

Incorporation of apical lymph node status into the seventh edition of the TNM classification improves prediction of prognosis in stage III colonic cancer

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Background: The node classification outlined in the seventh edition of the TNM classification is based solely on the number of metastasized lymph nodes. This study examined the prognostic value of apical lymph node (ALN) metastasis and the additional value of incorporating ALN status into a risk model based on the seventh edition.

Methods: This was a cohort study of patients with stage III colonic cancer who underwent tumour resection with dissection of regional (including apical) lymph nodes at 71 hospitals across Japan between 2000 and 2002. The main exposure was pathologically confirmed ALN metastasis, and the primary endpoint was cancer-specific death.

Results: ALN metastasis was present in 113 (8.3 per cent) of 1355 patients. During 5356 patient-years of follow-up (median 5.0 years), 221 instances (16.3 per cent) of cancer-specific death were observed. After adjustment for tumour and node classification (as described in the seventh edition of the TNM classification) and other prognostic factors, ALN metastasis was found to be independently associated with cancer-specific death (hazard ratio 2.29, 95 per cent confidence interval (c.i.) 1.49 to 3.52). Incorporation of ALN metastasis into the prognostic model based on the seventh edition of the TNM classification significantly improved discriminative performance for cancer-specific death (difference in concordance index 0.0146, 95 per cent c.i. 0.0030 to 0.0262) and risk reclassification for cancer-specific death at 5 years (category-free net reclassification improvement 19.4 (95 per cent c.i. 5.0 to 33.4) per cent).

Conclusion: Assessment of ALN metastasis provided independent prognostic information beyond that achievable with the seventh edition of the TNM classification in patients with stage III colonic cancer.

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Introduction

Accurate prognostic estimation of colorectal cancer is important for facilitating accurate decision-making in oncological management. The TNM classification developed by the American Joint Committee on Cancer and the International Union Against Cancer (UICC) is the most commonly used staging system worldwide. Under this system, lymph node staging is based only on the number of metastatic lymph nodes¹, providing a simple way of classifying patients and saving surgeons or pathologists the trouble of classifying retrieved lymph nodes by anatomical

location, such as paracolic, intermediate or apical area. However, the anatomical location of lymph nodes remains an important point from a prognostic perspective, especially as apical lymph nodes (ALNs) are considered the entry point for lymph node metastasis more proximal to the aorta (such as the para-aortic lymph node) or for haematogenous metastasis. Although ALN metastasis has high potential value as a marker for the prediction of future systemic metastasis and subsequent death, whether or not ALN metastasis has prognostic value remains unclear.

Several previous studies^{2–4} support the notion that the location of the metastasized lymph node has prognostic value. For example, the presence of inferior mesenteric artery (IMA) lymph node metastasis has been shown to predict para-aortic nodal recurrence in patients with cancer of the sigmoid colon or rectum². Other studies^{3,4} have shown the distribution of lymph node metastasis to be an independent predictor of overall survival in sigmoid colonic and rectal cancer. However, these previous reports were limited by the disease being restricted to a partial area of the colon and by being single-centre studies. In addition, these studies failed to show the value of incorporating the location of the metastasized lymph node into existing TNM classification-based prediction models.

In the present study, using Japanese multicentre registry data, the association between ALN metastasis and cancer-specific death in patients with colonic cancer was examined, and an assessment was made of whether the addition of ALN metastasis to the prognostic model based on the seventh edition of the UICC TNM classification (UICC7) improved the discrimination of cancer-specific death.

Methods

Approval was obtained to use the registry data of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) in this cohort study. The JSCCR registry project was approved by the institutional review board of Tochigi Cancer Centre. Patients diagnosed with colorectal cancer who underwent surgery at 89 member hospitals across different areas in Japan between January 2000 and December 2002 were registered voluntarily in the JSCCR registry. This nationwide registry is hospital-based (not population-based) and covered approximately 6.5 per cent of all patients with colorectal cancer in Japan between 2000 and 2002. Eligibility criteria for this study were: patients with colonic cancer who had curative resection with dissection of regional lymph nodes including the ALN; pathologically diagnosed stage III colonic cancer; and no distant metastasis. To maintain comparability between patients with or without ALN metastasis, patients with stage 0, I or II were not included in the study, as these disease stages do not involve ALN metastasis. The presence or absence of distant metastasis was usually determined using a combination of chest X-ray, abdominal ultrasonography, and abdominal (and chest) computed tomography⁵. Patients who had preoperative treatment and those with multiple primary cancers were excluded, as were patients with rectal cancer (defined as cancer of the bowel below the lower margin of the second sacral vertebra⁶) because

they have two main lymphatic drainage routes; specifically, both routes continuing to the root of the IMAs and the internal iliac arteries are involved in lymphatic spread. For correct determination of ALN metastasis, bilateral lymph node dissection surrounding the root of the internal iliac arteries is required, but is not always performed in practice as it is often complicated by voiding or sexual dysfunction. As informed consent to use existing registry data is not mandatory for observational studies in Japan, such consent was not obtained for the present study.

Lymph node staging and apical lymph node metastasis

For the JSCCR registry, data on the number and anatomical location of positive lymph nodes were collected, whereas only the anatomical location of positive lymph nodes had been used for staging according to the Japanese Classification of Colorectal Carcinoma between 2000 and 2002. For data on the number of positive nodes in the present study, lymph node staging was defined according to UICC7 and classified into four categories: N1a, N1b, N2a and N2b¹. The category of N1c was excluded because tumour deposit was not registered in the Japanese classification system at that time. The definition of ALN corresponds to the N3 station in the Japanese Classification of Colorectal Carcinoma⁶, which is located in the roots of major arteries, such as the iliocecal, right colic, middle colic and inferior mesenteric arteries. ALN metastases were considered to be present if the retrieved lymph nodes were found to contain tumours. In Japan, regional lymph node dissection usually includes dissection of the ALN, and surgeons assign lymph node stations during or after surgery in accordance with the rules of Japanese classification⁶. Fat clearance is not usually performed.

Cancer-specific death

Cause of death was categorized as defined by the JSCCR as death related to surgery, death specifically related to colonic cancer, death related to other primary cancer, death not related to cancer, or death of unknown cause. This outcome ascertainment is routine with the JSCCR registry and was performed independently from the study. Death specifically related to colonic cancer was defined as the primary outcome and referred to as cancer-specific death or mortality. Follow-up started from day 1 after surgery and ended on the date of death or of the patient's final visit to the hospital. In Japan, patients having curative resection generally continue regular outpatient visits for at least 5 years⁵, and patients are hospitalized before death,

so most deaths can be collected through dedicated surgical follow-up.

Measurement of other co-variables

Other clinical variables potentially useful in the prediction of cancer-specific death in the present study were age, sex, histological type and pathological T category. Histological type was dichotomized as 'well or moderately differentiated' and 'poorly differentiated, signet ring cell, or mucinous'. Pathological T category was classified into four categories according to the UICC7: T1–2, T3, T4a and T4b.

Statistical analysis

Demographic characteristics, histological type, pathological T category, UICC7-based lymph node staging, presence of ALN metastasis, and number of retrieved lymph nodes were described. Continuous variables and categorical variables were summarized as median (with 10th to 90th percentiles) and percentages respectively. Cancer-specific death during follow-up was described as number, proportion and incidence rate. Cancer-specific survival curves for those with and without ALN metastasis were estimated using the Kaplan–Meier method, with differences assessed by the log rank test. These analyses were stratified by each category of UICC7-based lymph node staging.

Effect measures in the present study were hazard ratios (HRs) for cancer-specific death estimated using Cox models. Two models were constructed: a risk model of UICC7-based lymph node staging (model 1) and a risk model of UICC7-based lymph node staging plus ALN status (model 2). To estimate adjusted HRs, all of the co-variables described above were entered into multivariable analyses. Facility clustering effects of these analyses were addressed using a robust variance estimator⁷, and the proportional hazards assumption was tested and verified for each co-variable.

Discrimination for the two risk models was conducted using Harrell's c index, which is similar to the area-under-the-curve statistic for receiver operating characteristic (ROC) curves but allows calculation of concordance in time-to-event data. The c indices of the two risk models and their difference were calculated with 2000-replication bootstrapping, and bias-corrected 95 per cent confidence intervals (c.i.) were reported. Both the bootstrapping technique used in the present study and the data-splitting technique estimate the likely performance of the prediction model on a new sample of patients from the present patient population⁸. However, bootstrapping

is more efficient than data splitting as it preserves the sample size, improving precision and power^{9,10}. Thus, 95 per cent c.i. for the c indices of the two risk models and their difference can be viewed as validated discrimination measures applied to a new sample from the same population^{9,10}.

The predicted risk of cancer-specific death at 5 years was estimated from a Cox model containing UICC7-based variables alone or UICC7-based variables plus ALN status. The predicted risk was determined by first running a Cox model to obtain the baseline survival function at 5 years¹¹, expressed as $S_0(5)$. A risk score for each value of UICC7-based variables, with or without ALN status, was then calculated by multiplying the observed value for the model parameter by its corresponding coefficient from the Cox model. The estimated probability of observing cancer-specific death at 5 years was then calculated using the formula: $P(5) = 1 - S_0(5) \times \exp(\text{risk score})$.

The potential for ALN status to improve risk prediction beyond a UICC7-based risk model (model 1) for cancer-specific death was assessed further based on category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as, to date, clinically relevant cut-off values for the risk of cancer-specific death are not available for patients with colonic cancer, and both category-free NRI and IDI are independent of arbitrarily defined risk thresholds¹². Category-free NRI is a measure for estimating overall improvement in reclassification of patients on incorporating ALN status into the UICC7-based risk model, and is calculated as the net proportion of patients whose predicted risk improved among those with (case) and without (control) cancer-specific death. For each patient, the predicted risk of cancer-specific death at 5 years was determined using the UICC7-based risk model, and the relative improvement in patient reclassification associated with ALN metastasis was then assessed. In contrast, IDI is a measure for examining the ability of ALN status added to the UICC7-based risk model to increase average sensitivity without reducing average specificity¹², and is calculated as improvement in the difference in predicted risk between patients with (case) and without (control) cancer-specific death. Any events outside the 5-year time frame were censored. Patients with censored data were treated as controls.

Sensitivity analyses were also conducted. First, cancer-specific death was evaluated using patients with complete data, considering deaths other than cancer-specific death as a competing risk according to the competing-risk regression model developed by Fine and Gray¹³. Second, cancer-specific death was analysed by imputing missing co-variable and lymph node staging

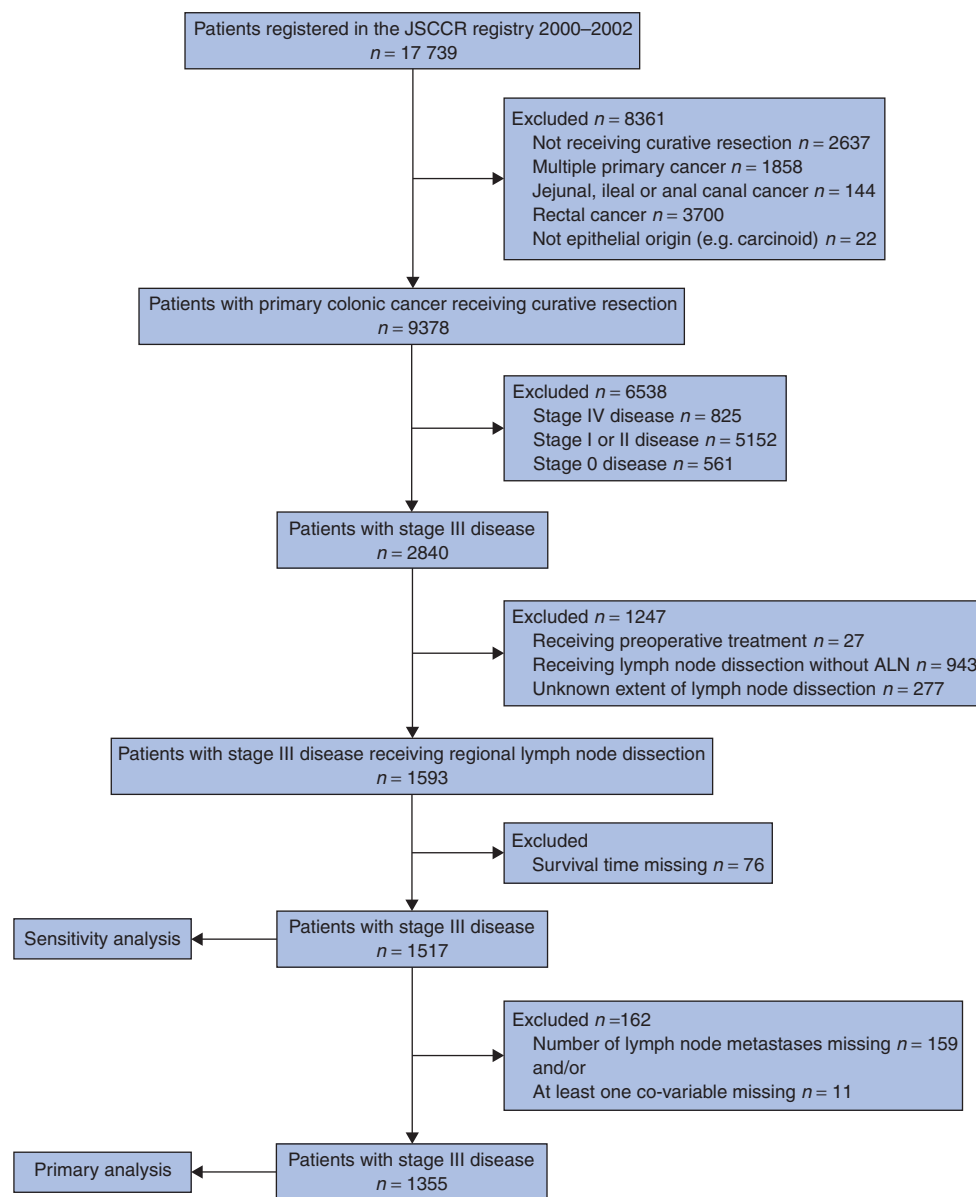


Fig. 1 Flow chart of the study population. JSCCR, Japanese Society for Cancer of the Colon and Rectum; ALN, apical lymph node

values. Multiple imputation using a chained equations method was used to estimate adjusted HRs^{14,15}. Multiple imputation with five imputed data sets using the `aregImpute` function in the `Hmisc` package was used for estimating difference in c indices of the two risk models, category-free NRI and IDI¹⁶. Third, all-cause death was analysed using patients with complete data.

All statistical analyses were conducted using R version 2.13.1 (www.r-project.org) and Stata[®] version 11.0 (StataCorp, College Station, Texas, USA). $P < 0.050$ was considered statistically significant.

Results

Of 17 739 patients in the JSCCR registry, 9378 with primary colonic cancer underwent curative resection (Fig. 1). Of those, 2840 had stage III disease, with at least 1593 undergoing regional lymph node dissection involving the ALN (277 had lymph node dissection of unknown extent). Seventy-six patients were excluded for missing data on survival time, and 162 for missing data on the number of lymph node metastases and/or at least one confounding variable. The remaining 1355 patients with stage III

Table 1 Baseline characteristics of the study population

	Total (n = 1355)	No ALN metastasis (n = 1242)	ALN metastasis (n = 113)
Age (years)*	65 (50, 77)	65 (50, 77)	67 (51, 77)
Sex ratio (M:F)	704:651	655:587	49:64
Histological type			
Well or moderately differentiated	1233 (91.0)	1145 (92.2)	88 (77.9)
Poorly differentiated/signet ring cell/mucinous	122 (9.0)	97 (7.8)	25 (22.1)
Pathological T category			
T1–2	100 (7.4)	96 (7.7)	4 (3.5)
T3	750 (55.4)	700 (56.4)	50 (44.2)
T4a	424 (31.3)	377 (30.4)	47 (41.6)
T4b	81 (6.0)	69 (5.6)	12 (10.6)
Lymph node staging according to UICC7			
N1a	534 (39.4)	523 (42.1)	11 (9.7)
N1b	466 (34.4)	433 (34.9)	33 (29.2)
N2a	226 (16.7)	203 (16.3)	23 (20.4)
N2b	129 (9.5)	83 (6.7)	46 (40.7)
ALN metastasis			
No	1242 (91.7)		
Yes	113 (8.3)		
No. of retrieved lymph nodes*	19 (8, 40)	19 (8, 40)	18 (7, 39)

Values in parentheses are percentages unless indicated otherwise; *values are median (10th to 90th percentile). ALN, apical lymph node; UICC7, International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition.

primary colonic cancer who had regional lymph node dissection in 71 institutions were entered into the primary analysis (85.1 per cent of 1593 patients with stage III disease who had regional lymph node dissection). Baseline characteristics of patients are presented in *Table 1*. Their median age was 65 years. Well or moderately differentiated adenocarcinoma was the dominant histological type (91.0 per cent). The most commonly assigned categories for pathological T and lymph node staging were T3 (55.4 per cent) and N1a (39.4 per cent). The median number of retrieved lymph nodes was 19.

Baseline characteristics were similar in patients with and in those without missing confounding variables or lymph node staging data (*Table S1*, supporting information), except for lymph node staging and ALN metastasis. As a group, their age and distributions of sex, histological type and pathological T category were similar.

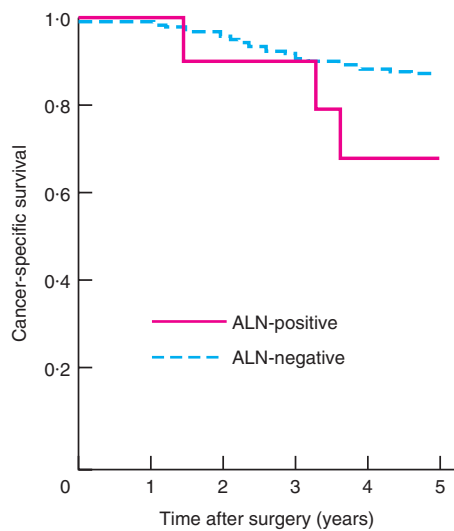
Overall, ALN metastasis was present in 113 (8.3 per cent) of the 1355 patients. Proportions of ALN metastasis were 2.1 per cent (11 of 534), 7.1 per cent (33 of 466), 10.2 per cent (23 of 226) and 35.7 per cent (46 of 129) in patients with N1a, N1b, N2a and N2b node categories respectively. As a group, patients with ALN metastasis had poorer histological type and more advanced pathological T and N categories than those without metastasis, whereas the median numbers of retrieved lymph nodes were similar, regardless of ALN metastasis (*Table 1*).

Over the course of the study a total of 5356 patient-years (mean 4.0 years, median 5.0 years) and 221 instances (16.3 per cent) of cancer-specific death were observed,

giving an incidence rate of cancer-specific death of 4.13 per 100 patient-years. The overall cancer-specific survival rate at 5 years was 81.0 per cent. When stratified based on UICC7 lymph node staging, cancer-specific survival at 5 years was worse in patients with ALN metastasis than in ALN-negative patients, with respective survival rates of 67.5 and 88 per cent for N1a ($P=0.068$), 62.5 and 83 per cent for N1b ($P=0.003$), 49.8 and 83 per cent for N2a ($P<0.001$), and 37 and 61 per cent for N2b ($P=0.008$) (*Fig. 2*).

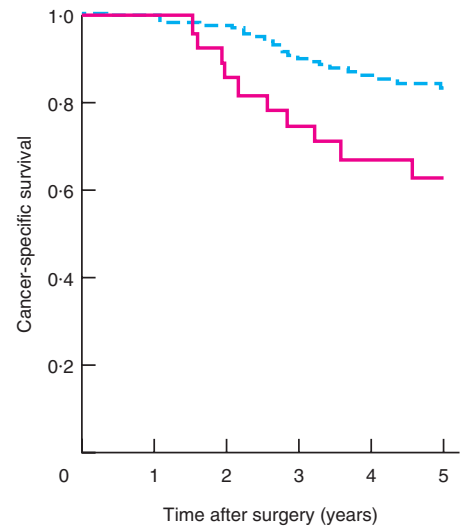
Associations between two lymph node staging models and cancer-specific death were attenuated slightly following adjustment for co-variables (*Table 2*). For model 1, category N2b was associated with higher cancer-specific mortality than N1a (adjusted HR 3.86, 95 per cent c.i. 2.28 to 6.53). For model 2, category N2b was still associated with higher cancer-specific mortality than N1a, but slightly less strongly than seen in model 1 (adjusted HR 2.98, 1.73 to 5.12). In the same model, the presence of ALN metastasis was associated with increased cancer-specific mortality (adjusted HR 2.29, 1.49 to 3.52). Sensitivity analyses in which non-cancer-specific deaths were considered as competing risks showed that adjusted HRs of lymph node staging and ALN metastasis were similar to those presented in *Table 2* (*Table S2*, supporting information). Cox models were therefore chosen for primary analysis of cancer-specific death, and further analyses were based on these models.

Harrell's c statistic was 0.694 (95 per cent c.i. 0.651 to 0.724) for the risk model based on UICC7 and 0.708



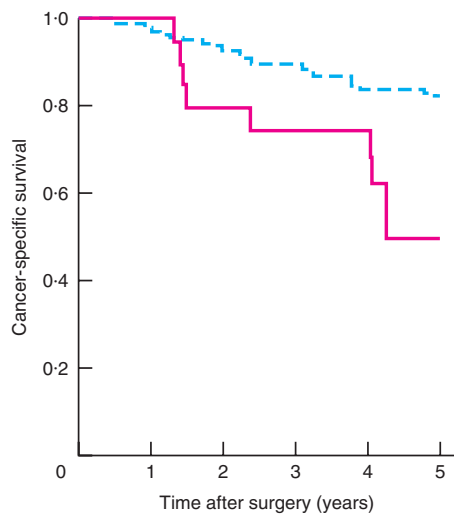
No. at risk						
ALN-positive	11	10	9	8	6	4
ALN-negative	523	489	454	404	362	315

a N1a



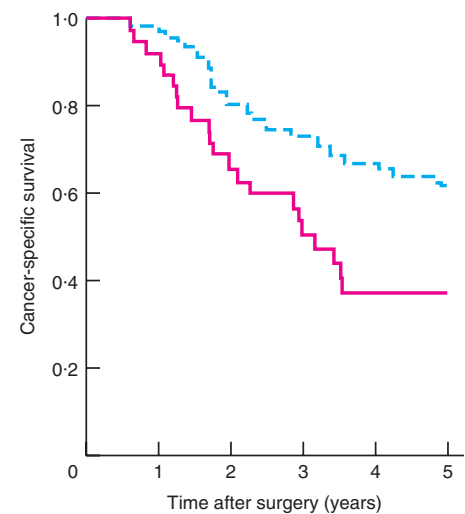
No. at risk						
ALN-positive	33	30	23	19	17	13
ALN-negative	433	406	383	332	299	270

b N1b



No. at risk						
ALN-positive	23	21	15	13	12	8
ALN-negative	203	188	172	153	136	119

c N2a



No. at risk						
ALN-positive	46	37	24	17	11	9
ALN-negative	83	78	61	54	47	39

d N2b

Fig. 2 Kaplan–Meier cancer-specific survival curves according to apical lymph node (ALN) status and International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition-based lymph node staging: **a** N1a, **b** N1b, **c** N2a, **d** N2b. **a** $P = 0.068$, **b** $P = 0.003$, **c** $P < 0.001$, **d** $P = 0.008$ (log rank test)

(0.666 to 0.737) for the model based on UICC7 and ALN status. Model 2 performed better than model 1 (Table 3), suggesting that the risk model based on UICC7 and ALN has better discrimination than that based on UICC7 alone.

Reclassification of risk was assessed for cancer-specific death after the addition of ALN status to the risk model based on UICC7 (Table 4). Both of the risks predicted using the UICC7-based model with or without addition of ALN

Table 2 Multivariable analysis of association between lymph node stage and cancer-specific death

	No. of patients (<i>n</i> = 1355)	Cancer-specific death			
		Unadjusted HR	<i>P</i>	Adjusted HR*	<i>P</i>
Model 1: UICC7					
Lymph node staging					
N1a	534	1.00 (reference)		1.00 (reference)	
N1b	466	1.41 (0.98, 2.01)	0.061	1.38 (0.94, 2.02)	0.102
N2a	226	1.63 (1.06, 2.52)	0.026	1.49 (0.97, 2.29)	0.069
N2b	129	4.74 (2.91, 7.71)	<0.001	3.86 (2.28, 6.53)	<0.001
Model 2: UICC7 + ALN status					
Lymph node staging					
N1a	534	1.00 (reference)		1.00 (reference)	
N1b	466	1.32 (0.93, 1.89)	0.123	1.31 (0.89, 1.93)	0.166
N2a	226	1.49 (0.97, 2.28)	0.066	1.39 (0.91, 2.12)	0.128
N2b	129	3.47 (2.13, 5.66)	<0.001	2.98 (1.73, 5.12)	<0.001
ALN metastasis					
No	1242	1.00 (reference)		1.00 (reference)	
Yes	113	2.58 (1.76, 3.78)	<0.001	2.29 (1.49, 3.52)	<0.001

Values in parentheses are 95 per cent confidence intervals. *Estimated from Cox models including age, sex, histological type and pathological T stage accounting for facility clustering effects. HR, hazard ratio; UICC7, International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition; ALN, apical lymph node.

Table 3 Concordance indices and their difference between the two prognostic models for cancer-specific death (1355 patients)

	Cancer-specific death (Harrell's <i>c</i>)*
Model 1: UICC7	0.694 (0.651, 0.724)
Model 2: UICC7 + ALN status	0.708 (0.666, 0.737)
Model 2 versus model 1 (difference in Harrell's <i>c</i>)	0.014 (0.005, 0.030)

Values in parentheses are 95 per cent confidence intervals calculated from 2000-replication bootstrapping with bias correction method. *Derived from Cox models including age, sex, histological type, pathological tumour stage and lymph node staging presented in *Table 2*. UICC7, International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition; ALN, apical lymph node.

status at the individual level were visualized as plots (*Fig. S1*, supporting information). Addition of ALN status to the UICC7-based model resulted in 28.5 per cent correct (up) and 71.5 per cent incorrect (down) reclassifications in the 221 patients with cancer-specific death. In contrast, 81.2 per cent correct (down) and 18.8 per cent incorrect (up) reclassifications were noted in the 1134 patients without cancer-specific death. Overall, 19.4 per cent of patients were correctly reclassified following the addition of ALN status ($P = 0.008$). Addition of ALN status to the UICC7-based model significantly improved stratification between patients with, and those without cancer-specific death ($P = 0.014$), indicating that the difference in average predicted risk between patients with cancer-specific death and those without increased by 0.0146 following incorporation of ALN status into the UICC7-based risk model.

In sensitivity analyses using imputed data for 1517 participants, the adjusted HR of ALN status for cancer-specific

Table 4 Category-free net reclassification improvement and integrated discrimination index for apical lymph node status added to the TNM UICC7-based risk model for cancer-specific death at 5 years (1355 patients)

	%	<i>P</i>
NRI		
Cases reclassified to higher risk	28.5	
Cases reclassified to lower risk	71.5	
Controls reclassified to lower risk	81.2	
Controls reclassified to higher risk	18.8	
Category-free NRI	19.4 (5.0, 33.4)	0.008
IDI	0.0146 (0.0030, 0.0262)	0.014

Values in parentheses are 95 per cent confidence intervals. Cases denote patients who had cancer-specific death at 5 years, whereas controls denote patients who did not experience cancer-specific death at 5 years or were censored before 5 years. UICC7, International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition; NRI, net reclassification improvement; IDI, integrated discrimination index.

death (*Table S3*, supporting information), the difference in the *c* indices of the two risk models (*Table S4*, supporting information), category-free NRI and IDI (*Table S5*, supporting information) were similar. When all-cause death was analysed among the 1355 patients, 290 instances (21.4 per cent) of all-cause death were observed (overall survival rate at 5 years 76.0 per cent). The results were similar to those for cancer-specific death (*Fig. S2* and *Tables S6–S8*, supporting information).

Discussion

In this multicentre cohort study of patients with stage III colonic cancer, pathologically confirmed ALN metastasis

was independently associated with cancer-specific death. In addition, incorporation of ALN metastasis into a prognostic model based on the seventh edition of the TNM classification significantly improved risk reclassification for cancer-specific death. Results were similar when all-cause death was examined as an outcome. The present findings suggest that identification of ALN metastasis by anatomical classification may provide additional prognostic value for risk stratification of cancer-specific death in patients with colonic cancer.

Findings from several previous studies support the prognostic value of anatomical classification of the metastasized lymph nodes. Indeed, one study² showed that IMA lymph node metastasis (an ALN metastasis) was associated with para-aortic node recurrence. However, participants in this previous study were restricted to patients with sigmoid colonic and rectal cancer, and the association between IMA lymph node metastasis and mortality was not examined. Another study³ showed that anatomical classification of the metastasized lymph node was independently associated with overall survival among patients with sigmoid colonic and rectal cancer. The importance of anatomical classification of metastasized lymph nodes in predicting overall survival was also shown among patients with colonic or rectal cancer^{4,17}. However, these previous studies have several shortcomings, such as their single-centre status, the fact that most had a relatively small sample size, their therapeutic heterogeneity (especially adjuvant chemotherapy) and, most importantly, their failure to examine the additive value of incorporating the anatomical classification of the metastasized lymph nodes into the existing TNM classification-based risk model. The present multicentre study involved 1355 patients with stage III colonic cancer from more than 71 facilities. In addition, the study focused on the prognostic importance of ALN metastasis and showed that incorporating the ALN into the UICC7-based risk model significantly improved predictive ability for both cancer-specific and all-cause mortality.

The authors believe that the present findings will influence the activity of surgeons and cancer researchers for several reasons. A more accurate staging system enables surgeons to provide detailed information to postoperative patients. Further, identification of those subgroups with a relatively poor prognosis may indicate the need for more extensive adjuvant therapy to such patients. The present findings may represent a basis for conducting a future study examining the effectiveness of dissecting ALNs for colorectal cancer. ALNs are considered the entry point for lymph node metastases more proximal to the aorta (such as the para-aortic lymph node) or for haematogenous metastasis, and thus their retrieval may offer prognostic benefit.

Indeed, complete mesenteric excision (CME) including the ALN has been proposed as a method of improving oncological outcomes¹⁸. However, CME is often associated with a greater technical requirement, involving high ligation of a major artery, and might therefore increase the incidence of postoperative complications. Further study is warranted to clarify the role of CME in apical lymph node dissection. The present study demonstrates that the TNM classification can be restructured based on available evidence to improve the accuracy of predicting patient prognosis¹⁹; incorporation of ALN metastasis into the risk model based on the present TNM classification can improve prognosis prediction. Of note, ALN was an important feature in the lymph node staging in the fourth edition of the TNM classification, but was dropped from the fifth edition owing to presumed lack of importance²⁰. The seventh edition of the TNM classification has been criticized for lack of an evidence base for changing the definitions of classifications (for example, tumour deposits) from those in previous editions²¹. Further studies on the additive impact of pathological findings on prognosis prediction are required to revise the TNM classification scientifically.

Several strengths of the present study warrant mention. This cohort study was conducted using a nationwide registry of major teaching hospitals across different areas of Japan, and the survival analyses accounted for variability in survival across the facilities using a robust variance estimator⁷. The study design and analysis plan ensure the generalizability of the findings. The relatively short, uniform, enrolment period prevented the findings from being confounded by advances in perioperative management or development of new anticancer agents such as oxaliplatin, which were not marketed in Japan between 2000 and 2002. The association between ALN metastasis and cancer-specific death might be less likely to be affected by competing risks, because Japanese patients tend to experience fewer cardiovascular disease risks than patients in Western countries²². Indeed, the results for sensitivity analyses with all-cause death as the outcome were similar to those in primary analyses. By calculating the difference in the *c* indices, category-free NRI and IDI, the present study was able to demonstrate that incorporating ALN status into the UICC7-based risk model not only improved the discriminative performance but also improved accuracy in risk reclassification for both cancer-specific and all-cause death.

However, the present study does have several limitations. Other potential confounders, such as tumour markers or degree of lymphatic vessel invasion or vascular invasion, could not be incorporated, which might have resulted in overestimation of the strength of the association between ALN metastasis and cancer-specific death. In addition,

the use of adjuvant chemotherapy could not be included. However, lack of adjustment for adjuvant chemotherapy tends to result in underestimation of the strength of the association between ALN metastasis and cancer-specific death, as adjuvant chemotherapy is more likely to be provided to those with more advanced lymph node staging involving the ALN. In addition, the N1c category of the seventh edition of the TNM classification could not be included in the present study, as tumour deposit was not used for staging between 2000 and 2002. Further study is warranted to examine the prognostic value of ALN metastasis. Among patients with cancer-specific death, the risk model based on UICC7 variables plus ALN status proved less accurate in its predictive ability than the model based on UICC7 alone, although ALN metastasis itself was an independent prognostic factor. Further research is needed to construct a more precise risk model.

ALN metastasis is a significant prognostic factor in stage III colonic cancer, and integration of ALN into the seventh edition of the TNM classification-based risk model improves the accuracy of prognosis prediction. ALN should therefore be incorporated into the next TNM classification for improved stratification of patient prognosis.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Predicted 5-year cancer-specific mortality risk from models including International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition (UICC7)-based variables with and without apical lymph node (ALN) status (Word document)

Fig. S2 Kaplan–Meier overall survival curves according to International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition (UICC7)-based lymph node staging (N1a to N2b) and apical lymph node (ALN) status (Word document)

Table S1 Baseline characteristics of patients with missing data for at least one co-variable or for lymph node stage (Word document)

Table S2 Association between lymph node stage and cancer-specific mortality in the complete data set of 1355 patients when competing risk was considered (Word document)

Table S3 Association between lymph node staging and cancer-specific death in the multiply imputed data set (1517 patients) (Word document)

Table S4 Concordance indices and their difference between the two prognostic models for cancer-specific death in the multiply imputed data set (1517 patients) (Word document)

Table S5 Category-free net reclassification improvement and integrated discrimination index for apical lymph node status added to the UICC7-based risk model for cancer-specific death at 5 years in the multiply imputed data set (1517 patients) (Word document)

Table S6 Association between lymph node staging and all-cause mortality (1355 patients) (Word document)

Table S7 Concordance indices and their difference between the two prognostic models for all-cause death (1355 patients) (Word document)

Table S8 Category-free net reclassification improvement and integrated discrimination index for apical lymph node status added to the UICC7-based risk model for all-cause death at 5 years (1355 patients) (Word document)