Original Article

Reasonable Follow Up Interval of Colonoscopy for Resected Stage I Colorectal Cancer Patient

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Key Words
Stage I colorectal cancer;
Colonoscopy;
Follow up

Purpose. Currently there is no consensus about surveillance guideline for resected stage I colorectal cancer. In this study, we try to investigate risk factor of stage of metachronous colorectal cancer and the reasonable colonoscopy follow up interval.
Materials and Methods. Between January 1995 and December 2015, total 17025 patients were diagnosed with colorectal cancer at the Linkou Chang Gung Memorial Hospital in Taiwan. Demographic data including sex, age, tumor location, index tumor location, original cancer's pathological characteristics; preoperative carcinoembryonic antigen level, and colonoscopy follow up interval were all collected for analysis with Pearson's chi-squared test and linear regression.
Results. Total 2558 patients were diagnosed with stage I colorectal cancer and underwent standard curative operations. We recorded total 31 patients had metachronous colorectal cancer. Family cancer history, age, gender, underlying disease such as hypertension, coronary artery disease, diabete mellitus, previous CEA level before operation, resection method, TMN stage T1 or T2, and its original tumor site had no statistical significance compare with stage of metachronous colorectal cancer ($p > 0.05$). Colonoscopy follow up interval do have association with metachronous cancer stage ($p = 0.036$). We get a regression curve equation. According to this equation, we may predict that if we want to control the second cancer within curable stage (within stage III), a reasonable follow up interval is 75 months. If we want to do more intensive surveillance in order to keep metachronous colorectal within stage II (No need of chemotherapy), a reasonable follow up interval is 52 months. Furthermore, if we follow colonoscopy every 8.4 months, the predict metachronous colorectal cancer stage would be within stage I.
Conclusions. Colonoscopy follow up interval do have association with metachronous cancer stage. The recommend follow up interval is 75 months.
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Over recent years, colorectal cancer (CRC) has become one of the most common cancer in Taiwan. According to the data of Taiwan Cancer Registry, CRC is the third leading cause of cancer-related

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death in Taiwan. With the introduction of a nationwide colorectal cancer screening by biennial fecal immunochemical testing for aged 50-69 years, rate of early colorectal cancer or stage I CRC has increased.[1]

The vast majority of studies exploring the benefits of posttreatment surveillance have been conducted in patients with resected stage II or III disease.[5-7] Although the question of a survival benefit is unsettled, periodic posttreatment endoscopic surveillance is suggested by major groups, including ASCO, ESMO, Cancer Care Ontario, the NCCN, the American Cancer Society (ACS).[6-8]

For resected stage I colorectal cancer, there are many different surveillance guidelines amount each expert group. According to ASCO,[8] Cancer Care Ontario,[10] the British Columbia Medical Association,[11] and the National Comprehensive Cancer Network (NCCN),[5] the surveillance of resected stage I colorectal cancer should be periodically colonoscopy examine only. And the European Society for Medical Oncology (ESMO) guidelines do suggest it should be the same surveillance policy amount stage I, II, and III colorectal cancer. Furthermore, some guidelines had even no description about surveillance for resected stage I CRCs.

Although stage I colorectal cancer is with promising outcome after resection, the 5 years' survival rate of resected stage I colorectal cancer is about 90%.[32] The goals of surveillance colonoscopy are two fold: to detect metachronous CRCs (non-anastomotic new tumors developing at least six months after the initial diagnosis), and detection of anastomotic recurrences of the initial primary cancer at a stage that would allow curative treatment. The local recurrence rate of resected stage I CRC is rare, so we follow up colonoscopy mainly focused on metachronous CRCs.

In general, current major guidelines available about colonoscopy surveillance for resected stage I colorectal cancer is about 1 year after operation, and then follow up every 3~5 years independently. However, colonoscopy is an invasive examine with the risk of perforation.[9] If we want to early detect metachronous colorectal cancer and balancing the risk of colonoscopy, how often should we perform colonoscopy examine for stage I colorectal cancer patient after curative resection?

Materials and Methods

Between January 1995 and December 2015, total 17025 patients were diagnosed with colorectal cancer at the Linkou Chang Gung Memorial Hospital in Taiwan. Total 2558 patients diagnosed with stage I colorectal cancer and underwent standard curative resection were included. All patients received the same postoperative follow up principles: do colonoscopy follow up at least at the first year after operation, and then follow up at different interval (around 3~5 years) depend on clinical condition and physician's judgement. All patients were under OPD follow up and telephone follow up by case managers. Amount these 2558 patients, 87 patients had lost follow up and 162 patients died of other disease. Up to December 2015, only 31 patients were found metachronous colorectal cancer and were enrolled in our study.

Demographic data including gender, age, family history, Co-morbidity, preoperative carcinoembryonic antigen level, operation type, index tumor cell differentiation, TMN-T stage, and index tumor location were all collected for analysis in these patients.

To investigate relationship between colonoscopy follow up interval (duration from last time tumor free colonoscopy examine to the newly diagnosis metachronous colorectal cancer) and its final pathologic diagnosis, we compared clinicopathological factors related to stage of metachronous colorectal cancer. Categorical data were compared by using Pearson's chi-squared test. Relationship between colonoscopy follow up interval and final pathological stage were analysis with linear regression. Statistical significance was defined as $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences version 20 (SPSS Inc. Chicago, USA).

Results

We recorded total 31 patients had metachronous colorectal cancer found via colonoscopy follow up

(Fig. 1). Amount them, no synchronous colorectal cancer was found neither while index tumor resection and follow up nor metachronous tumor resection and follow up. All of them were showed below (Table 1).

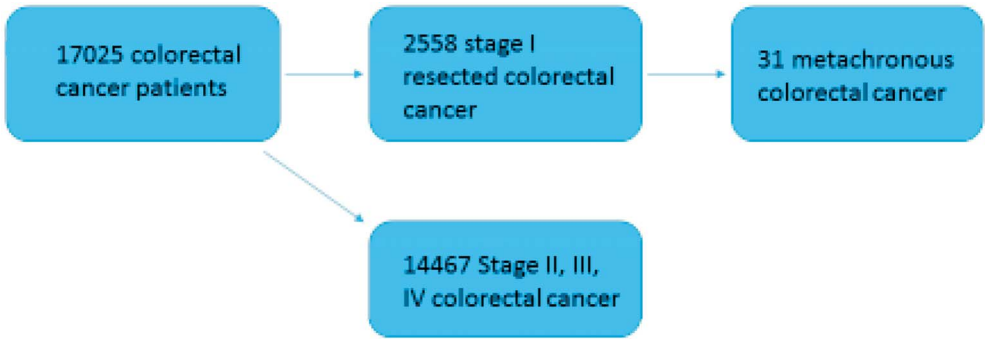

Fig. 1. From Jan 1995 to Dec 2015, total 31 patients enroll this study.

Table 1. Data character

Patient	Family history[a]	AGE[b]	Gender	Co-morbidity[c]			CEA[d]	Operation type	Tumor differ[e]	TMN (T)	Index tumor site	Time interval (month)	Stage of meta
				HTN	CAD	DM							
1	-	65	F	-	-	-	2.8	Radical	WDA	2	R	25	III A
2	-	85	M	-	-	-	3.5	Local	MDA	1	R	8[f]	Tis
3	-	73	M	-	-	-	3	Radical	MDA	1	T	6	Tis
4	-	71	M	-	-	-	1.6	Radical	MDA	2	S	12[f]	Tis
5	+	30	M	-	-	-	1.1	Radical	WDA	2	T	33	II A
6	-	48	M	-	-	-	3.3	Local	WDA	1	R	8	IV
7	-	65	F	+	-	-	0.8	Radical	WDA	1	S	27	III A
8	-	61	M	-	-	-	13.3	Radical	MDA	2	T	63	II B
9	-	70	M	-	-	-	1.5	Radical	WDA	2	R	11	II B
10	-	62	M	-	-	+	1.3	Radical	WDA	1	S	25	I B
11	-	69	M	-	-	-	2.8	Radical	MDA	2	R	10	Tis
12	-	66	F	+	-	+	7.3	Radical	MDA	1	R	12	Tis
13	-	66	M	+	-	-	5.2	Radical	MDA	2	R	8	III B
14	-	83	M	+	-	-	2.6	Local	MDA	1	R	13[f]	Tis
15	-	89	M	-	-	-	1.7	Radical	MDA	2	D	12[f]	I B
16	-	61	F	+	-	+	5.8	Local	MDA	1	R	26	I A
17	-	49	F	+	-	+	8	Radical	WDA	1	S	6	I A
18	-	75	M	+	-	-	1.9	Radical	WDA	2	T	53	III C
19	-	70	M	-	-	-	6	Radical	WDA	2	R	19	I A
20	-	61	M	+	-	-	2.4	Radical	WDA	1	S	16	III A
21	-	62	M	-	+	+	2.3	Radical	MDA	2	R	35	Tis
22	-	81	F	-	-	-	2.4	Radical	WDA	1	S	13	III B
23	-	79	M	+	+	-	2.3	Radical	MDA	1	A	14[f]	I B
24	-	61	M	-	-	-	1.8	Radical	MDA	2	R	6	Tis
25	-	55	F	-	-	-	1.3	Radical	MDA	2	R	37	I A
26	-	68	M	+	-	-	3.3	Radical	MDA	2	R	41	IV
27	-	82	M	-	-	-	4.3	Radical	PDA	2	R	18	I B
28	-	62	F	-	-	-	1.9	Radical	MDA	1	S	14	I B
29	-	78	M	-	-	-	2.5	Radical	WDA	2	R	13	Tis
30	+	52	F	-	-	-	1.3	Radical	MDA	2	A	11	I A
31	-	57	M	-	-	-	3.7	Radical	MDA	2	R	20	Tis

[a] Two patients had family history and compatible with hereditary nonpolyposis colorectal cancer (HNPCC); [b] Age while cancer diagnosed; [c] HTN: hypertension history; CAD: coronary artery disease history; DM: diabete mellitus history; [d] CEA: carcinoembryonic antigen level while 1st time cancer resection; [e] Tumor differentiation: WDA: well differentiated adenocarcinoma; MDA: moderate differentiated adenocarcinoma; PDA: poorly differentiated adenocarcinoma; [f] Metachronous colorectal cancer found via first time postoperative follow up colonoscopy.

We mainly focused on the final stage while metachronous colorectal cancer emerged. Two patients had family history, and they both meet HNPCC criteria. We compare it with metachronous CRC stage and found that there was no statistical significance (p = 0.858). We divided patients to three group according to their age, < 50, 50~75, and > 75. We compared each of them with metachronous CRC stage, and we get there was no statistical significance. By the same way, we analysis gender, co-morbidity such as hypertension, coronary artery disease, diabete mellitus, previous CEA level before operation, operation type, TMN stage T1 or T2, and its index tumor site, and then compared with metachronous CRC stage. The p value of those subgroup all > 0.05.

In our study, family history, age, gender, co-morbidity such as hypertension, coronary artery disease, diabete mellitus, previous CEA level before operation, operation type, TMN stage T1 or T2, and its index tumor site had no statistical significance compare with stage of metachronous colorectal cancer (p > 0.05) (Table 2).

However, the pathologic morphology of index cancer does have relationship with final pathology stage of metachronous cancer (p = 0.15). The more well differentiation, the more severe while found

Table 2. Risk factor for stage of metachronous cancer

Risk factor	Subgroup		Pearson association	p value
Family history (HNPCC)	Yes	2 (6.5%)	0.034	0.858
	No	29 (93.5)		
AGE[b]	< 50	3 (9.6%)	-0.21	0.257
	50~75	21 (67.7%)		
	> 75	7 (22.5%)		
Gender	Male	22 (70.9%)	-0.86	0.647
	Female	9 (29.0%)		
Hypertension	Yes	10 (32.2%)	0.243	0.188
	No	21 (67.7%)		
Coronary artery disease	Yes	2 (6.5%)	-1.32	0.479
	No	29 (93.5%)		
Diabete mellitus	Yes	5 (16.1%)	-2.5	0.175
	No	26 (83.8%)		
CEA	ng\mL		-0.35	0.852
Operation type	Local excision	4 (12.9%)	-1.08	0.564
	Radical resection	27 (87.0%)		
Tumor differentiation	Well	12 (38.7%)	-0.432	0.015[a]
	Moderate	18 (58.0%)		
	Poor	1 (3.2%)		
TMN-T staging	T1	13 (41.9%)	-0.15	0.934
	T2	18 (58.0%)		
Index tumor site	Ascending colon	2 (6.5%)	-0.205	0.268
	Transverse colon	4 (12.9%)		
	Descending colon	11 (3.2%)		
	Sigmoid colon	7 (22.5%)		
	Rectum	17 (54.8%)		
Colonoscopy follow up interval	Month		0.378	0.036[a]

[a] p < 0.05: statistic significant. [b] Age while cancer diagnosed.

metachronous colorectal cancer.

For survey the relationship between colonoscopy follow up interval and metachronous colorectal cancer stage, we defined stage Tis, Ia, Ib, IIa, IIb, IIIa, IIIb, IIIc, IV as 1 to 9. We obtained its log value and compared with the follow up time interval (month). We noted it do have significant association between them ($p = 0.036$).

We did further analysis for their distribution and get a regression curve (Fig. 2). And then we get the equation of this curve (Equation 1).

$$\log Stage = 0.009 * M + 0.225 \quad \text{(Eq. 1)}$$

Eq. 1. Relationship between stage and follow up interval. Stage: We defined stage Ois, Ia, Ib, IIa, IIb, IIIa, IIIb, IIIc, IV as 1 to 9. M = Follow up interval of colonoscopy (month).

Base on this curve, we may predict that if we want to control the second cancer within curable stage (within stage III), a reasonable follow up interval is 75 months. If we want to do more intensive surveillance in order to keep metachronous colorectal within stage II (no need of chemotherapy), a reasonable follow up interval is 52 months. Furthermore, if we follow colonoscopy every 8.4 months, the predict metachronous colorectal cancer stage would be within stage I.

Discussion

Patient with stage I colorectal cancer underwent curative resection are deemed to cure because of early treatment. However, they are still at risk of metachoronous colorectal cancer. The 5 years' survival rate of resected stage I colorectal cancer is about 90%.[31] In our study, amount 2309 resected stage I colorectal cancer patients whom were received regular follow up, there were 31 metachronous colorectal cancer. The incidence rate is 1.34%.

Whether resected stage I colorectal cancer should be follow up intensively or not, there were six of 12 randomized trials[12-23] and five separate meta-analyses[24-28] support a significant overall survival benefit for intensive posttreatment surveillance following potentially curative resection of CRC.

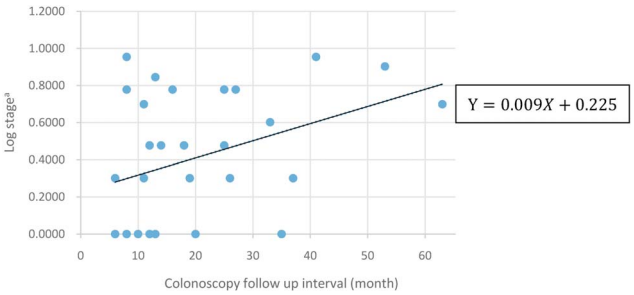

Fig. 2. Distribution and regression curve. [a] We defined stage Ois, Ia, Ib, IIa, IIb, IIIa, IIIb, IIIc, IV as 1 to 9. We obtained its log value and compared with the follow up time interval (month).

The best follow-up strategy is not established yet. Due to the stage I disease whose outcome is usually pretty well and make it difficult to detect difference between the more and less intensively followed groups.

According to ESMO guideline,[6] metachronous primary cancer could be detected with an incidence of 0.7% within the first 2 years after curative surgery. Park IJ et al. surveyed 5447 patients who underwent curative colorectal surgery due to colon cancer. They found 39 patients with metachronous colorectal cancer. The time interval between index and metachronous cancer ranged from 6 to 215 months (mean 39 months), with 13 (33.3%) patients diagnosed with metachronous cancer after 5 years.[33] However, the data above including all stage colorectal cancer. In our study, we focused on resected stage I colorectal cancer and survey the time interval between "last time negative colonoscopy survey" to "the time of metachronous colorectal cancer diagnosis". It is 6 to 63 months in our study. Nevertheless, the time interval between index and metachronous cancer in our study is 8 to 115 months.

In our study, we defined time interval as duration from last time tumor free colonoscopy examine to the newly diagnosis metachronous colorectal cancer. Amount 31 patients whom had metachronous colorectal cancer, 5 patients found metachronous cancer at first time follow up colonoscopy after curative resection (mean time interval is 11.8 months). Theoretically speaking, only one lesion and then status post curative resection, we can regard it as tumor free.

These 5 patients all received complete colonoscopy before index tumor resection, and revealed no synchronous colorectal cancer. Besides, the metachronous cancer stage of these 5 patients were Tis and IB, which were compatible with our result and suggestion (if we follow colonoscopy every 8.4 months, the predict metachronous colorectal cancer stage would be within stage I). They met our study purpose and did not against our final conclusion thus we analysis and discuss them with others together.

There are many risk factor of interval colorectal cancer. James M et al. reveal interval colon cancer does have relationship with aged ≥ 60 years, right colon, and colonoscopy complete or not.[29] Nevertheless, its' analysis data was colorectal cancer of all stage. In our study, patients with resected stage I colorectal cancer whom encounter metachronous colorectal cancer had no association with HNPCC history, age, gender, co-morbidity such as hypertension, coronary artery disease, diabete mellitus, operation type, TMN stage T1 or T2, and its original tumor site (all $p > 0.05$). It also had no association with preoperational CEA level ($p = 0.852$).

Index tumor differentiation did have association with the metachronous colorectal cancer's final stage. It showed moderate negative association, which means poor differentiated adenocarcinoma had better outcome compare with well differentiated adenocarcinoma if metachronous cancer emerged. We though it is due to limit data available. In our study, there was only one patient had poorly differentiated adenocarcinoma (primary cancer). And his final pathological staging of metachronous cancer is IB, which is better than part of other well differentiated adenocarcinoma or moderate differentiated adenocarcinoma.

We also found that colonoscopy follow up interval had significant association with metachronous colorectal cancer's final stage ($p = 0.036$). The longer the follow up interval, the more severe metachronous CRCs it turned out. Furthermore, we get a regression curve which showed as above (Fig. 2). Base on this curve, we may predict that if we want to control the second cancer within curable stage (beyond stage III), a reasonable follow up interval is 75 months. If we want to do more intensive surveillance in order to keep metachronous colorectal beyond stage II (No need of chemotherapy), a reasonable follow up interval is 52 months. Furthermore, if we follow colonoscopy every 8.4 months, the predict metachronous colorectal cancer stage would be beyond stage I base on over study.

Limit to the low incidence rate, the case number of this study is not big enough. And some extremity data will and do affect the result. Further large scale multicenter study may be necessary for more detail and precise recommendation.

Conclusions

In our study, the incidence rate of metachronous colorectal cancer amount the patients with resected stage I colorectal cancer is 1.34%. The follow up interval of colonoscopy do have association with the metachronous colorectal cancer stage. We get a regression curve (Eq. 1). According to this equation, if we wish to control metachronous colorectal cancer within curable stage (stage III), the reasonable follow up interval is 75 months.

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原　著

根除性手術後的第一期大腸癌病患合理的大腸鏡檢查追蹤間格

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目的　目前針對第一期大腸癌術後的病人，對於追蹤的準則並沒有統一的共識。在我們的研究中，我們嘗試著去尋找關於異時性大腸癌的嚴重程度的危險因子，以及合理的大腸鏡追蹤時間間格。

方法　從 1995 年 1 月到 2015 年 12 月，在台灣林口長庚醫院總共有 17025 個病人被診斷大腸癌，其中有 2258 位病人是第一期並且接受治癒性手術。在之後的追蹤裡，我們總共發現了 31 個病人有異時性大腸癌做進一步的分析。

結果　在我們的資料庫裡，異時性大腸癌的嚴重度跟家族癌症史、年齡、性別、合併症如高血壓心臟病及糖尿病、第一次切除大腸癌時的 CEA 數值、切除方式、T1 或 T2、以及原始大腸癌的位置沒有統計學上顯著的相關。

結論　大腸鏡追蹤的時間間格跟異時性大腸癌的嚴重程度有顯著相關，並且我們算出一條回歸曲線，根據這條曲線方程式，我們可以預測如果預期在發現異時性大腸癌時仍在可治癒的程度 (第三期以內)，合理的大腸鏡追蹤間格為 75 個月。

關鍵詞　第一期大腸癌、大腸鏡、追蹤。