

p53, nm23, VEGF

Prognostic Significance of p53, nm23 and VEGF Expression in Primary and Hepatic Colorectal Cancer Metastases Following Surgical Resection

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Purpose: The aim of this study is to analyze a correlation between related molecular markers and prognosis after curative resection for primary and hepatic metastatic colorectal cancer.

Methods: A total of 63 patients who have been resected either for primary and metastatic colorectal cancer between 1989 and 2000. All patients were completely followed up and recurrence and survival rates were analyzed. Affin embedded tumor tissues in primary and metastatic tumors were used for microtissue array and immunohistochemical staining of p53, nm23 and VEGF.

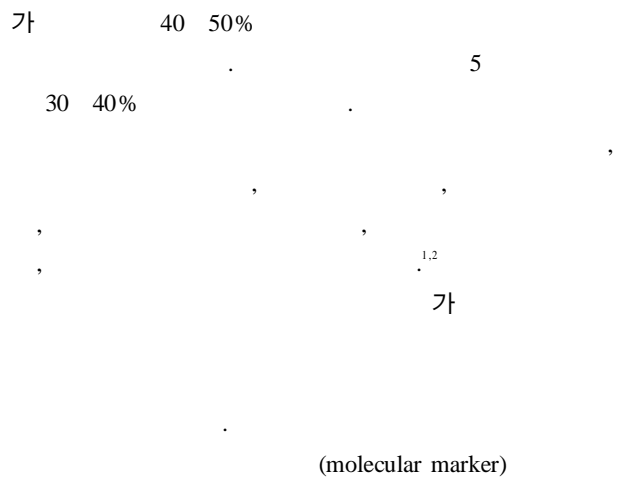
Results: Mean follow up period was 30.9 months. Recurrence was noted in 39/63 (61.9%) and 5 year survival was 27.7%. 5 year survival rates according to protein expression in primary tumor: p53 + / - : 24.6% vs 27.3%, nm23 + / - : 17.6% vs 38.9%, VEGF + / - : 38.8% vs 21.6% (P=0.16, 0.06, 0.9, respectively). 5 year survival according to protein expression in metastatic tumor, p53 + / - : 18% vs 59.2%, nm23 + / - : 38.2% vs 15.8%, VEGF + / - : 38.8% vs 21.6% (P=0.03, 0.35, 0.96, respectively). A patients recurred within 1 year after surgery (group I, N=23) were compared with patients who recurred 1 year after (group II, N=16). nm23 expression in primary tumor in each group of patients: + : 15/23 (65.2%), - : 8/23 (34.8%), + : 4/16 (25%), - : 12/16 (75%), respectively (P=0.013). But, p53, VEGF expression in primary tumor

showed no statistical significance. nm23 expression in metastatic tumor revealed no statistical significance between two groups of patients.

Conclusions: p53 expression in metastatic tumor and nm23 expression in primary tumor can predict poor prognosis after curative resection for primary and metastatic colorectal cancer. Molecular marker expression in primary and metastatic colorectal cancer can give us a reliable prognostic value. *J Korean Soc Coloproctol 2002;18:121-127*

Key Words: Colorectal cancer, Hepatic metastasis, p53, nm23, VEGF, Tissue microarray

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34

Brain Korea 21 Project for Medical Science, Yonsei University.

³⁻⁵ (metastasis cascade)

(adhesion)

molecules),

^{7,8} p53

DNA

1989 2000 6

⁸⁻¹²

63

p53 가

database

¹¹ , p53

가

100%

35

. Kang ¹² p53 angiogenic inducer vascular endothelial growth factor

SPSS (Version 10.0 for Windows, Chicago, IL, USA) Chi-square test ,

Kaplan-Meier

long-rank test

. P-value 0.05

VEGF

nm-23, p53, p53 가

Micro tissue array manual tissue array (Beecher Instruments, Silver Spring, MD, USA)

가

1 mm

3

Dukes

4 mm

5 10 mm

p53

가

^{6,7,9,10} p53

0.8 1 mm

slide 150

17p

53 kDa

. p53

Wild

cell cycle arrest DNA

type, clone DO-7, monoclonal mouse antibody (Dako A/S, Glostrup, Denmark) 1 : 100 , nm23

(apoptosis)

rabbit anti Human, both nm 23-H1, nm23-H2 (Dako A/S, Glostrup, Denmark) 1 : 50

p53

VEGF mouse anti-human VEGF monoclonal antibody (BD Biosciences Pharmingen, CA 92121, San Diego, USA) 1 :

. nm23

가 가

100

micro-

nm23-H2

가

17

(17q)

nm23-H1,

array Xylene, acetone, Alcohol

18.5 kDa, 17 kDa 152

10

. Cit-

rate buffer 25

가

PBS

10

PBS Strepstavidin

¹³⁻¹⁵

DAB chromogen (DAKO) 가

VEGF (Vascular Endothelial Growth Factor)

methyle green

¹⁶

p53, nm-23, VEGF

1)

43 : 20 (68.3% vs 31.7%)

가

57

가 48 (76.2%),

가 15 (23.8%)

30.9

(Table 1).

24, 9, S 13, 6
5, 1, 5

2)

p53 42 (66.7%),
40 (63.5%) . nm-23 28 (44.4%),
41 (61.5%), VEGF 14 (22.2%),
9 (14.3%)† (Table 2).

p53 31/48 (64.6%)/11/15 (73.3%) (P=0.53), nm23 2/48

Table 1. Patient characteristics (N=63)

	Frequency
Sex	
Male	43 (68.3%)
Female	20 (31.7%)
Age (year)	57.1±10.9
Synchronous metastasis	48 (76.2%)
Metachronous metastasis*	15 (23.8%)
Mean F/U period (month)	30.9±18.4

*Mean period in months = 12.6±4.8.

Table 2. Overall protein expression rate in primary and hepatic metastatic cancer (N=63)

	Primary tumor	Liver
p53	42 (66.7%)	40 (63.5%)
nm-23	28 (44.4%)	41 (61.5%)
VEGF	14 (22.2%)	9 (14.3%)

Table 3. Protein expression in the primary tumor according to synchronous or metachronous liver metastasis

		Synchronous (n=48)	Metachronous (n=15)	P-value
p53	(+)	31 (64.6%)	11 (73.3%)	0.53
	(-)	17 (35.4%)	4 (26.7%)	
nm-23	(+)	21 (43.8%)	7 (46.7%)	0.84
	(-)	27 (56.3%)	8 (53.3%)	
VEGF	(+)	10 (20.8%)	4 (26.7%)	0.63
	(-)	38 (79.2%)	11 (73.3%)	

(43.8%)/7/15 (46.7%) (P=0.84), VEGF 10/48 (20.8%)/4/15 (26.7%) (P=0.63) (Table 3).

p53 29/48 (60.4%)/11/15 (73.3%) (P=0.36), nm23 31/48 (64.6%)/10/15 (66.7%) (P=0.88), VEGF 7/48 (14.6%)/2/15 (13.3%) (P=0.90) (Table 4).

3)

39/63 (61.9%)

15.3±9.3

. 5 27.7%

39 가 15

(38.5%) 가 9 (23.0%), 5

(12.9%), 2 (5.1%), 가

8 (20.5%)

p53 26 (66.7%),

27 (69.2%), nm23 19 (48.7%), 24 (61.5%), VEGF

11 (28.2%), 6 (15.4%)

(P=0.9, 0.3,

0.1)(Table 5).

1 (N=23) 1 (N=16)

p53 18/23 (78.3%), 8/16 (50%)

Table 4. Protein expression in the metastatic tumor according to synchronous or metachronous liver metastasis

		Synchronous (n=48)	Metachronous (n=15)	P-value
p53	(+)	29 (60.4%)	11 (73.3%)	0.36
	(-)	19 (39.6%)	4 (26.7%)	
nm-23	(+)	31 (64.6%)	10 (66.7%)	0.88
	(-)	17 (35.4%)	5 (33.3%)	
VEGF	(+)	7 (14.6%)	2 (13.3%)	0.90
	(-)	41 (85.4%)	13 (86.7%)	

Table 5. Positive expression rate in primary and metastatic tumor in the recurrence after surgical resection (N=39)

	Primary tumor	Liver
p53	26 (66.7%)	27 (69.2%)
nm-23	19 (48.7%)	24 (61.5%)
VEGF	11 (28.2%)	6 (15.4%)

Table 6. Protein expression rate in the primary tumor according to recurrence time after surgical resection

		Recurrence		P-value
		< 1 year (n=23)	> 1 year (n=16)	
p53	(+)	18 (78.3%)	8 (50.0%)	0.06
	(-)	5 (21.7%)	8 (50.0%)	
nm-23	(+)	15 (65.2%)	4 (25.0%)	0.01
	(-)	8 (34.8%)	12 (75.0%)	
VEGF	(+)	5 (21.7%)	6 (37.5%)	0.28
	(-)	18 (78.3%)	10 (62.5%)	

Table 7. Protein expression rate in the metastatic tumor according to recurrence time after surgical resection

		Recurrence		P-value
		< 1 year (n=23)	> 1 year (n=16)	
p53	(+)	17 (73.9%)	10 (62.5%)	0.44
	(-)	6 (26.1%)	6 (37.5%)	
nm-23	(+)	14 (60.9%)	10 (62.5%)	0.91
	(-)	9 (39.1%)	6 (37.5%)	
VEGF	(+)	4 (17.4%)	2 (12.5%)	0.67
	(-)	19 (82.6%)	14 (87.5%)	

Table 8. 5 year survival rate according to protein expression in primary tumor

		Patient No.	Survival (%)	P-value
p53	(+)	42	24.6%	0.15
	(-)	21	27.3%	
nm-23	(+)	28	17.9%	0.06
	(-)	35	38.9%	
VEGF	(+)	14	34.3%	0.90
	(-)	49	23.1%	

5/23 (21.7%), 8/16 (50.0%) (P=0.06) . nm 23
 15/23 (65.2%), 4/16 (25%), 8/23
 (34.8%), 12/16 (75%) (P=0.013) . VEGF
 5/23 (21.7%), 6/16 (37.5%) 18/23 (78.3%),
 10/16 (62.5%) (P=0.28) (Table 6).

1 1
 p53 17/23 (73.9%), 10/16 (62.5%)

Table 9. 5 year survival rate according to protein expression in metastatic tumor

		Patient No.	Survival (%)	P-value
p53	(+)	40	18.0%	0.03
	(-)	23	59.6%	
nm-23	(+)	41	38.2%	0.35
	(-)	22	15.8%	
VEGF	(+)	9	38.8%	0.96
	(-)	54	21.6%	

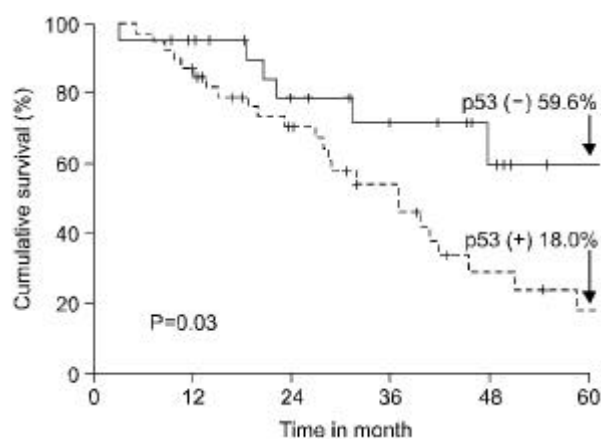


Fig. 1. Cumulative 5 year survival curve according to p53 expression in metastatic tumor.

6/23 (26.1%), 6/16 (37.5%) (P=0.44) . nm23
 14/23 (60.9%), 10/16 (62.5%)
 9/23 (39.1%), 6/16 (37.5%) (P=0.91) . VEGF
 4/23 (17.4%), 2/16 (12.5%), 19/23 (82.6%),
 14/16 (87.5%) (P=0.67) (Table 7).
 5
 p53 24.6% 27.3% (P=0.15), nm23
 17.6% 38.9% (P=0.06), VEGF
 34.3% 23.1% (0.9) 가 (Table 8).
 5 p53
 18.0% 59.6% (P=0.03) (Fig. 1), nm23
 38.2% 15.8% (P=0.35), VEGF
 38.8% 21.6% (P=0.96) (Table 9).

가

, , , , , Dukes stage, mutant p53 75 %
 , , , , , 가 p53 64.6%, 73.3%
 1 (P=0.53), 60.4%, 73.3% (P=0.36)
 . Yang 7 p53
 62.8% gene p53
 35.6%가 가 p53 가
 가 가 wild type p53
 가 p53
 가
 nm23
 p53 가
 p53 가 . Tullo 17 40
 19 (47.5%) p53 p53 mutation p53 wild type
 가 41%가 3 , wild p53 p53 5 p53
 14% 3 가 . p53, nm23, VEGF 1
 p53 (deletion) 251 codon, 252 codon p53 nm23 가 nm23
 . Yang 7 41% p53 nm23
 Kalenberg 18 60% De Jong 8 nuclear p53 expression p53, 83%,
 83%, 71% . Heide 19 EGFR 가 가 De Jong 8 p53,
 68%, 70% p53 TGF- 가 가
 . Belluco 9 72% p53 . Strum 20 41 BAX p53 gene 가
 p53 66.7%, 63.5% 가 p53 wild type BAX 가
 가 66.7%, 69.2% 가 . Belluco 9 50 p53
 Yao 10 p53 p53 21 , p53 53.2
 가 p53 . 2 41.7%, 78.6% p53
 . Pocard 23 p53
 2 Tullo 17 wild type p53 29% p53 80%,

40% . p53 angiogenetic effect가
 sensitivity
 가 60%, specificity가 82% .
 p53 VEGF
 . Kondo ¹¹
 angiogenesis가
 p53 VEGF p53
 Nitti ⁶ VEGF가 angiogenesis
 p53
 . VEGF
 p53 27 , p53 93
 p53
 가
 가

, Benhattar ²¹
 p53 . p53
 nm23 p53
 가 가
 가 가
 . Tabuchi ¹³ nm
 23-H1 가
 , Lee ¹⁴ nm23-H1 gene
 . Wang ¹⁵ nm23
 gene 가 가
 . Berney ²²
 nm23

Dukes B
 p53, VEGF, c-erbB-2
 가 p53
 nm23
 Vascular Endothelial Growth Factor (VEGF)
 cytokine
 . cytokine
 . Akagi ¹⁶ VEGF-C
 . VEGF-C가 VEGF tyrosine ki-
 nase receptor 3
 . VEGF tyrosine kinase receptor 2가
 angiogenesis
 . VEGF-C가 receptor 2

angiogenetic effect가
 VEGF
 . Kondo ¹¹
 angiogenesis가
 VEGF p53
 VEGF가 angiogenesis
 . VEGF
 p53
 p53
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 1
 nm23 nm23
 가
 nm23
 p53

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