Original Article

Use of Preoperative L3 Muscle Index to Predict Long Term Survival and in Hospital Complication of Stage I to III Colorectal Cancer

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Key Words
Colorectal cancer;
Sarcopenia;
Muscle index;
Survival

Purpose. Decrease of muscle mass is recognized as a poor prognostic factor in colorectal cancer. This study aimed to examine the association between computed tomography measured muscle index and the long term survival in resectable stage I to III colorectal cancers.
Materials and Methods. Data were collected retrospectively from medical records. There were total 236 patients underwent resection with curative intent at Keelung Chang Gung Memorial Hospital from 2006 to 2010. The muscle index was calculated by an open-saurce Image J software from National Institutes of Health U.S.A. (NIH). The cross-sectional muscle area in pre-op CT scan at the 3rd lumbar vertebral (L3) level normalized with patient's height represents the muscle index. The lowest quartile of L3 muscle index was classified as sarcopenia. Other potential predictors of survival were collected and analyzed by Kaplan-Meier curves and Cox proportional hazard models.
Results. For the lowest quartile of L3 muscle index, man lower than 36.59 cm^2/m^2 and woman lower then 36.64 cm^2/m^2 is defined as sarcopenia. The average follow-up duration was 71 months. The patients in sarcopenic group had worse 5-year overall survival rate than non-sarcopenic group (61.02% vs. 76.84%; log-rank test $p = 0.001$). Multivariate Cox regression analysis revealed that sarcopenia was independently associated with higher mortality rate (HR 2.524; 95% CI 1.4408-4.526; $p = 0.002$) in patients with colorectal cancer. There was no significant difference in in-hospital complication between two groups.
Conclusions. Preoperative L3 muscle index can be used to predict the long term survival in patient who undergoes surgical resection for stage I to III colorectal cancer. L3 muscle index less than the 25 percentile can be the prognostic threshold of sarcopenia in our population.
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Colorectal cancer has become one of the most commonly diagnosed cancers in the U.S. since 2003.[1] In Taiwan, with the good access to health care and the national policy of cancer screening, colorectal cancer became the most commonly diagnosis malignancy and more than 14,000 cases were detected in

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each year.[2] Despite the advancement of treatment, there is variation of prognosis in between patients with similar stages. There are several clinicopathological features related to poor prognosis like T4 lesion, inadequate lymph nodes harvest, poorly tumor differentiation, presence of lymphovascular invasion and perineural invasion. However, all these factors require surgical resection of the primary lesion to help determination. Thus it is important to find predictors preoperatively to estimate the prognosis of patients with colorectal cancer.

Skeletal muscle wasting (i.e. sarcopenia) is recognized as a marker of patient frailty and poor prognosis factor in many cancers.[3-5] There were bunch of literatures proposed the prognostic significance of sarcopenia in colorectal cancer recently.[6,7] However, the estimation of skeletal muscle wasting is variable and most of which depends on complicated software calculation. Here, we propose the utility of open source software "Image J" to calculate the skeletal muscle index at pre-operative computer tomography image at 3rd lumbar spine level. The lowest gender-specific quartile is defined as "sarcopenia". In the present study, we tried this simple method to evaluate the muscle mass from the pre-operative CT scans and presumed patients who had sarcopenia was associated with poor long term survival after surgery.

Materials and Methods

From January 2006 to December 2010, total 348 patients were diagnosed with colorectal adenocarcinoma and received standard resection at the Keelung branch of Chang Gung Memorial Hospital. We aimed to curative intent operation for the stage I to III colorectal cancer. There were 112 patients excluded from our study. These 112 patients include 59 patients had synchronous or metachronous metastatic lesions at the time of disgnosis; 14 patients who were diagnosed 2nd malignancy other than colorectal cancer; 16 patients who underwent emergent operation for obstruction or perforation; 9 patients who lack of pre-op CT or body height data, and 14 patients who loss follow-up within half year. The remaining 236 patients were enrolled in the study. The patient selection flow chart was presented (Fig. 1).

The data was collected from electronic inpatient and outpatient records in our department, included computed tomography images, demographic data (age, gender, height, weight, body mass index), preoperative laboratory data (white blood cell count, neutrophil to lymphocyte ratio, carcinoembryonic antigen, albumin, C-reactive protein), tumor-specific features (tumor location, size, and TNM staging), pathologic features (differentiation of the tumor, presentation of lymphovascular invasion and peri-neural invasion) and survival time.

In the study, we used L3 muscle index to quantized muscle mass. The skeletal muscle area was measured on CT scans performed within 30 days before surgery. We used the NIH software Image J to draw outlines of skeletal muscle in the cut of the L3 including paraspinal muscles (i.e. psoas major muscle, erector spinae muscles, quadratus lumborum muscle) and abdominal wall muscles (i.e. abdominal external oblique muscle, abdominal internal oblique muscle, transverse abdominal muscle, rectus adbominis muscle) and computed the cross-sectional area of each in centimeters squared (Fig. 2). The cross-sectional area of skeletal muscles (cm^2) at the L3 level was normalized by the square of the patient's height (m^2) to obtain the L3 muscle index (cm^2/m^2). All measurements were performed by a single trained surgical resident.

The Chi-square test and one-way analysis of variance (ANOVA) were used to compare characteristics

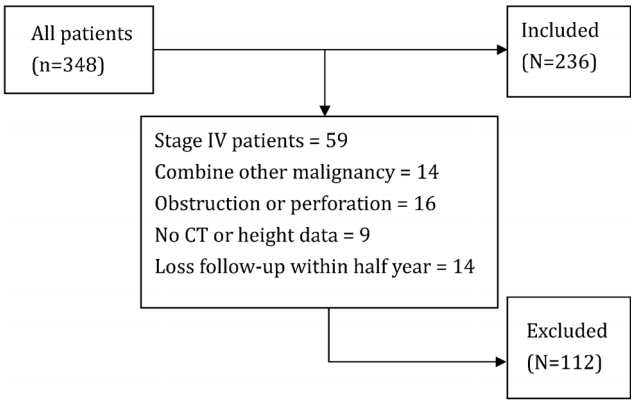


Fig. 1. Flow chart representing the patient selection process.

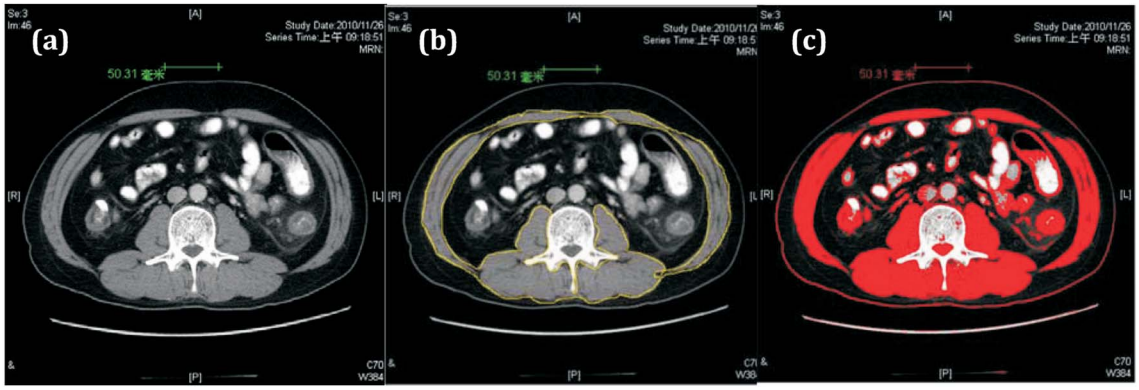


Fig. 2. An example of CT image analysis using NIH Image J software. (a) The original CT image, the scale is set using a known distance (5 cm), (b) Draw outlines of skeletal muscle in the cut of the 3rd lumbar vertebrae and calculate the area in cm^2, (c) The traditional method using muscle thresholds (-29 to +150 HU) to define cross area of skeletal muscle.

variable between groups. Survival curves were compared by using the Kaplan-Meier method and analyzed with log-rank test. Univariate Cox proportional hazards models was used to exam the potential predictors with 95% confidence intervals (CIs). Multivariate Cox proportional hazard model was used to quantify the hazard ratios (HRs) of quartiles of L3 index, gender, age at surgery, tumor size, histological features and TNM stages. A p-value of < 0.05 was considered to be statistically significant. All statistical analysis was performed using SPSS software (Version 22.0. SPSS Inc., Chicago, IL, USA).

Result

The characteristics of the 236 patients are displayed divided by gender in Table 1. The patients included 130 men (55.1%) and 106 women (44.9%). The mean age at diagnosis was 64.26 and 65.06 years respectively. The male group had higher body height (164.56 vs. 153.50 cm, $p < 0.05$), heavier body weight (64.31 vs. 56.07 kg, $p < 0.05$), but less L3 muscle index (44.35 vs. 47.39 cm^2/m^2, $p = 0.041$) compare to the female group. Women were seem to have a longer hospital stay and survival time, but did not reach statistical significance.

Considering the difference of body composition between genders, we divided the male and female patients respectively into quartiles according to the L3 muscle index. For example, Q1 presented patient with L3 index less than the 25 percentile either in male or female group. The comparisons of clinical factors among quartiles are shown in Table 2-1 and Table 2-2. We found that lower L3 muscle index was associated with serum CEA level higher than 10 mcg/L and less survival time.

We performed Kaplan-Meier analysis with the

Table 1. Basic characteristics of patients underwent surgery of colorectal cancer

Variable	All patient (n = 236)	Men (n = 130)	Women (n = 106)	p value[a]
Age of diagnosis (years)	64.62 ± 13.5[b]	64.26 ± 14.38	65.06 ± 12.43	0.654
Height (cm)	159.59 ± 8.43	164.56 ± 6.90	153.50 ± 5.72	< 0.001
Weight (kg)	60.60 ± 10.70	64.31 ± 10.34	56.07 ± 9.33	< 0.001
BMI (kg/m^2)	23.73 ± 3.39	23.67 ± 3.19	23.81 ± 3.62	0.756
L3 index (cm^2/m^2)	45.72 ± 11.40	44.35 ± 10.42	47.39 ± 12.34	0.041
Length of stay (days)	16.62 ± 8.35	15.75 ± 7.02	17.69 ± 9.65	0.076
Survival time (months)	71.15 ± 29.20	68.01 ± 31.98	75.00 ± 25.00	0.067

[a] Independent t-test. [b] Data are expressed as mean ± standard deviation for continuous variable.

Table 2-1. Skeletal muscle index and association with clinical parameters

Variable	L3 muscle index (quartile)				*p* value[a]
	Q1	Q2	Q3	Q4	
Gender					0.995
Men	33 (55.9%)	32 (54.2%)	33 (55.9%)	32 (54.2%)	
Women	26 (44.1%)	27 (45.8%)	26 (44.1%)	27 (45.8%)	
Age (years)					0.103
< 65	31 (52.5%)	32 (54.2%)	26 (44.1%)	20 (33.9%)	
≥ 65	28 (47.5%)	27 (45.8%)	33 (55.9%)	39 (66.1%)	
BMI[b] (kg/m^2)					0.602
< 18.5	2 (3.4%)	4 (6.9%)	4 (6.8%)	4 (6.9%)	
18.5-24	25 (43.1%)	33 (56.9%)	29 (49.2%)	26 (43.1%)	
≥ 24	31 (53.4%)	21 (36.2%)	26 (44.1%)	29 (50.0%)	
WBC[b] ($\times 10^3/\mu L$)	6.57 ± 1.97	7.39 ± 1.80	7.25 ± 2.62	7.05 ± 2.32	0.209
NLR[b]					0.909
< 5	29 (90.6%)	37 (86.0%)	28 (84.8%)	32 (86.5%)	
≥ 5	3 (9.4%)	6 (14.0%)	5 (15.2%)	5 (13.5%)	
CEA[b] (mcg/L)					0.036
< 10	39 (79.6%)	30 (73.2%)	44 (95.7%)	36 (83.7%)	
≥ 10	10 (20.4%)	11 (26.8%)	2 (4.3%)	7 (16.3%)	
Albumin (g/dl)					0.884
< 3.5	15 (27.3%)	19 (34.5%)	18 (31.6%)	16 (28.6%)	
≥ 3.5	40 (72.7%)	36 (65.5%)	39 (68.4%)	40 (71.4%)	
CRP[b] (mg/L)					0.878
< 10	20 (66.7%)	14 (66.7%)	14 (73.7%)	18 (75.0%)	
≥ 10	10 (33.3%)	7 (33.3%)	5 (26.3%)	6 (25.0%)	

[a] One way ANOVA and Chi-square test. [b] BMI: body mass index; WBC: white blood cell; NLR: neutrophil to lymphocyte ratio; CEA: carcinoembryonic antigen; CRP: C-reactive protein.

Table 2-2. Skeletal muscle index and association with clinical parameters

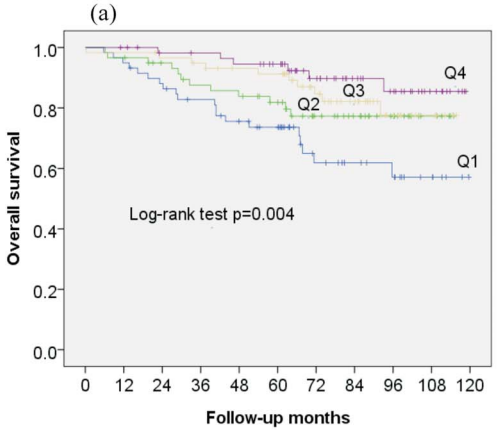
Variable	L3 muscle index (quartile)				*p* value
	Q1	Q2	Q3	Q4	
Tumor location					0.538
Colon	45 (76.3%)	50 (84.7%)	45 (76.3%)	44 (74.6%)	
Rectum	14 (23.7%)	9 (15.3%)	14 (23.7%)	15 (25.4%)	
Tumor size					0.985
< 5 cm	30 (50.8%)	32 (54.2%)	31 (52.5%)	32 (53.4%)	
≥ 5 cm	29 (49.2%)	27 (45.8%)	28 (47.5%)	27 (46.6%)	
Differentiation					0.628
Well	25 (43.1%)	21 (35.6%)	21 (36.2%)	21 (36.8%)	
Moderate	28 (48.3%)	33 (55.9%)	32 (55.2%)	35 (61.4%)	
Poor	5 (8.6%)	5 (8.5%)	5 (8.6%)	1 (1.8%)	
LVI[a]					0.690
Absent	22 (37.3%)	25 (42.4%)	23 (39.0%)	28 (47.5%)	
Present	37 (62.7%)	34 (57.6%)	36 (61.0%)	31 (52.5%)	
PI[a]					0.386
Absent	29 (49.2%)	27 (45.8%)	31 (52.5%)	36 (61.0%)	
Present	30 (50.8%)	32 (54.2%)	28 (47.5%)	23 (39.0%)	
TNM Stage					0.697
0	3 (5.1%)	3 (5.1%)	5 (8.5%)	1 (1.7%)	
1	13 (22.0%)	13 (22.0%)	13 (22.0%)	12 (20.3%)	
2	15 (25.4%)	15 (25.4%)	21 (35.6%)	21 (35.6%)	
3	28 (47.5%)	28 (47.5%)	20 (33.9%)	25 (42.4%)	
Adjuvant chemotherapy					0.871
Undone	18 (30.5%)	21 (35.6%)	18 (30.5%)	17 (28.8%)	
Done	41 (69.5%)	38 (64.4%)	41 (69.5%)	42 (71.2%)	
Complication in 30 days					0.953
Absent	50 (84.7%)	48 (81.4%)	49 (83.1%)	50 (84.7%)	
Present	9 (15.3%)	11 (18.6%)	10 (16.9%)	9 (15.3%)	
Length of stay					0.896
< 14 days	26 (44.1%)	25 (42.4%)	28 (47.5%)	24 (40.7%)	
≥ 14 days	33 (55.9%)	34 (57.6%)	31 (52.5%)	35 (59.3%)	
Survival time (months)	62.50 ± 30.86	68.61 ± 30.22	76.45 ± 25.61	77.03 ± 28.07	0.018

[a] LVI: lymphovascular invasion; PI: peri-neural invasion.

quartiles of L3 muscle index (Fig. 3-1). Patients in the Q1 group, who had lowest L3 muscle index, had significantly shorter survival time compared with Q2 to Q4 groups. According to the differences in each quartile, we defined Q1 (patient with L3 index less than the 25 percentile) as the sarcopenia group (Fig. 3-2), in which patients had worse overall survival rate than those in the non-sarcopenia group (5-year overall survival rate 61.02% vs. 76.84%; log-rank p = 0.001).

Univariate Cox proportional analysis found that worse survival was associated with sarcopenia, male gender, tumor size larger than 5 cm, presentation of lymphovascular invasion or perineural invasion and lymph nodes involvement (Table 3). In the multi-

(a)

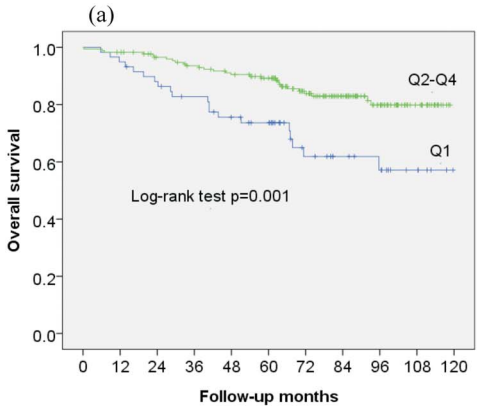


(b)

	3-year survival rate	5-year survival rate
Q1	77.97%	61.02%
Q2	79.66%	67.80%
Q3	91.52%	83.05%
Q4	89.83%	79.66%

Fig. 3-1. Kaplan-Meier curves for long-term survival according quartiles of muscle index. (a) In the left panels, Q1 represented the lowest quartile, (b) The 3-year and 5-year survival rate of each quartile.

(a)



(b)

	3-year survival rate	5-year survival rate
Sarcopenia (Q1)	77.97%	61.02%
Non-sarcopenia (Q2-4)	87.01%	76.84%

Fig. 3-2. Kaplan-Meier curves for long-term survival of sarcopenia and non-sarcopenia groups. (a) In the left panels, Q1 represented the sarcopenia group and Q2-4 represented the non-sarcopenia group, (b) The 3-year and 5-year survival rate of each group.

Table 3. Predictors of mortality in colorectal cancer

Variable	Univariate			Multivariate		
	HR	95% CI of HR	*p* value	HR	95% CI of HR	*p* value
Sarcopenia (L3 index < 25 percentile)	2.564	1.442-4.558	0.001	2.524	1.408-4.526	0.002
Male gender	1.825	1.001-3.326	0.050	2.133	1.161-3.921	0.015
Tumor size > 5 cm	3.084	1.153-3.766	0.015	1.378	0.750-2.531	0.302
Lymphovascular invasion	3.010	1.499-6.043	0.002	0.924	0.372-2.293	0.865
Peri-neural invasion	3.444	1.820-6.515	< 0.001	1.975	0.947-4.120	0.070
Lymph nodes involved (stage III disease)	1.617	1.308-2.000	< 0.001	1.465	1.120-1.916	0.005

variate Cox model, we found that sarcopenia (HR 2.524; 95% CI 1.4408-4.526; $p = 0.002$), male gender (HR 2.133; 95% CI 1.161-3.921; $p = 0.015$), and lymph nodes invasion (HR 1.465; 95% CI 1.120-1.916; $p = 0.005$) were independent predictors for patient survival.

Discussion

Sarcopenia, which is defined as the degenerative loss of skeletal muscle mass, quality, and strength, can be the result of either cachexia or other causes of weight loss such as malnutrition or malabsorption related to impaired gastrointestinal function.[8,9] This kind of muscle reduction is not uncommon in cancer patients, however, sarcopenia is rarely used as a parameter for preoperative assessment due to difficulty in measurement of quantity and quality of skeletal muscle.

In our study, we used a simplified method by using NIH Image J software to directly calculate the skeletal muscle area in CT images at routine pre-operative survey and obtain the L3 muscle index (cm^2/m^2) as representative. The obtained muscle index can be a prognostic factor to predict the prognosis of patients with stage I to III colorectal cancer before tumor resection. We found that patients with the muscle index less than the lowest quartile (Q1 group) (36.59 cm^2/m^2 in men and 36.64 cm^2/m^2 in woman as our database) had significant worse long-term survival rate. We may classify patients with the muscle index less than the first quartile as sarcopenia, which is a independent negative predictor as compare to TMN stage. By this way, we can get more prognostic information based on routine tumor survey without extra cost.

Muscle depletion has been recognized as a marker of poor prognosis in cancer patients,[3-5] implicated such as functional status,[10] chemotherapy toxicity,[11] and survival.[12] Richards et al. proposed sarcopenia in patients with colorectal cancer was related to skeletal muscle proteolysis caused by a systemic inflammatory response. This kind of muscle wasting can occur with or without loss of adipose tissue and may be independent to body weight.[6] From this point of view, sarcopenia is more like the pathological result of potential malignancy rather than nature aging.

There are several methods to quantify the degree of sarcopenia. In 1998, Baumgartner et al. performed dual-energy X-ray absorptiometry to evaluate muscle mass and established sarcopenia as appendicular skeletal muscle index (kg/m^2) being less than two standard deviations below the mean of a young reference group.[13] In 2008, Prado et al. proposed CT image analysis and discovered skeletal muscle index at 3rd lumbar spine cross section less than 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women predicted higher mortality in patients with solid tumors of the respiratory and gastrointestinal tracts.[12] Since that, CT image index became the main method to assess the skeletal muscle mass index and the values of sarcopenia were mostly based on this study. However, the ratio of muscle volume in body composition varied by race, geographical environment, and life style. The actual prevalence and reference value of sarcopenia in oriental people is seldom discussed in the past. In this study, we demonstrated not only the prognostic threshold of sarcopenia in our population but also providing a simplified method to access patients' muscle volume in daily practice.

In our population, men had more body weight but less muscle index than women, but there was no relationship in between muscle index and inflammatory makers like white blood cells count, neutrophil to the lymphocytes ratio, serum C-reactive protein. There were hypothesis that the sarcopenia is a candidate that related to chronic inflammation which induced by malignancy in patient.[6] However, from our present data, we cannot approve the association of sarcopenia to patient's chronic inflammation status that usually occurred in patient with solid malignancy.[14] JR Lieffers et al. reported sarcopenia could predict worse short-term outcome after primary resection of colorectal cancer including higher post-operative infection rate and longer length of stay.[7] In our data, complication rate within 30 days after operation was about 15.3% in sarcopenic group as compare to non-sarcopenic group which had 16.9% complication rate. All these complications include any degree of infection, ileus, and anastomosis leakage. The sarcopenic group had similar short-term complication rate and length of

stay as non-sarcopenic group which was not the same as previous report.

In our study, the most significant different in between the sarcopenic group and non-sarcopenic group was the overall survival. In the average 71 months follow-up duration, patients with the muscle index less than the first quartile experienced significant lower 5-year overall survival rate (61.02% vs. 76.84%; log-rank p = 0.001). In 2015, Yuji Miyamoto et al. used sex-specific quartiles to classify sarcopenic threshold of muscle index.[15] They observed patients in the first quartile of muscle index (less than 49.5 cm^2/m^2 in men and 42.1 cm^2/m^2 in woman) experienced significantly shorter 5-year overall survival rate (68% vs. 85% log-rank p = 0.015), compatible to our study results. However, the range of muscle index distribution was quite different.

The present study has some limitations that should be addressed. First, this is a retrospective study and all data collected from a regional institution. Second, whether skeletal muscle depletion due to the colorectal cancer candidate or other causes was difficult to determine.

Conclusions

We found that CT image based muscle index can be used to predict the long term survival in patients undergo curative intent surgical resection for stage I to III colorectal cancer. L3 muscle index less than the 25 percentile can be the prognostic threshold of sarcopenia in our population. The reason of muscle depletion in colorectal cancer patient would need further study to elucidate.

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Nil.

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原　著

利用術前肌肉質量指數預估大腸直腸癌存活率

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目的　在罹患大腸直腸癌的病人中，肌肉量的減少常被視為一項不良的預後因子。我們希望藉由術前的電腦斷層檢查來評估肌肉減少的程度，並驗證術前發現的肌減少症和大腸直腸癌術後存活率的關係。

方法　我們統計了從 2006 年 1 月到 2010 年 12 月共 236 位在基隆長庚醫院被確診為大腸直腸癌，並接受根治性切除手術的病人資料。利用美國國立衛生研究院發布的自由軟體 - Image J 來計算術前電腦斷層影像中，腰椎第三節橫截面的骨骼肌面積。此肌肉橫截面積以病人的身高做校正後可以得到肌肉質量指數。我們用肌肉質量指數來評估病人是否有肌減少症並預估其術後存活率。

結果　在我們的資料庫中，肌肉質量指數低於第一四分位數的病人 (男性低於 36.59 cm^2/m^2，女性低於 36.64 cm^2/m^2) 可視為有肌減少症。在平均 71 個月的追蹤期間，有肌減少症的病人組別有較差的五年存活率。而肌減少症對於存活率亦是獨立的變相因子。

結論　根據我們的結果，術前以電腦斷層影像計算出的肌肉質量指數可作為大腸直腸癌病人術後的預後評估因子。肌肉質量指數低於第一四分位數的病人可視為肌減少症並且有較差的五年存活率。

關鍵詞　大腸直腸癌、肌減少症、肌肉質量指數、存活率。