Free intraperitoneal tumor cells and outcome in gastric cancer patients: a systematic review and meta-analysis

Mathieu Pecqueux¹,*, Johannes Fritzmann¹,*, Mariam Adamu¹, Kristian Thorlund², Christoph Kahlert¹, Christoph Reißfelder¹, Jürgen Weitz¹ and Nuh N. Rahbari¹

¹ Department for Visceral, Thoracic and Vascular Surgery, University of Dresden, Dresden, Germany
² Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada

* These authors contributed equally to this work

Correspondence to: Nuh N. Rahbari, email: nuh.rahbari@uniklinikum-dresden.de

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ABSTRACT

Purpose: Despite continuously improving therapies, gastric cancer still shows poor survival in locally advanced stages with local recurrence rates of up to 50% and peritoneal recurrence rates of 17% after curative surgery. We performed a systematic review with meta-analyses to clarify whether positive intraperitoneal cytology (IPC) indicates a high risk of disease recurrence and poor overall survival in gastric cancer.

Methods: Multiple databases were searched in December 2014 to identify studies on the prognostic significance of positive intraperitoneal cytology in gastric cancer, including: Medline, Biosis, Science Citation Index, Embase, CCMed and publisher databases. Hazard ratios (HR) and associated 95% confidence intervals (CI) were extracted from the identified studies. A meta-analysis was performed using a random-effects model on overall survival, disease-free survival and peritoneal recurrence free survival.

Results: A total of 64 studies with a cumulative sample size of 12,883 patients were included. Cytology, quantitative real time polymerase chain reaction (PCR) or both were performed in 35; 21 and 8 studies, respectively. Meta analyses revealed free intraperitoneal tumor cells (FITC) to be associated with poor overall survival in univariate (HR 3.27; 95% CI 2.82 - 3.78) and multivariate (HR 2.45; 95% CI 2.04 - 2.94) analysis and poor peritoneal recurrence free survival in univariate (4.15; 95% CI 3.10 - 5.57) and multivariate (3.09; 95% CI 2.02 - 4.71) analysis. Subgroup analysis showed this effect to be independent of the detection method, Western or Asian origin or the time of publication.

Conclusions: FITC oder positive peritoneal cytology is associated with poor survival and increased peritoneal recurrence in gastric cancer.

INTRODUCTION

Every year around one million new cases of gastric cancer are diagnosed globally. In 2012, 723,000 people died from gastric cancer, ranking it the 4th most common cancer-related cause of death. Complete surgical resection together with perioperative chemotherapy represents the standard of care for curative treatment of patients with gastric cancer [1-3]. However, even after multimodal therapy up to 40% of the patients experience disease recurrence and up to 30% die within 12 months [4].

Peritoneal dissemination is a common cause of failure after curative treatment for gastric cancer. Peritoneal recurrence occurs in 17% of patients undergoing resection with curative intent and is associated with a dismal survival [5, 6]. Due to the frequent occurrence and the strong prognostic relevance of peritoneal metastases, detection of free intraperitoneal tumor cells (FITC) has been suggested as a prognostic and predictive biomarker in gastric cancer patients [7, 8]. Detection of FITC may help
to recognize those patients considered for curative therapy who are at high-risk for early tumor relapse and might benefit from intensified treatments such as hyperthermic intraperitoneal chemotherapy (HIPEC) [9]. Numerous studies have so far been conducted on the prognostic and predictive value of FITC in gastric cancer. Although FITC are found in 6-49% of gastric cancer patients considered for curative surgery [10-13], its predictive and prognostic value has remained unclear due to inconsistent detection techniques and results of the individual studies. This clinical uncertainty is reflected by inconsistent recommendations made by different guidelines on the use of FITC in the management of gastric cancer [1-3, 14].

To clarify the role of intraperitoneal lavage cytology as a prognostic biomarker in gastric cancer, we performed a systematic review with meta-analyses of studies on the prognostic significance of FITC detection in peritoneal lavage samples of patients with gastric cancer considered for curative therapy.
RESULTS

Baseline study characteristics

In total, we included 64 studies [10-13, 15-68] with a cumulative sample size of 12,883 patients (Figure 1). These studies had a median sample size of 134 (52 - 1297) patients and were published between 1978 and 2014 (Table 1). The included studies were conducted in Western institutions in 19% and in Asian institutions in 81%. Patients with stage IV disease were enrolled in 30 (47%) studies. The median follow up across all studies was 35 (18 - 82) months. FITC were detected by cytology in 43 (67%) studies (38 studies used Papanicolaou staining, 5 studies used H&E staining), by immunocytochemistry (ICC) in 5 (8%) studies and by RT-PCR in 29 (45%) studies (Table 2). The majority of studies used Carcinoembryonic antigen (CEA) for molecular tumor cell detection. In 22 studies CEA expression was analyzed and in seven studies CK20 expression was analyzed. Further markers included CK19, CD44, Caspase 9, MINT, MAGE, MMP 7, CA125, TGFβ, RegIV, FABP1, Muc2, IL-17 and CDH1. The detection rate of FITC across the included studies varied markedly (median: 23%; range 6% - 58%) and showed a strong association with patients’ stage of disease and in particular the inclusion of patients with overt peritoneal metastases. FITC were detected prior to resection in 62 (97%) studies and pre- as well as postoperatively in 2 (3%) studies. OS, DSS, DFS and PRFS was reported in 51 (80%), 7 (11%), 11 (17%) and 21 (33%) studies, respectively. Hazard ratios for multivariate analysis could be extracted in 21 studies (ten that performed cytology, eight that performed RT-PCR and three that performed both). Fifteen studies were graded with a low risk of bias (Appendix 1). Funnel plot analyses did not indicate significant publication bias for the analyzed outcomes (Appendix 2).

Figure 1: Flow diagram showing the selection process for relevant studies.
Prognostic value of FITC detection

Some 51 studies with a cumulative sample size of 11,005 patients reported on OS. The pooled analyses of the results from these studies showed a strong prognostic value of FITC detection (HR 3.27, 95% CI 2.82 - 3.78; n = 51; I² = 74%) (Figure 2). This result could be verified in the 35 studies with curatively resected patients and a cumulative sample size of 5908 (3.51; 3.01 - 4.08; n = 35; I² = 48%) (Table 3) [10-13, 16-19, 22, 24, 30-35, 37, 41, 44-49, 51, 56, 59, 60, 62, 65, 66, 68, 69]. Sensitivity analyses failed to identify a single study as a reason for the observed statistical heterogeneity. Meta-analysis of the results from 17 studies with multivariate analyses confirmed the prognostic association of FITC detection with reduced
Subgroup analyses

Subgroup analyses were performed to assess the impact of the detection method on the results. These analyses revealed a prognostic association of FITC detection by cytology with OS (3.03; 2.55 - 3.61; n = 35; I² = 78%) [10, 11, 13, 15-19, 21, 22, 24, 25, 28, 30, 33, 34, 38-41, 43, 44, 46, 47, 49-52, 57, 60, 61, 63, 65, 66,
Despite a lower number of studies we observed a more pronounced prognostic value for pooled analyses of studies using RT-PCR (3.64; 2.93 - 4.53; n = 19; I² = 49%).

Table 3: Subgroup analyses for overall survival in FITC positive patients and curatively resected FITC positive patients.

| Overall Survival | Overall Survival (Curative) |
|------------------|-----------------------------|
| HR               | 95% CI | Heterogeneity I² (%) | P-value | Included Studies | HR | 95% CI | Heterogeneity I² (%) | P-value | Included Studies |
| Total:           |        |                      |         |                 |    |        |                      |         |                 |
| Multivariate:    |        |                      |         |                 |    |        |                      |         |                 |
| Detection Method:|        |                      |         |                 |    |        |                      |         |                 |
| CY               |        |                      |         |                 |    |        |                      |         |                 |
| PCR              |        |                      |         |                 |    |        |                      |         |                 |
| Stage of disease|        |                      |         |                 |    |        |                      |         |                 |
| Advanced stage of disease | |                  |         |                 |    |        |                      |         |                 |
| Any stage        |        |                      |         |                 |    |        |                      |         |                 |
| Date of publication up to and including 2005 | |                  |         |                 |    |        |                      |         |                 |
| 2005             |        |                      |         |                 |    |        |                      |         |                 |
| Study population |        |                      |         |                 |    |        |                      |         |                 |
| Asian            |        |                      |         |                 |    |        |                      |         |                 |
| Western          |        |                      |         |                 |    |        |                      |         |                 |
| Size of study population |        |                      |         |                 |    |        |                      |         |                 |
| Median           |        |                      |         |                 |    |        |                      |         |                 |
| Risk of bias     |        |                      |         |                 |    |        |                      |         |                 |
| High             |        |                      |         |                 |    |        |                      |         |                 |
| Low              |        |                      |         |                 |    |        |                      |         |                 |
| Lavage fluid     |        |                      |         |                 |    |        |                      |         |                 |
| >150 ml          |        |                      |         |                 |    |        |                      |         |                 |
| <150 ml          |        |                      |         |                 |    |        |                      |         |                 |
| FITC positive (%)|        |                      |         |                 |    |        |                      |         |                 |
| Median           |        |                      |         |                 |    |        |                      |         |                 |
| Chemotherapy     |        |                      |         |                 |    |        |                      |         |                 |
| >25% adj. Chemor |        |                      |         |                 |    |        |                      |         |                 |
| <25% adj. Chemor |        |                      |         |                 |    |        |                      |         |                 |
| no adj. Chemor   |        |                      |         |                 |    |        |                      |         |                 |
| no reoad. Chemor |        |                      |         |                 |    |        |                      |         |                 |

Table 4: Subgroup analyses for disease free survival (DFS) and peritoneal recurrence free survival (PRFS) in FITC positive patients.

| DFS | PRFS |
|-----|------|
| HR  | 95% CI | Heterogeneity I² (%) | P-value | Included Studies | HR  | 95% CI | Heterogeneity I² (%) | P-value | Included Studies |
| Total: |        |                      |         |                 |    |        |                      |         |                 |
| Multivariate: |        |                      |         |                 |    |        |                      |         |                 |
| Detection Method: |        |                      |         |                 |    |        |                      |         |                 |
| CY |        |                      |         |                 |    |        |                      |         |                 |
| PCR |        |                      |         |                 |    |        |                      |         |                 |
| Stage of disease |        |                      |         |                 |    |        |                      |         |                 |
| Curative |        |                      |         |                 |    |        |                      |         |                 |
| Advanced |        |                      |         |                 |    |        |                      |         |                 |
| Not advanced |        |                      |         |                 |    |        |                      |         |                 |
| Date of publication up to and including 2005 | |                  |         |                 |    |        |                      |         |                 |
| 2005 |        |                      |         |                 |    |        |                      |         |                 |
| Study population |        |                      |         |                 |    |        |                      |         |                 |
| Asian |        |                      |         |                 |    |        |                      |         |                 |
| Western |        |                      |         |                 |    |        |                      |         |                 |
| Size of study population |        |                      |         |                 |    |        |                      |         |                 |
| Median |        |                      |         |                 |    |        |                      |         |                 |
| Risk of bias |        |                      |         |                 |    |        |                      |         |                 |
| High |        |                      |         |                 |    |        |                      |         |                 |
| Low |        |                      |         |                 |    |        |                      |         |                 |
| Lavage fluid |        |                      |         |                 |    |        |                      |         |                 |
| >150 ml |        |                      |         |                 |    |        |                      |         |                 |
| <150 ml |        |                      |         |                 |    |        |                      |         |                 |
| Cytology positive patients |        |                      |         |                 |    |        |                      |         |                 |
| Median |        |                      |         |                 |    |        |                      |         |                 |
| Chemotherapy |        |                      |         |                 |    |        |                      |         |                 |
| >25% adj. Chemor |        |                      |         |                 |    |        |                      |         |                 |
| <25% adj. Chemor |        |                      |         |                 |    |        |                      |         |                 |
| no adj. Chemor |        |                      |         |                 |    |        |                      |         |                 |
| no reoad. Chemor |        |                      |         |                 |    |        |                      |         |                 |

Legend: HR: Hazard Ratio; 95% CI: 95% confidence interval; CY = cytology; PCR = polymerase chain reaction

69]. Despite a lower number of studies we observed a more pronounced prognostic value for pooled analyses of studies using RT-PCR (3.64; 2.93 - 4.53; n = 19; I² = 49%). This difference reached statistical significance in the test of interaction for the subgroup of patients who...
underwent potentially curative resection ($p = 0.012$). The kind of detection method had no impact on the prognostic value with respect to DFS and PRFS (Table 3, Table 4).

We next evaluated the prognostic value of FITC in patients with advanced stages as compared to the entire patient cohort. Only one study reported outcome selectively for patients with early stage of disease (without lymph node metastases) [51]. There was a significant association of FITC detection with OS in patients with advanced disease as well as the entire cohort. However, in particular for patients who underwent a potentially curative resection, the magnitude of effect was lower in case of advanced disease (2.52; 2.10 - 3.02; $n = 12$; $I^2 = 24\%$)[16, 18, 25, 27, 30, 36, 47, 51, 59, 60, 65, 66] than

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**Figure 3: Treatment algorithm for gastric cancer**

- **Gastric cancer**
  - **T1 N0**
    - Consider endoscopic/limited resection
  - **>T1N0**
    - Laparoscopy + peritoneal lavage
      - FITC positive
        - **T2N0**: consider preoperative Chemotherapy
          - Laparoscopy + peritoneal lavage
            - FITC positive
              - low risk patients surgery (consider HIPEC)
                - Adjuvant Chemotherapy
            - high risk patients palliative Therapy
            - Adjuvant Chemotherapy
        - **>T2 and/or N+**:
          - Preoperative Chemotherapy
      - FITC negative
        - **>T2 and/or N+**:
          - Preoperative chemotherapy
      - **T2N0**:
        - surgery
          - Adjuvant Chemotherapy
    - Palliative Therapy
  - **Palliative**

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for studies including the entire population (3.23; 2.98 - 3.50; n = 27; F = 41%)[10-13, 17, 19, 22, 24, 31-35, 41, 45, 46, 48, 49, 51, 56, 59, 62, 65, 68, 69] (p = 0.014; test of interaction). The increased prognostic value of FITC detection in patients with less advanced disease was confirmed for PRFS (p = 0.008, test of interaction). There was not enough data for a pooled analysis of advanced disease for DFS (n = 2).

Previous studies suggested genetic differences between gastric cancers dependent on geographic location [74-76]. We therefore evaluated the prognostic value of FITC detection separately for these cohorts. These analyses showed a significant association between FITC detection and OS for Asian population (3.31; 2.77 - 3.95; n = 38; F = 78%) [11-13, 16, 18, 20-22, 24, 26, 30-35, 38, 40, 41, 43, 45, 46, 48, 52, 55-57, 60-68] as well as Western population (3.17; 2.50 - 4.01; n = 13; F = 48%) [10, 15, 17, 19, 28, 39, 44, 47, 49-51, 59, 69]. Significant associations for both cohorts were also present for patients who underwent a curative resection as well as the outcomes DFS and PRFS with no significant difference between both population as indicated by the tests of interaction.

Systemic chemotherapy has become common practice in the curative therapy of advanced gastric cancer [1, 77, 78], though the optimal regimen is still subject to intensive research [77]. Previous studies showed that 60-90% of FITC positive patients can be converted to FITC negative by neoadjuvant chemotherapy and thus improve survival [79, 80]. We therefore evaluated the prognostic value of FITC depending on the administration of neoadjuvant and adjuvant chemotherapy, respectively. These analyses revealed a strong association of FITC detection and OS, DFS and PRFS independent of the administration of neoadjuvant or adjuvant chemotherapy.

To exclude that the observed results were primarily caused by studies with low methodological quality, further analyses were stratified for the risk of bias. While studies with low (3.96; 2.92 - 5.38; n = 12; F = 63%)[11, 28, 38, 39, 47, 48, 51, 55, 65] and high risk of bias (3.08; 2.62 - 3.62; n = 39; F = 74%)[10, 13, 15-24, 26, 30-34, 40, 41, 43-46, 49, 50, 52, 56, 57, 59-64, 66-69] showed a significant prognostic value for FITC detection on OS, the effect was more pronounced in studies with low risk of bias (p = 0.15; test of interaction). The enhanced prognostic value reported in studies with a low risk of bias supports the validity of the finding that FITC detection represents a strong prognostic marker in gastric cancer.

**DISCUSSION**

This systematic review and meta-analysis shows a marked association of FITC with overall survival, disease free survival and peritoneal recurrence free survival of patients with gastric cancer scheduled for curative therapy.

Although the first studies on detection of FITC in gastric cancer patients have been published over 60 years ago [81], the role of FITC detection in the management of patients with gastric cancer has remained highly controversial. This may in part be explained by different study designs and insufficient statistical power of individual studies, in particular for subpopulations of patients with different extent of disease. In line with this, current gastric cancer treatment guidelines do not provide uniform recommendations on the use of peritoneal lavage. Although the majority of guidelines classify FITC detection as metastatic (M1) disease, these recommendations are based on single or a few individual studies, are limited to peritoneal lavage cytology and do not provide any standardization with respect to the sampling time and sampling/detection methodology (i.e. amount of lavage fluid, kind of staining). While the NCCN guidelines recommend a staging laparoscopy with peritoneal washings for cytology for stage IB and higher, the European ESMO, ESSO, ESTRO guidelines are less stringent and recommend a staging laparoscopy with or without peritoneal washings for malignant cells in these patients [1, 2]. Furthermore, there is no consensus regarding the consequences of a positive peritoneal cytology on patients’ clinical management. In the NCCN guidelines a positive peritoneal cytology is considered a criterion of unresectability for cure. The European guidelines do not comment on the consequences for surgical resection and the German guidelines state no relevance on patients’ further management [1, 2, 14]. As in these guidelines positive peritoneal cytology is classified as M1 disease and palliative treatment is recommended in M1 patients, there is urgent need to clarify which patients at what timepoint should undergo peritoneal lavage sampling by what methodology [26, 67, 73].

The results of the present meta-analysis confirm FITC as poor prognostic marker in patients with gastric cancer. Importantly, our results demonstrate the prognostic value of FITC detection to be dependent on the extent of disease. A more pronounced prognostic relevance is shown in patients with limited disease and a curative resection, respectively. Identification of strong prognostic markers might be useful in the management of gastric cancer patients in various ways. First, prognostic biomarkers might, moreover, serve as predictive biomarkers in patients considered for perioperative chemotherapy. Second, reliable prognostic information may be of particular help in decision-making for further treatment in elderly patients or patients with severe comorbidities who may be at increased risk for complications and poor outcome after multi-modal therapy. As total gastrectomy is associated with relevant morbidity and 90-day mortality, [82] a strong prognostic biomarker might be helpful to avoid surgery in high-risk patients with a poor prognosis. Third, it may be helpful in the management of young patients with excellent performance status who may be able to tolerate intensive therapy. Fourth, validation of FITC as...
strong prognostic biomarkers provide a valid scientific rationale for subsequent research to further characterize these cells on a molecular level. As targeted therapies are emerging for gastric cancer, [83] it is of particular interest, if molecular analysis of free intraperitoneal tumor cells might serve as a predictive biomarker for targeted agents in gastric cancer patients.

There is indeed increasing effort to identify patients with gastrointestinal malignancies and peritoneal metastases who benefit from intensified therapies such as HIPEC [84-86]. At present, these efforts mainly focus on patients with overt peritoneal metastases and showed promising results for colorectal cancer [87, 88]. The findings were much more modest for gastric cancer patients with overt peritoneal metastasis [89, 90] and may be explained by limitations to achieve complete cytoreduction [91]. These data suggest FITC positive gastric cancer without further distant metastasis as a promising subgroup of patients who might benefit from HIPEC. The first randomized controlled study to examine the benefit of extensive intraoperative peritoneal lavage followed by intraoperative chemotherapy in FITC positive gastric cancer showed promising results [92]. Further randomized controlled trials have already been initiated (ClinicalTrials.gov; NCT01683864). The results may redefine the treatment of FITC positive gastric cancer.

The optimal method of FITC detection remains to be determined. As outlined current guidelines are restricted to conventional cytology without providing further information on the kind of staining. Our results indicate a prognostic value of FITC detection by cytology as well as molecular techniques. To date, only few studies directly compared cytology by Papanicolaou staining with molecular detection by PCR [23, 29, 38, 53, 55-57, 59, 65]. Detection methods using PCR offer a considerably higher detection sensitivity at a marginally lower specificity (Appendix 3). This meta-analysis demonstrates a similar prognostic value for both detection methods. The results of the above studies imply a potential superiority of FITC detection by PCR, that needs to be substantiated within prospective trials before valid recommendations can be made in guidelines.

The use of peritoneal lavage in patients undergoing multimodal therapy remains a further question to be answered. While metabolic imaging has been proposed as a strategy for early response assessment in patients with cancers of the esophagogastric junction and stomach [93-95], peritoneal washings with detection of FITC may offer an additional or alternative approach. There is indeed evidence that clearance of positive peritoneal cytology by systemic chemotherapy is associated with improved outcome after surgical resection for gastric cancer [96, 97]. However, controlled clinical trials are required to clarify the benefit of surgical resection in patients who remain positive for FITC after chemotherapy.

One important question that needs answering is how to proceed with FITC positive patients with potentially curative gastric cancer. Considering the results of this meta-analysis we would like to propose a therapeutic algorithm (Figure 3). However, the feasibility and clinical utility of this algorithm needs to be tested in controlled clinical trials.

In conclusion, this meta-analysis reveals FITC detection as poor prognostic marker in gastric cancer patients scheduled for curative therapy. The prognostic value of FITC was noted across detection methods, administration of chemotherapy and geographic location, though a more pronounced effect was observed in patients with less advanced disease. These results support efforts to use FITC as a predictive biomarker and may contribute to the development of uniform international treatment guidelines with the ultimate aim to improve individualized therapy and outcomes of patients with gastric cancer.

**MATERIALS AND METHODS**

This systematic review was performed according to the recommendations of the PRISMA statement [98].

**Search strategy**

A systematic search of the following databases was performed in December 2014: Medline, Science Citation Index, Embase, CCMed, Publisher Database, ASCO abstracts. Additionally, clinical trial registries such as WHO International Clinical Trials Registry and ClinicalTrials.gov were searched. Search strategies included the Medical Subject Headings (MeSH) “Stomach Neoplasm”; “Peritoneal Lavage”; “Therapeutic Irrigation”; “Cytology” as well as the text terms “gastric cancer”, “peritoneal”; “washing”, “lavage” and “cytology” in various combinations. In addition, we searched the reference lists of relevant articles and review articles. No time and language restrictions were applied to the initial search. The identified titles and abstracts were screened for eligibility by two independent reviewers (MP and MA). Full articles of potentially relevant studies were obtained for detailed evaluation.

**Study inclusion and exclusion criteria**

Studies were included based on predefined selection criteria. Studies were eligible for inclusion, if they included patients with histologically proven gastric cancer and investigated the association of FITC with at least one of the following time-to-event outcomes: Overall survival (OS: date of surgery to date of death of any cause); disease specific survival (DSS: date of surgery to date of death due to gastric cancer); disease free survival (DFS: date of surgery to date of recurrence or death of any cause, whichever comes first), recurrence free survival
(RFS: date of surgery to date of recurrence) or peritoneal recurrence (PR: date of surgery to date of peritoneal recurrence). Peritoneal cytology may have included any standard staining technique (i.e. hematoxylin and eosin [H&E], Papanicolaou) performed on peritoneal fluid or peritoneal washings. Molecular detection methods may have included immunocytochemistry and any form of reverse-transcriptase polymerase chain reaction ([RT]-PCR). In contrast to DNA or protein markers, studies using peritoneal tumor mRNA markers were included, assuming a linear correlation between peritoneal tumor cell detection and extremely short-lived free mRNA molecules.

Exclusion criteria were met, if less than 50 peritoneal samples were analyzed, if the percentage of patients with peritoneal or distant metastasis was > 30%, if they were not published in a peer-reviewed journal, if the above mentioned definitions of peritoneal cytology or molecular diagnostic were not met or if no hazard ratio could be calculated for at least one of the above mentioned time-to-event outcomes.

Data extraction

The following data was extracted from every article: first author, year of publication, study type, enrolment period, sample size, patient age and sex, FITC detection rate, definition of positive peritoneal fluid/lavage, timing of FITC detection, detection protocol, target genes and antigens, chemotherapy (neoadjuvant and/or adjuvant, treatment regimen), duration of follow up, reported outcomes and the use of multivariate models. The data for each included article were extracted independently by two authors (MP and MA). Diverging results were resolved by discussion.

Assessment of study quality

Study quality was evaluated using the modified risk of bias tool recommended by the Cochrane Collaboration as described before [99, 100].

Statistical analyses

The synchronized extraction results were pooled statistically as effect estimates in meta-analyses. Hazard ratios (HR) and their corresponding standard errors (SE) were extracted for the individual time-to-event outcome parameters of the included studies. In case the HR together with their associated SE or confidence intervals (CI) were not provided for a certain outcome, HRs were calculated using different statistical methods based on the clinical and statistical data reported in the primary studies [101, 102].

The extracted HR were pooled using the generic inverse variance method of the Review Manager Version 5.3 software (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration, 2014). To adjust for expected inter-study heterogeneity (study populations, treatments, detection assays, definitions of FITC positivity, duration of follow-up, etc.) a random effects analysis model was applied, which is more conservative when determining confidence intervals (CI) around the pooled HR [103]. I^2 statistics was applied to assess the presence of statistical heterogeneity [104]. To explore reasons for statistical heterogeneity we performed sensitivity analyses, where the impact of single studies on the I^2 value is tested as well as “a priori” subgroup analyses [105]. The results of subgroup analyses were compared by tests of interaction [105]. To avoid double patient evaluation among studies that evaluated multiple detection assays and/or target genes, these parameters were combined where possible to keep a maximum of information. Otherwise, cytokeratins were prioritized over alternative tumor cell markers and immunohistochemistry over RT-PCR assays. Sensitivity analyses (by choosing the alternative study arm) were performed to assess the statistical impact of such prioritization. Publication bias was assessed using funnel plot analyses.

CONFLICTS OF INTEREST

No conflicts of interest exist.

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