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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Clinical impact of minimal cancer cell detection in various colorectal cancer specimens

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Abstract

Detection of cancer cells using molecular targets is achieved by combining immunochemical reactions with gene amplification techniques. This enables the detection of cancer cells in specimens that are traditionally determined to be cancer-free. These improvements in detection can lead to prognoses that are different from those derived by conventional pathological staging. Survival is worse when cancer cells are detected in regional lymph nodes compared to when the nodes are cancer-free. Furthermore, the circulating tumor cell (CTC) count increases as the cancer progresses. Consequently, there is a correlation between CTC count and prognosis. However, large-scale prospective studies are required to confirm this. The development of more convenient and cost-effective analysis techniques will facilitate the practical application of these findings.

Key words: Micrometastasis; Circulating tumor cell; Colorectal cancer; Prognosis; Molecular marker

Core tip: In patients with colorectal cancer (CRC), a more favorable prognosis can be achieved by curative resection. The depth of tumor invasion (T-category) and the extent of lymph node metastasis (N-category) are important prognostic factors for disease staging. With regard to metastatic CRC, an attempt should be made to determine whether it can be used as a monitoring marker for determining the response to chemotherapy.

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INTRODUCTION

In patients with colorectal cancer (CRC), a more favorable prognosis can be achieved by curative resection. The depth of tumor invasion (T-category) and the extent of lymph node metastasis (N-category) are important prognostic factors for disease staging. Approximately 25% of patients without lymph node or distant metastasis experience suffer recurrent disease. Therefore, obtaining a true node-negative diagnosis using conventional pathological guidelines is very difficult. It is possible to overlook occult metastasis if very few nodes are collected for examination[1-3]. Isolated tumor cells or micrometastases (MMs) within regional lymph nodes that are suspected markers of systemic tumor spread may be missed by conventional histopathological hematoxylin and eosin (HE) staining[4].

Cancer progression is also correlated with epithelial-to-mesenchymal transition, where cancer cells enter into lymphatic or blood vessels and migrate to distant organs in a mesenchymal state[5,6]. Circulating tumor cells (CTCs), which can be detected in peripheral blood (PB) by im-

munological or molecular techniques, are another indicator of disease progression[7,8].

The aim of the present review is to examine the current clinical significance of molecular tumor cell detection in lymph node specimens and PB samples.

REGIONAL LYMPH NODE TUMOR CELL DETECTION IN NODE-NEGATIVE CRC

Detection methods

It is quite difficult to detect lone cancer cells, or even clusters of such cells, using HE staining. Additionally, since conventional pathological examinations only assess one or two sections (including the maximal cutting surface) while determining the presence of lymph node metastasis, most lymph nodes remain unexamined. Special immunohistochemical (IHC) techniques and reverse transcriptase polymerase chain reaction (RT-PCR) can be used to identify MMs within lymph nodes[4], and several studies have employed IHC techniques using monoclonal antibodies directed against carcinoembryonic antigen (CEA) or cytokeratin (CK)[8,9]. Re-examination of regional lymph nodes using CK staining detected MMs in 39% patients with primary CRC in one study[10] and revealed occult metastases in 5.8% examined nodes in another study[9]. The MM detection rate has ranged from 4% to 31% in previous studies where only one section was examined from each lymph node[9,11,12]. In other studies where two or more sections from each lymph node were examined, the rate of MM detection was higher at 76%-100%[13,14]. Moreover, the MM detection rate in each lymph node increased with an increase in slice number from 1 to 2 to 5[15].

The CEA, CK, KRAS, and MUC2 genes are used for PCR[16-19], with 30%-50% of CRC specimens deemed to be node-negative actually instead being found to be positive when these markers are used. Recently, a novel one-step nucleic acid amplification (OSNA) assay using reverse-transcription loop-mediated isothermal amplification for gene amplification was developed[20]. In the OSNA assay, the supernatant of a homogenized lymph node solution is analyzed directly without mRNA purification, enabling rapid detection via an automated gene amplification detector. This is, therefore, a more convenient method for application in a clinical setting compared with conventional RT-PCR[21].

Prognostic significance and tumor cell detection in node-negative CRC

Significant correlations between the detection of tumor cells and survival have been reported by some studies[9,22,23], whereas others have failed to demonstrate any such correlation[10-12,15,24-26]. Recent meta-analyses indicated that molecular tumor cell detection has a prognostic impact on overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS). Subgroup analyses of studies that enrolled patients with stage Ⅱ CRC only showed that tumor cell detection was associated with poor OS, DSS, and DFS. Molecular tumor cell detection was also associated with poorer OS, DSS, and DFS in studies with an inadequate average lymph node count. In studies that examined at least 12 resected lymph nodes, a similar association was observed between tumor cell detection and poor OS, DSS, and DFS. However, DFS was the only outcome measure with sufficient available data for evaluating the prognostic impact of tumor cell detection dependent upon the administration of adjuvant therapy. These subgroup analyses showed that cancer cell-positive lymph nodes were associated with a less favorable DFS among patients, regardless of whether or not they underwent adjuvant chemotherapy[4].

CIRCULATING TUMOR CELLS IN CRC

Detection methods

CTCs and lymph node MMs are detected by targeting nucleic acids associated with epithelial or oncogenic genes or by their immunoreactivity to cell surface proteins[7]. Targets include the cancer cell markers CEA, CKs, hTERT, and CD133[27,28].

Recently, the CellSearch™ System (Veridex, Huntingdon Valley, PA) was developed for the detection of small numbers of CTCs; the system can detect CTCs in a 7.5-mL PB sample. In one study, the prevalence of CTCs was determined in blood samples taken from 199 patients with nonmalignant diseases, 964 patients with metastatic carcinomas, and 145 healthy donors. In the 2183 blood samples obtained from the 964 patients with metastatic carcinomas, the number of CTCs ranged from 0-23618 per 7.5 mL of blood; 36% (781/2183) samples had two or more CTCs. The rate of detection of two or more CTCs in different cancers was as follows: 57% (107/188) for prostate cancers, 37% (489/1316) for breast cancers, 37% (20/53) for ovarian cancers, 30% (99/333) for colorectal cancers, 20% (34/168) for lung cancers, and 26% (32/125) for other cancers[29].

Prognostic value in resectable and metastatic CRC

Several reports have noted a correlation between RT-PCR-based CTC detection in patients with stage Ⅰ-Ⅲ disease and DFS and OS[30-32]. Wong *et al*[32] employed an assay of immunomagnetic separation and reported that an increase in the number of CTCs was associated with recurrence. Meta-analyses have also detected significant correlations between CTC detection and poor recurrence-free survival and OS[7]. Detection of CTCs in PB is indicative of a poor prognosis in patients with primary CRC.

CTC counts obtained with the CellSearch™ system reportedly predict the response of metastatic breast, colorectal, and prostate cancers to chemotherapy[29]. In metastatic CRC, patients with three or less CTCs or less after the initiation of chemotherapy have better PFS and OS[33]. Matsusaka *et al*[34] reported that many patients had three CTCs or less after the initiation of oxaliplatin-based chemotherapy, and that these patients also showed better PFS and OS compared with patients with more

Table 1 Prognostic value of resectable and metastatic colorectal cancer

Detection method	Objectives	Correlation	Ref.
RT-PCR	Stage Ⅰ Ⅱ Ⅲ	DFS	[30]
RT-PCR	Stage Ⅰ Ⅱ Ⅲ	DFS, OS	[31]
RT-PCR	Stage Ⅰ Ⅱ Ⅲ	RFS	[28]
Immunomagnetic	Stage Ⅰ Ⅱ Ⅲ	Recurrence	[33]
RT-PCR	Stage Ⅰ Ⅱ Ⅲ	DFS, OS	[32]
CellSearch	mCRC	PFS, OS	[34]
CellSearch	mCRC	PFS, OS	[35]
CellSearch, RT-PCR	mCRC	OS	[36]
CellSearch	mCRC	PFS, OS	[37]
CellSearch	mCRC	OS	[38]

DFS: Disease-free survival; OS: Overall survival; PFS: Progression-free survival; RT-PCR: Reverse transcriptase polymerase chain reaction; RFS: Recurrence-free survival.

CTCs. Some reports have indicated that CTC counts obtained using the same system are prognostic biomarkers of PFS and OS[35-37]. Recently, the detection of circulating endothelial cells in the PB by the CellSearch™ system before chemotherapy has been reported to predict the efficacy of bevacizumab[38] (Table 1).

Future directions and clinical significance of minimal cancer cell detection

Even though meta-analyses have shown the utility of tumor cell detection in node-negative lymph nodes, large-scale prospective studies are required to elucidate the correlation between lymph node MM and prognosis. If such a correlation is proven, then studies to ascertain the equality of staging for MM and conventional metastasis will also be needed. The development of a low-cost, convenient method of detection is also desirable to facilitate practical application of these findings.

Prospective studies of CTC detection in stage Ⅱ and Ⅲ CRC are also required. The first aim should be to clarify whether the CTC count can be used to identify patients who are likely to experience recurrence and whether it can be used as a monitoring marker similar to CEA. The next aim should be to ascertain whether CTC can be used to determine stage Ⅱ patients who are at a high risk of recurrence and consequently require adjuvant chemotherapy. If possible, an investigation should be performed to ensure that chemotherapy is avoided by stage Ⅲ patients considered to be at a low risk of recurrence.

With regard to metastatic CRC, an attempt should be made to determine whether it can be used as a monitoring marker for determining the response to chemotherapy.

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