Number of Lymph Node Metastases May Indicate the Regimen for Adjuvant Chemotherapy in Patients with Stage III Colorectal Cancer

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Abstract. *Background: Adjuvant chemotherapy (ACT) may prevent recurrence in patients with stage III colorectal cancer (CRC). However, only 10% of patients benefit from ACT and no effective indicators exist to predict which patients are likely to benefit. The present study validated metastatic lymph node (MLN) number as a new indicator for ACT. Patients and Methods: We retrospectively reviewed 173 patients with stage III CRC, who were classified by Union for International Cancer Control (UICC) stage or N category, and analyzed their overall survival (OS) and disease-free survival (DFS) according to stage, number of MLNs and ACT use. Results: Among 173 patients, we found 65 with only one MLN (N1a). For N1a patients treated with ACT, the 5-year OS rate was 100%; the 3-year DFS rate was 92.7% for those treated with oral ACT. Conclusion: The number of MLNs is a simple indicator for ACT in patients with stage III CRC. For patients with only one MLN, oral chemotherapy is a good option.*

The year 2012 saw more than 14 million people diagnosed with cancer and 8 million cancer-related deaths. Colorectal cancer (CRC) is the third most common type of cancer and the fourth most common cause of cancer mortality worldwide (1). Improved multimodal treatments, including surgery, radiotherapy, chemotherapy, and molecular-targeting therapy, have been found to increase chances of cure or prolonged survival in CRC. Progress in chemotherapy has prolonged survival of patients with CRC (2). Patients with unresectable or metastatic CRC have a median survival time of almost 30 months (3). Chemotherapy is a critical therapy for CRC.

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For patients with stage III CRC with local metastatic lymph nodes (MLNs) but not distant metastases, adjuvant chemotherapy (ACT) is recommended. Recurrence reportedly occurred in 20-40% of Japanese patients with stage III CRC after R0 surgery (4). The aim for ACT is to prevent such recurrence. However, only 10% of patients with stage III CRC reportedly benefit from ACT (5), whereas 70% of patients do not experience relapse without ACT, and 20% suffer recurrence even with ACT. Thus, selecting patients who should receive ACT is difficult.

Regimens commonly used for adjuvant chemotherapies are FOLFOX (5-fluorouracil/leucovorin plus oxaliplatin) (6), XELOX (capecitabine plus oxaliplatin) (7) and oral uracil and tegafur plus leucovorin. However, these regimens have side-effects, most notably, oxaliplatin-induced neuropathy.

To date, no evidence indicates which patients would benefit from ACT. For 70% of patients with stage III CRC who do not benefit from ACT, its use may increase their suffering while wasting medical resources. A means of identifying patients who are likely to benefit from ACT is required.

In the present study, we evaluated MLN number as an indicator for ACT.

Patients and Methods

Patients. We enrolled 173 Japanese patients who were diagnosed with stage III sporadic CRC and who underwent colorectal surgery in the Department of Surgery and Science, Kyushu University Hospital from 2000 to 2011. Written informed consent for the study was obtained from each patient.

The patients were divided into three groups by stage–IIIA, IIIB or IIIC–according to the Union for International Cancer Control 7th TNM classification (8) and then further classified by MLN number as N1a (1 MLN), N1b (2-3 MLNs), or N2 (≥4 MLNs).

Statistical analysis. We performed statistical analysis using JMP 9.0 software (SAS institute, Cary, NC, USA). The χ^2 test, Fisher's exact test and one-way ANOVA were used as appropriate. A value of $p<0.05$ was considered to be significant. Kaplan–Meier analysis was used to analyze overall survival (OS) and disease-free survival (DFS).

Table I. *Patients' characteristics*.

Factors	Patients (n=173)
Age (mean±SD), years	65.6±12.7
Gender, n (%)	
Male	97 (56.1)
Female	76 (43.9)
Depth, n (%)	
T1	7 (4.0)
T2	32 (18.5)
T3	107 (61.8)
T4a	24 (13.9)
T4b	3 (1.7)
N Category, n (%)	
N1a	65 (37.5)
N1b	66 (38.1)
N2	42 (24.3)
Stage, n (%)	
IIIA	33 (19.1)
IIIB	118 (68.2)
IIIC	22 (12.7)
Adjuvant therapy, n (%)	
Without	57 (33.0)
With	116 (67.0)
Regimen, n (%)	
Oral	89 (76.7)
mFOLFOX6	15 (12.9)
XELOX	12 (10.3)

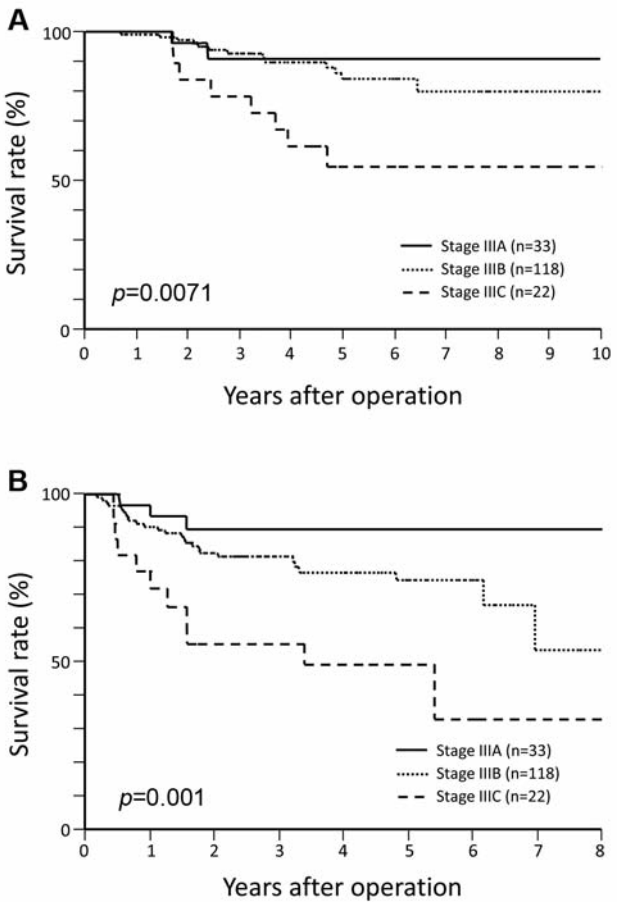

Figure 1. *Survival curves for 173 patients with stage III colorectal cancer by stage. A: Overall survival. The five-year overall survival rate was 90.7% for stage IIIA, 84.1% for stage IIIB and 54.7% for stage IIIC patients. B: Disease-free survival. The three-year DFS rate was 89.7% for stage IIIA, 74.4% for stage IIIB and 48.9% for stage IIIC patients.*

Results

Patients' characteristics. This study included 97 men and 76 women with a mean age of 65.6 years (range=31-89 years). Of these patients, 65 had only one MLN (N1a) and 42 had four or more MLNs (N2); 33 had stage IIIA disease, 118 had stage IIIB and 22 had stage IIIC. Of the 116 patients who underwent ACT, 89 received oral chemotherapy such as tegafur/leucovorin, 15 received modified (m)FOLFOX6 and 12 received XELOX (Table I).

Overall survival and disease-free survival by disease stage. We first validated OS and DFS by disease stage (Figure 1). The 5-year OS rates were: stage IIIA: 90.7%; stage IIIB: 84.1%; and stage IIIC: 54.7% (p=0.0071; Figure 1A). The 3-year DFS rates were: stage IIIA: 89.7%; stage IIIB: 74.4%; and stage IIIC: 48.9% (p=0.001; Figure 1B).

Overall survival and disease-free survival by number of MLNs. We then validated OS and DFS by the number of MLNs (Figure 2). The 5-year OS rates were: N1a: 91.8%; N1b: 83.7%; and N2: 59.7% (Figure 2A). The 3-year DFS rates were: N1a: 86.0%; N1b: 86.8%; and N2: 53.4% (Figure 2B); notably, the 3-year DFS rates did not significantly differ between the N1a and N1b patients. The 6-year DFS rates were: N1a: 86.0%; N1b: 75.8%; and N2: 40.0%.

ACT and oral chemotherapy in N1a patients. As the 5-year OS in N1a patients was above 90%, we next considered the effect of ACT for these patients. Out of 65 N1a patients, 40 (61.5%) underwent ACT, all 40 of whom were still alive 5 years after their surgeries (Figure 3). Thus, 5-year OS rates were 100% for patients who underwent ACT and 73.1% for those did not (p=0.0018, Figure 3A), indicating that ACT benefits patients with only one MLN. We then verified which regimen benefited N1a patients. ACT regimens used for N1a patients were oral chemotherapy such as tegafur/leucovorin: 29 patients; XELOX: six patients; and mFOLFOX6: five patients. Although these therapies did not significantly differ in OS, oral chemotherapy such as tegafur/leucovorin led to a better DFS rate among these three therapies (Figure 3B),

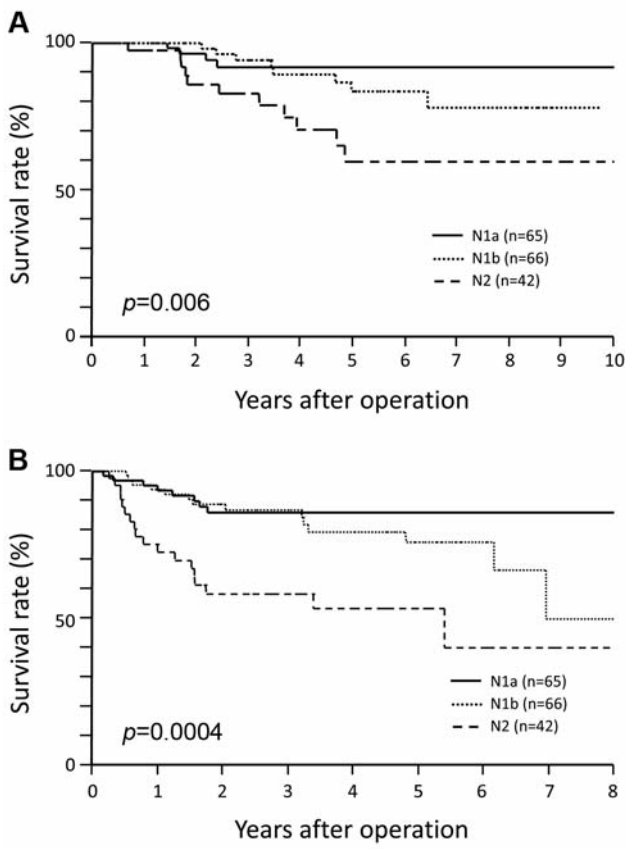

Figure 2. *Survival curves for 173 patients with stage III colorectal cancer by number of lymph node metastases. A: Overall survival; the 5-year overall survival rate was 91.8% for N1a, 83.7% for N1b and 59.7% for N2 patients. B: Disease-free survival; the 3-year disease-free survival rate was 86.0% for N1a, 86.8% for N1b and 53.4% for N2 patients.*

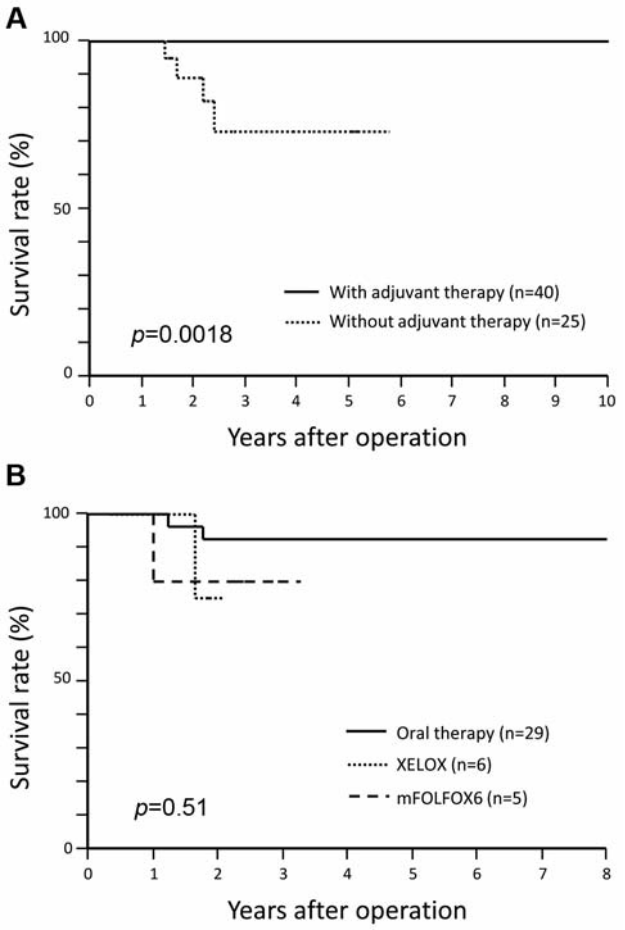

Figure 3. *Survival curves for N1a patients by adjuvant chemotherapy. A: Overall survival of 65 colorectal cancer patients with only one metastatic lymph node number; (MLN) by adjuvant chemotherapy. The 5-year overall survival rate of patients with adjuvant therapy was 100%. B: Disease-free survival by use of adjuvant chemotherapy. The 3-year disease-free survival rate in patients treated with oral therapy was 92.7%.*

indicating that for N1a patients, ACT is important and oral chemotherapy with tegafur/leucovorin is a good choice.

ACT in patients with two or more MLNs, for whom multidrug chemotherapy may be required. We then validated effects of ACT for the 108 patients with two or more MLNs. Out of these patients, 32 patients received no ACT, 60 patients had oral chemotherapy with tegafur/leucovorin, six patients had XELOX therapy and 10 patients had mFOLFOX6 therapy. Patients who underwent ACT had better prognoses (Figure 4A, p=0.013), but did not differ in DFS (data not shown). The 3-year DFS rates for patients who received oral chemotherapy (74.5%) were the same as those who received no ACT (76.5%); whereas 3-year DFS rates were 100% for patients who received XELOX and 80% for those on mFOLFOX6 (Figure 4B). Oral chemotherapy is apparently not enough for patients with two or more MLNs; multi-drug ACT regimens might be necessary for these patients.

Discussion

Patients with CRC and only one MLN should receive ACT. Oral chemotherapy with tegafur/leucovorin might be enough for these patients. For patients with two or more MLNs, XELOX or mFOLFOX6 is necessary.

The first randomized prospective clinical trial for adjuvant therapy in CRC was the 1988 NSABP C-01 study (9), showing that significant DFS and OS benefits could be achieved with postoperative ACT in patients with stage II or III CRC who underwent curative resection. In 1990, the 5-FU/levamisole regimen was recognized as a standard ACT regimen; and 5-FU/leucovorin became a standard ACT regimen after the NSABP C-03 (21) and IMPACT studies (1). The NSABP C-04 study showed that 5-FU/leucovorin

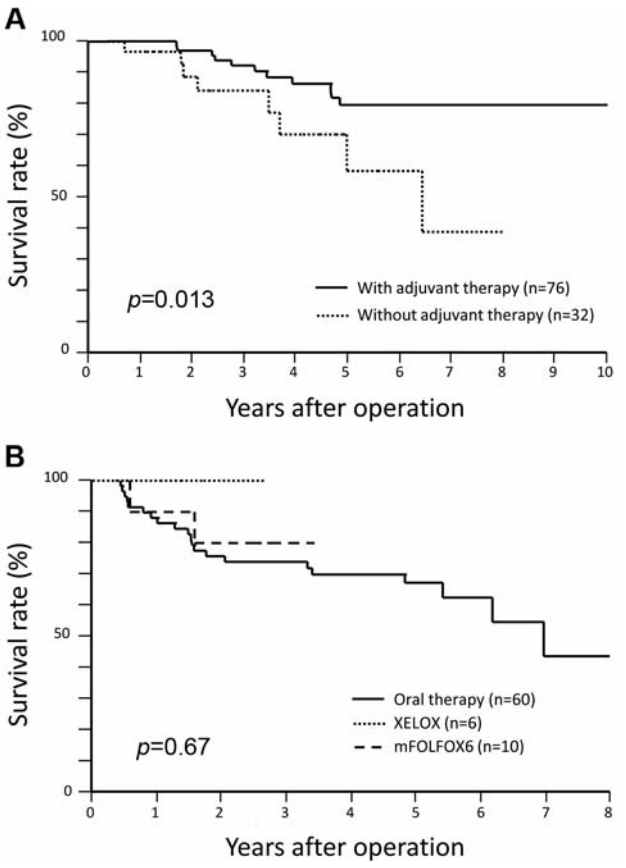

Figure 4. *Survival curves for patients with ≥2 lymph node metastases by adjuvant chemotherapy. A: Overall survival of 108 colorectal cancer patients with ≥2 lymph node metastases by adjuvant chemotherapy. The 5-year overall survival rate of patients who received adjuvant therapy was 79.9%. B: Disease-free survival by adjuvant chemotherapy regimen.*

gave longer DFS and OS than did 5-FU/levamisole, leading 5-FU/leucovorin to become a more widely used ACT regimen for CRC. After the MOSAIC study showed that oxialiplatin increases effectiveness of 5-FU/leucovorin (10, 11), the FOLFOX regimen, and the NO16968 study (12) showed that XELOX is an effective ACT regimen, FOLFOX and XELOX became commonly used ACT regimens. However, their oxaliplatin component can lead to peripheral neuropathy. Andre *et al*. reported that this neuropathy continues in 15% of patients after 4 years of ACT (11), with no effective treatment; this side-effect might influence how ACT is selected for patients with stage III disease.

In this study, we found that patients with only one MLN may benefit from oral chemotherapy such as tegafur/leucovorin, with less toxicity. The NSABP C-06 study compared the relative efficacy of tegafur/leucovorin as ACT for stage II/III CRC with an intravenous, weekly bolus 5-FU plus leucovorin regimen and showed them to give similar DFS and OS rates (13). Shimada *et al*. also reported that the JCOG0205 trial (14) showed non-inferior DFS for tegafur/leucovorin compared with standard 5-FU/levofolinate for patients with stage III CRC who underwent Japanese D2/D3 lymph node dissection. The main side-effect of tegafur/leucovorin was alanine aminotransferase elevation. They concluded that tegafur/leucovorin should be an oral treatment option for this patient population. These trials support our data that N1a patients benefit from UFT/LV. This result may allow selection of patients who would not suffer from peripheral neuropathy from oxaliplatin.

This study focused on the number of MLNs but some studies have focused on the importance of the lymph node ratio (LNR) (15), *i.e*. the ratio of positive lymph nodes to total retrieved lymph nodes, which is reportedly a prognostic factor in stage III CRC (16-18) with implications for adjuvant therapy (19). The LNR might be useful when fewer than 12 lymph nodes are retrieved but it requires a cut-off, that is complicated to decide on and differs in each report. O'Shea *et al*. reported that increasing the number of retrieved lymph nodes does not necessarily increase the number of positive lymph nodes (20). Schiffmann *et al*. also showed that using the LNR rather than the N category of the TNM system seemed to have no benefit if the number of subgroups is not increased (21). These reports support the use of the number of MLNs as an easy indicator for choosing ACT in patients with CRC.

In conclusion, the number of MLNs is a simple indicator for ACT in patients with stage III CRC. For patients with only one MLN, oral tegafur/leucovorin is a good therapy option.

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