Prognostic significance of isolated tumor cells in patients with colorectal cancer in recent 10-year studies (Review)

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Abstract. Circulating tumor cells (CTCs) that detach from the primary tumor and move into the circulation are detected in patients with metastatic cancer. The discovery of such cancer cells has been used as a predictor of recurrence and prognosis, although a consensus regarding such applications has not been reached. Peritoneal cytology may be used for identifying high risk of recurrence or mortality, whereas the intraoperative presence of tumor cells in drainage veins, bone marrow, or the liver is not always useful for evaluating the prognosis. The reported positive rate for tumor cells in the peripheral blood of patients with colorectal cancer, including metastasis, has varied from 10 to 80%; however, numerous studies have demonstrated significant differences in the recurrence and mortality rates between patients with and without isolated tumor cells (ITCs) in the peripheral blood. However, the clinical significance of CTCs as an absolute prognostic factor has not been elucidated, since the measurement methodologies and/or the number of cases differed between the studies. Future prospective studies including larger patient populations may elucidate the utility of routine detection of ITCs in daily practice.

Contents

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1. Introduction

Biomarkers predictive of the prognosis of colorectal cancer have been investigated using various materials and methods. With advances in immunohistochemistry (IHC) and molecular biology, occult tumor cells, including micrometastases in lymph nodes and circulating tumor cells (CTCs) in the peripheral blood, have been detected in patients with gastrointestinal and breast cancers (1-5). By applying highly sensitive and specific diagnostic techniques, several prospective studies suggested that the presence of isolated tumor cells (ITCs) in peripheral areas, drainage veins and the bone marrow is associated with poor outcomes in colorectal cancer patients (6-9). ITCs are single tumor cells or small clusters of cells, ≤0.2 mm in greatest dimension, detectable by routine hematoxylin and eosin staining or IHC. Several reviews and meta-analyses evaluated clinical studies on ITCs in lymph nodes, peripheral blood, bone marrow and liver and suggested the prognostic significance of such cells in colorectal cancer patients (10-15).

To elucidate the findings of previous clinical studies assessing the prognostic value of disseminated tumor cells (DTCs) in patients with colorectal cancer, we investigated English literature over the past 10 years, using computer searches of PubMed with the following key words: 'colorectal cancer', 'micrometastasis', 'occult metastasis', 'circulating tumor cell', 'disseminated tumor cell', 'isolated tumor cell', 'lymph node', 'peritoneal cavity', 'peripheral blood', 'drainage vein', 'bone marrow', 'liver', 'prognosis', and 'survival'. After reading all the abstracts and reviewing the available studies, a total of 87 studies were collected and included in this review.

2. Tumor cells in lymph nodes

Between January, 2002 and March, 2012, a total of 31 studies assessed the prognostic value of tumor cells in histologically negative lymph nodes of patients with colorectal cancer (Table I) (16-46). The studies investigated a total of 4,080 patients with colorectal (n=20), colon (n=7) and rectal (n=4) cancer, with a median cohort size of 105 patients. The majority of the studies detected tumor cells using a marker of cytokeratin (CK) and IHC techniques.

Positive rates for tumor cells in histologically negative lymph nodes varied considerably among these studies, ranging from 5 to 88% (median, 30%). With median follow-up periods of 24-128 months (median, 60 months), 16 out of

Table I. Tumor cells in negative lymph nodes.

Author (year)	Cases	Tumor	Stage	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Rosenberg, *et al* (2002)	85	CRC	I/II	CK20	RT-PCR	52	86[a]	R: 34 vs. 7%; M: 22 vs. 5%	Yes	(16)
Choi, *et al* (2002)	93	CRC	II	MNF116	IHC	31	66	R: 17 vs. 14%	No	(17)
Noura, *et al* (2002)	64	CRC	II	CEA	RT-PCR	30	80	R: 39 vs. 12%; M: 22 vs. 5%	Yes	(18)
Merrie, *et al* (2003)	141	CC	II	CK20	RT-PCR	34	42	M: HR 2.7	Yes	(19)
Shimoyama, *et al* (2003)	57	RC	I/II	CK7/8/CAM5.2	IHC	19	NA	R: 45 vs. 22%	Yes	(20)
Palma, *et al* (2003)	38	CRC	II	AE1/AE3	IHC	16	75	R: 71 vs. 76[b]	No	(21)
Fisher, *et al* (2003)	399	CRC	I/II	AE1/AE3	IHC	18	NA	R: HR 1.19; M: HR 0.94	No	(22)
Bukholm, *et al* (2003)	156	CC	II	CAM5.2	IHC	38	NA	M: HR 4.4	Yes	(23)
Kronberg, *et al* (2004)	90	CRC	I/II	AE1/AE3	IHC	29	91	R: 23 vs. 20%; M: 19 vs. 10%	No	(24)
Laso, *et al* (2004)	21	CRC	I/II	AE1/AE3	IHC	38	57	M: 55 vs. 77[b]	No	(25)
Rosenberg, *et al* (2004)	85	CRC	I/II	CEA/CK20	IHC	27	86	M: 28 vs. 9%	Yes	(26)
Mukai, *et al* (2005)	124	CRC	II	AE1/AE3	IHC	17	>60	R: 65 vs. 10%; M: 38 vs. 8%	Yes	(27)
Lee, *et al* (2006)	121	CRC	I/II	MNF116	IHC	50	57	R: 17 vs. 15%	No	(28)
Garcia-Saenz, *et al* (2006)	105	CRC	II	AE1/AE3	IHC	25	60	R: 23 vs. 20%	No	(29)
Messerini, *et al* (2006)	395	CRC	IIA	CK20	IHC	38	128	R: 22 vs. 22%	No	(30)
Wang, *et al* (2007)	55	RC	I/II	CK20	IHC	18	56	R: 50 vs. 20%	Yes	(31)
Hara, *et al* (2007)	144	RC	I/II	AE1/AE3	IHC	24	81	R: 24 vs. 17%	No	(32)
Fleming, *et al* (2007)	56	RC	I/II	CAM5.2	IHC	18	98	R: 10 vs. 17%	No	(33)
Steinert, *et al* (2008)	90	CRC	I/II	CK18	IHC	46	61	R: NS	No	(34)
Davies, *et al* (2008)	105	CRC	I/II	AE1/AE3	IHC	47	48	R: 16 vs. 18%	No	(35)
Park, *et al* (2008)	160	CC	I/II	CK20	IHC	5	46	R: 20 vs. 15%; M: 8 vs. 7%	No	(36)
Bosch-Roig, *et al* (2008)	39	CC	II	AE1/AE3	IHC	10	82[a]	R: 50 vs. 17%; M: 50 vs. 6%	Yes	(37)
Koyanagi, *et al* (2008)	67	CRC	I/II	CK20/cMET	RT-PCR	40	34	R: 37 vs. 61; M: 43 vs. 57[b]	Yes	(38)
Waldman, *et al* (2009)	257	CRC	I/II	GUCY2C	RT-PCR	88	24	R: 21 vs. 6%	Yes	(39)
van Schaik, *et al* (2009)	72	CC	I/II	LU5	IHC	24	68	R: 49 vs. 28%; M: 38 vs. 21%	Yes	(40)
Uribarrena-Amezaga, *et al* (2010)	85	CRC	I/II	AE1/AE3	IHC	36	NA	R: 32 vs. 22%	No	(41)
Haince, *et al* (2010)	123	CC	I/II	GUCY2C	RT-PCR	20	53	R: 33 vs. 16%	Yes	(42)
Faerden, *et al* (2011)	126	CC	I/II	CAM5.2	IHC	31	60	R: 23 vs. 7%	Yes	(43)
Oh, *et al* (2011)	124	CRC	II	AE1/AE3	IHC	27	36	R: 14 vs. 7%; M: 4 vs. 2%	No	(44)
Hyslop, *et al* (2011)	291	CRC	I/II	GUCY2C	RT-PCR	40	24	R: 41 vs. 2%	Yes	(45)
Mescoli, *et al* (2012)	312	CRC	I/II	MNF116	IHC	59	63	R: 14 vs. 5%	Yes	(46)

[a]Mean, [b]survival (months). CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; CK, cytokeratin; CEA, carcinoembryonic antigen; GUCY, guanylate cyclace HR, hazard ratio; IHC, immunohistochemistry; RT-PCR, reverse transcriptase-polymerase chain reaction; NA, not available; R, recurrence rate; M, mortality rate; NS, not significant.

the 31 studies (52%) demonstrated a significant difference in recurrence and/or mortality rates between patients with and without ITCs in lymph nodes.

3. Tumor cells in the peritoneal cavity

During the same period, 13 studies assessed the prognostic value of tumor cells in the peritoneal cavity of patients with colorectal cancer (Table II) (34,47-58). The studies investigated a total of 2,434 colorectal cancer patients (median, 125 patients). The majority of these studies used standard cytological methods to detect tumor cells in peritoneal lavage samples.

Positive rates for tumor cells in the peritoneal cavity varied among studies, ranging from 2 to 33% (median, 17%). The median follow-up period was 47 months (range, 25-103 months) and 9 out of the 13 studies (69%) demonstrated significant differences in recurrence and/or mortality rates between patients with and without ITCs in the peritoneal cavity.

4. Tumor cells in the peripheral blood

A total of 22 studies assessed the prognostic value of tumor cells in the peripheral blood of patients with colorectal cancer (Table III) (38,59-79). The studies included a total of 2,857 patients (median, 103 patients), most of whom had colorectal cancer, with the exception of 2 patients with colon and 1 with rectal cancer only. A total of 13 studies included patients with stage I/II/III disease (Dukes' A/B/C), whereas 9 included patients with stage IV disease (Dukes' D). The majority of the studies detected tumor cells using a carcinoembryonic antigen (CEA) or CK marker and reverse transcriptase-polymerase chain reaction (RT-PCR), IHC, immunomagnetic assay (IMA), or membrane assay (MA) techniques.

Positive rates for tumor cells in the peripheral blood ranged from 10 to 62% (median, 38%). Following the exclusion of 9 studies on stage IV patients, the positive rate for tumor cells among the studies was 22-62% (median, 36%). With a median follow-up period of 40 months (range, 24 to >70 months), 15 out of the 22 studies (68%) demonstrated significant differences in recurrence and/or mortality rates between patients with and without ITCs in the peripheral blood. Among the 14 studies including only stage I/II/III patients, 12 (86%) demonstrated a prognostic value of ITCs.

5. Tumor cells in drainage veins

Six studies assessed the prognostic value of tumor cells in drainage veins sampled from the mesenteric or portal vein during surgery (Table IV) (63,65,80-83). The studies investigated patients with colorectal cancer, including a total of 638 patients (median, 94 patients). Tumor cells were detected using a CEA marker and RT-PCR.

The positive rate for tumor cells in the drainage vein varied from 11 to 49% (median, 43%). With a median follow-up period of 46 months (range, 30 to ≥60 months), 4 out of the 6 studies (67%) demonstrated a significant difference in recurrence and/or mortality rates between patients with and without ITCs in the drainage veins.

Table II. Tumor cells in the peritoneal cavity.

Author (year)	Cases	Tumor	Stage or depth of invasion	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Guller, *et al* (2002)	39	CRC	I-III	CEA/CK20	RT-PCR	28	31	R: 82 vs. 7%..	Yes	(47)
Yamamoto, *et al* (2003)	189	CRC	T3/T4	TC	CYT	6	103	R: 55 vs. 26%	Yes	(48)
Kanellos, *et al* (2003)	110	CRC	T1-T3	TC	CYT	20	>60	M: 32 vs. 20%	No	(49)
Bosch, *et al* (2003)	53	CRC	I-III	CK20	CYT/ICC	25	37	R: 62 vs. 28%	Yes	(50)
Baskaranathan, *et al* (2004)	281	CRC	I-IV	TC	CYT	9	49[a]	R: 35 vs. 14%	Yes	(51)
Lloyd, *et al* (2006)	125	CRC	I/II	CEA/CK20	RT-PCR	33	25	R: 29 vs. 4%..	Yes	(52)
Kanellos, *et al* (2006)	95	CRC	I-III	TC	CYT	26	>60	M: 36 vs. 30%	No	(53)
Gozalan, *et al* (2007)	67	CRC	I-IV	TC	CYT	9	>24	R: 50 vs. 31%	No	(54)
Steinert, *et al* (2008)	132	CRC	I-III	CK18	CYT/ICC	22	61	R: NS	No	(34)
Katoh, *et al* (2009)	91	CRC	III	TC	CYT	11	>24.	R: 30 vs. 9%[b]; M: 86 vs. 21%.	Yes	(55)
Noura, *et al* (2009)	697	CRC	0-III	TC	CYT	2	91[a]	R: 63 vs. 17%; M: 50 vs. 13%	Yes	(56)
Nishikawa, *et al* (2009)	410	CRC	T3/T4	TC	CYT	8	36	R: 60 vs. 30%; M: 79 vs. 32%	Yes	(57)
Temesi, *et al* (2012)	145	CRC	T1-T4	TC	CYT	17	47	R: 56 vs. 23%	Yes	(58)

[a]Mean, [b]local/peritoneal recurrence. CRC, colorectal cancer; CEA, carcinoembryonic antigen; CK, cytokeratin; TC, tumor cell; RT-PCR, reverse transcriptase-polymerase chain reaction; CYT, cytology; ICC, immunocytochemistry; R, recurrence rate; M, mortality rate; NS, not significant.

Table III. Tumor cells in the peripheral blood.

Author (year)	Cases	Tumor	Stage	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Bessa, *et al* (2003)	66	CRC	I-III	CEA	RT-PCR	55	36	R: 22 vs. 23%	No	(59)
Giacomelli, *et al* (2003)	41	CRC	I-IV	EGFR	RT-PCR	39	36	R: 94 vs. 4%	Yes	(60)
Chen, *et al* (2004)	42	CRC	II-IV	GCC	RT-PCR	29	36	R: 50 vs. 7%	Yes	(61)
Zhang, *et al* (2005)	58	CRC	I-III	CK20	RT-PCR	45	>12	M: 55 vs. 33%	Yes	(62)
Sadahiro, *et al* (2005)	93	CRC	I-III	CEA	RT-PCR	39	59	R: 6 vs. 19%	No	(63)
Douard, *et al* (2006)	121	CRC	I-IV	CGM2	RT-PCR	48	NA	R: 28 vs. 29%	No	(64)
Iinuma, *et al* (2006)	167	CRC	I-IV	CEA/CK20	RT-PCR	10	30	R: NS	No	(65)
Koch, *et al* (2006)	90	CRC	II	CK20	RT-PCR	25	58	R: 28 vs. 10%	Yes	(66)
Katsumata, *et al* (2006)	57	CC	I-IV	CK20	RT-PCR	42	>70	R: 25 vs. 12%	No	(67)
Allen-Mersh, *et al* (2007)	113	CRC	I-III	CEA/VK20	RT-PCR	31	46	R: HR 8.66	Yes	(68)
Sadahiro, *et al* (2007)	200	CRC	I-III	CEA	RT-PCR	22	52	R: 45 vs. 22%	Yes	(69)
Koch, *et al* (2007)	45	RC	I-IV	CK20	RT-PCR	38	51	M: 34 vs. 13%	No	(70)
Wang, *et al* (2007)	157	CRC	I-III	CEA/CK19/20	MA	57	36	M: 50 vs. 12%	Yes	(71)
Friederichs, *et al* (2007)	37	CRC	I-IV	CK20	RT-PCR	30	40	M: 45 vs. 15%	No	(72)
Uen, *et al* (2007)	194	CRC	II	CEA/CK19/20	MA	27	40	R: 85 vs. 8%	Yes	(73)
Uen, *et al* (2008)	438	CRC	I-III	CEA/CK19/20	MA	31	44	R: 68 vs. 16%	Yes	(74)
Yie, *et al* (2008)	51	CRC	I-IV	Survivin	RT-PCR	41	36	R: 48 vs. 17%	Yes	(75)
Koyanagi, *et al* (2008)	34	CRC	I-III	CK20/cMET	RT-PCR	47	34	M: 36 vs. 50[b]	Yes	(38)
Wong, *et al* (2009)	132	CRC	I-III	CK20	IMA	62	24	M: 52 vs. 17%	Yes	(76)
Vardakis, *et al* (2011)	265	CRC	II-III	CEA	RT-PCR	37	34	R: 37 vs. 12%; M: 24 vs. 12%	Yes	(77)
Lu, *et al* (2011)	141	CC	II/III	CEA/CK19/20	MA	36	62	R: 73 vs. 12%	Yes	(78)
Iinuma, *et al* (2011)	315	CRC	II/III	CEA/CK19/20	RT-PCR	24	37[a]	R: HR 3.04; M: HR 3.20	Yes	(79)

[a]Mean, [b]survival (months). CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; GCC, guanylyl cyclase C; CGM2, carcinoembryonic gene member 2; CK, cytokeratin; RT-PCR, reverse transcriptase-polymerase chain reaction; IMA, immunomagnetic assay; MA, membrane assay; HR, hazard ratio; NA, not available; R, recurrence rate; M, mortality rate; NS, not significant.

Table IV. Tumor cells in drainage veins.

Author (year)	Cases	Tumor	Stage	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Sunouchi, *et al* (2003)	37	CRC	I-IV	CEA	RT-PCR	43	33	R: 25 vs. 5%[b]; M: 31 vs. 5%	Yes	(80)
Akashi, *et al* (2003)	80	CRC	I-III	CEA	RT-PCR	44	52[a]	R: 20 vs. 5%	No	(81)
Sadahiro, *et al* (2005)	49	CRC	I-III	CEA	RT-PCR	49	59	R: 7 vs. 21%	No	(63)
Iinuma, *et al* (2006)	167	CRC	I-IV	CEA/CK20	RT-PCR	34	30	R: HR 1.744; M: HR 1.517	Yes	(65)
Kanellos, *et al* (2006)	108	CRC	I-III	CEA	RT-PCR	11	>60	R: 50 vs. 15%	Yes	(82)
Shimada, *et al* (2012)	197	CRC	II/III	CEA/CK/CD133	RT-PCR	62	37	R: HR 1.13/1.25[c]; M: HR 2.28/1.49[c]	Yes	(83)

[a]Mean, [b]liver and lung, [c]Dukes' B/C. CRC, colorectal cancer; CEA, carcinoembryonic antigen; CK, cytokeratin; CD113, cluster of differentiation 113; RT-PCR, reverse transcriptase-polymerase chain reaction; R, recurrence rate; M, mortality rate; HR, hazard ratio.

Table V. Tumor cells in the bone marrow.

Author (year)	Cases	Tumor	Stage	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
O'Connor, *et al* (2005)	49	CRC	I-III	CK18	ICC	29	55	R: 29 vs. 31%	No	(84)
Koch, *et al* (2006)	90	CRC	II	CK20	RT-PCR	28	58	R: 5 vs. 17%	No	(66)
Steinert, *et al* (2008)	140	CRC	I-III	CK18	CYT/ICC	64	61	M: 17 vs. 20%	No	(34)
Flatmark, *et al* (2011)	235	CRC	I-III	EpCAM	IMA/ICC	17	112	R: HR 3.0	Yes	(85)

CRC, colorectal cancer; CK, cytokeratin; EpCAM, epithelial cell adhesion molecule; ICC, immunocytochemistry; RT-PCR, reverse transcriptase-polymerase chain reaction; IMA, immunomagnetic assay; CYT, cytology; R, recurrence rate; M, mortality rate; HR, hazard ratio.

Table VI. Tumor cells in the peripheral blood of stage IV patients.

Author (year)	Cases	Tumor	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Vlems, *et al* (2003)	22	CRC	CK20	RT-PCR	15	18	R: 75 vs. 64%	No	(86)
Fruhauf, *et al* (2005)	18	CRC	A45B/B3	IHC	56	31[a]	R: 76 vs. 10%	Yes	(87)
Koch, *et al* (2005)	37	CRC	CK20	RT-PCR	30	38	M: 71 vs. 50%	Yes	(88)
Topal, *et al* (2005)	20	CRC	CEA/CK20	RT-PCR	80	37	NA	No	(89)
Cohen, *et al* (2008)	413	CRC	CK8/18/19	CSS	26	11	R: 5 vs. 8[b]; M: 9 vs. 19[c]	Yes	(90)
Cohen, *et al* (2009)	413	CRC	CK8/18/19	CSS	26	26	R: 4 vs. 8[b]; M: 9 vs. 21[c]	Yes	(91)
Tol, *et al* (2010)	451	CRC	CK8/18/19	CSS	29	17	R: 8 vs. 10[b]; M: 13 vs. 22[c]	Yes	(92)
Rahbari, *et al* (2011)	63	CRC	CK20	RT-PCR	57	23	R: 58 vs. 44%	Yes	(93)
Pilati, *et al* (2012)	50	CRC	CD133	RT-PCR	50	36	R: 88 vs. 24%; M: HR 2.611	Yes	(94)

[a]Mean, [b]relapse-free survival (months), [c]overall survival (months). CRC, colorectal cancer; CK, cytokeratin; CD113, cluster of differentiation 113; CEA, carcinoembryonic antigen; RT-PCR, reverse transcriptase-polymerase chain reaction; IHC, immunohistochemistry; CSS, CellSearch system; R, recurrence rate; M, mortality rate; NA, not available; HR, hazard ratio.

Table VII. Tumor cells in the bone marrow of patients with liver metastasis.

Author (year)	Cases	Tumor	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Bjørnland, *et al* (2003)	29	CRC	MOC31	IMA	7	18	M: 50 vs. 12%	Yes	(95)
Vlems, *et al* (2003)	22	CRC	CK20	RT-PCR	23	18	R: 80 vs. 65%	No	(86)
Koch, *et al* (2005)	37	CRC	CK20	RT-PCR	16	38	R: 75 vs. 51%	Yes	(88)
Schoppmeyer, *et al* (2006)	30	CC	CK	ICC	50	43	M: 47 vs. 53%	No	(96)
Vogelaar, *et al* (2010)	44	CRC	CK20	RT-PCR	20	24	R: HR 4.11; M: HR 6.40	Yes	(97)
Buxhofer-Ausch, *et al* (2010)	45	CRC	A45B/B3	ICC	22	35	R: 30 vs. 22%	No	(98)
Hinz, *et al* (2012)	71	CRC	CK20	RT-PCR	23	41	R: 22 vs. 45[a]	Yes	(99)

[a]Recurrence-free survival (months). CRC, colorectal cancer; CC, colon cancer; CK, cytokeratin; IMA, immunomagnetic assay; RT-PCR, reverse transcriptase-polymerase chain reaction; ICC, immunocytochemistry; M, mortality rate; R, recurrence rate; HR, hazard ratio.

6. Tumor cells in the bone marrow

Four studies assessed the prognostic value of tumor cells in the bone marrow (Table V) (34,66,84,85). The studies included a total of 514 colorectal cancer patients (median, 115 patients). These studies detected tumor cells using a CK marker and immunocytochemistry (ICC) or RT-PCR techniques.

Positive rates of tumor cells in the bone marrow varied from 17 to 64% (median, 29%). With a median follow-up of 60 months (range, 55-112 months), only 1 in 4 studies (25%) demonstrated a significant difference in recurrence and/or mortality rates between patients with and without ITCs in the bone marrow.

7. Isolated tumor cells in stage IV patients

We identified 9 studies assessing the prognostic value of tumor cells in the peripheral blood of patients with metastatic colorectal cancer (Table VI) (86-94). The positive rate of tumor cells in the peripheral blood varied from 15 to 80% (median, 30%). Median follow-up was 25 months (range, 11 to ≥38 months) and 7 studies (78%) demonstrated a significant difference in recurrence and/or mortality rates between patients with and without ITCs in the peripheral blood.

Seven studies assessed the prognostic value of tumor cells in the bone marrow of patients with liver metastasis (Table VII) (86,88,95-99). The median positive rate for tumor cells in peripheral blood was 22% (range, 7-50%). The median follow-up period was 35 months (range, 18 to ≥43 months) and 4 studies (57%) demonstrated a significant difference in recurrence and/or mortality rates between patients with and without ITCs in the bone marrow.

Five studies assessed the prognostic value of tumor cells in the normal liver tissue of patients with liver metastasis, excluding 1 study comprising only stage I/II/III patients (Table VIII) (89,100-103). The positive rate for tumor cells in the peripheral blood varied considerably among the studies (10-70%; median, 37%). With a median follow-up period of 44 months (range, 1 to ≥5 months), 3 studies (60%) demonstrated significant differences in recurrence and/or mortality rates between patients with and without ITCs in the normal liver tissue.

8. Conclusion

Although IHC and molecular techniques are useful for detecting tumor cells in histologically negative lymph nodes, the prognostic significance of such cells is equivocal among recent 10-year studies (104). Peritoneal cytology during curative resection ocasionally detects tumor cells and may be useful in identifying a high risk of recurrence or mortality, whereas the presence of tumor cells during surgery in the drainage vein, bone marrow, or liver is not always useful for evaluating the prognosis (105).

Recent studies demonstrated that identifying ITCs in the peripheral blood is useful for estimating the outcome of patients with localized as well as metastatic cancer (106,107). ITCs in the peripheral blood may be measured using the CellSearch system (4,5,108-112) and future prospective studies based on large patient samples and long-term follow-up may elucidate

Table VIII. Tumor cells in the normal liver tissue of patients with liver metastasis.

Author (year)	Cases	Tumor	Marker	Method	Positive rate (%)	Follow-up (months)	Recurrence/ mortality rate	Prognostic value	(Refs.)
Yokoyama, *et al* (2002)	46	CRC	CK20	IHC	70	44	R: 69 vs. 16%; M: 78 vs. 36%	Yes	(100)
Schimanski, *et al* (2003)	16	CRC	K-ras	RT-PCR	50	NA	M: 165 vs. 240[a]	Yes	(101)
Linnemann, *et al* (2004)	54	CRC	K-ras	RT-PCR	26	>1	R: 71 vs. 30%; M: 64 vs. 25%	Yes	(102)
Topal, *et al* (2005)	19	CRC	CEA/CK20	RT-PCR	37	37	NA	No	(89)
Koch, *et al* (2007)	100	CRC	CK20	RT-PCR	10	55	R: 11 vs. 23%; M: 20 vs. 23%	No	(103)

[a]Overall survival (months). CRC, colorectal cancer; CK, cytokeratin; CEA, carcinoembryonic antigen; IHC, immunohistochemistry; RT-PCR, reverse transcriptase-polymerase chain reaction; NA, not available; R, recurrence rate; M, mortality rate.

the utility of routine examination for ITCs in the daily practice of colorectal cancer surgery.

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