The utility or lack thereof regarding serum p53 antibody for detecting ulcerative colitis-associated colorectal cancer in the era of immunosuppressive therapy.

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Abstract

Background: Serum anti-p53 antibodies (Abs) have been considered useful for the early detection of ulcerative colitis-associated colorectal cancer (CAC). However, since the spread of immunosuppressive therapy for ulcerative colitis (UC) treatment in the 2010s, we have experienced a low prevalence of anti-p53 Abs in UC patients. The present study thus examined the utility of serum p53 Abs for detecting CAC in the era of immunosuppressive therapy. Methods: A series of 320 consecutive surgical cases of UC patients between April 2008 and March 2019 were enrolled in this study. Patients with no serum anti-p53 Abs data were excluded. Of the 250 patients analyzed, 219 had no carcinoma or dysplasia (Group non-CAC), and 31 had carcinoma or dysplasia (Group CAC). Serum anti-p53 Abs were detected with an enzyme-linked immunosorbent assay. Immnohistochemical detection was performed in Group CAC. Immunosuppressive therapy included a history of medication with prednisolone >20 mg/day, immunosuppressant drugs, immunomodulator drugs or biologic therapies for UC. Results: Immunosuppressive therapy was performed in 98.1% of Group non-CAC and 80.6% of Group CAC. There were no marked differences in serum anti-p53 Abs positivity between Groups non-CAC and CAC (8.7% vs. 3.2%, p =0.30). p53 staining positivity was noted in 90.3% of Group CAC, and the rate of serum p53 positivity was significantly lower in patients with immunosuppressive therapy than in those without in Group CAC (0.0% vs. 16.7%, p =0.04). Conclusions: The utility of serum p53 Abs for detecting CAC is dubious in the era of immunosuppressive therapy.

Background

Mutations in the p53 tumor suppressor gene are the most frequently reported somatic gene alterations in human cancer[1-3]. In the ulcerative colitis (UC)-associated dysplasia-carcinoma sequence, p53 gene mutations are early events in 50% of patients with UC compared with approximately 10% of adenomas related to the typical adenoma-carcinoma sequence[4,5]. Mutations in the p53 gene was observed in 50%-85% of colonic tissue specimens of UC with dysplasia or colorectal cancer[5]. These mutations result in the accumulation of the p53 protein, which causes p53 overexpression in tissue. There have been many reports of p53 overexpression in cases of ulcerative colitis-associated colorectal cancer (CAC)[5,6].

Apart from the detection of p53 gene mutations and p53 overexpression associated with CAC, in the 1990's it was reported that serum anti-p53 antibodies were detected as serum IgG antibodies which occur due to an antigen-antibody reaction to p53 protein. The usefulness of measuring serum anti-p53 Antibodies (Abs) in various malignant tumors has been suggested[7-11]. Compared with conventional tumor markers, anti-p53 Abs is useful for detecting early colorectal cancer[12]. Yoshizawa et al. reported the usefulness of measuring serum anti-p53 Abs in CAC in 2007[13]. This assessment subsequently became eligible for health insurance coverage in Japan that same year.

However, since the spread of immunosuppressive therapy for UC treatment in the 2010s, we have experienced a low prevalence of anti-p53 Abs in UC patients with CAC. To our knowledge no data are available in the literature concerning the usefulness of serum p53 Abs for CAC since immunosuppressive

therapy became common for UC treatment. The present study therefore explored whether or not serum p53 Abs are useful for detecting CAC in the era of immunosuppressive therapy.

Methods

Study population

From April 2008 to March 2019, 320 consecutive patients who underwent surgical resection for UC were collected from Yokohama City University Medical Center in Japan. The exclusion criterion was no data on serum anti-p53 Abs before the operation. A total of 250 patients were analyzed in this study. We divided the patients into two groups: Group non-CAC included those who underwent surgery for severe or intractable colitis and had not been diagnosed with carcinoma or dysplasia histologically by a biopsy or surgical specimen, and Group CAC included those who had been diagnosed with carcinoma or dysplasia. Of these 250 UC patients, 219 (87.6%) were in Group non-CAC, and 31 (12.4%) were in group CAC (Fig. 1). The history of other cancer, smoking habit and family history of colorectal cancer (CRC) were reviewed. The clinicopathological features of UC, such as the age at the operation, duration of disease, extension of disease and medications, were collected from the medical records.

An enzyme-linked immunosorbent assay (ELISA) for Anti-p53 Abs and conventional tumor makers

An ELISA for the detection of anti-p53 Abs in serum was carried out with a commercially available ELISA kit (MESACUP anti-p53 test; Medical & Biological Laboratories, Nagoya, Japan). In brief, serum samples and calibrators were added to each well of a microwell plate coated with wild-type human p53 or control protein. Samples were incubated on the plate for 60 min (20-30 ℃). After washing, a peroxidase-conjugated anti-human IgG anti-p53 Abs was added, followed by further incubation for another 60 min (20-30 ℃). After washing again, the substrate was added, and the plate was incubated again for 30 min (20-30 ℃). A stop solution was then added to each well to stabilize the color development. The value in each sample was determined by comparing the optical density of the sample to that of the anti-p53 standard. The cut-off value was 1.3 U/ml, according to a previous colorectal cancer study[12, 14, 15].

The carcinoembryonic antigen (CEA) levels were measured with a CEA-2 enzyme immune assay (EIA) kit (Elecsys CEAII; Roche Diagnostics K.K., Tokyo, Japan) following the manufacturer's instructions with a cut-off value of 5.0 ng/ml. The cancer antigen 19-9 (CA19-9) levels were measured with a CA19-9 EIA kit (Elecsys CA19-9; Roche Diagnostics K.K.) with a cut-off value of 37 U/ml.

Immunohistochemistry

For those patients revealed to have dysplasia or CRC by colonoscopy, we also evaluated the p53 status with immunohistochemistry using biopsied or surgical specimens. In brief, paraffin-embedded tissue

samples were cut into serial sections of 3-4 μm thickness, placed on coated slides and deparaffinized through a series of xylene and ethanol baths. The slides were then incubated with anti-p53 primary antibodies (DO-7; DAKO, Glostrup, Denmark), followed by biotin-conjugated goat antibody against mouse as a secondary antibody (E0433; DAKO). The following steps were performed using a standard ABC method (Elite ABC kit, Vectastain; Vector Laboratories, Burlingame, CA, USA): 3,3-Diaminobenzidine was used as substrate for the peroxidase enzyme reaction (Vectastain; Vector Laboratories), and all slides were counterstained with hematoxylin and observed under a microscope (CH40; Olympus, Tokyo, Japan).

Immunosuppressive therapy

In this study, we defined immuno-suppressive therapy as a patient with a medical history of receiving prednisolone exceeding 20 mg per day for the equivalent of 2 weeks or more, immunosuppressant drugs (including cyclosporine and tacrolimus), immunomodulator drugs (including 6-mercaptopurine, azathioprine and methotrexate) or biologic therapies (including infliximab and adalimumab) for UC treatment. According to a previous report, these therapies induced an immunocompromised state in inflammatory bowel disease patients.

Statistical analyses

Differences between categorical variables were tested using Pearson's chi-squared test, and differences between continuous variables were tested using the Mann-Whitney U test. Statistical analyses were performed using the SPSS statistical software program, version 22.0 (SPSS Inc., Chicago, IL, USA). All tests were 2-sided, and values less than 0.05 were considered statistically significant.

Results

Serum anti-p53 Abs and the clinicopathological features of the study population

The demographic and biochemical characteristics of the subjects in all studied groups are shown in Table 1. There were no significant differences in the positivity of serum anti-p53 Abs between Group non-CAC and Group CAC (8.7% vs. 3.2%, p=0.30). The age at operation in Group non-CAC was lower than that in Group CAC (40 years vs. 50 years, p=0.02). The duration of disease differed significantly between Group non-CAC and Group CAC (6 years vs. 17 years, p=0.01), and patients with >8 years since the UC onset were less frequent in Group non-CAC than in Group CAC (25.1% vs. 87.1%, p<0.01). Immunosuppressive therapy was performed in 98.1% of Group non-CAC and 80.6% of Group CAC.

There were no significant differences between the groups in the gender, age at UC onset, disease extent, history of other cancer, smoking, family history of CRC, serum CEA or serum CA19-9.

Serum anti-p53 Abs and tissue p53 overexpression in Group CAC

The serum anti-p53 Abs and tissue p53 overexpression in Group CAC are shown in Table 2. p53 overexpression in tumor tissue was noted in 90.3% of Group CAC. Both serum anti-p53 Abs and tissue p53 overexpression were positive only in Patient 3, who was diagnosed with CRC and did not undergo immunosuppressive therapy.

Association between anti-p53 Abs and immunosuppressive therapy

The association between anti-p53 Abs and immunosuppressive therapy is shown in Table 3. The rate of positivity for anti-p53 Abs was significantly lower in those who underwent immunosuppressive therapy before their operation than in those who did not undergo immunosuppressive therapy before their operation in Group CAC. (0.0% vs. 16.7%, p=0.04).

Discussion

We analyzed a total 250 UC patients, including 31 patients with carcinoma or dysplasia. The rate of positivity for serum anti-p53 Abs was only 3.2% in patients with carcinoma or dysplasia and 8.7% in those without carcinoma or dysplasia. Our study clarified that serum anti-p53 Abs measurement does not aid in the detection of CAC.

Lu et al. showed in their meta-analysis that p53 expression was positive in cases of UC associated with carcinoma and dysplasia[6]. The frequency of anti-p53 Abs in patients with tumors is strictly correlated with the frequency of p53 mutations[17]. There is generally a good correlation between the presence of anti-p53 Abs and the p53 accumulation and/or mutations in a tumor[18-20]. Previous studies reported that the presence of anti-p53 Abs in UC with carcinoma or dysplasia was significantly more frequent than in UC without carcinoma or dysplasia (40.0%-61.5% vs. 12.8%-13.3%). Therefore, measuring anti-p53 Abs may aid in the early detection of carcinoma or dysplasia in UC patients [13,20].

However, in the present study, the p53 expression was positive in 90.3% of UC patients with carcinoma or dysplasia, but anti-p53 Abs was positive in only 3.2% of UC patients with carcinoma or dysplasia. The rate of p53 overexpression was thus high in tumors despite a low prevalence of serum anti-p53 Abs in UC with carcinoma or dysplasia. Some reports have demonstrated the high rate of p53 mutations in tumors and the low prevalence of anti-p53 Abs [21-23]. One factor associated with this observation is immunological malformation that influence the difference in anti-p53 Abs prevalence among patients with p53 mutant tumors[21-23]. Over the past decade, UC patients have tended to develop immunological malformation because immunosuppressive therapy has been used more frequently and earlier in the disease course to treat UC[24]. In addition to steroid therapy, immunomodulatory drugs,

immunosuppressant drugs and biologic therapy (specifically anti-tumor necrosis factor [anti-TNF]) have been key to the treatment of UC, as the efficacy of immunomodulatory drugs for UC maintenance therapy was reported in a meta-analysis in 2012[25], and that of biological therapies was reported in 2011[26].

Some reports have suggested that immunosuppressive therapy might induce a low antibody response rate to various vaccines, because immunosuppressive therapy plays a role at various points of the inflammation cytokine cascade[27-30]. We considered that the low prevalence of anti-p53 Abs might be caused by a low antibody response to p53 protein induced by immunosuppressive therapy in UC patients, as the positivity for anti-p53 Abs was significantly lower in patients with immunosuppressive therapy than in those without immunosuppressive therapy among UC patients with cancer or dysplasia.

Several limitations associated with the present study warrant mention. First, some cases did not have anti-p53 Abs measured before the operation, particularly emergent surgical cases. We therefore excluded these cases from this study. Second, this was a small-scale single-institutional study, wholly comprising Japanese patients. A large-scale multi-institutional study is thus needed.

Conclusions

There was no marked difference in the serum anti-p53 Abs between UC cases with carcinoma or dysplasia and those without carcinoma or dysplasia. Serum p53 Abs are not associated with p53 immunoreactivity in CAC patients with immune-suppressive therapy. The utility of serum p53 Abs for detecting CAC is dubious in the era of immunosuppressive therapy.

Abbreviations

Abs: antibodies; CA19-9: carbohydrate antigen 19-9; CAC: ulcerative colitis-associated colorectal cancer; CEA: carcinoembryonic antigen; CRC; colorectal cancer; EIA: enzyme immune assay; ELISA: enzyme-linked immunosorbent assay; Group non-CAC: patients who underwent surgery for severe or intractable colitis and had not been diagnosed with carcinoma or dysplasia histologically by a biopsy or surgical specimen; Group CAC: patients who had been diagnosed with carcinoma or dysplasia; UC: ulcerative colitis

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine and the institutional review board of each participating hospital before the study was initiated. Because the type of this study was a retrospective chart review, the need for written consent was waived by an IRB. Informed consent was obtained in the form of opt-out on the website. All patients' chart records were anonymized prior to analyses.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no conflicts of interest for this work.

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The authors received no funding for this study.

Authors' contributions

KT and HK contributed to the study design. All authors contributed to the data collection, data analysis, and interpretation. KT and HK contributed to the statistical analyses. All authors contributed to the writing or review of the report and approved the final version.

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None

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Tables

Table.1 Characteristics of Study population

Variables	Group non-CAC N=219	Group CAC N=31	*p* value
Gender, n (%)	125 (57.1)	23 (74.2)	0.07
Male	94 (43.9)	8 (25.8)	
Female			
Age at operation (years), mean±SD	40±17.7	50±16.6	0.02
Duration of disease(years), mean±SD	6±6.5	17±9.2	0.01
>8 years, n (%)	55 (25.1)	27 (87.1)	<0.01
Age at UC onset (years), mean±SD	33.6±17.2	32.4±15.6	0.26
Disease extent , n (%)	208 (95.0)	29 (93.5)	0.74
Extensive colitis	11 (5.0)	2 (6.5)	
Left-sided colitis	0	0	
Proctitis			
History of other cancer , n (%)	5 (2.3)	0	0.40
Smoking, n (%)	33 (15.1)	8 (25.8)	0.13
Immunosuppressive therapy, n (%)	215 (98.1)	25 (80.6)	<0.01
Family history of CRC, n (%)	11 (5.0)	4 (12.9)	0.08
Serum anti- p53 antibodies positive, n (%)	19 (8.7)	1 (3.2)	0.30
Serum CEA (ng/ml), positive, n (%)	18 (8.2)	2 (6.5)	0.73
Serum CA 19-9 (U/ml, positive, n (%)	10 (4.5)	2 (6.5)	0.65

Group non-CAC; Ulcerative colitis without carcinoma or dysplasia, Group CAC; Ulcerative colitis with carcinoma or dysplasia; UC; Ulcerative Colitis, CRC; colorectal cancer; CEA; Carcinoembryonic antigen, CA19-9; carbohydrate antigen 19-9.

Table.2 Clinicopathologic Characteristics of Ulcerative colitis with cancer or dysplasia

Patients	Sex	Age	Duration	Immunosuppressive therapy	Histology	Stage	p53 Overexprassion	Anit-p53 antibodies	Serum CEA	Serum CA19-9
1	F	83	43	-	tub1		+	-	+	-
2	F	29	13	-	tub1		+	-	-	+
3	M	37	11	-	tub1		+	+	-	-
4	M	72	15	-	tub1		+	-	-	-
5	M	19	4	-	tub1		+	-	-	-
6	M	60	28	-	HGD	n.a.	+	-	-	-
7	M	39	18	PSL	tub2		+	-	+	-
8	M	82	4	IM, PSL	tub2		-	-	-	-
9	M	65	25	IM, PSL	tub2		-	-	-	-
10	M	46	21	IM, PSL	tub2		+	-	-	-
11	M	51	16	IM, PSL	muc		+	-	-	-
12	M	50	24	Bio, PSL	tub1		+	-	-	-
13	M	42	11	Bio	tub1		+	-	-	-
14	M	35	16	IM	tub1		+	-	-	+
15	M	38	21	IM	tub1		+	-	-	-
16	F	35	16	PSL	tub2		+	-	-	-
17	F	55	15	PSL	tub1		+	-	-	-
18	M	48	19	PSL	tub1		+	-	-	-
19	M	45	16	PSL	tub1		+	-	-	-
20	M	41	24	Bio, PSL	tub1	0	+	-	-	-
21	F	52	12	PSL	tub2	0	+	-	-	-
22	F	38	8	IM, Bio, IS, PSL	tub1	0	-	-	-	-
23	M	40	15	Bio, PSL	HGD	n.a.	+	-	-	-
24	M	75	18	IM, Bio, IS, PSL	HGD	n.a.	+	-	-	-
25	M	63	37	PSL	HGD	n.a.	-	-	-	-
26	M	72	26	PSL	HGD	n.a.	+	-	-	-
27	M	70	4	PSL	HGD	n.a.	+	-	-	-
28	M	51	31	PSL	LGD	n.a.	+	-	-	-
29	F	35	11	IM, PSL	LGD	n.a.	+	-	-	-
30	M	62	14	IM, Bio, IS, PSL	LGD	n.a.	+	-	-	-
31	F	27	6	PSL	LGD	n.a.	+	-	-	-

M; male, F; female, PSL; prednisolone, IM; immunomodulator drugs, Bio; biologic therapies, IS; immunosuppressant drugs, tub2; moderately differentiated tubular adenocarcinoma, tub1; well differentiated tubular adenocarcinoma, HGD; high grade dysplasia, LGD; low grade dysplasia, n.a.; not applicable, CEA; Carcinoembryonic antigen, CA19-9; carbohydrate antigen 19-9.

Table.3 Association between anti-p53 antibodies and immuno-suppressive therapy

Group CAC N=31	Serum Anti-p53 antibodies (+)	Serum Anti-p53 antibodies (-)	*p* value
Immunosuppressive therapy (-) N=6	1 (16.7%)	5 (83.3%)	0.04
Immunosuppressive therapy (+) N=25	0 (0.0%)	25 (100.0%)	

Group CAC; Ulcerative colitis with carcinoma or dysplasia.

Figures

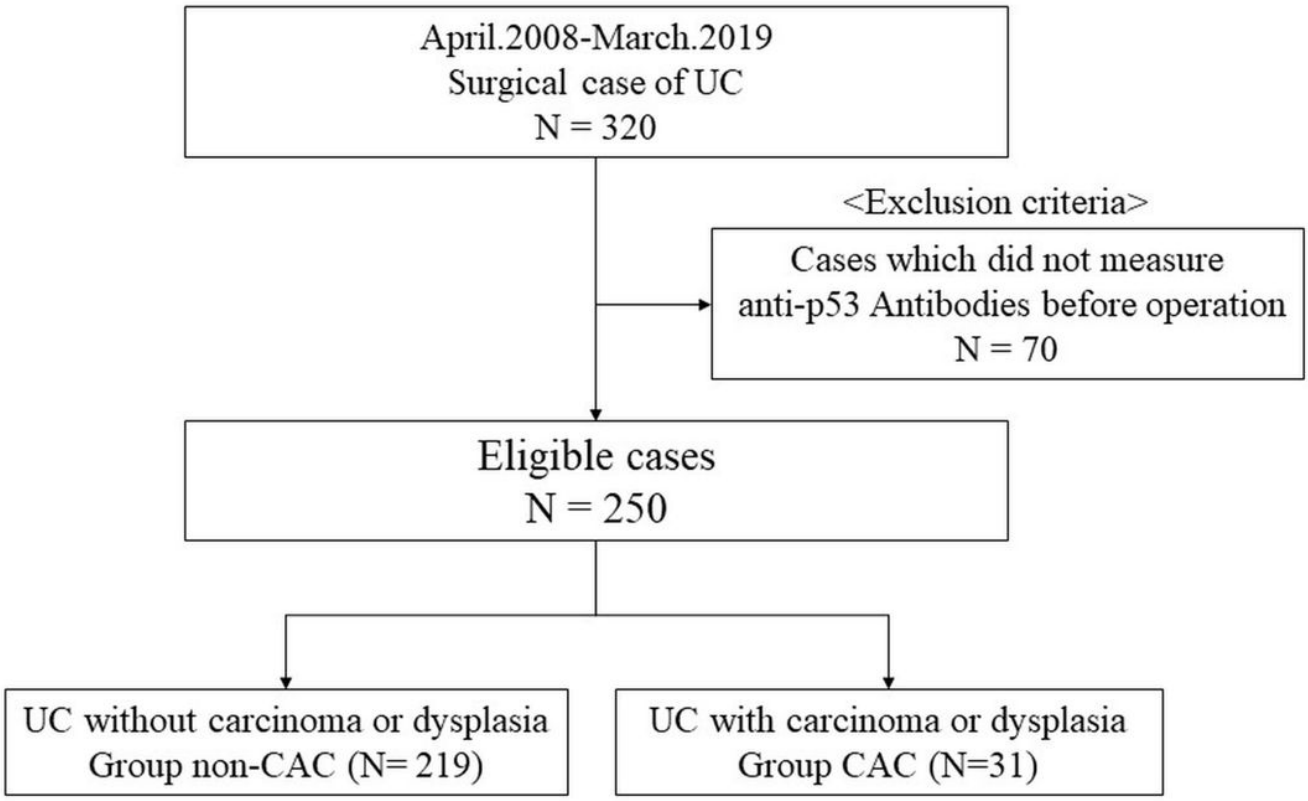

Figure 1

Outline of patient selection. UC: Ulcerative colitis.