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REVIEW ARTICLE

A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer

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Abstract
Background There is lack of uniformity in the utilization of peritoneal cytology in gastric cancer management. The identification of intraperitoneal free cancer cells (IFCCs) is believed to confer poor prognosis. However, while some of these patients are palliated, others may undergo more aggressive therapies. In this review, we aimed to identify and synthesize findings on the use of peritoneal cytology in predicting peritoneal recurrence and overall survival in curative gastric cancer patients.
Methods Electronic literature searches were conducted using Medline, EMBASE, and the Cochrane Central Register of Controlled Trials from January 1, 1998 to December 31, 2009. We determined the accuracy, sensitivity, and specificity of peritoneal cytology in predicting peritoneal recurrence based on four techniques—conventional cytology, immunoassay, immunohistochemistry, and reverse transcriptase-polymerase chain reaction. Recurrence rates and overall survival rates for curative patients were determined, based on positivity or negativity for IFCCs.
Results Twenty-eight articles were included. All four techniques showed wide variations in accuracy, sensitivity, and specificity in predicting peritoneal recurrence. Recurrence rates for patients positive for IFCCs ranged from 11.1 to 100%, while those negative for IFCCs had recurrence rates of 0–51%. Overall survival was significantly reduced for patients with positive IFCCs. Short follow-up periods and possible duplication of results may limit result interpretation.
Conclusion The presence of IFCCs appears to increase the risk of peritoneal recurrence and is associated with worse overall survival in gastric cancer patients. Further incorporation of peritoneal cytology in clinical decision-making in gastric cancer depends on the development of a consistently accurate and rapid IFCC detection method.

Keywords Gastric cancer · Cytology · Peritoneal cavity · Recurrence · Survival

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Introduction

The assessment of peritoneal lavage or ascitic fluid in gastric cancer patients serves to identify patients who, despite no evidence of gross peritoneal disease, have intraperitoneal free cancer cells (IFCCs). The identification of IFCCs in gastric cancer patients has been used to predict the risk of peritoneal cancer recurrence and predict overall survival [1–3]. Patients with IFCCs have a poorer prognosis compared to those with no IFCCs [4, 5].With peritoneal dissemination being the most common pattern of metastasis and recurrence in gastric carcinoma, the identification of IFCCs seems prudent [1]. To this end, the most recent TNM classification has included IFCC detection as part of the staging process, denoting M1 disease [6]. Traditionally, these patients were considered only for palliation [7]; however, newer strategies have employed more aggressive multimodal therapies in the neoadjuvant [7, 8] and adjuvant settings [9–12] with some evidence of improved outcome [7, 8, 10–12].

There is lack of consensus regarding the incorporation of peritoneal cytology into the algorithm of gastric cancer treatment. The *Japanese Gastric Cancer Association (JGCA)* includes the cytological examination of fluid in their staging system [13]. Peritoneal cytology at the time of diagnostic laparoscopy is recommended by the Society of American Gastroenterologists and Endoscopic Surgeons (SAGES) [14], while the European Society for Medical Oncology (ESMO) [15] considers this step optional. The current National Comprehensive Cancer Network (NCCN) guidelines do not explicitly incorporate peritoneal cytology into the gastric cancer treatment algorithm, despite later considering positive peritoneal cytology a criterion of unresectability for cure [16].

The methods of detecting IFCCs represent yet another area of evolution. Traditionally, conventional cytological evaluation of peritoneal fluid (Papanicolaou or hematoxylin and eosin stains) has been employed. Low sensitivity and a poor negative predictive value of this method have heralded the development of advanced techniques in detecting IFCCs—immunoassays, immunohistochemistry (IHC), and reverse transcriptase-polymerase chain reaction (RT-PCR). It has been suggested that these tools have better sensitivity in detecting IFCCs with better correlation to peritoneal recurrence [17–20].

This systematic review aims to assess the value of IFCCs in predicting peritoneal recurrence and overall survival in gastric cancer patients treated with curative intent, and to determine which method, if any, is preferable for the prediction of both peritoneal recurrence and overall survival for curative gastric cancer.

Methods

Data sources

Electronic literature searches were conducted in Medline and EMBASE from January 1, 1998 to December 31, 2009 according to the search algorithm presented in Appendix A in the electronic supplementary material (ESM). Search terms included [exp Stomach Cancer/ or (((gastric or stomach) adj1 cancer$) or ((gastric or stomach) adj1 carcinoma) or ((gastric or stomach) adj1 adenocarcinoma) or ((gastric or stomach) adj1 neoplasm$)).mp.] and [Laparoscopy/ or peritoneal lavage/ or laparoscopic surgery/ or Laparotomy/] or [clinical trial/ or controlled clinical trial/ or exp comparative study/ or meta analysis/ or multicenter study/ or exp practice guideline/ or randomized controlled trial/] not [review or case report/ or *gastrointestinal stromal tumor/ or exp B cell lymphoma/ and "marginal zone".mp.]. A separate search of the Cochrane Central Register of Controlled Trials (1998–2009) was performed using the search term "gastric cancer". Studies were limited to English language articles. No attempt was made to locate unpublished material.

Study selection and review process

To be eligible, studies had to meet the following criteria: (1) examined ascitic or lavage fluid of patients with gastric cancer for IFCCs; (2) provided data on peritoneal recurrence and overall survival; (3) reported a minimum of 30 human patients with confirmed histology of gastric adenocarcinoma who underwent curative resections; and (4) were prospective studies, retrospective studies, or case series. Studies were excluded according to the following exclusion criteria: (1) studies where gastric adenocarcinoma data could not be extracted from pooled results; (2) studies using animal models; (3) studies with no patient follow-up data; and (4) review articles, meta-analyses, abstracts, conference proceedings, editorials/letters, and case reports. No age, gender, or staging restrictions were employed. All electronic search titles, selected abstracts; and full-text articles were independently reviewed by a minimum of two reviewers (NC, PL, and LL). Reference lists from review papers and relevant articles were also examined for additional studies that met our inclusion criteria. Disagreements on study inclusion/exclusion were resolved with a consensus meeting.

Data extraction

A systematic approach to data extraction was used to produce a descriptive summary of participants, interventions, and study findings. The first reviewer (PL) independently

extracted the data and a second reviewer (RC) checked the data extraction. No attempt was made to contact authors for additional information.

Data analysis

Many definitions were found for the calculation of accuracy, sensitivity, and specificity. Therefore, these values were re-calculated from the original numbers provided in each included publication when possible. Accuracy was defined as follows: (number of true positives + number of true negatives)/(number of true positives + false positives + true negatives + false negatives) × 100. Sensitivity was calculated as follows: (number of true positives)/(number of true positives + number of false negatives) × 100. Specificity was defined as follows: (number of true negatives)/(number of true negatives + number of false positives) × 100. Descriptive characteristics including country of origin, study type, number of patients, patient characteristics, disease stage, and the technique used for peritoneal cell analysis were also collected for each included study.

Results

Search results

A total of 1129 abstracts/citations were identified from the electronic and hand searches for preliminary review. After removal of duplicates and screening for relevant titles and abstracts, a total of 435 articles were submitted for a full-text review. Twenty-eight articles [21–48] on peritoneal cytology for gastric cancer which satisfied the inclusion and exclusion criteria were included in the review (Fig. 1). The descriptive characteristics of each included study are presented in Appendix B in the ESM.

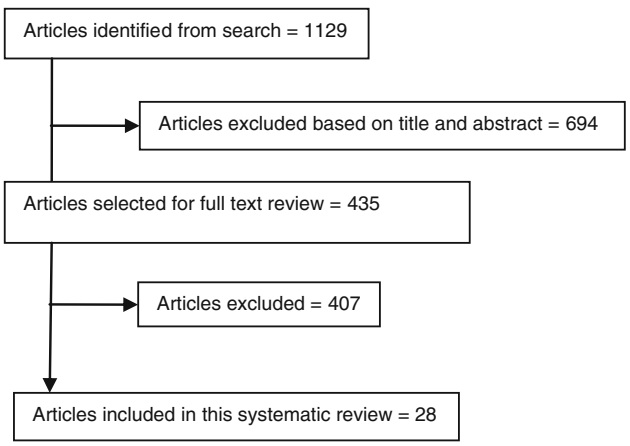

Fig. 1 Article selection flow

Study and patient characteristics

Sixteen studies were prospective [24–27, 29–31, 33, 35, 37, 39, 41–45], while the remaining 12 were retrospective [21–23, 28, 32, 34, 36, 38, 40, 46–48]. Tumor stage was described in all but one study [35]. One article included only locally advanced tumors [24]. The remainder included both early and advanced cancers [21–23, 25–48].

IFCCs were identified by conventional cytology in 17 articles [21, 23, 24, 30–35, 39, 41, 42, 44–48], immunoassay in 6 articles [26, 33, 35, 43, 45, 46], IHC in 4 articles [22, 37, 40, 44], and RT-PCR in 14 articles [24, 25, 27–30, 35, 36, 38, 41, 42, 45–47]. Further details of the specific analyses can be viewed in Appendix B in the ESM.

Study findings

Study findings are summarized in Tables 1, 2, 3, 4, 5, 6, and 7. The outcome measures of interest included the accuracy, sensitivity, and specificity of conventional cytology, immunoassay, IHC, and RT-PCR in predicting peritoneal recurrence through the identification of IFCCs; peritoneal recurrence rates in curative gastric cancer patients with positive and negative IFCCs; and overall survival in curative gastric cancer patients with positive and negative IFCCS.

Prediction of peritoneal recurrence

Of the 17 articles where conventional cytology was used to detect IFCCs, 11 commented on the risk of peritoneal recurrence [23, 24, 30, 31, 33, 41, 42, 44–47]. Table 1 summarizes the results, with conventional cytology predicting peritoneal recurrence with an accuracy of 73–91.9%, sensitivity of 11.1–80%, and specificity of 86.4–100%.

Four of the six articles using immunoassay to detect IFCCs commented on peritoneal recurrence [33, 43, 45, 46]. Based on these articles, the accuracy, sensitivity, and specificity of immunoassay in predicting peritoneal recurrence was 72–95, 23–100, and 81–92.9%, respectively (Table 2).

Table 3 summarizes the results of the four articles involving IHC [22, 37, 40, 44], with a calculated accuracy, sensitivity, and specificity of IHC in predicting peritoneal recurrence of 54.8–76.7, 22.1–75, and 76.9–97.3%, respectively.

Eleven studies evaluated the use of RT-PCR in predicting peritoneal recurrence [24, 25, 28–30, 38, 41, 42, 45–47]. RT-PCR predicted peritoneal recurrence with an accuracy of 61–89.7%, sensitivity of 31–100%, and specificity of 58.8–95% (Table 4).

Table 1 The use of IFCCs identified by conventional cytology in predicting peritoneal recurrence in curative gastric cancer patients

Study	*N* of M0 patients	Median follow-up	TNM classification	Accuracy (%)	Sensitivity (%)	Specificity (%)
Euanorasetr and Lertsithichai [23]	97	1995–2005[a]	T1-4;NX;M0	85.6[c]	61[d]	100[d]
Fujii et al. [24]	49	16 months[b]	T3-4;NX;M0	77.6[c]	33.3[c]	97.1[c]
Kodera et al. 1998 [30]	123	NR	T1-4;N0-3;M0	85.1[c]	62.5[c]	86.4[c]
Kodera et al. 1999 [31]	91	25.3 months	T2-4;N0-2;M0	89[c]	80[c]	97.5[c]
Li et al. [33]	64	39 months	T1-4;NX;M0	90.6[d]	73.7[d]	97.8[d]
Sugita et al. [41]	111	NR	T1-4;NX;M0	87.6[c]	11.1[c]	93.3[c]
Tokuda et al. [42]	136	27.3 months	T1-4;N0-2;M0	91.9[c]	31.3[c]	100[c]
Vogel et al. [44]	47	45.3 months	T1-4;NX;M0	76.7[c]	42.9[c]	87[c]
Wang et al. [45]	40	25 months	T1-4;N0-3;M0	75[c]	33.3[c]	92.9[c]
Yonemura et al. 2001 [46]	230	40.8 months	T1-4;NX;M0	73[d]	46[d]	94[d]
Yonemura et al. 2001 [47]	152	28.8 months	T1-4;NX;M0	79[c]	46[c]	95[c]

IFCCs intraperitoneal free cancer cells, *N* number, *NR* not reported/necessary information not provided

[a] Study period

[b] Minimum follow-up

[c] Calculated by literature review study team

[d] Calculations published in original manuscript

Table 2 The use of IFCCs identified by immunoassay in predicting peritoneal recurrence in curative gastric cancer patients

Study	*N* of M0 patients	Median follow-up (months)	TNM classification	Accuracy (%)	Sensitivity (%)	Specificity (%)	Cut-off level
Li et al. [33]	64	39	T1-4;NX;M0	85.9[a,c]	94.7[a,c]	82.2[a,c]	210 ng/g[a]
Tsutsumi et al. [43]	60	NR	T0-4;NX;M0	95[a,b]	100[a,b]	92.9[a,c]	100 ng/g[a]
Wang et al. [45]	40	25	T1-4;N0-3;M0	82.5[a,b]	66.7[a,b]	89.3[a,b]	200 ng/g[a]
Yonemura et al. [46]	230	40.8	T1-4;NX;M0	72[a,c]	23[a,c]	81[a,c]	5 ng/ml[a]

IFCCs intraperitoneal free cancer cells, *N* number, *NR* not reported/necessary information not provided

[a] Carcinoembryonic antigen (CEA)

[b] Calculated by literature review study team

[c] Calculations published in original manuscript

Table 3 The use of IFCCs identified by immunohistochemistry in predicting peritoneal recurrence in curative gastric cancer patients

Study	*N* of M0 patients	Median follow-up (months)	TNM classification	Accuracy (%)	Sensitivity (%)	Specificity (%)
de Manzoni et al. [22]	168	64	T1-4;N0-3;M0	54.8[a,c]	22.1[a,c]	97.3[a,c]
Nekarda et al. [37]	118	64	T1-4;N0-2;M0	NR	37[a,d]	97[a,d]
Rosenberg et al. [40]	346	70	T1-4;N0-2;M0	70.2[a,c]	36.1[a,c]	85.1[a,c]
Vogel et al. [44]	47	45.3	T1-4;NX;M0	76.7[b,c]	75[b,c]	76.9[b,c]

IFCCs intraperitoneal free cancer cells, *N* number, *NR* not recorded/necessary information not provided

[a] Ber-EP4

[b] HEA-125

[c] Calculated by literature review study team

[d] Calculations published in original manuscript

Peritoneal recurrence rates by detection of IFCCs

Nineteen studies compared the peritoneal recurrence rates in the subset of curative patients with positive versus negative IFCCs [22–25, 28–31, 37–47]. The studies included a variety of analysis techniques, as shown in Table 5. Recurrence rates for patients positive for IFCCs ranged from 11.1 to 100%, while those negative for IFCCs

Table 4 The use of IFCCs identified by RT-PCR in predicting peritoneal recurrence in curative gastric cancer patients

Study	*N* of M0 patients	Median follow-up (months)	TNM Classification	Accuracy (%)	Sensitivity (%)	Specificity (%)
Fujii et al. [24]	49	16[g]	T3-4;NX;M0	75.5[a,h]	100[a,h]	64.7[a,h]
Hara et al. [25]	126	NR	T1-4;N0-2;M0	89.7[c,h]	80[c,h]	90.5[c,h]
Ito et al. [28]	86	38	T1-4;NX;M0	87.2[a,h]	84.6[a,h]	87.6[a,h]
Katsuragi et al. [29]	80	32	T1-4;N0-3;M0	NR	64.9[a,i], 51.4[b,i], 81.1[c,i]	82.3[a,i], 81[b,i], 79.7[c,i]
Kodera et al. 1998 [30]	123	NR	T1-4;N0-3;M0	77.7[a,h]	100[a,h]	76.4[a,h]
Oyama et al. [38]	163	27	T1-4;N0-3;M0	85.3[a]	87.5[a,h]	85.2[a,h]
Sugita et al. [41]	111	NR	T1-4;NX;M0	61[c,h]	88.9[c,h]	58.8[c,h]
Tokuda et al. [42]	136	27.3	T1-4;N0-2;M0	88.2[a,h]	93.8[a,h]	87.5[a,h]
Wang et al. [45]	40	25	T1-4;N0-3;M0	80[a,h]	50[a,h]	92.9[a,h]
Yonemura et al. 2001 [46]	230	40.8	T1-4;NX;M0	73[a,i], 77[d,i]	31[a,i], 57[d,i]	95[a,i], 89[d,i]
Yonemura et al. 2001 [47]	152	28.8	T1-4;NX;M0	70[e,h], 79[f,h]	33[e,h], 62[f,h]	88[e,h], 88[f,h]

IFCCs intraperitoneal free cancer cells, *RT-PCR* reverse transcriptase-polymerase chain reaction, *N* number, *NR* not reported/necessary information not provided

[a] CEA

[b] Cytokeratin 20 (CK20)

[c] CEA + CK20

[d] CEA + cytology

[e] Matrix metalloproteinase-7 (MMP-7)

[f] MMP-7 + cytology

[g] Minimum follow-up period

[h] Calculated by literature review study team

[i] Calculations published in original manuscript

had recurrence rates of 0–51%. Minimum follow-up was 16 months, while median follow-up varied from 25 to 70 months. Statistical comparisons between recurrence rates for patients positive and negative for IFCCs were made in eight studies [22, 24, 31, 38, 44–47]. All eight studies noted that patients identified as positive for IFCCs had statistically significant higher peritoneal recurrence rates compared to their negative counterparts.

Overall survival for curative gastric cancer patients positive and negative for IFCCs

Tables 6 and 7 show the 2- and 5-year overall survival rates, respectively, for curative gastric cancer patients positive and negative for IFCCs. Twenty-four articles provided data on 2-year overall survival [21–32, 34–36, 38–40, 42–44, 46–48], while six articles reported 5-year overall survival rates [23, 32, 33, 37, 39, 40]. All articles found that overall survival was significantly reduced for patients with positive IFCCs.

Discussion

The role of peritoneal lavage and ascitic fluid assessment for the detection of IFCCs in gastric cancer patients continues to evolve. Current guidelines are inconsistent in their recommendations. SAGES recommends peritoneal cytology at the time of diagnostic laparoscopy, but fails to indicate the impact of the results on management decisions [14]. NCCN guidelines suggest that patients with positive peritoneal cytology be treated with palliative therapy [16]. The Japanese currently use peritoneal cytology for staging and prognostic purposes [13]. However, in Japan, staging laparoscopy is not a standard practice, nor are the results always available at the time of surgery to allow for clinical decision-making. ESMO makes no recommendations for the use of peritoneal cytology [15]. The numerous experimental studies conducted and the vast array of analytical tools evaluated support the belief that IFCC detection is a potentially useful tool for clinical decision-making. However, the management of patients with IFCCs still remains debatable. Challenging the traditional palliative approach to patients with IFCCs [16], some authors suggest that the early detection and eradication of IFCCs may improve patient outcome [20]. The identification of IFCCs, in medically fit patients, has the potential to impact decisions regarding both neoadjuvant and adjuvant treatment strategies, with more aggressive treatments likely being employed in IFCC-positive patients [49].

Table 5 Peritoneal recurrence rates in curative gastric cancer patients positive and negative for IFCCs

Study	*N* of M0 patients	TNM classification	Recurrence rates for IFCC + patients (%)	Recurrence rates for IFCC − patients (%)	Median follow-up	Statistical significance (*P*)
de Manzoni et al. [22]	168	T1-4;N0-3;M0	91[c,l]	51[c,l]	64 months	<0.001[m]
Euanorasetr and Lertsithichai [23]	97	T1-4;NX;M0	100[a,m]	19[a,m]	1995–2005[j]	NR
Fujii et al. [24]	49	T3-4;NX;M0	56[a,m], 83.3[b,m]	0[a,m], 23.3[b,m]	16 months[k]	0.00003[a,m], 0.002[b,m]
Hara et al. [25]	126	T1-4;N0-2;M0	42.1[e,l]	1.9[e,l]	NR	NR
Ito et al. [28]	86	T1-4;NX;M0	55[b,m]	3[b,m]	38 months	NR
Katsuragi et al. [29]	80	T1-4;N0-3;M0	65.2[e,l]	10[e,l]	32 months	NR
Kodera et al. 1998 [30]	123	T1-4;N0-3;M0	20.8[a,l], 19.5[b,l]	2.4[a,l], 0[b,l]	NR	NR
Kodera et al. 1999 [31]	91	T2-4;N0-2;M0	80[a,l]	2.5[a,l]	25.3 months	<0.0001[m]
Nekarda et al. [37]	118	T1-4;N0-2;M0	91[c,l]	38[c,l]	64 months	NR
Oyama et al. [38]	163	T1-4;N0-3;M0	23.3[b,l]	0.8[b,l]	27 months	SS
Ribeiro et al. [39]	220	T1-3;N0-2;M0	100[a,l]	NR	64 months	NR
Rosenberg et al. [40]	346	T1-4;N0-2;M0	51[c,l]	24.6[c,l]	70 months	NR
Sugita et al. [41]	111	T1-4;NX;M0	11.1[a,l], 14.5[f]	6.7[a,l], 1.4[f,l]	NR	NR
Tokuda et al. [42]	136	T1-4;N0-2;M0	100[a,l], 50[b,l]	8.4[a,l], 0.9[b,l]	27.3 months	NR
Tsutsumi et al. [43]	60	T0-4;NX;M0	85.7[b,l]	0[b,l]	NR	NR
Vogel et al. [44]	47	T1-4;NX;M0	50[a,m], 66.7[d,m]	16.7[a,m], 4.8[d,m]	45.3 months	0.0009[a,m], 0.12[d,m]
Wang et al. [45]	40	T1-4;N0-3;M0	66.7[a,m], 72.7[b,m], 75[b,m]	23.5[a,m], 13.8[b,m], 7.4[b,m]	25 months	<0.001[m]
Yonemura et al. 2001 [46]	230	T1-4;NX;M0	76[h,m]	21[h,m]	40.8 months	<0.0001[m]
Yonemura et al. 2001 [47]	152	T1-4;NX;M0	85[a,l], 57[g,l], 68[i,l]	20[a,l], 26[g,l], 17[i,l]	28.8 months	<0.001[a,m], <0.01[g,i,m]

IFCCs intraperitoneal free cancer cells, *N* number, *NR* not reported/necessary information not provided, *SS* statistically significant, + positive, − negative

[a] Conventional cytology, Immunoassay

[b] CEA (RT-PCR)

[c] Ber-EP4 (immunohistochemistry)

[d] HEA-125 (immunohistochemistry)

[e] Reverse transcriptase-polymerase chain reaction

[f] CEA/CK20 (RT-PCR)

[g] MMP-7 (RT-PCR)

[h] Conventional cytology and CEA

[i] Conventional cytology and MMP-7

[j] Study period

[k] Minimum follow-up

[l] Calculated by literature review study team

[m] Calculations published in original manuscript

Methods of detection of IFCCs and their limitations

The accuracy of IFCC detection is critical for prognostication and clinical decision-making. No single test has been found to be uniformly accurate in identifying IFCCs. As such, testing methodology has not been standardized. In our review, wide variations in accuracy between different analytical methods and even between similar methods highlight the ongoing issue. According to our review, the sensitivities of conventional cytology, immunoassay, IHC, and RT-PCR in predicting peritoneal recurrence vary considerably (11.1–80, 23–100, 22.1–75, and 31–100%, respectively). Such low sensitivities suggest that a significant number of patients negative for IFCCs are developing recurrence. Indeed, this is shown in Table 5, with up to 51% [22] of patients who had negative IFCC results developing peritoneal recurrence. Even with more sensitive detection techniques, the tests are failing to identify IFCCs, a shortcoming that has significant management and survival implications. IFCC detection by conventional cytology has been the gold standard to date, and this method has been included in the JGCA [13]. Cytology has, however,

Table 6 2-Year overall survival for curative gastric cancer patients positive and negative for IFCCs

Study	*N* of M0 patients	TNM classification	Overall survival for IFCC + patients (%)	Overall survival for IFCC − patients (%)	Statistical significance (*P*)
Bentrem et al. [21]	371	T1-4;N0-2;M0	28[a]	80[a]	<0.0001[b]
de Manzoni et al. [22]	168	T1-4;N0-3;M0	12[a]	55[a]	<0.001[b]
Euanorasetr and Lertsithichai [23]	97	T1-4;NX;M0	45[a]	95[a]	<0.001[b]
Fujii et al. [24]	49	T3-4;NX;M0	38[a]	90[a]	SS
Hara et al. [25]	126	T1-4;N0-2;M0	58[a]	85[a]	<0.0001[b]
Irinoda et al. [26]	89	T1-4;N0-3;M0	60[a]	100[a]	SS
Ishii et al. [27]	51	T1-4;N0-3;M0	40[a]	70[a]	0.0069[b]
Ito et al. [28]	86	T1-4;NX;M0	55[a]	88[a]	<0.0001[b]
Katsuragi et al. [29]	80	T1-4;N0-3;M0	65[a]	98[a]	<0.0001[b]
Kodera et al. 1998 [30]	123	T1-4;N0-3;M0	28[a]	80[a]	0.014[b]
Kodera et al. 1999 [31]	91	T2-4;N0-2;M0	0[a]	88[a]	<0.0001[b]
Kodera et al. 2001 [32]	34	T1-4;N0-3;M0	0[a]	48[a]	0.0380[b]
Miyashiro et al. [34]	417	T2-4;N1-3;M0	40[a]	60[a]	<0.0001[b]
Mori et al. [35]	179	NR	18[a]	85[a]	<0.0001[b]
Nakanishi et al. [36]	82	T1-4;NX;M0	37[a]	85[a]	<0.01[b]
Oyama et al. [38]	163	T1-4;N0-3;M0	80[a]	98[a]	<0.001[b]
Ribeiro et al. [39]	220	T1-3;N0-2;M0	0[a]	75[a]	0.00001[b]
Rosenberg et al. [40]	346	T1-4;N0-2;M0	75[a]	95[a]	<0.001[b]
Tokuda et al. [42]	136	T1-4;N0-2;M0	50[a]	95[a]	<0.0001[b]
Tsutsumi et al. [43]	60	T0-4;NX;M0	30[a]	95[a]	NR
Vogel et al. [44]	47	T1-4;NX;M0	45[a]	82[a]	0.007[b]
Yonemura et al. 2001 [46]	230	T1-4;NX;M0	0[a]	60[a]	<0.0001[b]
Yonemura et al. 2001 [47]	152	T1-4;NX;M0	0[a]	60[a]	<0.001[b]; 0.002[b]
Yoshikawa et al. [48]	149	T1-4;N0-2;M0	30[a]	72[a]	<0.0001[b]

IFCCs intraperitoneal free cancer cells, *N* number, *NR* not reported/necessary information not provided, *SS* statistically significant, + positive, − negative

[a] Estimated based on survival curves

[b] Calculations published in original manuscript

Table 7 5-Year overall survival for curative gastric cancer patients positive and negative for IFCCs

Study	*N* of M0 patients	TNM classification	Overall survival for IFCC + patients (%)	Overall survival for IFCC − patients (%)	Statistical significance (*P*)
Euanorasetr and Lertsithichai [23]	97	T1-4;NX;M0	0[b]	75[b]	<0.001[b]
Kodera et al. 2001 [32]	34	T1-4;N0-3;M0	0[a]	30[a]	0.0380[b]
Li et al. [33]	64	T1-4;NX;M0	15.4[a]	60.5[a]	<0.05[b]
Nekarda et al. [37]	118	T1-4;N0-2;M0	8[b]	60[b]	0.0001[b]
Ribeiro et al. [39]	220	T1-3;N0-2;M0	0[a]	50[a]	0.00001[b]
Rosenberg et al. [40]	346	T1-4;N0-2;M0	35[b]	71.9[b]	<0.001[b]

IFCCs intraperitoneal free cancer cells, *N* number, + positive, − negative

[a] Estimated based on survival curves

[b] Calculations published in original manuscript

been criticized for its low sensitivity and the interpretive challenge of differentiating well-differentiated carcinoma cells from benign mesothelial cells [17, 18]. Sensitivities for cytology can vary greatly among institutions because of pathologists' experience, inter-observer variability, and the diagnostic criteria used [30].

IHC may be a useful ancillary test performed on conventional cytological preparations. IHC techniques have demonstrated improved detection rates of up to 14% over conventional cytology [19]. Recently developed molecular biologic approaches, commonly using RT-PCR, have the potential to replace conventional morphologic techniques due to their improved sensitivity and discriminatory value [20]. Seven of eight studies [24, 30, 41, 42, 45–47] included in our review that compared RT-PCR to other methods noted the improved sensitivity of RT-PCR over other methods in detecting IFCCs. Despite the apparent superiority of RT-PCT in detecting IFCCs, limitations do exist. These include the illegitimate transcription of tumor-associated genes in non-cancer cells included in the specimen, the deficient expression of marker genes in IFCCs, and the potential for limited sampling of IFCCs from the specimen [30]. Some authors have demonstrated both low sensitivity [47] and low specificity [24] in IFCC detection when using carcinoembryonic antigen (CEA), the traditional target molecule for RT-PCR detection. This has prompted the investigation of newer molecules to serve as markers. The problem of sacrificing specificity in order to improve sensitivity, as demonstrated by positivity in T1 cancers [28], is likely to plague other markers as well.

A separate staging procedure, with its added cost and complication risks, is often required when assessing IFCCs [21]. For example, the time needed for gene amplification limits the usefulness of RT-PCR in intraoperative decision-making [50]. Current experimental studies which aim to identify a rapid, accurate, and cost-effective detection method are ongoing. The transcription-reverse transcription concerted reaction (TRC) system, as described by Ishii et al. [27] and Ohashi et al. [51], and the LightCycler system described by Kodera et al. [52] have shown promise in IFCC detection by providing results in as little as 1–2 h. Cost, however, still remains a considerable limitation.

Until an improved method of IFCC detection can be established, the intended use of the results obtained may help to guide the clinician in choosing an optimal detection method. Tests with improved sensitivity often compromise specificity, and vice versa. For example, high sensitivity is essential in cases where aggressive therapy for IFCC-positive patients is being considered, and needs to be taken into consideration when the method of IFCC detection is chosen.

Prognostic significance of IFCCs

The use of multiple methods of IFCC detection and the varied accuracies of these methods can make interpretation of the significance of results challenging. Factors contributing to this difficulty include the unknown natural history of IFCCs and the use of varying cut-off values during analysis. The factors responsible for IFCC proliferation and the progression of metastatic disease, as well as the degree and duration of dormancy of these cells, remain unknown [20]. IFCCs may well be identified in patients who have not been noted to develop recurrence. Here, the duration of follow-up becomes a factor. With follow-up periods as low as 16 months noted in our review, the recurrence rates of IFCC-positive patients may have been underestimated. In addition, shifting cut-off values to improve sensitivity will ultimately reduce specificity in IFCC detection, resulting in higher false-positive results [53].

The wide variation in peritoneal recurrence rates and survival rates for patients positive and negative for IFCCs demonstrates the challenge in result interpretation (Tables 5, 6, 7). It is difficult to make recommendations for clinical decision-making based on such varied results. Encouraging 5-year survival rates of 35% for patients with IFCCs, as reported by Rosenberg et al. [40], would support a more aggressive treatment strategy. However, such rates were not borne out by the majority of studies. Despite variability in results, all included studies uniformly showed that patients positive for IFCCs had a significantly higher risk of peritoneal recurrence and lower survival rates compared to those negative for IFCCs. The detection of IFCCs is clearly associated with a poor prognosis. The question remains as to the appropriate treatment strategy for those patients with IFCCs.

Implications of IFCCs in treatment

Through the designation as Stage IV disease [6, 13] and the well-established associated poor prognosis [4, 5], patients with IFCCs have traditionally been offered palliative care [7, 16]. However, some groups suggest that the prognosis of patients with positive IFCCs can be improved through early identification and treatment. Intraperitoneal chemotherapy has been demonstrated to be prophylactic against peritoneal recurrence and to result in improved survival [10, 54]. Both neoadjuvant and adjuvant treatment strategies are currently being evaluated.

Lorenzen et al. [8] demonstrated that gastric cancer patients whose IFCC status was converted from positive to negative following neoadjuvant therapy had an improved median survival (36.1 vs. 9.2 months; $P = 0.002$) and longer 2-year survival (71.4 vs. 25%; $P = 0.002$) compared to persistently IFCC-positive patients. This may be a useful marker of biologic responsiveness to chemotherapy, allowing surgeons to selectively offer aggressive resection to patients in whom there is a response to induction chemotherapy. Also, the use of extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy has been demonstrated, in a randomized controlled trial, to improve the 5-year survival of advanced gastric cancer patients positive for IFCCs [11].

A recent study by Mezhir et al. [55] has proposed an approach to these patients that appears reasonable under these circumstances where lack of level 1 data fails to support a specific treatment plan. Patients with M1 disease based solely on IFCC positivity undergo chemotherapy for 6–12 months. If there has been no clinical progression, repeat peritoneal cytology is performed. Patients who remain positive for IFCCs are treated palliatively. Patients who become IFCC-negative have repeat laparoscopy after a further 3–6 months. If they revert to M1 status, they are treated palliatively. If they remain IFCC-negative and have good performance status, they are considered for gastrectomy. Mezhir et al. [55] stress the importance of both patient performance and re-evaluation, after an adequate amount of time has been given for either progression of disease or eradication, in determining the aggressiveness of treatment. Using this strategy, they reported a resection rate of 74% (20 of 27) for IFCC-positive patients who were converted to negative cytology, with a 2.5-year median disease-specific survival for those resected [55]. Given the lack of significant prospective data for treatment outcomes for IFCC-positive patients, it is clear that more clinical trials are needed to determine the optimal treatment for these patients.

Our review suffers from several limitations. Both the use of various methods for IFCC detection and the use of differing cut-off values make the pooling of data impossible and the subsequent interpretation of results difficult. In addition, the short median follow-up periods in the majority of studies may falsely decrease the recurrence rates and overestimate survival results. It was not always possible to determine whether the patients included in papers by a similar author were duplicated. The conclusions, therefore, must be made in this context.

Conclusion

Despite the limitations of this systematic review, it appears that the identification of IFCCs is of prognostic value, irrespective of the detection methodology used. Their presence is associated with a risk of peritoneal recurrence and worse overall survival, and may be an important factor in treatment decision-making. Although RT-PCR appears to be a superior method of detecting IFCCs compared to morphologically based methods, it still has limitations related to cost, timeliness, and sampling. In order for IFCCs to be relevant in clinical decision-making, IFCC detection methods need to be accurate, reliable, cost-effective, and effective during a single procedure.

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