Factors Influencing the Number of Lymph Nodes Harvested for Stage I-III Colorectal Cancer in Thai Patients

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Abstract

Introduction: Lymph node (LN) status is the most important predictor of survival in non-metastatic colorectal cancer (CRC). Recent guidelines recommend that a minimum of 12 nodes be examined for accurate staging. Three major classes of factors may influence the number of LN examined, including surgeon, pathologist and tumor/host factors.

Objectives: To identify factors influencing the number of LN harvested for stage I-III CRC in Thai patients and to review the adequacy of LN harvested by one surgeon.

Patients and Methods: A retrospective study of stage I-III CRC patients who underwent curative-intent resection by one surgeon was performed. Patients who underwent subtotal or total colectomy and patients who had preoperative chemoradiation were excluded. Variability in the quality of surgical technique was reduced by including patients who had operations performed by one surgeon only.

Results: From January 2001 to February 2008, 278 patients including 135 (49%) males and 143 (51%) females were eligible for analysis. The mean age was 62.3 years (SD, 11.8 years). There were 157 colon cancers (56.5%) and 121 rectal cancers (43.5%). The mean number of LN harvested was 17.3 nodes (18.7 nodes for colon cancer and 15.4 nodes for rectal cancer) with a median of 15 nodes (colon cancer, 16 nodes; rectal cancer, 14 nodes). Overall, 41 patients (15%) had inadequate LN harvest (<12 nodes; colon cancer, 8%; rectal cancer, 24%). Multivariable analysis revealed that factors associated with inadequate LN harvest included older age (>70years), left-sided colon or rectal cancer and early T-stage.

Conclusions: Excluding surgeon and pathologist factors, the number of harvested LNs in Thai patients was affected by patient and tumor factors, including age, location of tumor and T-stage. The high proportion of adequate LN harvest in the present study was probably due to a high volume caseload and the uniformly good quality of surgery as performed by one surgeon.

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INTRODUCTION

Tumor stage is the most important determinant of prognosis in colorectal cancer (CRC) and is the basis of all management guidelines,[1] allowing meaningful comparison of outcomes between institutes.[2] Lymph node (LN) metastasis is the most important predictor of survival in non-metastatic CRC.[3-7] The diagnosis of a lymph node (LN)-negative CRC should imply a good prognosis. However, the outcomes for stage II disease remain variable. About 20%-30% of patients with stage II CRC still develop recurrent disease.[3,4,8-10] Understaging of the disease is believed, at least partially, to explain some of these failures.[11]

The number of LNs examined is a significant factor in the accurate staging of CRC. Recent guidelines from the National Cancer Institute,[12] the American Joint Committee on Cancer (AJCC)[13] and the International Union Against Cancer (UICC)[14] recommend that a minimum of 12 LNs be recovered for accurate staging.

The purpose of this study was to identify factors influencing the number of lymph nodes harvested for stage I-III colorectal cancer in Thai patients and to review the adequacy of lymph nodes harvested after curative-intent resection of colorectal cancer by one surgeon.

PATIENTS AND METHODS

A retrospectively study of patients who had histological proof of adenocarcinoma of the colon or rectum, with TNM stage I-III disease and who underwent oncologic resection with curative-intent (R0) was performed. All operations were performed by one surgeon (CE). Patients with distant metastasis (stage IV disease), underwent palliative resection (R1-2), subtotal, total colectomy, proctocolectomy (patients with multiple CRC, HNPCC or FAP), or had pre-operative chemoradiation therapy were excluded.

All tumors were staged according to the TNM staging system. The clinicopathologic data including age, gender, tumor location, T-stage, TNM stage, tumor grading, presence or absence of angiolymphatic or perineural invasion, number of LNs harvested, and number of positive-nodes were reviewed.

Location of the colon cancer was categorized as right-sided (cecum, ascending colon, hepatic flexure and transverse colon) or left-sided (splenic flexure, descending colon and sigmoid colon). Comparisons of clinicopathologic characteristics between colon and rectal cancer patients, and between inadequate and adequate LN harvested (<12 or ≥12 nodes) were undertaken.

Continuous variables were summarized as mean and standard deviation (SD) or median (range) or both as appropriate. Categorical variables were summarized as counts and percentages. Continuous variables were contrasted between the two groups using unpaired t-test or Wilcoxon rank-sum test as appropriate, or between three or more groups using ANOVA or Kruskal-Wallis tests as appropriate. Categorical variables were contrasted between two or more groups using the chi-square test. Multivariable analysis for determining important predictors of total harvested lymph nodes was done using multiple linear regressions. Factors associated with total harvested lymph nodes <12 and factors associated with positive lymph nodes were determined using logistic regression analyses. The result of each statistical test was considered significant if the two-sided p-value was 0.05 or less. All statistical analyses were performed using Stata version 9 (Stata Corp, College Station, TX, USA).

RESULTS

From January 2001 to February 2008, 278 CRC patients underwent oncologic resection with curative-intent (R0) by one surgeon (CE) at Ramathibodi Hospital and were eligible for analysis. Overall, 135 (49%) were male and 143 (51%) were female. The mean age at diagnosis was 62.3 years (SD, 11.8 years). There were 157 colon cancers (56.5%) and 121 rectal cancers (43.5%). Of the 157 colon cancers, 63 (40%) were right-sided and 94 (60%) were left-sided (Table 1). For all patients, the mean number of LN harvested was 17.3 nodes (colon cancer, 18.7 nodes; rectal cancer, 15.4 nodes) and the median number was 15 nodes (colon cancer, 16 nodes; rectal cancer, 14 nodes) (Tables 1, 2).

The proportions of patients in stage II and III disease were 37% and 40%, respectively (43% and 34% for colon cancer; 31% and 48% for rectal cancer) (Tables 1, 2). The majority of patients with colon cancer presented with stage II disease (43%) and well or moderately differentiated tumor (94%). The

Table 1 Clinicopathological characteristics of patients (N = 278)

Characteristics	Number (%)
Mean age (SD)	62.3 years (11.8)
Male / Female	135/143 (49/51)
Location of tumor	
Right-sided colon	63 (23)
Cecum & descending colon	35 (13)
Hepatic flexure	24 (9)
Transverse colon	4 (1)
Left-sided colon	94 (34)
Splenic flexure and descending colon	11 (4)
Sigmoid colon	83 (30)
Rectum	121 (43)
T- stage	
T1	10 (4)
T2	61 (22)
T3	156 (56)
T4	51 (18)
N - stage	
N0	165 (59)
N1	74 (27)
N2	39 (14)
TNM - stage	
I	64 (23)
II A	69 (25)
II B	34 (12)
III A	9 (3)
III B	64 (23)
III C	38 (14)
Angiolymphatic or perineural invasion (yes)	55 (20)
Grade of tumor	
Well differentiated	186 (67)
Moderately differentiated	66 (24)
Poorly or undifferentiated	26 (9)
Total lymph nodes harvested	
Median (range)	15 (4-69)
Mean (SD)	17.3 (7.8)
Number of positive lymph nodes	
Median (range)	0 (0-37)
Mean (SD)	1.6 (3.8)

majority of patients with rectal cancer presented with stage III disease (48%) and well or moderately differentiated tumor (87%) (Table 2).

Factors influencing LN harvest in CRC

The number of LNs harvested decreased with increased age, male gender, left-sided colon or rectal cancer, early T-stage, early TNM stage and poorly or undifferentiated tumor (Table 3). There was no significant correlation between the number of LNs harvested and the presence of angiolymphatic invasion, perineural invasion or the positive-node status (Table 3). On multivariable analysis, age, location of tumor, TNM staging and grade of tumor remained significantly related to the number of LNs harvested (Table 4).

In the present study, 12 cases (8%) of colon cancer patients and 29 cases (24%) of rectal cancer patients had inadequate LN harvest (<12 nodes). Overall, 41 patients (15%) had inadequate LN harvest (Table 5). Factors associated with inadequate LN harvest are shown in Table 6. On multivariable analysis, inadequate LN harvest was associated with older age, left-sided colon and rectal cancer, and early T-stage (Table 7).

Effect of LN harvest on the identification of LN metastasis

A total of 111 patients (40%) had one or more LN metastasis. These patients had the same median number of nodal harvest as those without metastasis (15 nodes vs 15 nodes, respectively) (Table 3). Factors associated with positive-nodes are shown in Table 8.

From the multivariable analysis, factors associated with positive nodes included advanced T-stage, presence of angiolymphatic or perineural invasion, and decreased number of LNs harvested (Table 9).

DISCUSSION

Since the first CRC classification proposed by Dukes in 1932,[15] LN metastasis has been shown to adversely affect survival in CRC patients. LN involvement is the strongest prognostic factor in patients with non-metastatic CRC.[3-7] In the current AJCC /UICC TNM staging system, the classification of LN metastasis is based on the number of LNs involvement.

A complete evaluation of the LN basin which collects lymphatic drainage from the affected segment of the bowel is important for accurate identifying LN involvement and to confirm the completeness of surgical resection.[16] Retrieving a high number of LNs increases the probability that, if present, positive LNs will be detected.[17-19]

Numerous studies have shown that survival of patients with CRC is related to number of LNs examined.[4-6,16,20-44] Two mechanisms might explain

Table 2 Characteristics of colon and rectal cancers (N = 278)

Characteristics	Colon cancer (N = 157)	Rectal cancer (N = 121)	p-value*
Mean age (SD)	63.8 years (11.0)	60.3 years (12.6)	0.012
Gender: number (%)			0.025
Male	67 (43)	68 (56)	
Female	90 (57)	53 (44)	
T- stage: number (%)			0.001
T1	6 (4)	4 (3)	
T2	32 (20)	29 (24)	
T3	77 (49)	79 (65)	
T4	42 (27)	9 (7)	
N- stage: number (%)			0.087
N0	102 (65)	63 (52)	
N1	35 (22)	39 (32)	
N2	20 (13)	19 (16)	
TNM - stage: number (%)			0.015
I	37 (24)	27 (22)	
II A	38 (25)	31 (26)	
II B	28 (18)	6 (5)	
III A	2 (1)	7 (6)	
III B	33 (21)	31 (26)	
III C	19 (12)	19 (16)	
Angiolymphatic or perineural invasion: number (%)			0.776
Yes	32 (20)	23 (19)	
No	125 (80)	98 (81)	
Grade of tumor: number (%)			0.137
Well differentiated	110 (70)	76 (63)	
Moderately differentiated	37 (24)	29 (24)	
Poorly or undifferentiated	10 (6)	16 (13)	
Total lymph nodes harvested			0.001
Median (range)	16 (5-69)	14 (4-39)	
Mean (SD)	18.7 (8.5)	15.4 (6.2)	
Number of positive lymph nodes			0.026
Median (range)	0 (0-37)	0 (0-18)	
Mean (SD)	1.4 (4.2)	1.8 (3.3)	

*p - values by t-test, Wilcoxon rank - sum test or chi - square test as appropriate

this relation. The first is stage migration. Because LN metastasis may go unidentified in patients in whom only a small number of LNs have been harvested leading to possible understaging, inappropriate treatment might have been given.[7,19,45] Thus, with higher number of LNs examined, the risk of missed nodal metastasis should be lowered. This would lead to upstaging stage I or II to stage III disease. Even in stage III disease, stage migration can occur leading from substages IIIA (T1-2, N1) or IIIB (T3-4, N1) to IIIC (T1-4, N2). The distinction between N1 and N2 is prognostically important,[3,4,46-48] and may also be of value when choosing more potent adjuvant chemotherapy.[3,4] Another explanation is that a more complete resection of tumor and the draining nodes would have less residual disease and possibly a better outcome.[7,16,19,45] The surgeon was, in fact, an important variable in the outcome.

The minimum number of LNs needed to be examined to accurately stage individuals with CRC is

Table 3 Factors influencing number of lymph nodes harvested, univariable analysis

Characteristics	Number of subjects (%)	Number of lymph nodes harvested: Median (range)	p-value*
Age			0.024
≤ 70 years	215 (77)	16 (4-69)	
> 70 years	63 (23)	14 (7-31)	
Gender			0.004
Male	135 (49)	14 (4-53)	
Female	143 (51)	16 (5-69)	
Location of tumor (I)			< 0.001
Right-sided colon	63 (23)	22 (5-69)	
Left-sided colon	94 (34)	14 (7-42)	
Rectum	121 (43)	14 (4-39)	
Location of tumor (II)			0.001
Colon	157 (57)	16 (5-69)	
Rectum	121 (43)	14 (4-39)	
T - stage			< 0.001
T1	10 (4)	11 (5-18)	
T2	61 (22)	13 (4-39)	
T3	156 (56)	16 (4-53)	
T4	51 (18)	18 (9-69)	
TNM - stage			< 0.001
I	64 (23)	14 (4-39)	
II (II A-B)	103 (37)	16 (8-69)	
III (III A-C)	111 (40)	15 (4-42)	
Angiolymphatic or perineural invasion			0.135
Yes	55 (20)	16 (4-53)	
No	223 (80)	15 (4-69)	
Grade of tumor			0.027
Well differentiated	186 (67)	14.5 (4-69)	
Moderately differentiated	66 (24)	16 (5-53)	
Poorly or undifferentiated	26 (9)	18 (10-42)	
Positive lymph nodes			0.765
Yes	111 (40)	15 (4-42)	
No	167 (60)	15 (4-69)	

*p - values by Kruskal - Wallis rank test.

controversial and have ranged from 6 to 40 nodes.[9,13,21-23,25,29,49-59] In 1990, the Working Party Report to the World Congress of Gastroenterology, published in 1991,[60] recommended the evaluation of at least 12 LNs, a recommendation that was subsequently used by the National Cancer Institute in USA.[12] The UICC[14]/AJCC,[13] the Dutch CRC treatment guidelines,[61] and the College of American Pathologists[52] also recommended the examination of a minimum of 12 LNs. In addition, the American College of Surgeons, the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN) and the National Institute of Clinical Excellence (NICE)[62] have endorsed the 12 nodes minimum.

Despite this recommendation, five population-based studies found that only 13% to 47.7% of patients with CRC received adequate LN evaluation.[3-5,40,61] At best, 61% to 67% of patients undergo adequate LN evaluation for CRC,[2,63] suggesting that a large number of patients with CRC are being staged inadequately.

Table 4 Factors influencing number of harvested nodes, multivariable analysis

Characteristics	Number of lymph nodes increase (decrease)	95% CI	p-value*
Age			
> 70 years	Reference	-	
≤ 70 years	2.86	0.89 to 4.84	0.005
Location of cancer			
Right side of colon	Reference	-	
Left side of colon	<- 5.78	- 3.54 to - 8.07	<0.001
Rectum	<- 6.99	- 4.84 to - 9.13	<0.001
Stage of cancer			
I	Reference	-	
II [IIA-B]	4.40	2.20 to 6.60	<0.001
III [IIIA-C]	2.05	<- 0.15 to 4.24	0.068
Grade of cancer			
Well differentiated	Reference	-	
Moderately differentiated	0.45	<- 1.53 to 2.44	0.652
Poorly or Undifferentiated	3.82	0.89 to 6.76	0.011

Table 5 Lymph nodes harvested, stage, and location of tumor

Number of lymph nodes	All patients N = 278	Colon cancer N = 157	Rectal cancer N = 121	Stage I-II N = 167	Stage III N = 111
< 12	41 (15 %)	12 (8 %)	29 (24 %)	28 (17%)	13 (12%)
≥ 12	237 (85 %)	145 (92 %)	92 (76 %)	139 (83%)	98 (88%)

Table 6 Factors associated with harvested lymph nodes < 12, univariable analysis

Factors	Odds Ratio (95 % CI)	p-value
Age (per years increase)	1.04 (1.01 - 1.07)	0.013
Gender (Male)	2.04 (1.04 - 4.04)	0.042
Location of tumor		
Right-sided colon (reference category)	1	-
Left-sided colon	8.22 (1.03 - 65.3)	0.046
Rectum	19.5 (2.59 - 147)	0.004
T - stage		
T1 (reference category)	1	-
T2	0.325 (0.082 - 1.28)	0.109
T3	0.061 (0.015 - 0.243)	< 0.001
T4	0.027 (0.004 - 0.181)	< 0.001
Grade of tumor		
Well differentiated (reference category)	1	-
Moderately differentiated	0.447 (0.179 - 1.20)	0.086
Poorly or undifferentiated	0.179 (0.023 - 1.37)	0.097
TNM - stage		
I (reference category)	1	-
II	0.067 (0.022 - 0.206)	< 0.001
III	0.221 (0.103 - 0.477)	< 0.001
Angiolymphatic or perineural invasion (Yes)	0.658 (0.262 - 1.65)	0.373
Positive lymph nodes ≥ 1 (Yes)	0.659 (0.325 - 1.36)	0.247

Table 7 Factors associated with harvested lymph nodes < 12, multivariable analysis

Factors	Odds Ratio (95% CI)	p-value
Age (per years increase)	1.06 (1.02 - 1.10)	0.004
Location of tumor		
Right-sided colon (reference category)	1	-
Left-sided colon	10.2 (1.12 - 93.1)	0.039
Rectum	36.4 (4.03 - 329)	0.001
T - stage		
T1 (reference category)	1	-
T2	0.191 (0.039 - 0.949)	0.043
T3	0.031 (0.006 - 0.160)	< 0.001
T4	0.044 (0.006 - 0.350)	0.003

Table 8 Factors associated with positive lymph nodes, univariable analysis

Factors	Odds Ratio (95% CI)	p-value
Age (per year increase)	0.989 (0.969 - 1.01)	0.296
Gender (Male)	0.892 (0.552 - 1.44)	0.641
Location of tumor		
Right-sided colon (reference category)	1	-
Left-sided colon	0.856 (0.438 - 1.67)	0.648
Rectum	1.55 (0.829 - 2.89)	0.170
T - stage		
T 1 - 2 (reference category)	1	-
T 3 - 4	6.69 (3.16 - 14.2)	< 0.001
Grade of tumor		
Well differentiated (reference category)	1	-
Moderately differentiated	1.55 (0.877 - 2.74)	0.132
Poorly or undifferentiated	2.98 (1.28 - 6.94)	0.011
Angiolymphatic or perineural invasion (Yes)	4.14 (2.21 - 7.76)	< 0.001
Number of lymph nodes harvested (per node increase)	0.987 (0.956 - 1.02)	0.413

Table 9 Factors associated with positive lymph nodes, multivariable analysis

Factors	Odds Ratio (95% CI)	p-value
T - stage		
T 1 - 2 (reference category)	1	-
T 3 - 4	6.65 (3.00 - 14.7)	< 0.001
Angiolymphatic or perineural invasion (Yes)	3.19 (1.63 - 6.23)	0.001
Number of lymph nodes harvested (per node increase)	0.950 (0.914 - 0.987)	0.009

One Canadian study by Wright et al. in 2004[64] showed that only 58% of pathologists were aware of guidelines for LN retrieval in CRC and only 25% knew that a minimum of 12 nodes is necessary for accurate designation of node negativity.

The College of American Pathologists[65] has established guidelines in 2000 for pathologic evaluation of CRC resection specimens that all grossly negative or equivocal LNs be submitted in their entirety for microscopic examination. If fewer than 12 LNs are found, additional techniques, such as fat clearance, may be needed to identify more LNs and that this fact should be communicated in the pathology report. Similarly, in 2007, the Santa Monica Conference[66] recommended that if <12 LNs are found on initial examination, the pathologist should re-examine the specimen. If <12 LNs are still found on re-examination, the pathologist should document this in the pathology report. Some authors, and the American Society of Clinical Oncology in 2004[67] have suggested that chemotherapy be administered to any patient who cannot be reliably declared node negative.[23,40]

The 3 classes of factors that may influence number of LNs examined include the quality of the surgery, the thoroughness of pathologic analysis and the differences in the host and tumor biology.[16,19,43,68-71] Surgeon factors have been found to be associated with the number of LNs recovered[27,68] and long-term survival.[72-74] Numerous studies have shown that high surgeon workload and surgical specialization improve outcomes in CRC through improved surgical technique and management.[75-80] In the present study, the variability in the quality of surgical technique was reduced by restricting patient-subjects to those operated on by one of the authors (CE).

In the present study, the same team of pathologists from the Department of Pathology examined surgical specimens for LNs, using the same technique for LN assessment. Hence the variability associated with the pathologist factor has also been minimized. Hospital case volume, which can influence both the surgeon and the pathologist, is also associated with the number of LN recovered.[16,43] Regardless of the pathologist who performed the LN evaluation, surgeon is the most important factor in increasing the total number of LNs examined.

The present study identified a number of important patient and tumor-related factors associated with the number of LNs harvested. These included age, gender, location of tumor, T-stage, TNM-stage and grade of tumor. Angiolymphatic or perineural invasion and positive node status were not significant factors. Increasing age has been associated with decreased LN yields,[5,9,19,27,31] but the reasons for this are unclear. Some have suggested that the elderly may have physiologic differences that result in fewer LNs in the resected specimens.[3] There is evidence that the size of LNs is reduced from lymphoid tissue atrophy[31] as patients get older, and this may make it more difficult to identify and retrieve the LNs.[19,81] Alternatively, surgeons may perform less extensive operations due to greater co-morbidity in older patients.[19,45]

A difference in the number of LNs harvested between men and women has been reported in many studies,[3,5,9,25,61,82] but the reasons for this are also unclear. A possible explanation is the gender differences in the pelvic anatomy that affect surgical resection, resulting in a lower likelihood of men having adequate LN harvest.[83,84] But some authors could not demonstrate this association.[19,31]

The location of tumor may also be important in LN recovery. The explanation is that right-sided specimens often contain larger amount of mesentery.[9,17,26,27,49,68] Due to the anatomy of the bowel, right-sided specimens are usually longer than the left-sided specimens and this may make it easier to identify more LNs.[2,9,27,43,68,83-86] Although it is generally agreed that tumors on the right-side are associated with higher number of LNs examined,[5,9,23,26-27,49,68,87] this was not seen in some studies.[19,28]

Similar to other studies,[2,5,19] the present study demonstrated that LN yields were higher in patients with more advanced T-stage. In the present study, T1 tumors were associated with a median number of LNs harvested of 11 nodes compared with a median yield of 18 nodes associated with T4 tumor (Table 3). The reason for this finding is unclear. It may be that tumor-draining nodes undergo inflammatory changes that make them larger and easier to identify or that new LNs appear due to the antigenic challenge of a more advanced tumors.[2,5,18-19,24]

Similarly, the median LN yield increased with TNM stage from 14 nodes for stage I compared with 15 nodes for stage III disease (Table 3).

Numerous studies have demonstrated that the number of LNs examined increases with higher

stage.[5,18-19,50,88]

The finding that patients with higher number of LNs examined were more likely to have nodal metastasis were reported in previous studies.[11,18,23,35,43] But this finding was not supported in the present study. One large multicenter study,[21] one population-based study,[37] as well as other studies[20] have not demonstrated an increased proportion of LN-positive patients in the setting of larger number of LNs harvested, indicating that upstaging is an inadequate explanation of the phenomenon. Indeed, the number of positive or negative LNs examined is likely to reflect underlying tumor biology.[41]

The overall rate of adequate LN harvest (>12 nodes) in our study was 85%, higher than that of all other previous reports. The reason was that, generally, population-based studies include surgeons of variable skills, and the number of LNs harvested would reflect results from both highly-skilled and less skilled surgeons. In the present study, a single-surgeon, with a large case volume and long experience, can achieve a much higher proportion of adequate LN clearance. This is also brought out quite clearly when the proportion of adequate LN harvest in the present study is compared with that of a previous report from the same department: 85% vs 73.3% (92% vs 78.8% for colon cancer; 76% vs 67.3% for rectal cancer).[89] The explanation is that the variability of surgical skills in a multi-surgeon study (which included colorectal surgeons, general surgeons, and surgical residents) tended to lower the rate of adequate LN harvest.

Conclusions

Assessing as many LNs as possible is important in CRC, but LN yields will vary in relation to many factors. Excluding surgeon and pathologist factors, the number of LN harvested in Thai patients was related to patient/tumor factors which included age, tumor location, TNM stage, and tumor grading. A greater proportion of adequate number of LNs harvested (>12 nodes) in the present study when compared with previous studies was probably due to the focus on the operative results of only one experienced surgeon.

Although many authors recommend that patients with node-negative tumors but inadequate LN clearance be considered for adjuvant chemotherapy, this suggestion does not address the underlying problem, which is to increase the number of retrieved LNs. Since the number of LNs examined will vary according to many factors, the assignment of a specific number of LNs as representing adequate LN dissection is arbitrary. Rather, the surgeon should perform an appropriate oncologic resection and the pathologist should retrieve as many nodes as possible for examination.

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