

## Original Article

# Analysis of colonic adenomas recurrence after adenoma removes

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**Abstract:** Objective: Some neoplasms are missed in colonoscopy procedures make the colonic adenoma surveillance intervals difficult to put into practice. Our research tried to avoid the influence of missed neoplasms, analyzed the adenoma recurrence and provided surveillance suggestion for patients after polypectomy or other endoscopic therapy. Methods: A total of 303 patients with colonic adenoma and lesions remove between 2005 and 2009 were respectively analyzed, all patients were suggested colonoscopy within 6 months after initial colonoscopy and removed missed adenomas. Every patient underwent surveillance colonoscopies every 1-2 years to detect the adenomas recurrence. Results: The median recurrence time was 23 months, male patients, patients older than 60 years, patients with extracolonic tumor history; with alcohol history and patients with  $\geq 3$  adenomas has high risk of adenoma recurrence. Conclusions: The first surveillance colonoscopy are suggested 24 months after initial colonoscopy, if patients are male patients, older than 60 years, with extracolonic tumor history or drinking history in the mean time, shorter surveillance interval are suggested.

**Keywords:** Colonic adenoma, recurrence, colonoscopy

### Introduction

The incidence of colorectal cancer (CRC) in China has increased significantly in recent years. Colorectal neoplasia screening and removal by colonoscopy is an effective strategy for reducing CRC incidence and mortality [1, 2]. There are no provided guidelines for colonoscopy surveillance intervals after polypectomy based on the characteristics of the neoplasia on initial colonoscopy in China. The main reason for surveillance intervals difficultly putting into practice is some neoplasms being missed in colonoscopy procedures. 20-50% patients who have adenoma removed during the initial colonoscopy will be found to have recurrent adenoma on a surveillance colonoscopy within 3-5 years [3-6].

Patients in our hospital were suggested colonoscopy within 6 months after initial colonoscopy and removed missed adenomas. All adenomas detected at subsequent colonoscopies performed within 6 months of the baseline colonoscopy were considered to be adenomas missed on the initial colonoscopy. After

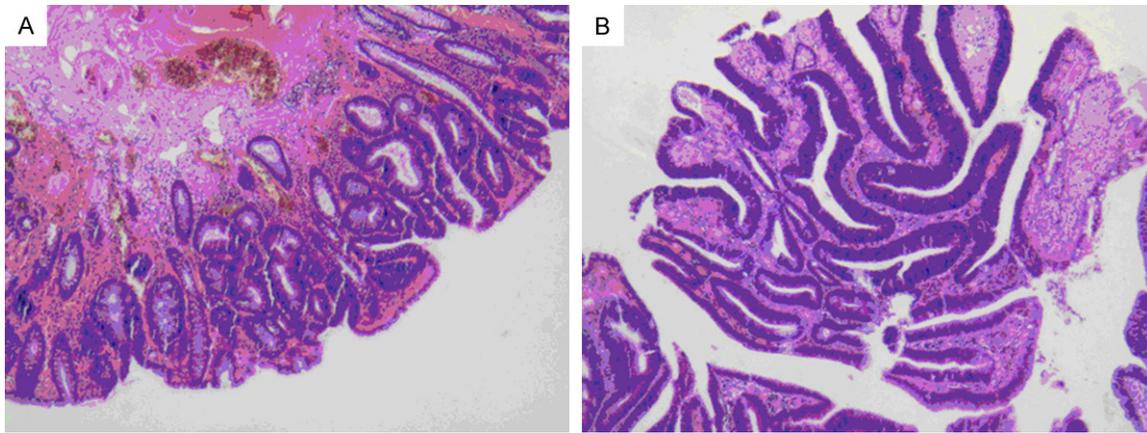
removed all the baseline adenomas by two times endoscopic examination and treatment, patients were followed up regularly and recorded the actual recurrence of adenoma. The aim of our study was retrospectively analyzed the cumulative recurrence rates, median recurrence time of colonic adenoma and main influential factors for adenoma recurrence based on the features of adenomas detected on initial colonoscopy, provided surveillance suggestion for Chinese patients with colonic adenoma after polypectomy or other endoscopic therapy.

### Materials and methods

#### Study population

Our retrospective study initial collection information from 806 patients with adenomas accepted polypectomy or endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) from 2005-2009. Patients should met the following included criteria: 1) at least one surveillance colonoscopy was performed within 6 months after the initial colo-

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**Figure 1.** The pathological images of non-advanced adenoma ,advanced adenoma with high grade intraepithelial neoplasia. A. Non-advanced adenoma; B. This lesion is advanced adenoma with high grade intraepithelial neoplasia.

noscopy, with the aim of removing missed adenomas; 2) complete colonoscopy was performed at every examination; 3) the surveillance interval was 1-2 years. The excluded criteria were: 1) no surveillance colonoscopy was performed within 6 months after the initial colonoscopy to remove missed adenomas; 2) at least one uncomplete colonoscopy was performed; 3) patients couldn't finish surveillance every 1-2 years; 4) patients with familial adenomatous polyposis, inflammatory bowel disease, or colorectal cancer in initial colonoscopy were excluded. 303 patients met the included criterion. This study was conducted in accordance with the declaration of Helsinki. Ethic Committee of Peking University People's Hospital approved the research protocol.

### Data collection

In the course of this study, we reviewed all colonoscopy and pathology reports and collected data on the adenoma's number, size, and pathology, patients' age and sex, patients' colonic carcinoma history, extracolonic tumor history, family history of colonic carcinoma, family history of extracolonic tumor, smoking history, alcohol history.

### Endoscopic process

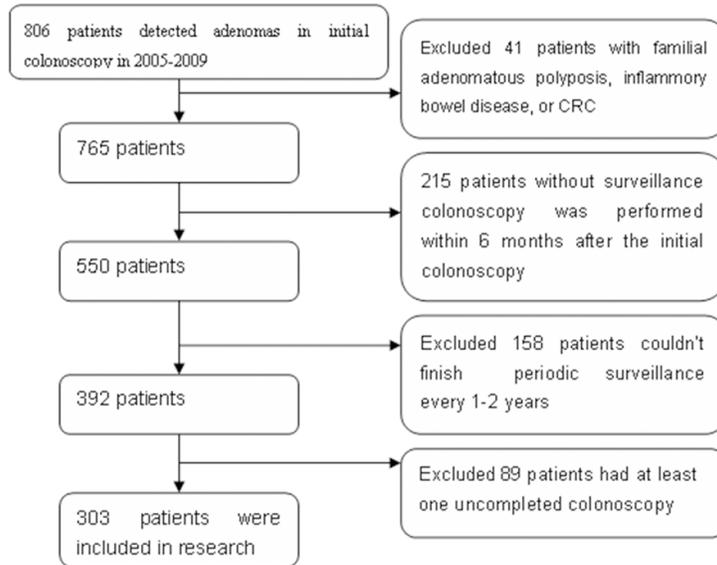
All colonoscopies were performed by 2 experienced endoscopists. A complete colonoscopy was considered to include: colonoscopy reaching the cecum, a good bowel preparation, and removal of all visualized lesions by colonos-

copic polypectomy or EMR, or ESD. All polypectomy, EMR and ESD were also performed by 2 experienced endoscopists, both doctors performed endoscopic treatment more than 7 years. The size of the adenoma was estimated with an opened biopsy forceps (7 mm) or measured after resection.

### Pathological evaluation

All pathology was evaluated by 2 experienced pathological doctor. When there was a discrepancy, a third referee pathologist reviewed the material. Patients were classified based on the most advanced histologic lesion. Histopathology features of the adenoma were evaluated by 2 specialist gastrointestinal pathologist according to the colorectal neoplasia classification of the World Health Organization recommendations. Our study classified adenomas pathology in two ways. One classified adenoma into advanced adenomas group and without advanced adenomas group, the other classified adenoma into high grade intraepithelial neoplasia group and without high grade intraepithelial neoplasia group. Advanced adenoma was considered to be adenoma that had one or more of the following features: a tubular adenoma 10 mm or larger in diameter, villous or tubulovillous adenoma, or the presence of high-grade dysplasia. Adenomas without above features were classified into without advanced adenomas group (**Figure 1**). High grade intraepithelial neoplasia means severe dysplasia and carcinoma in situ, low grade intraepithelial neoplasia means mild and moderate dysplasia.

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**Figure 2.** The included procedure of 303 patients.

According to the definition, advanced adenomas sometimes accompany with high grade intraepithelial neoplasia (**Figure 1**).

### Statistical analysis

Statistical package for the SPSS version 13.0 were used for the statistical analysis, life table analysis were used to identify the cumulative recurrence rates of adenoma. Kaplan-Meier analyses with log-rank test were used to identify univariate predictors of adenoma recurrence and compare differences between cumulative recurrence curves. Multivariate analysis was conducted using Cox proportional hazard model.

### Results

#### Baseline characteristics

806 patients detected adenomas in initial colonoscopy and accepted endoscopic treatment in our hospital in 2005-2009 were included, The mean ( $\pm$  standard deviation, SD) age at the index colonoscopy was  $63.56 \pm 9.45$  years (range 20-92 years). The excluded patients included: 41 patients with familial adenomatous polyposis, inflammatory bowel disease, or CRC in initial colonoscopy, 215 patients without surveillance colonoscopy was performed within 6 months after the initial colonoscopy, 158 patients couldn't finish periodic surveillance every 1-2 years. 89 patients had at least

one uncompleted colonoscopy.

**Figure 2** showed the procedure of patient's included. **Table 1** showed the characteristics of study cohort.

#### Recurrent polyps

The median follow up time is 46 months. The median recurrence time was 23 months, by life table analysis the cumulative recurrence rates of adenoma at the surveillance examination were 52%, 62%, and 75% for the surveillance intervals 0-2, 2-5, 5-8 years, respectively (**Table 2**). More than 50% patients have adenoma recurrence in 2 years.

#### Factors of adenoma recurrence

By Kplan-Meier method, six characteristics (age, sex, colonic carcinoma history, extracolonic tumor history, alcohol history, adenomas' number at baseline status) survival curve distribution difference have significant difference ( $P < 0.01$ ). Different groups median recurrence time and survival curve distribution difference see **Table 3**.

Above 6 characteristic were introduced into multivariate analysis, gender, age, extracolonic tumor history, alcohol history and adenomas' number at baseline status were the independent prognostic factors for adenoma recurrence (**Table 4**). Patients older the 60 years had high adenoma recurrence risk than patients younger than 60 (HR 1.359,  $P = 0.011$ ), patients with extracolonic tumor history had high adenoma recurrence risk than patients without extracolonic tumor history (HR 5.180,  $P < 0.001$ ), patients with alcohol history had high risk than patients without alcohol history (HR 2.022,  $P = 0.001$ ), patients had more than 3 colonic adenomas at initial colonoscopy had high adenoma recurrence risk than patients had  $\leq 2$  adenomas (HR 1.811,  $P < 0.001$ ), the female patients had lower recurrence risk than male patients (HR 0.632,  $P = 0.001$ ). The median recurrence time for male patients, patients older than 60 years, patients with extracolonic tumor history, patients with alcohol history and patients with  $\geq 3$  adenomas at baseline status were  $19 \pm 1.28$  months,  $22 \pm$

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**Table 1.** Characteristics of Study Cohort

	Sex		Colonic carcinoma history		Extracolonic tumor history		Family history of colonic carcinoma		Family history of extracolonic tumor		Smoking history		Alcohol history		Adenomas' number at baseline status (≥3)		Adenoma size			High grade IN*		Advanced adenoma	
	Male	Female	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	<1 cm	1-2 cm	>2 cm	Yes	No	Yes	No
n	171	132	16	287	13	289	17	286	27	276	97	206	54	249	226	77	192	84	27	58	245	228	75
%	56.43	43.56	5.28	94.72	4.29	95.38	5.61	94.39	8.91	91.09	32.01	67.99	17.82	82.18	74.59	25.41	63.37	27.72	8.91	19.14	80.86	75.25	24.75

**Table 3.** Different groups median recurrence time and survival curve distribution difference

Characteristic	Age (years)		Sex		Colonic carcinoma history		Extracolonic tumor history		Family history of colonic carcinoma		Family history of extracolonic tumor		Smoking history		Alcohol history		Adenomas' number at baseline status (≥3)		Adenoma size			High grade IN*		Advanced adenoma	
	<60	≥60	Male	Female	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	<1 cm	1-2 cm	>2 cm	Yes	No	Yes	No
	Median recurrence time (months)	36	22	19	36	14	27	10	25	14	24	26	24	19	24	12	26	24	81	24	24	24	24	24	25
Standard error	3.17	1.36	1.28	2.60	1.63	2.19	2.27	2.43	0.76	2.24	4.67	1.80	2.77	2.68	2.27	2.24	0.90	0.00	3.45	3.17	3.20	3.04	3.62	2.64	1.76
95% confidence interval	Lower limit	29.78	19.34	16.48	30.91	10.80	22.70	5.55	20.27	12.52	19.61	16.84	20.46	13.59	18.74	7.54	21.62	22.24	17.23	17.78	17.71	18.03	16.90	19.81	20.56
	Upper limit	42.21	24.66	21.52	41.09	17.20	31.30	14.44	29.76	15.48	28.39	35.16	27.54	24.42	29.26	16.46	30.38	25.75	30.76	30.22	33.29	29.97	31.10	30.19	27.44
Survival curve distribution difference	P value	0.001		0.000	0.000		0.000		0.033		0.959		0.033		0.000		0.000	0.398				0.313	0.374		

IN: intraepithelial neoplasia.

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**Table 2.** 10-year disease-specific survival life-table

Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval
0	303	0	303.000	0	0.00	1.00	1.00	0.00
1	303	7	299.500	86	0.29	0.71	0.71	0.03
2	210	15	202.500	66	0.33	0.67	0.48	0.03
3	129	7	125.500	13	0.10	0.90	0.43	0.03
4	109	22	98.000	10	0.10	0.90	0.39	0.03
5	77	11	71.500	2	0.03	0.97	0.38	0.03
6	64	30	49.000	14	0.29	0.71	0.27	0.03
7	20	13	13.500	1	0.07	0.93	0.25	0.04
8	6	1	5.500	0	0.00	1.00	0.25	0.04
9	5	2	4.000	3	0.75	0.25	0.06	0.05

**Table 4.** Multivariate analysis: risk factors of adenomas recurrence

	Age	Sex	Colonic carcinoma history	Extracolonic tumor history	Alcohol history	Adenomas' number at baseline status	
B	0.333	-0.458	0.502	1.645	0.704	0.594	
SE	0.130	0.144	0.241	0.252	0.209	0.162	
Wald	6.503	10.146	4.340	42.634	11.33	13.432	
P value	0.011	0.001	0.057	0.000	0.001	0.000	
HR	1.395	0.632	1.653	5.180	2.022	1.811	
95.0% CI for HR	Lower	1.080	0.477	1.030	3.162	1.342	1.318
	Upper	1.801	0.838	2.651	8.488	3.048	2.488

1.36 months,  $10 \pm 2.27$  months,  $12 \pm 2.27$  months and  $24 \pm 0.9$  months, respectively. The cumulative hazard of adenoma recurrence accords to extracolonic tumor history, adenomas' number at baseline status and alcohol history by Kaplan-Meier method see **Figures 3-5**.

### Discussion

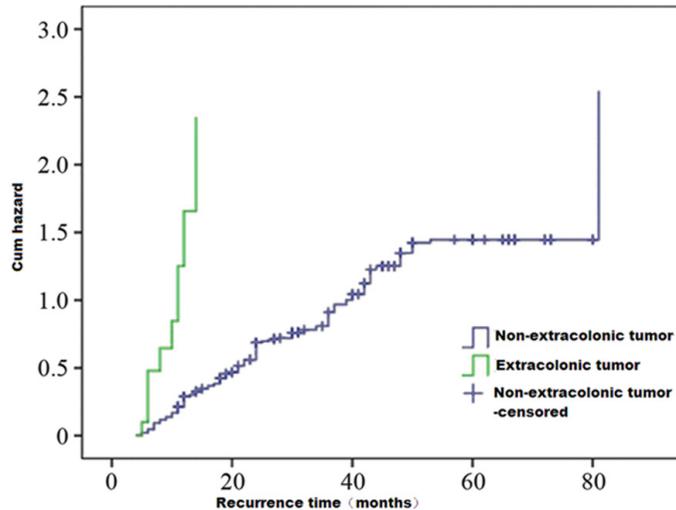
American guideline for colonoscopy surveillance after polypectomy in 2006 recommended repeat screening colonoscopy at 10 years for patients with no neoplasia at baseline and surveillance at 5 years or more for patients with 1 or 2 small (10 mm) tubular adenomas and at 3 years in patients with advanced neoplasia or more than 2 adenomas [7]. A recommendations for surveillance intervals after removal of cancer or adenomas with high-grade dysplasia range from 1 to 3 years [8].

In European guideline [9], Patients with three or four small adenomas or at least one adenoma of size  $\geq 10$  mm and  $< 20$  mm are at intermedi-

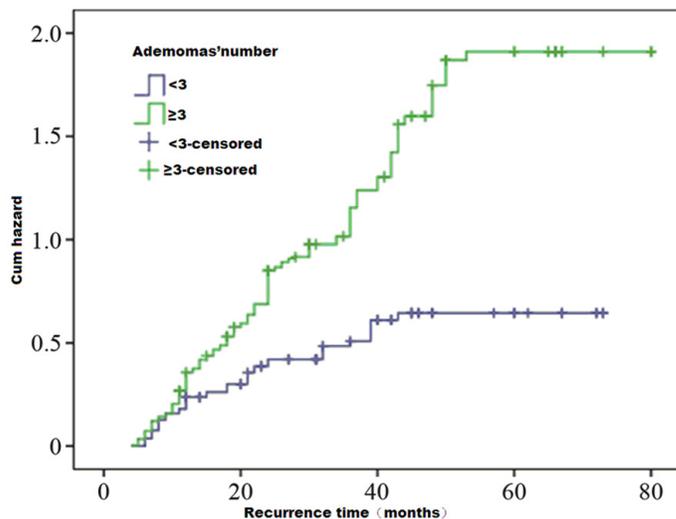
ate risk and should be offered surveillance at 3-yearly intervals. After one negative exam, the interval can be extended to 5 years. After two consecutive normal exams, the patient can return to routine screening. If either of the following is detected at any single examination (at baseline or follow-up): 5 or more adenomas, or an adenoma  $\geq 20$  mm, the patient is at high risk and an extra examination should be undertaken within 12 months, to check for missed synchronous lesions, before initiating 3-yearly surveillance. After two consecutive normal exams, the interval can be extended to 5-yearly. In the absence of evidence on the safety of stopping surveillance in the high risk group, surveillance should continue.

There is no provided guidelines for colonoscopy surveillance intervals after polypectomy based on the characteristics of the neoplasia on initial colonoscopy in China. One important reason is adenomas always being missed on account of poor bowel preparation, meandering lumen of colon, size of adenoma, short examining time, the experience of endoscopic doctor [10-12]. Missed adenomas always

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**Figure 3.** The cumulative hazard of adenoma recurrence according to extracolonic tumor history by Kaplan-Meier method ( $P < 0.001$ ).



**Figure 4.** The cumulative hazard of adenoma recurrence according to adenomas' number at baseline status by Kaplan-Meier method ( $P < 0.001$ ).

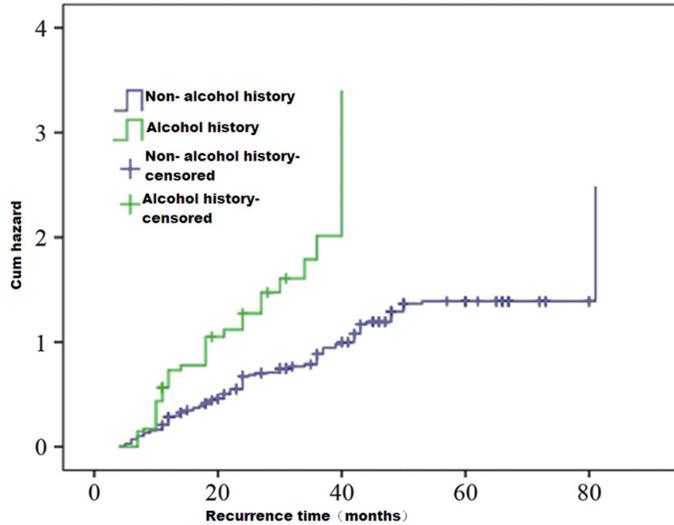
affected the colonic adenoma's surveillance and establish screening recommendations. Patients in our hospital were suggested colonoscopy within 6 months after initial colonoscopy and removed missed adenomas. All adenomas detected at subsequent colonoscopies performed within 6 months of the baseline colonoscopy were considered to be adenomas missed on the initial colonoscopy. Followed the patients from this time point and recorded the actual recurrence rate of adenoma, we resolve the influence of the missed adenoma

on screening colonoscopy, made sure calculate accurately the recurrence rate of colonic adenoma.

In one research among the 1023 patients with colorectal polyp at baseline, 553 underwent a surveillance colonoscopy. The mean time interval from baseline colonoscopy to first surveillance examination was  $3.42 \pm 1.45$  years. The recurrence rates were 50.5% and 32.9% for all polyps and adenomas, respectively [13]. In our research, by life table analysis the cumulative recurrence rates of adenoma were 52%, 62%, and 75% for the surveillance intervals 0-2, 2-5, 5-8 years, respectively. this results is similar with another Chinese research [14]. More than 50% patients have adenoma recurrence in 2 years, Based on our results, a 2-year follow-up of patients after polypectomy could be effective in preventing the recurrence of adenoma.

In multivariate analysis of our study, gender, age, extracolonic tumor history, drinking history and adenoma number at initial examination were the independent prognostic factors for recurrence. Older age, male and adenoma number  $\geq 3$  had been found to be associated with an increased risk of adenoma recurrence in several studies, we have similar results with other studys [8, 15]. In Viel et al study, the number of polyps at baseline was the only significant predictor for both polyp recurrence and adenoma recurrence [13]. In another study, male patients had a higher risk of recurrence than female patients. Patients with  $\geq 10$  mm adenoma at baseline colonoscopy were more likely to have recurrent adenomas than those with  $< 10$  mm adenoma. Patients with  $\geq 4$  adenoma at baseline colonoscopy had also an increased risk for recurrent adenomas. Multivariable analysis showed that  $\geq 10$  mm sized and  $\geq 4$  adenomas at baseline colonoscopy were independent predictors of adenoma recurrence at subsequent colonoscopy [16]. In Laiyemo et al study, age 65-69 years, age  $\geq 70$  years, and

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**Figure 5.** The cumulative hazard of adenoma recurrence according to alcohol history by Kaplan-Meier method ( $P=0.001$ ).

male sex were positively associated with proximal only adenoma recurrence [17].

Our study showed extracolonic tumor history increasing risk of adenoma recurrence. there were no previous literature had similar results. Eleven extracolonic tumor history were exposed in our research: one thymic carcinoma, one adrenal carcinoma, two thyroid papillary carcinoma, one esophageal carcinoma, two mammary carcinoma, two endometrial carcinoma, one laryngeal carcinoma, one hepatic carcinoma. We reviewed previous literatures, some study reported the relationship between extracolonic tumor history or precancerous lesion with colonic lesion. One research recommended patients with esophageal carcinoma accept colonoscopy surveillance, especially patients with high BMI, smoking history, drinking history [18]. In another study, patients with colonic adenoma, dysplasia or colonic adenocarcinoma have high risk of Barrett esophagus [19]. Peutz-Jeghers patients always have high risk of mammary carcinoma [20]. But no published literatures reported extracolonic tumor have significant relationship with colonic adenoma recurrence. We don't know the exactly reason of the high colonic adenoma recurrence risk in patients with extracolonic tumor. We just described the phenomenon, try to enlarge the cases to future research.

In previous research, some reported the relationship between colonic adenoma, colon ade-

nocarcinoma and alcohol. 212 patients with colorectal adenoma were analyzed in Song et al research [21]. When compared to the non-drinker group, the alcohol drinker group represented significantly high odds ratios for advanced adenoma, and multiple adenoma. In another study, a total of 30 studies with 26145 incident colon adenocarcinoma cases were included. Overall, an increase of 25 g (two drinks) per day of alcohol consumption was related to an increased risk of colon adenocarcinoma [22]. Rueda et al work confirms that the use of alcohol and tobacco is associated with an earlier onset of colon pathology [23]. But no previous researchs reported the relationship between alcohol and colonic adenoma recur-

rence. In our research, drinking history found to be associated with an increased risk of adenoma recurrence.

Based on the colonic adenoma media recurrence time in our study, 19 months for male patients, 22 months for patients older than 60 years, male patients older than 60 years should be offered first surveillance after 19 months after initial colonoscopy. If patients are with extracolonic tumor history or drinking history in the mean time (media recurrence time is 10 months for patients with extracolonic tumor history, 12 months for patients with drinking history), we suggest shorten the first surveillance time to 10-12 months. The median recurrence time of patients with adenoma  $\geq 3$  is equal to the suggested surveillance time, 24 months.

Two analysis showed patients with advanced adenomas has high recurrence rate than patients with adenoma without advanced pathology [24, 25]. However, some other studies had different results, the recurrence of adenoma hadn't significant relation with adenoma pathology [26]. In our study, adenomas were classified into advanced adenomas group and without advanced adenomas group, in another way were classified into high grade intraepithelial neoplasia group and without high grade intraepithelial neoplasia group. but both didn't showed relation between adenoma pathology and adenoma recurrence.

Limitations of our study included the retrospective analysis, small sample size, single center. our study was not designed to determine whether risk stratification in European guideline would modify the risk of newly discovered neoplasia during surveillance.

Our study tries to provide data for Chinese colonic adenoma surveillance. The first surveillance colonoscopy were suggested perform 24 months after initial colonoscopy, if patients are male patients, older than 60 years, or with extracolonic tumor history or drinking history in the mean time, shorter surveillance interval are suggested.

### Disclosure of conflict of interest

None.

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