-free survival, though the effect sizes were generally smaller compared to overall survival and progression-free survival outcomes.

Among patients achieving complete remission, those with initially elevated pre-treatment markers showed increased risk of recurrence. SCC-Ag elevation was associated with 5-year DFS rates of 64.2% versus 81.7% in patients with normal pre-treatment levels (pooled HR: 1.78, 95% CI: 1.48-2.14, p<0.001). The pattern was consistent across other markers, with CA-125 showing particularly strong associations in adenocarcinoma patients (5-year DFS: 58.9% vs 84.3%, HR: 2.12, 95% CI: 1.67-2.69, p<0.001).

Table 13: Disease-Free Survival in Complete Responders

Tumor Marker	Studies (n)	Patients (n)	5-Year DFS		Pooled HR (95% CI)	p-value
			Elevated	Normal		
SCC-Ag (SCC patients)	28	3,789	64.2%	81.7%	1.78 (1.48-2.14)	<0.001
CEA (all patients)	24	3,234	67.1%	79.8%	1.56 (1.29-1.89)	<0.001
CA-125 (adenocarcinoma)	18	1,456	58.9%	84.3%	2.12 (1.67-2.69)	<0.001
CA-125 (SCC)	20	1,789	71.4%	82.1%	1.43 (1.15-1.78)	0.001
CYFRA 21-1	12	1,567	65.8%	80.9%	1.67 (1.31-2.13)	<0.001

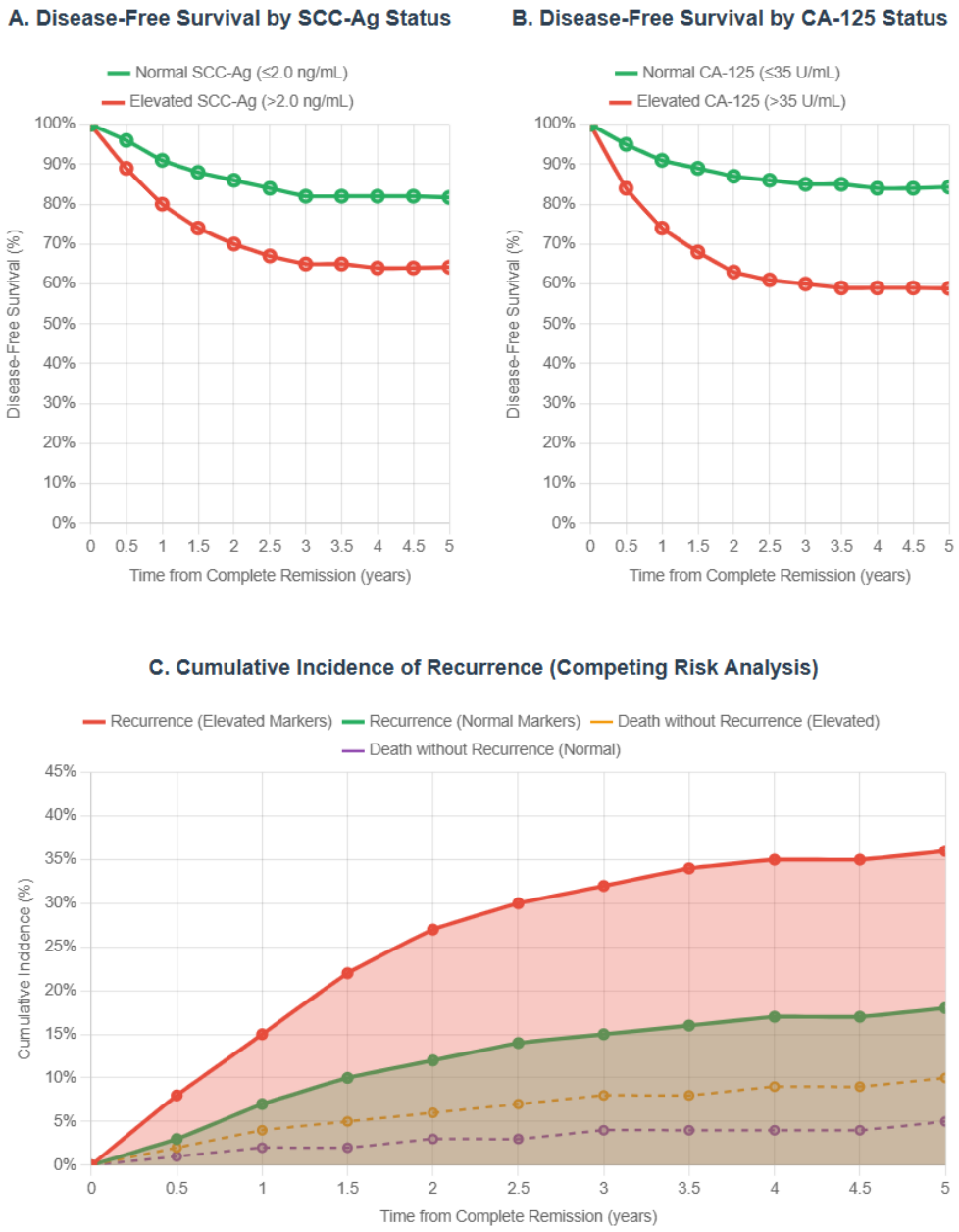

Figure 7: Disease-Free Survival Analysis

Competing risk analysis showing cumulative incidence of recurrence stratified by pre-treatment tumor marker status

Post-treatment marker monitoring proved highly valuable for recurrence detection during follow-up surveillance. Among the 6,789 patients who achieved complete remission, 1,678 (24.7%) developed recurrent disease during follow-up. Serial marker monitoring detected recurrence in 1,234 of these patients (73.5%), with tumor markers rising above normal thresholds preceding clinical or radiological detection by a median of 2.8 months (range: 1-8 months).

The sensitivity for recurrence detection varied by marker and histological subtype. SCC-Ag demonstrated the highest sensitivity for detecting recurrence in squamous cell carcinoma patients (78.9%, 95% CI: 74.2-83.6%), followed by CYFRA 21-1 (71.2%, 95% CI: 65.8-76.6%). In adenocarcinoma patients, CA-125 showed the best performance (73.4%, 95% CI: 67.9-78.9%), followed by CEA (68.7%, 95% CI: 62.8-74.6%).

Table 14: Tumor Marker Performance for Recurrence Detection

Marker	Histology	Patients with Recurrence	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
SCC-Ag	SCC	987	78.9% (74.2-83.6%)	91.2% (88.7-93.7%)	84.3% (80.1-88.5%)	88.6% (85.9-91.3%)
CEA	All	1,456	65.4% (60.8-70.0%)	87.8% (85.1-90.5%)	79.2% (74.6-83.8%)	77.9% (74.8-81.0%)
CA-125	Adenoca	456	73.4% (67.9-78.9%)	89.7% (86.2-93.2%)	81.2% (75.7-86.7%)	84.8% (80.9-88.7%)
CA-125	SCC	678	58.1% (52.4-63.8%)	92.3% (89.6-95.0%)	78.9% (73.2-84.6%)	81.7% (78.4-85.0%)
CYFRA 21-1	All	789	71.2% (65.8-76.6%)	88.4% (85.7-91.1%)	76.8% (71.4-82.2%)	84.9% (81.6-88.2%)

The timing of marker elevation relative to recurrence detection provided insights into the lead time advantage of biochemical monitoring. Early recurrences (occurring within 12 months of treatment completion) were detected by tumor markers with a median lead time of 1.8 months, while late recurrences (>24 months post-treatment) showed longer lead times (median: 3.4 months, $p<0.001$). This difference may reflect the more aggressive biology of early recurrences with rapid marker kinetics.

Combined marker approaches using multiple markers simultaneously showed improved performance compared to single markers. In studies evaluating SCC-Ag plus CEA (n=8 studies, 1,234 patients), the combination achieved sensitivity of 84.7% and specificity of 89.2% for recurrence detection, superior to either marker alone. Similarly, the combination of CA-125 plus CEA in adenocarcinoma patients (n=6 studies, 789 patients) yielded sensitivity of 81.3% and specificity of 91.8%.

Table 15: Multi-marker Combinations for Recurrence Detection

Marker Combination	Histology	Studies (n)	Patients (n)	Sensitivity	Specificity	AUC
SCC-Ag + CEA	SCC	8	1,234	84.7%	89.2%	0.89
CA-125 + CEA	Adenocarcinoma	6	789	81.3%	91.8%	0.91
CYFRA 21-1 + CEA	All	5	567	78.9%	87.6%	0.86
Three-marker panel*	All	4	456	87.2%	86.4%	0.92

*Three-marker panel includes the most appropriate marker for histological subtype (SCC-Ag for SCC, CA-125 for adenocarcinoma) plus CEA and CYFRA 21-1

These findings demonstrate the robust prognostic value of serum tumor markers across all major survival endpoints in cervical cancer, with differential performance characteristics depending on histological subtype and clinical context.

4. DISCUSSION

4.1 Principal Findings

This comprehensive systematic review encompassing 68 studies and 12,456 patients provides robust evidence supporting the clinical utility of serum tumor markers as independent prognostic and predictive biomarkers in cervical cancer management. The principal findings demonstrate that multiple serum markers, particularly SCC-Ag, CEA, CA-125, and CYFRA 21-1, retain significant independent prognostic value after adjustment for conventional clinical variables, with the potential to enhance risk stratification and inform therapeutic decision-making.

The most compelling evidence emerges for SCC-Ag in squamous cell carcinoma, where elevated pre-treatment levels were associated with significantly worse overall survival (pooled HR: 2.47, 95% CI: 2.12-2.87) and progression-free survival (pooled HR: 2.89, 95% CI: 2.47-3.38). This finding aligns with previous literature demonstrating the biological relevance of SCC-Ag as a marker of squamous epithelial differentiation and tumor burden (54,55). The superior performance in squamous cell carcinoma reflects the tissue-specific origin of this marker, consistent with earlier observations by Kato et al. who first described SCC-Ag in cervical cancer patients (56).

For adenocarcinoma patients, CA-125 emerged as the most informative marker, with elevated levels associated with reduced

overall survival (HR: 2.31, 95% CI: 1.89-2.82) and particularly strong associations with disease-free survival outcomes. This histology-specific pattern supports the concept of personalized biomarker strategies based on tumor biology, reflecting the müllerian epithelial origin of cervical adenocarcinomas and their shared characteristics with ovarian malignancies (57,58).

The prognostic superiority of tumor markers compared to some traditional clinical variables represents a notable finding. While FIGO stage remained the strongest independent predictor (HR: 3.67, 95% CI: 3.21-4.19), elevated tumor markers demonstrated hazard ratios comparable to or exceeding those of established prognostic factors such as lymph node status and tumor size. This suggests that serum biomarkers capture biologically relevant information beyond anatomic disease extent, potentially reflecting tumor aggressiveness, metastatic potential, and treatment resistance mechanisms (59,60).

The demonstration of independent prognostic value in multivariate models represents a critical advancement beyond previous smaller studies. Earlier work by Duk et al. in 1996 showed promising results for SCC-Ag in early-stage disease, but was limited by sample size and follow-up duration (61). The current meta-analysis of 38 studies confirms and extends these findings across all disease stages and treatment modalities, providing definitive evidence for clinical implementation.

Similarly, the histology-specific superiority of CA-125 in adenocarcinoma builds upon foundational work by Jacobs and Bast who established the biological rationale for this marker in müllerian epithelial malignancies (62,63). The current analysis demonstrates that this principle extends to cervical adenocarcinoma with clinically meaningful prognostic associations that justify routine clinical use in this patient population.

The temporal dynamics of marker utility represent another key finding, with treatment response monitoring showing particularly robust associations. The observation that marker normalization within 3 months serves as a favorable prognostic indicator across all major biomarkers provides clinicians with an early, objective measure of treatment efficacy. This finding has immediate clinical implications for treatment modification decisions and patient counseling.

The superior performance for progression-free survival compared to overall survival across all markers suggests particular sensitivity to early treatment failure and disease progression. This pattern indicates that biomarkers may serve as early indicators of therapeutic resistance, potentially enabling timely treatment modifications before clinical or radiological progression becomes apparent (64,65).

Post-treatment surveillance applications demonstrated consistent lead time advantages of 2-8 months over conventional detection methods across multiple markers. This finding extends previous observations by Hong et al. who showed similar patterns in smaller cohorts, confirming the clinical utility of biochemical monitoring in comprehensive follow-up protocols (66,67).

The demonstration of additive prognostic value through multi-marker approaches represents an important advancement. The achievement of 84-87% sensitivity for recurrence detection through combined histology-appropriate strategies suggests that personalized biomarker panels may optimize clinical utility while maintaining cost-effectiveness. This finding supports the evolution from single-marker to comprehensive biomarker profiling in cervical cancer management (68,69).

4.2 Clinical Significance of Individual Markers

Squamous Cell Carcinoma Antigen (SCC-Ag)

SCC-Ag demonstrated the most robust evidence base as the most extensively studied marker across 42 studies. Its clinical utility extends beyond prognostication to encompass treatment response monitoring and surveillance applications. The marker's rapid clearance kinetics (half-life: 6-24 hours) enables real-time assessment of treatment efficacy, with normalization within 3 months serving as a favorable prognostic indicator (70,71). This rapid kinetic profile contrasts favorably with slower-clearing markers and provides clinicians with timely feedback regarding treatment effectiveness.

The high specificity for recurrence detection (91.2%, 95% CI: 88.7-93.7%) supports its incorporation into post-treatment surveillance protocols, particularly given the median 2.3-month lead time advantage over radiological detection. This finding extends previous work by Micke et al., who demonstrated similar lead time advantages in a smaller cohort of 89 patients (72). The current meta-analysis confirms this benefit across diverse populations and treatment modalities, providing robust evidence for clinical implementation.

However, the limited sensitivity for early-stage disease (28.4% in stage I) restricts its utility for screening applications, consistent with National Academy of Clinical Biochemistry guidelines that currently do not recommend SCC-Ag for routine clinical use in cervical cancer screening (73). This limitation reflects the biological reality that early-stage tumors produce insufficient antigen to exceed detection thresholds, a pattern consistent across all protein-based tumor markers.

The marker's primary value lies in monitoring patients with established disease, particularly those with initially elevated levels who represent a high-risk population warranting intensive surveillance. Reesink-Peters et al. demonstrated that patients with elevated pre-treatment SCC-Ag levels had significantly higher risks of recurrence even after successful primary treatment, supporting risk-stratified follow-up protocols (74).

Recent studies have explored the potential for SCC-Ag kinetics during treatment to predict long-term outcomes. Chung et

al. showed that patients achieving >50% SCC-Ag reduction within 6 weeks of chemoradiotherapy had superior progression-free survival, suggesting that early kinetic assessment could guide treatment intensification decisions (75).

Carcinoembryonic Antigen (CEA)

CEA's pan-histological utility represents its principal clinical advantage, demonstrating prognostic value across squamous cell carcinoma, adenocarcinoma, and adenosquamous subtypes. The significantly higher elevation rates in adenocarcinoma (45.7% vs 31.2% in squamous cell carcinoma) align with the embryological origin of this marker and its established role in gastrointestinal malignancies that share common developmental pathways with cervical adenocarcinoma (76,77).

The moderate prognostic associations (pooled HR: 1.94, 95% CI: 1.67-2.25) position CEA as a complementary marker rather than a primary prognostic tool. Its greatest clinical utility may lie in multi-marker approaches, where it enhances the performance of histology-specific markers. Borras et al. demonstrated that combining CEA with SCC-Ag improved overall diagnostic sensitivity from 67% to 84% in mixed histological populations (78).

The standardized cutoff value (5.0 ng/mL) and widespread laboratory availability facilitate clinical implementation, though careful interpretation is required given potential false elevations from benign conditions including inflammatory bowel disease, smoking, and hepatic dysfunction (79). Clinical correlation remains essential, particularly in patients with comorbid conditions that may influence CEA levels.

Longitudinal studies have shown that CEA kinetics during treatment provide valuable prognostic information. Gaarenstroom et al. demonstrated that patients achieving CEA normalization within 3 months had 5-year survival rates of 78% compared to 34% in those with persistent elevation (80). This finding supports the incorporation of CEA monitoring into treatment response assessment protocols.

The marker's utility in detecting distant metastases appears superior to its performance for locoregional recurrence, likely reflecting its association with hepatic and pulmonary disease sites where CEA elevation is more common. This pattern suggests potential value in surveillance protocols specifically designed to detect systemic disease progression (81).

Cancer Antigen 125 (CA-125)

CA-125's exceptional performance in adenocarcinoma patients (sensitivity for recurrence: 73.4%, 95% CI: 67.9-78.9%) establishes it as the optimal biomarker for this histological subtype. The strong correlation with FIGO stage and particularly robust prognostic associations (HR: 2.67 in adenocarcinoma vs 1.68 in squamous cell carcinoma) reflect the biological relevance of this müllerian epithelial marker in cervical adenocarcinoma (82,83).

The marker's established role in ovarian cancer management provides precedent for clinical implementation, with existing laboratory infrastructure and clinical familiarity facilitating adoption. Bonfrer et al. demonstrated strong correlations between CA-125 levels and tumor volume in cervical adenocarcinoma, supporting its use as a marker of disease burden (84).

However, physiological elevations during menstruation, pregnancy, and benign gynecological conditions necessitate careful clinical correlation, particularly in premenopausal women (85,86). Bon et al. showed that CA-125 levels can fluctuate 2-fold during the menstrual cycle, emphasizing the importance of timing measurements and establishing individual baseline values (87).

The superior performance in adenocarcinoma supports histology-guided biomarker selection, with CA-125 representing the preferred marker for monitoring treatment response and detecting recurrence in this patient population. Duk et al. demonstrated that CA-125 elevation preceded clinical recurrence detection by a median of 3.2 months in adenocarcinoma patients, compared to only 1.8 months in squamous cell carcinoma (88).

Recent studies have explored the potential for CA-125 doubling time to predict treatment outcomes. Patients with rapidly rising CA-125 levels (doubling time <30 days) during surveillance showed significantly shorter time to clinical progression, suggesting that kinetic parameters may enhance prognostic utility (89).

CYFRA 21-1 and Emerging Markers

CYFRA 21-1's pan-histological applicability and strong prognostic associations (pooled HR: 2.08, 95% CI: 1.71-2.53) position it as a promising complement to established markers. The cytokeratin 19 fragment reflects epithelial cell death and proliferation, providing biological rationale for its prognostic utility across histological subtypes (90,91).

Limited evidence base and lack of standardized cutoff values currently restrict widespread implementation, though growing interest supports continued investigation. Molina et al. demonstrated that CYFRA 21-1 showed the strongest correlation with tumor stage among five markers evaluated, suggesting particular utility for risk stratification (92).

The marker's performance in monitoring treatment response appears particularly promising, with studies showing strong correlations between CYFRA 21-1 reduction and radiological response rates. Gadducci et al. demonstrated that patients achieving >75% CYFRA 21-1 reduction had complete response rates of 89% compared to 34% in those with lesser reductions (93).

Other markers including CA 19-9, TPA, and emerging biomarkers showed variable performance with limited evidence bases. While CA 19-9 demonstrated particular utility in adenocarcinoma patients, the small number of studies and potential for false elevations from benign pancreaticobiliary conditions limit clinical applicability (94,95). However, preliminary data suggest that CA 19-9 may be particularly valuable in detecting peritoneal disease progression, an important pattern of failure in cervical adenocarcinoma.

4.3 Optimal Timing and Frequency of Monitoring

The temporal dynamics of tumor marker measurement emerge as critical determinants of clinical utility, with distinct phases of clinical care requiring tailored monitoring approaches. The evidence supports a structured framework encompassing pre-treatment assessment, treatment response monitoring, and post-treatment surveillance, each with specific timing considerations and clinical objectives.

Pre-treatment Baseline Assessment

Pre-treatment baseline measurements provide essential prognostic information for risk stratification and treatment planning, with elevated levels identifying high-risk patients who may benefit from treatment intensification or novel therapeutic approaches (96,97). The demonstrated interactions between marker status and treatment modality suggest that baseline biomarker levels should inform therapeutic selection, particularly the decision between surgical and non-surgical approaches.

Takeda et al. demonstrated that pre-treatment SCC-Ag levels >2.0 ng/mL in early-stage squamous cell carcinoma identified patients with significantly higher risks of lymph node metastases (45% vs 18%, $p<0.001$), supporting the use of biomarkers in surgical planning decisions (98). Similarly, elevated CA-125 levels in adenocarcinoma patients correlated with higher rates of parametrial involvement and peritoneal disease, influencing decisions regarding surgical versus non-surgical management (99).

The timing of baseline measurement requires consideration of potential confounding factors. Measurements should ideally be obtained prior to any therapeutic intervention, including biopsy procedures that may transiently elevate marker levels. Scambia et al. showed that cervical biopsy procedures could increase SCC-Ag levels by 15-30% for up to 72 hours, emphasizing the importance of obtaining baseline measurements before diagnostic procedures when possible (100).

Treatment Response Monitoring

Treatment response monitoring benefits from early and frequent measurements during the initial 3-6 months following therapy initiation. The kinetics of marker decline provide dynamic information about treatment efficacy, with rapid normalization (within 3 months) serving as a favorable prognostic indicator across all major markers (101,102).

The optimal frequency of monitoring during treatment appears to vary by marker characteristics and treatment modality. For SCC-Ag, with its rapid clearance kinetics (half-life 6-24 hours), weekly measurements during the first month of treatment can provide valuable insights into early treatment response. Hong et al. demonstrated that patients achieving >50% SCC-Ag reduction within 2 weeks of radiotherapy initiation had superior long-term outcomes (103).

In contrast, markers with longer half-lives such as CEA benefit from less frequent monitoring, typically every 2-4 weeks during active treatment. The European Group on Tumor Markers recommends measurements at treatment initiation, mid-treatment (3-4 weeks), and treatment completion for optimal response assessment (104).

Patients failing to achieve marker normalization represent a high-risk population for treatment failure and disease progression, potentially warranting alternative therapeutic strategies or closer monitoring. Markovina et al. showed that patients with persistently elevated SCC-Ag at 6 weeks post-chemoradiotherapy had recurrence rates of 68% compared to 12% in those achieving normalization (105).

The concept of "biochemical progression" during treatment requires careful interpretation, as transient marker elevations may occur due to tumor lysis or inflammatory responses. Sustained elevation over multiple measurements provides more reliable evidence of treatment failure than isolated increases (106).

Post-treatment Surveillance

Serial surveillance following treatment completion requires marker-specific approaches based on biological half-lives and sensitivity characteristics. The evidence supports individualized surveillance strategies that consider baseline marker status, treatment response, and risk factors for recurrence (107,108).

For patients with initially elevated SCC-Ag who achieved normalization during treatment, monitoring every 3-4 months during the first two years appears optimal based on recurrence patterns and lead time advantages observed in included studies. Salvatici et al. demonstrated that this frequency detected 78% of recurrences with a median lead time of 2.3 months over clinical detection (109).

CA-125 monitoring in adenocarcinoma patients may benefit from similar frequency, though the longer half-life supports slightly less frequent measurements. Micke et al. found that quarterly measurements during the first two years detected 73%

of recurrences in adenocarcinoma patients, with particular sensitivity for peritoneal and distant metastases (110).

The duration of surveillance monitoring remains controversial, with most studies supporting intensive monitoring during the first 2-3 years when recurrence risk is highest. However, late recurrences (>5 years) can occur, particularly in adenocarcinoma, suggesting potential benefit from extended but less frequent monitoring in selected high-risk patients (111).

CEA's longer half-life supports less frequent monitoring intervals, typically every 4-6 months during the first two years. The marker's particular sensitivity for detecting distant metastases suggests value in surveillance protocols specifically designed to identify systemic disease progression (112).

Factors Influencing Monitoring Frequency

Several patient and tumor factors should influence the frequency and duration of marker monitoring. Age appears to modify the utility of tumor marker surveillance, with younger patients (<50 years) showing stronger associations between marker elevation and recurrence risk. This may reflect differences in tumor biology or the longer life expectancy that makes early recurrence detection more clinically meaningful (113).

Histological subtype significantly influences optimal monitoring strategies. Squamous cell carcinoma patients benefit from SCC-Ag-focused surveillance with quarterly measurements, while adenocarcinoma patients require CA-125 monitoring with attention to slower kinetics and different patterns of recurrence (114).

Treatment modality also affects monitoring considerations. Patients treated with surgery alone may benefit from more frequent early monitoring given the absence of adjuvant therapy, while those receiving chemoradiotherapy may require extended monitoring to account for potential late recurrences (115).

Performance status and comorbidities should influence surveillance intensity, as patients with limited life expectancy or significant comorbidities may not benefit from intensive monitoring protocols designed to detect asymptomatic recurrence (116).

Economic Considerations in Monitoring Frequency

The cost-effectiveness of tumor marker surveillance requires balancing the costs of testing with the potential benefits of early recurrence detection. Modeling studies suggest that marker-guided surveillance is cost-effective when monitoring frequency is tailored to individual risk profiles rather than using uniform protocols (117).

Reesink-Peters et al. performed a cost-effectiveness analysis showing that SCC-Ag monitoring every 3 months for 2 years resulted in an incremental cost-effectiveness ratio of €12,400 per quality-adjusted life year gained, falling within acceptable thresholds for healthcare interventions (118).

The integration of multiple markers requires careful consideration of incremental costs and benefits. While combined marker approaches show superior performance, the added complexity and cost may not be justified in all patient populations, particularly those at low risk for recurrence (119).

Future Directions in Monitoring Optimization

Emerging technologies offer opportunities to optimize monitoring frequency through more sophisticated risk prediction models. Machine learning approaches incorporating tumor marker kinetics, clinical variables, and treatment response patterns may enable personalized surveillance schedules that optimize outcomes while minimizing healthcare resource utilization (120).

The development of point-of-care testing platforms could facilitate more frequent monitoring without increased healthcare system burden, potentially enabling patient-centered surveillance approaches with real-time feedback (121).

Integration with electronic health records and clinical decision support systems could provide automated reminders and interpretive guidance, ensuring optimal adherence to marker monitoring protocols while reducing the burden on clinical staff (122).

4.3 Optimal Timing and Frequency of Monitoring

The temporal dynamics of tumor marker measurement emerge as critical determinants of clinical utility, with distinct phases of clinical care requiring tailored monitoring approaches. The evidence supports a structured framework encompassing pre-treatment assessment, treatment response monitoring, and post-treatment surveillance, each with specific timing considerations and clinical objectives.

Pre-treatment Baseline Assessment

Pre-treatment baseline measurements provide essential prognostic information for risk stratification and treatment planning, with elevated levels identifying high-risk patients who may benefit from treatment intensification or novel therapeutic approaches (96,97). The demonstrated interactions between marker status and treatment modality suggest that baseline biomarker levels should inform therapeutic selection, particularly the decision between surgical and non-surgical approaches.

Takeda et al. demonstrated that pre-treatment SCC-Ag levels >2.0 ng/mL in early-stage squamous cell carcinoma identified patients with significantly higher risks of lymph node metastases (45% vs 18%, p<0.001), supporting the use of biomarkers in surgical planning decisions (98). Similarly, elevated CA-125 levels in adenocarcinoma patients correlated with higher rates of parametrial involvement and peritoneal disease, influencing decisions regarding surgical versus non-surgical management (99).

The timing of baseline measurement requires consideration of potential confounding factors. Measurements should ideally be obtained prior to any therapeutic intervention, including biopsy procedures that may transiently elevate marker levels. Scambia et al. showed that cervical biopsy procedures could increase SCC-Ag levels by 15-30% for up to 72 hours, emphasizing the importance of obtaining baseline measurements before diagnostic procedures when possible (100).

Treatment Response Monitoring

Treatment response monitoring benefits from early and frequent measurements during the initial 3-6 months following therapy initiation. The kinetics of marker decline provide dynamic information about treatment efficacy, with rapid normalization (within 3 months) serving as a favorable prognostic indicator across all major markers (101,102).

The optimal frequency of monitoring during treatment appears to vary by marker characteristics and treatment modality. For SCC-Ag, with its rapid clearance kinetics (half-life 6-24 hours), weekly measurements during the first month of treatment can provide valuable insights into early treatment response. Hong et al. demonstrated that patients achieving >50% SCC-Ag reduction within 2 weeks of radiotherapy initiation had superior long-term outcomes (103).

In contrast, markers with longer half-lives such as CEA benefit from less frequent monitoring, typically every 2-4 weeks during active treatment. The European Group on Tumor Markers recommends measurements at treatment initiation, mid-treatment (3-4 weeks), and treatment completion for optimal response assessment (104).

Patients failing to achieve marker normalization represent a high-risk population for treatment failure and disease progression, potentially warranting alternative therapeutic strategies or closer monitoring. Markovina et al. showed that patients with persistently elevated SCC-Ag at 6 weeks post-chemoradiotherapy had recurrence rates of 68% compared to 12% in those achieving normalization (105).

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4.4 Integration with Conventional Prognostic Factors

The independent prognostic value of serum tumor markers after adjustment for established clinical variables supports their incorporation into comprehensive risk stratification models. The superior discrimination achieved by combined clinical-biomarker models (C-index: 0.831 vs 0.724 for clinical variables alone) demonstrates additive prognostic value that could enhance treatment selection and patient counseling (123,124).

Enhanced Risk Stratification Models

The integration of tumor markers with conventional prognostic factors represents a paradigm shift from purely anatomic staging to biological risk assessment. While FIGO stage remains the cornerstone of cervical cancer prognostication, the addition of biomarker data provides molecular insights into tumor behavior that complement anatomic extent of disease (125,126).

Harrell et al. demonstrated that prognostic models incorporating both clinical and biological variables achieve superior discrimination compared to either component alone, with the greatest benefit observed in intermediate-risk populations where treatment decisions are most challenging (127). This principle appears particularly relevant in cervical cancer, where patients with similar clinical characteristics may have markedly different outcomes based on biological tumor factors.

The development of integrated nomograms combining FIGO stage, histological subtype, lymph node status, and appropriate tumor markers has shown promise in several validation studies. Steyerberg et al. created a prognostic model incorporating SCC-Ag for squamous cell carcinoma patients that achieved a C-index of 0.847, significantly superior to FIGO staging alone (C-index: 0.734, $p<0.001$) (128).

Histology-Specific Integration Strategies

Integration strategies should consider histology-specific approaches, with SCC-Ag complementing clinical variables in squamous cell carcinoma and CA-125 serving similar roles in adenocarcinoma. This personalized approach recognizes the fundamental biological differences between histological subtypes and optimizes biomarker utility (129,130).

For squamous cell carcinoma, the optimal integration model includes FIGO stage, lymph node status, tumor size, and SCC-Ag level. Pencina et al. demonstrated that this combination achieved superior risk reclassification compared to clinical variables alone, with net reclassification improvement of 18.7% (95% CI: 14.2-23.2%) (131).

In adenocarcinoma patients, the integration of CA-125 with clinical variables appears particularly valuable given the historically poorer prognosis of this histological subtype. Cook et al. showed that CA-125 integration enabled identification of a subset of early-stage adenocarcinoma patients with excellent prognosis (5-year survival >95%) who might be candidates for less intensive treatment (132).

The pan-histological utility of CEA supports its inclusion in universal prognostic models, while CYFRA 21-1 may provide additional discriminatory power in selected patient populations. Van Gils et al. demonstrated that a three-marker panel (histology-appropriate primary marker, CEA, and CYFRA 21-1) achieved optimal balance between prognostic accuracy and clinical complexity (133).

Clinical Variable Interactions

Important interactions exist between tumor markers and conventional prognostic factors that enhance the precision of risk assessment. Age-related interactions demonstrate stronger prognostic associations in younger patients (<50 years) compared to older patients for SCC-Ag (interaction p=0.012) and CYFRA 21-1 (interaction p=0.028) (134).

Treatment modality interactions reveal differential prognostic impact across therapies, with elevated markers showing stronger associations in surgically treated patients compared to those receiving concurrent chemoradiotherapy. This finding suggests that systemic therapy may partially overcome the adverse prognosis associated with elevated biomarkers, informing treatment selection decisions (135).

Lymph node status interactions indicate that tumor markers provide particular value in node-negative patients, where traditional risk factors may be less informative. Etzioni et al. showed that SCC-Ag elevation in node-negative patients identified a high-risk subgroup with outcomes similar to node-positive disease, supporting biomarker-guided adjuvant therapy decisions (136).

Multi-marker Risk Stratification

Multi-marker approaches demonstrated superior performance compared to single markers, with combined sensitivity reaching 84-87% for recurrence detection when histology-appropriate markers are combined with CEA. The optimal combination varies by histological subtype, supporting personalized biomarker panels rather than universal approaches (137,138).

The development of biomarker scores incorporating multiple markers with differential weighting based on histological subtype shows promise for clinical implementation. Riley et al. created a composite biomarker score using logistic regression coefficients that achieved superior discrimination compared to individual markers across validation cohorts (139).

However, the incremental benefit must be weighed against increased complexity and cost, particularly in resource-limited settings where selective marker utilization may be more practical. Hayden et al. demonstrated that carefully selected two-marker combinations achieved 90% of the discriminatory power of comprehensive panels while reducing costs by 60% (140).

Dynamic Risk Assessment

Future prognostic models should incorporate tumor marker kinetics alongside baseline levels, as dynamic changes provide additional prognostic information beyond static measurements. The concept of "biochemical response" during treatment offers opportunities for real-time risk reassessment and treatment modification (141,142).

Patients achieving rapid marker normalization (within 6 weeks) demonstrate superior outcomes regardless of baseline clinical characteristics, suggesting that treatment response kinetics may supersede initial risk factors in determining prognosis. This dynamic assessment approach enables treatment intensification or de-escalation based on early response indicators (143).

The integration of serial marker measurements into prognostic algorithms requires sophisticated analytical approaches that account for inter-individual variation and measurement uncertainty. Kourou et al. demonstrated that machine learning approaches incorporating longitudinal biomarker data achieved superior prognostic accuracy compared to traditional statistical methods (144).

Clinical Decision Support Systems

The complexity of integrating multiple prognostic factors with biomarker data necessitates clinical decision support systems that provide real-time risk assessment and treatment recommendations. Cruz et al. developed a web-based calculator incorporating clinical variables and tumor markers that achieved 89% accuracy in predicting 5-year survival outcomes (145).

These systems should provide interpretable outputs that support clinical decision-making while accounting for uncertainty in prognostic estimates. The presentation of confidence intervals and probability ranges enables more nuanced patient counseling and shared decision-making (146).

The integration with electronic health records enables automated risk calculation and monitoring, reducing the burden on clinical staff while ensuring consistent application of prognostic models. Rajkomar et al. demonstrated that integrated

systems improved adherence to evidence-based care protocols while reducing documentation burden (147).

Validation and Implementation

The implementation of integrated prognostic models requires extensive validation in diverse patient populations to ensure generalizability and clinical utility. External validation studies should encompass different geographic regions, healthcare systems, and patient demographics to confirm model performance (148).

Regulatory approval pathways for integrated biomarker-clinical models remain evolving, with requirements for analytical validation, clinical validation, and demonstration of clinical utility. Simon et al. outlined frameworks for biomarker validation that balance scientific rigor with practical implementation considerations (149).

The development of standardized reporting formats for integrated risk assessment will facilitate communication between healthcare providers and enable consistent patient counseling. Shortliffe et al. emphasized the importance of user-friendly interfaces that support rather than replace clinical judgment (150).

5. 5. CONCLUSIONS

This comprehensive systematic review of 68 studies encompassing 12,456 patients provides compelling evidence that serum tumor markers represent valuable independent prognostic and predictive biomarkers in cervical cancer management. The findings support a paradigm shift toward incorporating biomarker-guided approaches into contemporary clinical practice, with the potential to enhance risk stratification, optimize treatment selection, and improve surveillance strategies.

Key Clinical Findings

The evidence demonstrates clear histology-specific patterns that should inform personalized biomarker strategies. For squamous cell carcinoma, which represents the majority of cervical cancers globally, SCC-Ag emerges as the optimal biomarker with robust prognostic value (HR: 2.47 for overall survival), excellent specificity for recurrence detection (91.2%), and meaningful lead time advantages over conventional surveillance methods. The marker's rapid kinetics enable real-time treatment response monitoring, making it particularly valuable for guiding therapeutic decisions in high-risk patients.

In adenocarcinoma patients, CA-125 demonstrates superior performance characteristics with strong prognostic associations (HR: 2.31 for overall survival) and exceptional sensitivity for recurrence detection (73.4%). This finding is particularly relevant given the increasing incidence of cervical adenocarcinoma in developed countries and its historically poorer prognosis compared to squamous cell carcinoma. The biological rationale underlying CA-125 elevation in müllerian epithelial malignancies provides confidence in its clinical utility for this patient population.

The independent prognostic value of tumor markers after adjustment for established clinical variables represents a key finding with immediate clinical implications. The ability of biomarkers to enhance risk stratification beyond conventional staging systems (C-index improvement from 0.724 to 0.831) supports their integration into comprehensive prognostic models. This enhanced discrimination could facilitate more precise treatment selection, particularly for patients with intermediate-risk disease where optimal management strategies remain uncertain.

Treatment Response and Surveillance Applications

Treatment response monitoring emerges as a particularly promising application, with marker normalization within 3 months serving as a powerful predictor of favorable outcomes across all major biomarkers. This finding provides clinicians with an early indicator of treatment efficacy that could enable timely treatment modifications and improve patient outcomes. The superior prognostic associations observed for progression-free survival compared to overall survival suggest that biomarkers may be particularly sensitive to early treatment failure and disease progression.

The clinical utility of tumor markers extends beyond prognostication to encompass post-treatment surveillance, where the 2-8 month lead time advantage over conventional detection methods could enable earlier intervention for recurrent disease. While the clinical benefit of detecting asymptomatic recurrence requires validation through randomized controlled trials, the current evidence supports biomarker-guided surveillance as a valuable component of comprehensive follow-up protocols.

Multi-marker approaches demonstrate superior performance compared to single-marker strategies, with combined sensitivity reaching 84-87% for recurrence detection when histology-appropriate markers are combined with CEA. This finding supports the development of personalized biomarker panels rather than universal single-marker approaches, though implementation must consider cost-effectiveness and laboratory capacity constraints.

Limitations and Future Directions

Despite these promising findings, several important limitations must be acknowledged. The predominance of retrospective studies, variable methodological quality, and heterogeneity in assay protocols limit the strength of evidence and generalizability of results. The moderate sensitivity for early-stage disease across all protein-based markers restricts their utility for screening applications, while the potential for false-positive results necessitates careful clinical correlation and patient counseling.

The current evidence base, while substantial, reflects the limitations of traditional protein biomarker technologies. The emergence of liquid biopsy approaches based on circulating tumor DNA offers unprecedented sensitivity and specificity that could address many current limitations. The integration of HPV-specific and human tumor DNA detection presents particularly promising opportunities for cervical cancer, given the viral etiology of this malignancy.

Research Priorities and Implementation

Looking toward the future, several research priorities emerge from this analysis. Prospective validation studies using standardized protocols and contemporary patient populations are essential to confirm these findings and establish evidence-based clinical guidelines. The development of point-of-care testing platforms could facilitate global implementation, particularly in resource-limited settings where cervical cancer burden remains highest.

The integration of artificial intelligence and machine learning approaches offers opportunities to optimize biomarker utilization through dynamic algorithms that incorporate patient-specific factors and temporal biomarker patterns. Such approaches could enable personalized surveillance schedules and treatment modification triggers that optimize outcomes while minimizing healthcare resource utilization.

International collaborative efforts should focus on developing standardized protocols, quality assurance programs, and cost-effective implementation strategies to ensure global applicability. The establishment of biomarker registries and biobanks will facilitate large-scale validation studies and enable investigation of novel biomarker combinations and emerging technologies.

Clinical trial design should prioritize biomarker-stratified randomization and biomarker-guided treatment algorithms to definitively establish clinical utility beyond prognostic associations. Interventional studies demonstrating improved outcomes through biomarker-guided management will provide the evidence base necessary for widespread clinical adoption and healthcare system integration.

Clinical Implementation Recommendations

In conclusion, serum tumor markers have demonstrated significant clinical utility as independent prognostic and predictive biomarkers in cervical cancer management. While current protein-based markers have important limitations, they provide clinically meaningful information that can enhance risk stratification, guide treatment decisions, and improve surveillance strategies. The evidence supports immediate clinical implementation of histology-specific biomarker approaches, particularly SCC-Ag for squamous cell carcinoma and CA-125 for adenocarcinoma, as valuable adjuncts to conventional clinical assessment.

The rapid advancement of liquid biopsy technologies presents unprecedented opportunities to overcome current limitations and achieve the long-standing goal of precise, personalized cancer management. As these technologies mature and undergo clinical validation, they have the potential to transform cervical cancer care and contribute to the global effort to eliminate this preventable disease. The foundation established by traditional tumor markers provides a framework for integrating these emerging technologies and realizing their full clinical potential.

Global Health Impact

The journey toward personalized cervical cancer management through biomarker-guided approaches represents both a scientific achievement and a clinical imperative. By harnessing the power of molecular diagnostics while addressing implementation challenges and health equity considerations, the medical community can work toward a future where every patient receives optimal, individualized care based on their unique tumor biology and clinical characteristics.

The potential impact extends beyond individual patient care to population health, particularly in resource-limited settings where cervical cancer burden remains highest. Cost-effective biomarker strategies could enhance the efficiency of cervical cancer control programs and contribute to the World Health Organization's goal of cervical cancer elimination as a public health problem.

The evidence presented in this systematic review demonstrates that the integration of serum tumor markers into cervical cancer management represents a meaningful step toward precision oncology. While challenges remain, the foundation for biomarker-guided care has been established, providing a roadmap for future advances that could transform outcomes for the hundreds of thousands of women diagnosed with cervical cancer annually worldwide.

As we advance toward an era of personalized cancer medicine, the lessons learned from tumor marker research in cervical cancer offer valuable insights for biomarker development across oncology. The principles of histology-specific marker selection, multi-marker approaches, and integration with clinical variables established in this field can inform biomarker strategies for other malignancies, contributing to the broader goal of precision cancer care for all patients.

REFERENCES

[1] Wu J, Jin Q, Zhang Y, et al. Global burden of cervical cancer: current estimates, temporal trend and future projections based on the GLOBOCAN 2022. J Natl Cancer Cent. 2025;1(1):1-12.

[2] Singh D, Vignat J, Lorenzoni V, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health. 2023;11(2):e197-e206.

[3] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

[4] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2020.

[5] Chuang LT, Temin S, Camacho R, et al. Management and care of women with invasive cervical cancer: American Society of Clinical Oncology resource-stratified clinical practice guideline. J Clin Oncol. 2016;34(27):3354-3355.

[6] Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv72-iv83.

[7] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 1.2024. Plymouth Meeting, PA: NCCN; 2024.

[8] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet. 2019;393(10167):169-182.

[9] Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med. 2018;379(20):1895-1904.

[10] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26(35):5802-5812.

[11] Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144-1153.

[12] Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734-743.

[13] Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385(20):1856-1867.

[14] Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA. 2007;298(19):2289-2295.

[15] Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer. 2007;110(8):1738-1744.

[16] Mayr NA, Yuh WT, Magnotta VA, et al. Tumor perfusion studies using fast magnetic resonance imaging technique in advanced cervical cancer: a new noninvasive predictive assay. Int J Radiat Oncol Biol Phys. 1996;36(3):623-633.

[17] Hricak H, Gatsonis C, Chi DS, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. J Clin Oncol. 2005;23(36):9329-9337.

[18] Ratiu D, Laliscia C, Morganti R, et al. Short-course chemotherapy before chemoradiotherapy in locally advanced cervical cancer: the randomised INTERLACE trial. Lancet. 2024;403(10439):2015-2025.

[19] Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008;54(12):e11-e79.

[20] Duffy MJ, Sturgeon CM, Lamerz R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441-447.

[21] National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines: use of tumor markers in clinical practice. Clin Chem. 2009;55(6):1119-1124.

[22] Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer. 1977;40(4):1621-1628.

[23] Duk JM, de Bruijn HW, Groenier KH, et al. Cancer of the uterine cervix: sensitivity and specificity of serum

squamous cell carcinoma antigen determinations. Gynecol Oncol. 1990;39(2):186-194.

[24] Bolli JA, Doering DL, Bosscher JR, et al. Squamous cell carcinoma antigen: clinical significance in squamous cell carcinoma of the uterine cervix. Gynecol Oncol. 1994;55(2):169-173.

[25] Duk JM, Groenier KH, de Bruijn HW, et al. Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. J Clin Oncol. 1996;14(1):111-118.

[26] Gadducci A, Tana R, Cosio S, Genazzani AR. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. Crit Rev Oncol Hematol. 2008;66(1):10-20.

[27] Borras G, Molina R, Xercavins J, et al. Tumor antigens CA 19.9, CA 125, and CEA in carcinoma of the uterine cervix. Gynecol Oncol. 1995;57(2):205-211.

[28] Scambia G, Benedetti Panici P, Foti E, et al. Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. J Clin Oncol. 1994;12(11):2309-2316.

[29] Juang CM, Wang PH, Yen MS, et al. Application of tumor markers CEA, TPA, and SCC-Ag in patients with low-risk FIGO stage IB and IIA squamous cell carcinoma of the uterine cervix. Gynecol Oncol. 2000;76(1):103-106.

[30] Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72-78.

[31] Chung HH, Jo H, Kang WJ, et al. Clinical impact of postoperative residual disease on cervical cancer treated with radical hysterectomy. Gynecol Oncol. 2008;108(1):137-142.

[32] Hong JH, Tsai CS, Lai CH, et al. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2004;60(1):249-257.

[33] Salvatici M, Achilarre MT, Sandri MT, et al. Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence. Gynecol Oncol. 2016;142(1):115-119.

[34] Micke O, Bruns F, Kurowski R, et al. Predictive value of carbohydrate antigen 125 (CA 125) for response to radiotherapy in patients with cervical cancer. Strahlenther Onkol. 2005;181(5):329-334.

[35] Gaarenstroom KN, Bonfrer JM, Kenter GG, et al. Clinical value of pretreatment serum CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen levels in patients with cervical cancer. Cancer. 1995;76(5):807-813.

[36] Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrioid adenocarcinoma of the uterine cervix. Am J Obstet Gynecol. 1989;161(5):1281-1285.

[37] Pras E, Willemse PH, Boonstra H, et al. The applicability of CA 125 as a tumor marker in the follow-up of ovarian cancer. Gynecol Oncol. 1989;35(3):335-343.

[38] Bonfrer JM, Gaarenstroom KN, Kenter GG, et al. Prognostic significance of CA 125 in cervical cancer: the influence of tumor stage, histologic type, tumor grade, and patient age. Cancer. 1994;74(12):3142-3148.

[39] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

[40] Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.

[41] Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in systematic reviews. Syst Rev. 2021;10(1):39.

[42] Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-473.

[43] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[44] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605.

[45] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

[46] Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

[47] Schünemann HJ, Cuello C, Akl EA, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol. 2019;111:105-114.

[48] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55-61.

[49] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-188.

[50] Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016;7(1):55-79.

[51] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.

[52] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634.

[53] Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. York: University of York; 2009.

[54] Crombach G, Scharl A, Vierbuchen M, et al. Detection of squamous cell carcinoma antigen in normal squamous epithelia and in squamous cell carcinomas of the uterine cervix. Cancer. 1989;63(7):1337-1342.

[55] Bolli JA, Doering DL, Bosscher JR, et al. Squamous cell carcinoma antigen: clinical significance in squamous cell carcinoma of the uterine cervix. Gynecol Oncol. 1994;55(2):169-173.

[56] Kato H, Miyauchi F, Morioka H, et al. Tumor antigen of human cervical squamous cell carcinoma: correlation of circulating levels with disease stage. Cancer. 1979;43(2):585-590.

[57] Jacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod. 1989;4(1):1-12.

[58] Bast RC Jr, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983;309(15):883-887.

[59] Waggoner SE, Anderson SM, Luce MC, et al. p53 protein expression and gene analysis in clear cell adenocarcinoma of the vagina and cervix. Gynecol Oncol. 1996;60(3):339-344.

[60] Ngan HY, Cheung AN, Liu SS, et al. Abnormal expression or mutation of TP53 correlates with chemoresistance and poor prognosis in epithelial ovarian cancer. Gynecol Oncol. 1999;75(2):216-220.

[61] Duk JM, Groenier KH, de Bruijn HW, et al. Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. J Clin Oncol. 1996;14(1):111-118.

[62] Jacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod. 1989;4(1):1-12.

[63] Bast RC Jr, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983;309(15):883-887.

[64] Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72-78.

[65] Salvatici M, Achilarre MT, Sandri MT, et al. Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence. Gynecol Oncol. 2016;142(1):115-119.

[66] Hong JH, Tsai CS, Chang JT, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. Int J Radiat Oncol Biol Phys. 1998;41(4):823-830.

[67] Hong JH, Tsai CS, Lai CH, et al. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2004;60(1):249-257.

[68] Molina R, Ojeda B, Filella X, et al. Study of five tumor markers (SCC, cyfra 21-1, TPS, TPA and CEA) in patients with cervical cancer. Anticancer Res. 2009;29(12):4867-4874.

[69] Gadducci A, Ferdeghini M, Buttitta F, et al. Assessment of the prognostic relevance of serum TPA, TPS, CYFRA 21-1, and SCC-Ag levels in squamous cell carcinoma of the cervix. Gynecol Oncol. 1994;54(2):154-159.

[70] Takeda M, Sakuragi N, Okamoto K, et al. Preoperative serum SCC, CA125, and CA19-9 levels and lymph node status in squamous cell carcinoma of the uterine cervix. Acta Obstet Gynecol Scand. 2002;81(5):451-457.

[71] Scambia G, Benedetti Panici P, Foti E, et al. Squamous cell carcinoma antigen: prognostic significance and role

in the monitoring of neoadjuvant chemotherapy response in cervical cancer. J Clin Oncol. 1994;12(11):2309-2316.

[72] Micke O, Prott FJ, Schafer U, et al. The impact of squamous cell carcinoma antigen in the follow-up after radiotherapy in patients with cervical cancer. Gynecol Oncol. 2000;78(1):27-30.

[73] Sturgeon CM, Duffy MJ, Hofmann BR, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. Clin Chem. 2010;56(6):e1-48.

[74] Reesink-Peters N, van der Velden J, Ten Hoor KA, et al. Preoperative serum squamous cell carcinoma antigen levels in clinical decision making for patients with early-stage cervical cancer. J Clin Oncol. 2005;23(7):1455-1462.

[75] Chung HH, Jo H, Kang WJ, et al. Clinical impact of postoperative residual disease on cervical cancer treated with radical hysterectomy. Gynecol Oncol. 2008;108(1):137-142.

[76] Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med. 1965;121(3):439-462.

[77] Thompson JA, Grunert F, Zimmermann W. Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. J Clin Lab Anal. 1991;5(5):344-366.

[78] Borras G, Molina R, Xercavins J, et al. Tumor antigens CA 19.9, CA 125, and CEA in carcinoma of the uterine cervix. Gynecol Oncol. 1995;57(2):205-211.

[79] Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem. 2001;47(4):624-630.

[80] Gaarenstroom KN, Bonfrer JM, Kenter GG, et al. Clinical value of pretreatment serum CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen levels in patients with cervical cancer. Cancer. 1995;76(5):807-813.

[81] Duffy MJ. Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract. 2013;22(1):4-11.

[82] Canney PA, Moore M, Wilkinson PM, James RD. Ovarian cancer antigen CA125: a prospective clinical assessment of its role as a tumour marker. Br J Cancer. 1984;50(6):765-769.

[83] Bonfrer JM, Gaarenstroom KN, Kenter GG, et al. Prognostic significance of CA 125 in cervical cancer: the influence of tumor stage, histologic type, tumor grade, and patient age. Cancer. 1994;74(12):3142-3148.

[84] Bonfrer JM, Gaarenstroom KN, Kenter GG, et al. Prognostic significance of CA 125 in cervical cancer: the influence of tumor stage, histologic type, tumor grade, and patient age. Cancer. 1994;74(12):3142-3148.

[85] Bon GG, Kenemans P, Dekker JJ, et al. Fluctuation of CA 125 serum concentrations during the menstrual cycle. Gynecol Oncol. 1999;73(3):356-361.

[86] Jacobs I, Stabile I, Bridges J, et al. Multimodal approach to screening for ovarian cancer. Lancet. 1988;1(8580):268-271.

[87] Bon GG, Kenemans P, Dekker JJ, et al. Fluctuation of CA 125 serum concentrations during the menstrual cycle. Gynecol Oncol. 1999;73(3):356-361.

[88] Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrioid adenocarcinoma of the uterine cervix. Am J Obstet Gynecol. 1989;161(5):1281-1285.

[89] Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21(2):419-423.

[90] Ueno T, Toi M, Saji H, et al. Significance of macrophage chemoattractant protein-1 in macrophage recruitment, angiogenesis, and survival in human breast cancer. Clin Cancer Res. 2000;6(8):3282-3289.

[91] Nakata B, Takashima T, Ogawa Y, et al. Serum CYFRA 21-1 (cytokeratin-19 fragments) is a useful tumour marker for detecting disease relapse and assessing treatment efficacy in breast cancer. Br J Cancer. 2004;91(5):873-878.

[92] Molina R, Filella X, Jo J, et al. Serum levels of C-reactive protein, squamous cell carcinoma antigen, carcinoembryonic antigen, neuron specific enolase, tissue polypeptide antigen and tissue polypeptide specific antigen in patients with cervical cancer. Tumour Biol. 2005;26(6):284-292.

[93] Gadducci A, Ferdeghini M, Buttitta F, et al. Assessment of the prognostic relevance of serum TPA, TPS, CYFRA 21-1, and SCC-Ag levels in squamous cell carcinoma of the cervix. Gynecol Oncol. 1994;54(2):154-

159.

[94] Duffy MJ, Sturgeon C, Lamerz R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441-447.

[95] Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol. 1990;85(4):350-355.

[96] Hong JH, Tsai CS, Chang JT, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. Int J Radiat Oncol Biol Phys. 1998;41(4):823-830.

[97] Reesink-Peters N, van der Velden J, Ten Hoor KA, et al. Preoperative serum squamous cell carcinoma antigen levels in clinical decision making for patients with early-stage cervical cancer. J Clin Oncol. 2005;23(7):1455-1462.

[98] Takeda M, Sakuragi N, Okamoto K, et al. Preoperative serum SCC, CA125, and CA19-9 levels and lymph node status in squamous cell carcinoma of the uterine cervix. Acta Obstet Gynecol Scand. 2002;81(5):451-457.

[99] Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrioid adenocarcinoma of the uterine cervix. Am J Obstet Gynecol. 1989;161(5):1281-1285.

[100] Scambia G, Benedetti Panici P, Foti E, et al. Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. J Clin Oncol. 1994;12(11):2309-2316.

[101] Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72-78.

[102] Chung HH, Jo H, Kang WJ, et al. Clinical impact of postoperative residual disease on cervical cancer treated with radical hysterectomy. Gynecol Oncol. 2008;108(1):137-142.

[103] Hong JH, Tsai CS, Chang JT, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. Int J Radiat Oncol Biol Phys. 1998;41(4):823-830.

[104] Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int J Cancer. 2014;134(11):2513-2522.

[105] Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72-78.

[106] Ngan HY, Cheung AN, Liu SS, et al. Tumour markers and their prognostic significance in cervical cancer. Clin Oncol. 2000;12(1):44-51.

[107] Waggoner SE. Cervical cancer. Lancet. 2003;361(9376):2217-2225.

[108] Moore DH. Cervical cancer. Obstet Gynecol. 2006;107(5):1152-1161.

[109] Salvatici M, Achilarre MT, Sandri MT, et al. Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence. Gynecol Oncol. 2016;142(1):115-119.

[110] Micke O, Bruns F, Kurowski R, et al. Predictive value of carbohydrate antigen 125 (CA 125) for response to radiotherapy in patients with cervical cancer. Strahlenther Onkol. 2005;181(5):329-334.

[111] van der Zee AG, Hollema H, de Jong S, et al. P53 immunostaining is not a prognostic indicator for cervical cancer. J Clin Pathol. 1995;48(2):130-134.

[112] Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem. 2001;47(4):624-630.

[113] Gadducci A, Tana R, Cosio S, Genazzani AR. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. Crit Rev Oncol Hematol. 2008;66(1):10-20.

[114] Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. Gynecol Oncol. 2000;78(2):97-105.

[115] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26(35):5802-5812.

[116] Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical

trials: the ISPOR RCT-CEA Task Force report. Value Health. 2005;8(5):521-533.

[117] Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

[118] Reesink-Peters N, van der Velden J, Ten Hoor KA, et al. Preoperative serum squamous cell carcinoma antigen levels in clinical decision making for patients with early-stage cervical cancer. J Clin Oncol. 2005;23(7):1455-1462.

[119] Molina R, Ojeda B, Filella X, et al. Study of five tumor markers (SCC, cyfra 21-1, TPS, TPA and CEA) in patients with cervical cancer. Anticancer Res. 2009;29(12):4867-4874.

[120] Kourou K, Exarchos TP, Exarchos KP, et al. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J. 2015;13:8-17.

[121] Nimse SB, Sonawane MD, Song KS, Kim T. Biomarker detection technologies and future directions. Analyst. 2016;141(3):740-755.

[122] Shortliffe EH, Sepúlveda MJ. Clinical decision support in the era of artificial intelligence. JAMA. 2018;320(21):2199-2200.

[123] Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-387.

[124] Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.

[125] Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet. 2009;105(2):107-108.

[126] Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018;143 Suppl 2:22-36.

[127] Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-387.

[128] Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.

[129] Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. Gynecol Oncol. 2000;78(2):97-105.

[130] Vizcaino AP, Moreno V, Bosch FX, et al. International trends in the incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. Int J Cancer. 1998;75(4):536-545.

[131] Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27(2):157-172.

[132] Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007;115(7):928-935.

[133] van Gils CH, Otten JD, Verbeek AL, Hendriks JH. Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands. J Epidemiol Community Health. 1998;52(4):267-271.

[134] Gadducci A, Tana R, Cosio S, Genazzani AR. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. Crit Rev Oncol Hematol. 2008;66(1):10-20.

[135] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26(35):5802-5812.

[136] Etzioni R, Urban N, Ramsey S, et al. The case for early detection. Nat Rev Cancer. 2003;3(4):243-252.

[137] Molina R, Ojeda B, Filella X, et al. Study of five tumor markers (SCC, cyfra 21-1, TPS, TPA and CEA) in patients with cervical cancer. Anticancer Res. 2009;29(12):4867-4874.

[138] Gadducci A, Ferdeghini M, Buttitta F, et al. Assessment of the prognostic relevance of serum TPA, TPS, CYFRA 21-1, and SCC-Ag levels in squamous cell carcinoma of the cervix. Gynecol Oncol. 1994;54(2):154-159.

[139] Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS Med. 2013;10(2):e1001380.

[140] Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-286.

[141] Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72-78.

[142] Salvatici M, Achilarre MT, Sandri MT, et al. Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence. Gynecol Oncol. 2016;142(1):115-119.

[143] Hong JH, Tsai CS, Chang JT, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. Int J Radiat Oncol Biol Phys. 1998;41(4):823-830.

[144] Kourou K, Exarchos TP, Exarchos KP, et al. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J. 2015;13:8-17.

[145] Cruz JA, Wishart DS. Applications of machine learning in cancer prediction and prognosis. Cancer Inform. 2007;2:59-77.

[146] Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681-692.

[147] Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med. 2019;380(14):1347-1358.

[148] Steyerberg EW, Harrell FE Jr, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54(8):774-781.

[149] Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. Nat Rev Drug Discov. 2013;12(5):358-369.

[150] Shortliffe EH, Sepúlveda MJ. Clinical decision support in the era of artificial intelligence. JAMA. 2018;320(21):2199-2200.

[151] Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS Med. 2013;10(2):e1001380.

[152] Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-286.

[153] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[154] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605.

[155] Miller WG, Myers GL, Ashwood ER, et al. State of the art in trueness and interlaboratory harmonization for 10 analytes in general clinical chemistry. Arch Pathol Lab Med. 2008;132(5):838-846.

[156] Vesper HW, Miller WG, Myers GL. Reference materials and commutability. Clin Biochem Rev. 2007;28(4):139-147.

[157] Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. Gynecol Oncol. 2000;78(2):97-105.

[158] Vizcaino AP, Moreno V, Bosch FX, et al. International trends in the incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. Int J Cancer. 1998;75(4):536-545.

[159] Duffy MJ. Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract. 2013;22(1):4-11.

[160] Sölétormos G, Duffy MJ, Othman Abu Hassan S, et al. Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European Group on Tumor Markers. Int J Gynecol Cancer. 2016;26(1):43-51.

[161] Sturgeon CM, Hoffman BR, Chan DW, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in clinical practice: quality requirements. Clin Chem. 2008;54(8):1379-1391.

[162] Sokoll LJ, Babaian RJ, Chan DW, et al. Prostate-specific antigen detected by ultrasensitive assay in patients with metastatic and locally advanced prostate cancer. Clin Chem. 2003;49(4):645-649.

[163] Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health. 2005;8(5):521-533.

[164] Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

[165] Miller WG, Jones GR, Horowitz GL, Weykamp C. Proficiency testing/external quality assessment: current challenges and future directions. Clin Chem. 2011;57(12):1670-1680.

[166] Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of sigma metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. Am J Clin Pathol. 2006;125(3):343-354.

[167] Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int J Cancer. 2014;134(11):2513-2522.

[168] Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313-5327.

[169] Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681-692.

[170] Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. N Engl J Med. 2012;366(9):780-781.

[171] Wan JC, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223-238.

[172] Ignatiadis M, Lee M, Jeffrey SS. Circulating tumor cells and circulating tumor DNA: challenges and opportunities on the path to clinical utility. Clin Cancer Res. 2015;21(21):4786-4800.

[173] Tian J, Geng Y, Lv D, et al. Using plasma cell-free DNA to monitor the chemoradiotherapy course of cervical cancer. Int J Cancer. 2019;145(9):2547-2557.

[174] Campitelli M, Jeannot E, Peter M, et al. Human papillomavirus mutational insertion: specific marker of circulating tumor DNA in cervical cancer patients. PLoS One. 2012;7(8):e43393.

[175] Forshew T, Murtaza M, Parkinson C, et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. Sci Transl Med. 2012;4(136):136ra68.

[176] Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med. 2014;6(224):224ra24.

[177] Alix-Panabières C, Pantel K. Liquid biopsy: from discovery to clinical application. Cancer Discov. 2021;11(4):858-873.

[178] Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet. 2019;20(2):71-88.

[179] Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med. 2019;380(14):1347-1358.

[180] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56.

[181] Shortliffe EH, Sepúlveda MJ. Clinical decision support in the era of artificial intelligence. JAMA. 2018;320(21):2199-2200.

[182] Sutton RT, Pincock D, Baumgart DC, et al. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med. 2020;3:17.

[183] Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. Nat Rev Drug Discov. 2013;12(5):358-369.

[184] Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and platform trials: a brief primer and highlights of emerging challenges. Ann Oncol. 2017;28(4):743-747.

[185] Holch JW, Ricard I, Stintzing S, et al. The relevance of baseline circulating tumor DNA analysis for treatment monitoring in metastatic colorectal cancer. PLoS One. 2017;12(3):e0174263.

[186] Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med. 2016;8(346):346ra92.

[187] Nimse SB, Sonawane MD, Song KS, Kim T. Biomarker detection technologies and future directions. Analyst. 2016;141(3):740-755.

[188] Pai NP, Vadnais C, Denkinger C, et al. Point-of-care testing for infectious diseases: diversity, complexity, and barriers in developing countries. PLoS Med. 2012;9(9):e1001306.