Predictors of endoscopic recurrence in resected patients with Crohn's disease in a long-term follow-up cohort: History of multiple previous resections and residual synchronous disease in the remnant intestine

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Cite this article as: *Erzin Y, Şişman G, Hatemi İ, et al. Predictors of endoscopic recurrence in resected patients with Crohn's disease in a long-term follow-up cohort: History of multiple previous resections and residual synchronous disease in the remnant intestine. Turk J Gastroenterol 2020; 31(4): 282-8.*

ABSTRACT

Background/Aims: *This study aimed to determine the predictors of endoscopic recurrence in a cohort of patients with Crohn's disease (CD) with prior intestinal resections.*

Materials and Methods: *The charts of the patients with CD were reviewed in a retrospective manner. Eighty-three patients were eligible for the final analysis. Demographic features of these patients and time between resection and colonoscopy, presence of any macroscopic residual disease in the remnant intestine, and postoperative medications were noted. Rutgeerts score was used to define postoperative endoscopic recurrence.*

Results: *The patients' mean age±SD at their final colonoscopy was 42.81±11.99 yr; and 37 of 83 patients (45%) were female. The mean follow-up time between resection and the final colonoscopy was 51.16±51.08 months. A total of 51 of 83 patients (61%) were in endoscopic remission (i0, i1); whereas 32 (39%) had an endoscopic recurrence (i2, i3, i4). History of multiple resections (χ^2=6.12; p=0.013) and the presence of any postoperative residual disease in the remnant intestine (χ^2=5.86; p=0.015) were risk factors; whereas the regular use of azathioprine (AZA) was significantly more common among patients without recurrence (χ^2=4.515; p=0.034). In an age-sex adjusted Cox regression analysis history of multiple resections, presence of any postoperative residual disease proved to be independent risk factor for endoscopic recurrence, whereas the regular use of AZA proved to be ineffective.*

Conclusion: *In a retrospective long-term follow-up cohort of resected patients with CD, having multiple resections for CD and the presence of any residual synchronous disease after ileocolonic resection were identified as risk factors for endoscopic recurrence; the latter was never reported in previous studies.*

Keywords: *Crohn's disease, intestinal resection, endoscopic recurrence, risk factors*

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory intestinal disease of unknown etiology that frequently requires surgical bowel resection because of refractory activity in spite of medical treatment or complications such as stricture and/or fistulae. Approximately 80% of patients need intestinal resection during their lifetime contributing to the economic burden of the disease (1). Unfortunately, CD can be palliated, but it cannot be cured by surgery because inflammation tends to return in areas adjacent to those that were previously removed. Postoperative recurrence is common; and many patients require repeat operations, reoperation rates ranging from 10% to 35% at 5 years, 20% to 45% at 10 years, and 45% to 55% at 20 years (2).

The main clinical problem is how to individualize and tailor the postoperative treatment. Although postoperative recurrence is common in CD, not all but some of the determinants of disease recurrence remain as a matter of debate. Several patients with CD experience frequent recurrences, while others have prolonged periods of remission after surgery. Thus defining individual risk factors for postoperative recurrence would be useful to identify patients at a high risk and to determine strategies for medical therapy after surgery to prevent

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Received: ***September 11, 2013*** *Accepted:* ***December 13, 2013***

DOI: ***10.5152/tjg.2020.136680***

fatal outcomes of repeated resections like short bowel syndrome.

The real answer is behind somewhere in the long-term follow-up of cohorts of our daily clinical practice. Therefore, this study aimed to determine the predictors of endoscopic recurrence in a cohort of patients with CD with prior intestinal resections in a dedicated tertiary referral center for inflammatory bowel diseases (IBD), regularly run for more than 15 years.

MATERIALS AND METHODS

The local ethics committee of Istanbul University Cerrahpaşa School of Medicine approved the study. The charts of patients with IBD between 1997 and 2012 retrospectively were reviewed in our clinic that has been regularly run by our team of gastroenterologists, surgeons, and radiologists for more than 15 years. Of 1500 charts of patients with IBD, 537 patients with CD were identified. A total of 104 of 537 patients (19%) with CD had a history of prior intestinal resection. Of 104, 21 (20%) were either lost to follow-up or had no postoperative colonoscopy; so 83 patients were eligible for the final analysis.

Surgery

All patients had either an ileocecal resection with ileotransversostomy or an ileal resection with subtotal colectomy and ileosigmoidostomy or ileoproctostomy. All these operations were performed by our surgeons (BB, IH), providing macroscopic disease-free margins. If a defunctioning ileostomy was performed, the time until the ileostomy closure was deducted from the total follow-up time. Additionally, the presence of any residual synchronous lesions regarding the whole remnant intestine was determined either intraoperatively or according to the preoperative investigations like gastroscopy, colonoscopy, or enteroclysis.

Demography of patients

Demographic characteristics of patients are summarized in Table 1. Age at disease onset, at resection, at the last postoperative colonoscopy; time between the resection and last colonoscopy; presence of family history for IBD; sex; disease location; behavior according to Montreal classification (3); presence of perianal fistulae; presence of any macroscopic residual disease in the remnant intestine; postoperative smoking status and intensity; and dosage, duration, and postoperative starting time of medications were noted.

Table 1. Demographic characteristics of the patients with CD with prior intestinal resections.

	Patients (n=83)
Mean age at the last postoperative colonoscopy (yr)*	42.81±11.99
Mean age at disease onset (yr) *	33.14±11.66
Mean age at operation (yr) *	36.32±11.23
Number and proportion of female subjects (%)	37(45)
Mean postoperative follow-up period till the last colonoscopy (months)	51.16±51.08
Number and proportion of patients with multiple intestinal resections (%)	13 (16)
Number and proportion of subjects with endoscopic recurrence (%)	32 (39)
Number and proportion of postoperative active smokers (%)	27 (33)
Number and proportion of disease location: Ileal	20 (24)
Colonic	8 (10)
Ileocolonic	54 (65)
Upper gastrointestinal	1 (1)
Number and proportion of patients with perianal fistulae (%)	26 (31)
Number and proportion of reason for resection: Structuring disease (1)	45 (54)
Penetrating disease (2)	29 (35)
Both (1+2)	9 (11)
Number and proportion of patients with no postoperative residual disease (%)	45 (54)
Number and proportion of patients with any extraintestinal manifestation (%)	16 (19)

*Values represent means±SD

Postoperative medications

We actually consider intestinal resection for CD as a marker of aggressive disease course; so apart from the presence of well-determined risk factors in the guidelines, our postoperative policy has been to offer immunosuppressive treatment (azathioprine or AZA in nearly all cases) to all cases for more than a decade. However, some of the patients refused AZA treatment because of personal concerns about late side effects; some of them were not offered AZA because of concerns about regular follow-up; and some of them stopped AZA because of side effects or loss of patients' adherence. Thus, in this retrospective cohort, any postoperative usage of AZA for shorter than 3 months was accepted as having not used the drug. Use for more than 3 months was accepted as having used the drug but only if the patient had used AZA in at least 85% of the postoperative time period till the final colonoscopy; this was defined as its regular use. Shorter use of AZA due to various reasons was regarded as having not used the drug regularly. According to whether it was started within 3 months of surgery, the postoperative starting time of AZA was stratified as early or late.

Colonoscopy

The postoperative follow-up colonoscopies were performed in our unit after an overnight fast of 12 h by our gastroenterologists (YE, IH, and AFC). The choice of sedation was made at the discretion of the endoscopist. Conscious sedation with midazolam and meperidine or monitored anesthesia with propofol was preferred according to the patients' cardiovascular risk status. Rutgeerts score (4) was used to define postoperative endoscopic recurrence. Patients disclosing i0–i1 were accepted in endoscopic remission, whereas i2-i3-i4 were regarded as endoscopic recurrence. During chart reviews, these endoscopic findings were again judged by at least two experienced gastroenterologists to prevent false scores. None of the included patients had a permanent ileostomy. If a patient had multiple colonoscopies during postoperative follow-up, the latest colonoscopy was regarded as the final one (namely end of follow-up period); but if any of these showed endoscopic recurrence, the earliest colonoscopy disclosing recurrence was accepted as the final one. Thus, any colonoscopies and treatments after endoscopic recurrence were ignored.

Statistical analysis

Data were collected into a Statistical Package for Social Sciences (SPSS) version 21 for Windows (IBM Corp.; Armonk, NY, USA), and they were expressed as means, with SD of the mean calculated when appropriate. Differences between means were analyzed by Student's t-test or Mann-Whitney U test; and the $\chi 2$ test was used to compare the prevalences between groups. The effect of risk factors on the time from resection to the final colonoscopy was quantified by the hazard ratios (HR) from the final Cox model with forward conditional method. A generous significance level threshold of 0.15 was used to prevent premature elimination of important risk factors. Value of $p<0.05$ was regarded as significant.

RESULTS

Table 2 shows demographic characteristics of patients with and without endoscopic recurrence. The mean age (±SD) at disease onset of patients with recurrence was 32.59±13.54 yr and of patients without recurrence (NS) was 33.49±10.43 yr. The mean age (±SD) at resection of patients with recurrence was 35.53±12.07 yr and of patients without recurrence (NS) was 36.82±10.77 yr. The mean time (±SD) between the resection and the latest postoperative colonoscopy was 54.18±45.42 months for patients with recurrence and 49.27± 54.68 months for those without recurrence, disclosing no significant difference. A total of 31% of patients with recurrence and 52% of patients without recurrence were female (p=NS) disclosing no significant difference either. There was a trend for female predominance in the recurrence-free group. The proportion of active smokers in the postoperative period showed no significant difference, although smoking was more common among patients with recurrence (Table 2).

No differences were noted between both groups regarding the use, duration of 5-ASA, and metronidazole (MTZ). The mean postoperative start time of AZA and any postoperative use of it were not significantly different between both groups, although its regular use (defined as its use in at least 85% of the postoperative period) was significantly more common in the group without endoscopic recurrence ($\chi^{2=}4.515$; p=0.034). Reoperated patients were significantly more common in the group with endoscopic recurrence ($\chi^{2=}6.12$; p=0.013) (Figure 1), and the presence of any postoperative residual disease was significantly more common among patients with recurrence ($\chi^{2=}5.86$; p=0.015) (Figure 2).

In an age-sex adjusted forward conditional Cox regression analysis entered the variables history of multiple resections, presence of any postoperative residual disease, and the regular use of AZA only the first two variables proved to be independent predictors of recurrence

Table 2. Comparisons via univariate analysis between resected 83 patients with CD with and without postoperative endoscopic recurrence.

	Recurrence positive	Recurrence negative	p
Number of patients (%)	32 (39)	51 (61)	NA
Mean age at disease onset (yr)*	32.59±13.54	33.49±10.43	NS
Mean age at resection (yr)*	35.53±12.07	36.82±10.77	NS
Duration of disease (yr)*	10.59±5.13	9.09±6.23	NS
Mean age at the last postoperative colonoscopy (yr)*	43.18±13.32	42.58±11.20	NS
Time between resection and last colonoscopy(months)	54.18±45.42	49.27±54.68	NS
Female patients' number (%)	10 (31)	27 (53)	NS
Number of patients with a family history of IBD (%)	1 (3)	8(16)	NS
Localization of disease: number of patients (%)			
Ileum	5 (16)	15 (29)	NS
Colon	4 (13)	4 (8)	NS
Ileocolonic	22 (69)	32 (63)	NS
Upper gastrointestinal	1 (3)	0 (0)	NS
Behavior of disease: number of patients (%)			
Stenosing	20 (63)	25 (49)	NS
Penetrating	10 (31)	19 (37)	NS
Stenosing + penetrating	2 (6)	7 (14)	NS
Number of patients with perianal fistulae (%)	11 (34)	15 (29)	NS
Active smokers' number (%)**	11/26 (42)	16/48 (33)	NS
Number of patients with MTZ use of at least 3 months after resection (%)	2 (6)	4 (8)	NS
Number of patients with postoperative use of 5-ASA (%)	10 (31)	21 (41)	NS
Number of patients with regular postoperative use of 5-ASA (%)***	1 (3)	5 (10)	NS
Number of patients with postoperative use of AZA (%)	20 (63)	37 (73)	NS
Mean postoperative start time of AZA (months) (range)	18.20 (1–132)	11.06 (1–108)	NS
Number of patients AZA started within 3 months of surgery (%)	7 (21.9)	19 (37.3)	NS
Number of patients with regular postoperative use of AZA (%)***	4 (12)	17 (33)	0.034
Number of patients with a history of multiple resections (%)	9 (28)	4 (8)	0.013
Number of patients with any postoperative residual disease in remnant intestine (%)	20 (62)	18 (35)	0.015

*Values represent means±SD
** Only patients with a questionnaire about smoking habits were included
***The regular use of the relevant drug means its use at least at 85% of the postoperative period until the final colonoscopy
NA: Not available; NS: Not significant

[p=0.049; HR:2.23 (1.003-4.94), for a history of multiple resections], [p=0.019; HR:2.45 (1.155-5.181), for the presence of any postoperative residual disease].

DISCUSSION

In extensive reviews and some classic studies, the probability of having surgery in the course of CD is reported as high as 78%-91% (5-7). Unfortunately, postsurgical remission tends to be short lived; and in most of the series, about 50% of resected patients undergo repeated surgery within 20 yr (8, 9). Ultimately, when assessed endoscopically, there are studies reporting postoperative recurrence rates as high as 100% at 3 yr (10).

In retrospective assessment of our cohort, the mean follow-up period between resection and the latest postoperative colonoscopy was 51.16±51.08 months (approximately 4 yr), and the endoscopic recurrence rate was just 39%, despite the fact that only 20 of 83 patients (24%) had a regular use of AZA. Considering higher rates of en-

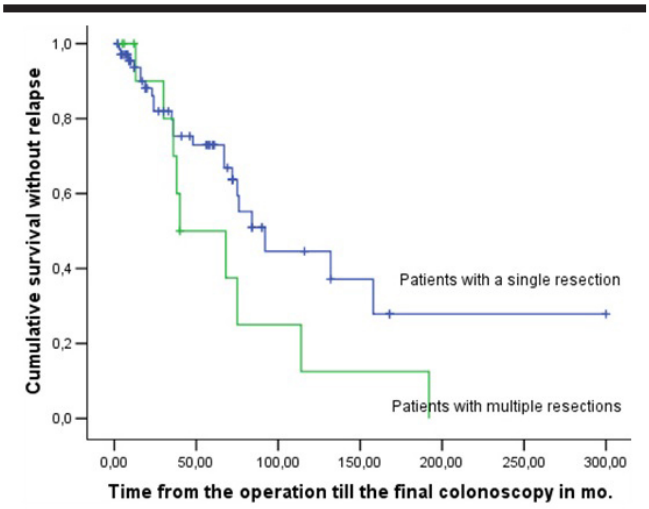

Figure 1. Kaplan-Meier survival analysis of endoscopic recurrence-free survival according to having a history of multiple or single resection. The mean time to recurrence was 71.82±18.97 months in the group with multiple resections, and 136.64±22.73 months in the group with a single resection. Cox multivariate regression analysis revealed that having a history of multiple resections was associated with a worse outcome regarding endoscopic recurrence [HR=2.23, 95% CI (1.003-4.94), p=0.049].

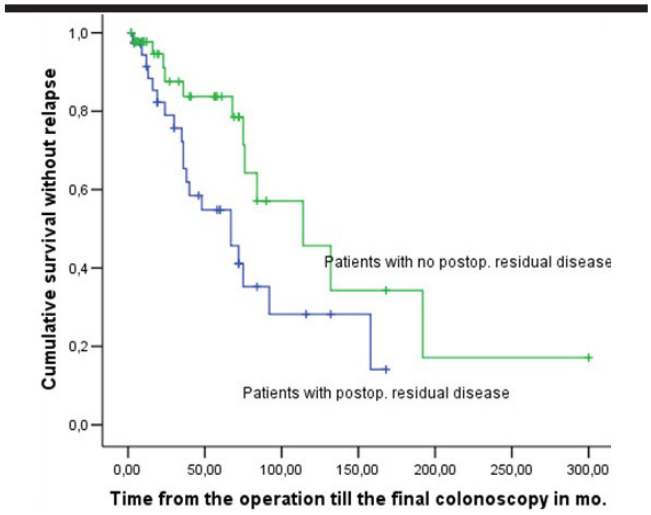

Figure 2. Kaplan–Meier survival analysis of time to endoscopic recurrence by group with and without any postoperative residual disease in the remnant intestine. The mean time to recurrence was 136.34±25.96 months in the group with no residual disease, and 78.31±11.55 months in the group with any residual disease. Cox multivariate regression analysis revealed that having any residual disease in the remnant intestine was associated with endoscopic recurrence [HR: 2.45, 95% CI (1.155-5.181) p=0.019].

doscopic recurrence in previous studies, like the one reported by Domenech et al. (11), in which all patients were put under AZA treatment immediately after the resection (the recurrence rates were 44%, 53%, 69%, and 82%, at 1, 2, 3, and 5 yr, respectively), the relative low postoperative recurrence rate in our cohort may add to the speculation in favor of a milder disease course in developing countries compared to the developed ones. However, this difference might arise from the prospective nature of that study, in which each step, like the starting time of AZA or timing of follow-up endoscopies had been planned in advance and strictly controlled. Nevertheless, that study lacks a control group. Regarding our study, we think that our retrospective cohort is more likely to reflect the results of daily routine practice with all its shortcomings like irregular outpatient visits, follow-up colonoscopies, and insufficient patients' adherence to their treatment regimens.

Another unanswered question about the postoperative recurrence is the timing of resection after the diagnosis of CD. Early surgery for CD is defined as major surgery within 3 years of diagnosis, except major surgeries like compulsory operations for acute perforations and/or obstruction at the time of diagnosis (12). It is still not clear whether early surgery is a protective factor or a predictor of postoperative recurrence. However, limited information suggests that early ileocecal resection has a positive effect on preventing clinical recurrence (13). In our series, 21 of 83 patients (25%) had a resection at the time of diagnosis, and if they are excluded, 33 of the remaining 62 patients (53%) had an early resection. The comparison of these two groups (62 patients) with and without early surgery did not disclose any difference regarding postoperative recurrence. Actually, a more aggressive course could be expected in the early operated group, and this could be biased by a trend toward a more aggressive treatment approach in the early operated group. However, there was no difference regarding postoperative length and regularity of AZA use in both groups (data not shown). Thus, we did not observe any effect of timing of surgery on postoperative recurrence in this retrospective cohort.

Although several studies have examined potential risk factors for recurrence after surgery, conflicting data exist for the age at onset, sex, and duration of the disease (14). These parameters were not found to be predictive of recurrence in this study (Table 2). Actually, there was a non-significant trend toward female predominance in the group without recurrence (53% vs. 31%). This could be because that smoking is a more common habit among men in our country (15), and actually active smoking rate was higher among men but it did not reach a significant difference (29%-42% for women and men, respectively).

Smoking is a widely accepted risk factor for postoperative recurrence (16). We only evaluated patients those who had filled a questionnaire about smoking habits (74 patients), and the active smoking rate was 42% vs. 33% in the group with and without recurrence, respectively. Thus, in concordance with the current literature, smoking was more frequent among patients with recurrence but reached statistical significance, probably due to relative low sample size.

Prior intestinal surgery has been reported as a risk factor for recurrence (17). In concordance with this, the proportion of patients with multiple resections was significantly higher among patients with recurrence compared to the recurrence-free group (28% vs. 8%), approximately disclosing a twofold risk. Therefore, having multiple resections for CD may be an indicator of an aggressive disease course. Although penetrating disease behavior [18] and perianal location (19) have been indicated as predictors of recurrence in some previous studies, we did not observe any effect of both variables on it (Table 2).

According to ECCO consensus report, it is recommended that prophylaxis is best started within 2 weeks of surgery, although an early start has not been proven superior to later treatment (14). Considering postoperative AZA treatment, we did not notice any difference regarding postoperative starting time between both groups with or without endoscopic recurrence. Even when we stratified the groups according to whether AZA was started within 3 months of surgery, we did not observe any significant difference regarding endoscopic recurrence (Table 2). Actually, it could be speculated about our retrospective data that the early initiation (within 3 months of surgery) of AZA could be biased by the fact that more aggressive cases (patients with a younger age, second resection, penetrating disease behavior, postoperative active smoking etc.) were chosen by our staff for this treatment arm; but when we analyzed our data, we did not observe any significant difference between patients with and without early postoperative administration of AZA regarding above-mentioned well-known risk factors for recurrence (data not shown). Thus, our data look equally distributed.

Any use of AZA other than regular between both groups was not significant as well. However, when an arbitrary limit of at least 85% of the time between the resection and final colonoscopy was applied to define the regular AZA use, a slight significant difference was noted in favor of preventing endoscopic recurrence. Unfortunately, this effect did not persist in Cox regression analysis.

In a recent meta-analysis, at one year, thiopurines were found to be superior both to placebo and 5-ASA compounds in preventing endoscopic recurrence (i2-4) but not the severe ones (i3-4), (20). In concordance with this, in a recent open-label prospective study, in which patients after curative intestinal resection were treated with daily AZA starting immediately after the surgery, the cumulative probabilities of endoscopic recurrence was as high as 69%-82% at 3 and 5 yr, respectively (11). Although the authors mentioned that their uncontrolled results indicated AZA to delay endoscopic recurrence, the clinical value of this "delay" depends on how one considers the natural postoperative recurrence rate. Nevertheless, the lack of long-term endoscopic follow-up data in post-resection patients with CD makes it plausible whether and/or when initially nominated endoscopic recurrence goes as further as to the level of re-operative stage under AZA treatment. This might underestimate the possible protective effect of AZA like delaying repeated resections. However, it is a matter of fact that time to intestinal surgery did not change despite the more frequent use of immunosuppressants in patients with CD from the end of the 1990s (21). Unfortunately, all these results taken together raise concerns about the efficacy of postoperative use of AZA on the natural course of CD.

In this retrospective study, we did not observe any positive effect of 5-ASA and MTZ on endoscopic recurrence (Table 2). Regarding MTZ, any postoperative use of the drug was not different between both groups, but only a few patients could use it for at least 3 months after surgery, thus making our results open to a type 2 error regarding this subgroup. Nevertheless, even the well-known study of Rutgeerts et al. (22) using MTZ for 3 months after resection could not show any beneficial effect of the drug on endoscopic recurrence at 3 months and 3 years after surgery. Only the clinical recurrence rate was reduced at one year subsiding during their follow-up. Actually, the drugs tested to date to prevent postoperative CD recurrence including different 5-ASA formulations, nitro-imidazole antibiotics, steroids, and AZA, convincingly have not been shown promising (23).

From our point of view, the most interesting finding of this study was that the presence of any postoperative residual disease came out as the most important independent predictor of endoscopic recurrence [HR:2.45 (1.155-5.181)]. Although it was reported that residual microscopic disease at resectional margins had no influence on the recurrence rate (24), our patients all after ileocolonic resection with macroscopic disease-free margins but with any macroscopic synchronous residual disease were under increased risk for recurrence. When both

groups (with and without residual disease) were separately analyzed, no differences were detected regarding sex, postoperative smoking status, and any or the regular use of AZA (data not shown). This could possibly be explained by the presence of a source of ongoing systemic inflammatory power that may simplify the recurrence in the neoterminal ileum. To our best knowledge, this parameter has never been investigated in previous studies, maybe having had influenced their results.

In conclusion, our results suggest that postoperative AZA use is not protective against the endoscopic recurrence of CD. The presence of a residual synchronous lesion after the resection and having a history of multiple resections were the only postoperative endoscopic recurrence indicators.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Approval Date: 05.07.2012, Decision Number: B.30.2.İST.0.30.90.00/18966).

Informed Consent: Written informed consent was obtained from parents and patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.Z.E.; Design - Y.Z.E, A.F.Ç. ; Supervision – A.F.Ç.; Resource A.F.Ç.; Materials – A.F.Ç., B.B., İ.H., U.K.; Data Collection and/or Processing - Y.Z.E., G.Ş.; Analysis and/or Interpretation - Y.Z.E., A.D.; Literature Search – G.Ş.; Writing - Y.Z.E.; Critical Reviews - İ.H., A.F.Ç.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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