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 ≥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 difficulty 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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noscopy, with the aim of removing missed ade-
nomas; 2) complete colonoscopy was per-
formed at every examination; 3) the surveil-
ance interval was 1-2 years. The excluded cri-
teria were: 1) no surveillance colonoscopy was
performed within 6 months after the initial
colonoscopy to remove missed adenomas; 2)
at least one incomplete colonoscopy was
performed; 3) patients couldn’t finish surveil-
lance every 1-2 years; 4) patients with familial
adenomatous polyposis, inflammatory bowel
disease, or colorectal cancer in initial colonos-
copy 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 col-
clected data on the adenoma’s number, size, and
pathology, patients’ age and sex, patients’
colectomy or EMR, or ESD. All poly-
pectomy, 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 esti-
imated with an opened biopsy forceps (7 mm)
measured after resection.

Pathological evaluation

All pathology was evaluated by 2 experienced
pathological doctor. When there was a dis-
crepancy, a third referee pathologist reviewed
the material. Patients were classified based
on the most advanced histologic lesion. His-
topathology features of the adenoma were
evaluated by 2 specialist gastrointestinal path-
ologist according to the colorectal neoplasia
classification of the World Health Organiza-
tion recommendations. Our study classified ade-
nomas pathology in two ways. One classified ade-
noma into advanced adenomas group and with-
out advanced adenomas group, the other clas-
sified adenoma into high grade intraepithelial
neoplasia group and without high grade
intraepithelial neoplasia group. Advanced ade-
noma 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 intraep-
ithelial neoplasia means severe dysplasia and
carcinoma in situ, low grade intraepithelial neo-
plasia means mild and moderate dysplasia.

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 neopla-
sia.
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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 (± standard deviation, SD) age at the index colonoscopy was 63.56±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 Kaplan-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 without extracolonic tumor history (HR 5.180, 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 ≥3 adenomas at baseline status were 19 ± 1.28 months, 22 ±
Table 1. Characteristics of Study Cohort

<table>
<thead>
<tr>
<th>Sex</th>
<th>Colonic carcinoma history</th>
<th>Extracolonic tumor history</th>
<th>Family history of colonic carcinoma</th>
<th>Family history of extracolonic tumor</th>
<th>Smoking history</th>
<th>Alcohol history</th>
<th>Adenomas' number at baseline status (≥3)</th>
<th>Adenoma size</th>
<th>High grade IN*</th>
<th>Advanced adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>171</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>&lt;1 cm</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Female</td>
<td>132</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>≤1 cm</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>%</td>
<td>56.43</td>
<td>43.56</td>
<td>5.28</td>
<td>94.72</td>
<td>4.29</td>
<td>5.61</td>
<td>94.39</td>
<td>8.91</td>
<td>91.09</td>
<td>17.82</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Colonic carcinoma history</th>
<th>Extracolonic tumor history</th>
<th>Family history of colonic carcinoma</th>
<th>Family history of extracolonic tumor</th>
<th>Smoking history</th>
<th>Alcohol history</th>
<th>Adenomas' number at baseline status (≥3)</th>
<th>Adenoma size</th>
<th>High grade IN*</th>
<th>Advanced adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median recurrence time (months)</td>
<td>&lt;60</td>
<td>36</td>
<td>22</td>
<td>19</td>
<td>36</td>
<td>14</td>
<td>27</td>
<td>10</td>
<td>25</td>
<td>14</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Standard error</td>
<td>3.17</td>
<td>1.36</td>
<td>1.28</td>
<td>2.60</td>
<td>1.63</td>
<td>2.19</td>
<td>2.27</td>
<td>2.43</td>
<td>0.76</td>
<td>2.24</td>
<td>4.67</td>
<td>1.80</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>29.78</td>
<td>19.34</td>
<td>16.48</td>
<td>30.91</td>
<td>10.80</td>
<td>22.70</td>
<td>5.55</td>
<td>20.27</td>
<td>12.52</td>
<td>19.61</td>
<td>16.84</td>
<td>20.46</td>
</tr>
<tr>
<td>Survival curve distribution</td>
<td>P value</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.033</td>
<td>0.959</td>
<td>0.033</td>
<td>0.000</td>
<td>0.000</td>
<td>0.398</td>
<td>0.313</td>
</tr>
</tbody>
</table>

IN: intraepithelial neoplasia.
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Table 2. 10-year disease-specific survival life-table

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

Table 4. Multivariate analysis: risk factors of adenomas recurrence

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

1.36 months, 10 ± 2.27 months, 12 ± 2.27 months and 24 ± 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 ≥10 mm and <20 mm are at intermediate 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 ≥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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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 ± 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 ≥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 ≥10 mm adenoma at baseline colonoscopy were more likely to have recurrent adenomas than those with <10 mm adenoma. Patients with ≥4 adenoma at baseline colonoscopy had also an increased risk for recurrent adenomas. Multivariable analysis showed that ≥10 mm sized and ≥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 ≥70 years, and
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 colon 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 adenocarcinoma 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 recurrence. 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 ≥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.
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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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References


