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ORIGINAL ARTICLE

Does body mass index impact the number of LNs harvested and influence long-term survival rate in patients with stage III colon cancer?

Yi-Hung Kuo · Kam-Fai Lee · Chih-Chien Chin · Wen-Shih Huang · Chung-Hung Yeh · Jeng-Yi Wang

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Abstract
Background The aim of this study is to evaluate whether different body mass index (BMI) values affect lymph node (LN) retrieval and whether such variations influence long–term survival in Asian patients.
Method From January 1995 to July 2003, 645 stage III colon cancer patients were enrolled in our study. Patients were stratified into four groups: Obese (BMI $\geq$ 27 kg/m^2), overweight (24 $\leq$ BMI < 27 kg/m^2), normal (18.5 $\leq$ BMI < 24 kg/m^2), and underweight (BMI < 18.5 kg/m^2).
Results Mean BMI in the cohort was 23.3 kg/m^2. Mean number of LNs harvested was 23.1, 19.5, 19.8 and 28.1 in the normal, overweight, obese and underweight groups, respectively. There was a significant difference in the mean number of LNs harvested when comparing the overweight and underweight groups to the normal group (p=0.013 and p=0.04, respectively). Females were overrepresented in the underweight group (p=0.011), and patients who had proximal colon cancers were more frequently underweight (p=0.018). The mean number of LNs harvested varied by cases of right hemicolectomy (p=0.009) and proximal cancer location (p=0.009) for different BMI groups. Multivariate analysis showed that underweight, proximal colon cancer, well- or moderately differentiated adenocarcinoma and stage IIIC cancer were significant variables for adequate LN recovery. BMI was not significantly associated with relapse-free survival (p=0.523) or overall survival (p=0.127).
Conclusion BMI is associated with LN harvest but is not an independent variable in stage III colon cancer survival.

Keywords BMI · LNs harvested · Colon cancer · Survival rate

Introduction

Colorectal cancer is one of the most common malignancies in Taiwan. According to the TNM staging system proposed by the American Joint Committee on Cancer (AJCC), the absence or presence of metastatic lymph nodes (LNs) and their number play an important role in colorectal cancer and influence cancer staging, therapy and outcome prediction. Current studies have shown that the number of total LNs harvested is an independent prognostic factor [1, 2]. LN harvest number of 12 or more is associated with increased long-term survival in stages II and III colon cancer [3]. When at least 12 LNs have been examined and all have been found to be negative, a staging of N0 is more than 90 % accurate [4]. Variations in the number of LNs harvested in colorectal specimens could be attributed to differences in anatomy, surgical technique used, use of

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Y.-H. Kuo · C.-C. Chin (✉) · W.-S. Huang · C.-H. Yeh
Division of Colon and Rectal Surgery,
Department of Surgery, Chang Gung Memorial Hospital,
6 West Chia-Pu Road, Putz City,
Chiayi 61363, Taiwan, Republic of China
e-mail: ccchin@adm.cgmh.org.tw

C.-C. Chin · W.-S. Huang · J.-Y. Wang
Graduate Institute of Clinical Medical Science,
Chang Gung University,
Taoyuan 33305, Taiwan, Republic of China

K.-F. Lee
Department of Pathology, Chang Gung Memorial Hospital,
6 West Chia-Pu Road, Putz City,
Chiayi 61363, Taiwan, Republic of China

neoadjuvant therapy for advanced rectal cancer and pathology procedures [5–8]. The differences in the number of LNs harvested seem to be multifactorial, and a few studies in Medline have assessed whether the number of LNs harvested is affected by the patient's body mass index (BMI). In 2000, Dhar et al. [9] reported that being obese or overweight influenced regional LN dissection in T2/T3 gastric cancers and that BMI was an independent predictor of disease recurrence. Only a few small population-based studies have investigated the impact of obesity on the number of LNs harvested in colon or rectal cancer surgery. LN retrieval was not affected by BMI in three of these studies [10–12]. One of them was an abstract presented at the American Society of Clinical Oncology 2006 meeting [12]. However, in two reports, the total number of lymph nodes removed decreased significantly with increasing BMI in colorectal cancer surgery [13], and there was a significant reduction in the mean number of LNs harvested in short specimens of rectal resection in obese patients [14]. The aim of our study was to evaluate whether differences in BMI influence the number of LNs harvested in stage III colon cancer in a larger population and whether differences could be found in relapse-free survival (RFS) and overall survival among different BMI groups.

Materials and method

From January 1995 to July 2003, a total of 645 patients with histologically confirmed stage III adenocarcinoma of the colon underwent elective surgery for cancer curability at Chung Gung Memorial Hospital. This is a retrospective analysis by a single institution, of a prospectively maintained data collection. All patients underwent routine hemogram, carcinoembryonic antigen (CEA) tests, colonofiberoscopy, chest X-ray, abdominal computer tomography (CT) and/or ultrasound of the liver preoperatively. At post radical resection of colon cancer, all patients were followed up by physical examination; a CEA follow-up every 3–6 months; regular chest X-ray and abdominal ultrasound and/or CT of the chest, abdomen and pelvis every year; and colonofiberoscopy every 1–3 years. In order to decrease variability of this study, cases of rectal cancer, any malignancy other than colon adenocarcinoma, emergent surgery and surgery for recurrent adenocarcinoma and metachronous or synchronous colon adenocarcinoma were excluded. Tumour location, histology and differentiation, surgical procedure and the numbers of harvested and metastatic LNs were evaluated for each patient. The surgical resection included resection of the affected segment of colon and en block resection of associated draining lymph nodes to the original level of the primary blood supply to the colonic segment. The high ligations at ileocolic and middle colic root were performed during right hemicolectomy (RH), and they were performed at the root of the inferior mesentery artery (IMA) during anterior resection (AR). During left hemicolectomy (LH), ligation of the left colic artery was done, but the IMA root was preserved to provide a blood supply to the rectosigmoid junction. All of the resection margins in each surgical procedure were 5 cm over the proximal and distal parts of the colon cancer. The specimen was fixed in 10 % formalin solution and then processed for paraffin block. Two pathologists identified the tumour and nodes by visual inspection and palpation. In this study, we did not evaluate the variations by different surgeons and pathologists. Special fat clearance, immunohistochemistry, or genetic methods were not routinely used. All patients with colon cancer were staged according to the AJCC's sixth edition TNM staging system [15]. Based on AJCC guidelines, the number of harvested or examined LNs ≥12 was defined as an adequate lymphadenectomy. Mucinous adenocarcinoma was identified if >50 % of the tumour volume was composed of mucin. Because of differences between Western and Asian populations, a BMI of ≥30 kg/m^2 in Western populations equals a BMI ≥27 kg/m^2 in the Chinese population in terms of fat component [16]. Therefore, we did not use the classifications for BMI adopted by the National Institutes of Health and the World Health Organization [39]. We instead adopted the BMI recommendation of the Department of Health Executive Yuan, R.O.C. (Taiwan). Patients were stratified into four groups: Obese (BMI ≧27 kg/m^2), overweight (24 ≤ BMI <27 kg/m^2), normal (18.5 ≤ BMI <24 kg/m^2), and underweight (BMI <18.5 kg/m^2). Our classification of BMI was similar to the report of Shibakita et al. in 2010 [13]. Patients were divided into three categories in their report; high BMI (BMI ≥24 kg/m^2), middle BMI (BMI <24 kg/m^2) and low BMI (BMI <21 kg/m^2). In our study, we evaluated the possible influence of nodal harvest in patients having different BMIs in a single institution. We stratified the 645 patients enrolled in this study by BMI into four groups: normal, overweight, obese and underweight. All patients in this study were followed up until death or September 2008. The end points of long-term study outcome were overall survival (OS) and relapse-free survival. OS was calculated by death from any aetiology. RFS was defined as the time from surgery to the first recurrence or distant metastasis.

Statistical analysis

Student's *t* test was applied to compare continuous variables, and Pearson's chi-square test was used for categorical variables. Logistic regression was used to evaluate the association between LN recovery and clinicopathological factors. Survival curves were made using the Kaplan–Meier method and were compared using the log-rank test. Cox regression was used for multivariate analyses of survival. All p values were two tailed and considered statistically significant if <0.05.

Results

A total of 645 patients (315 male, 330 female) with stage III colon cancer who underwent elective curative surgery were included in this study. The mean age of the cohort was 61.4 years. Mean BMI in the entire cohort was 23.3 kg/m^2 (range 12.8–37.7 kg/m^2). There were 332 patients (51.5 %) in the normal group, 173 patients (26.8 %) in the overweight group, 88 patients (13.6 %) in the obese group and 52 patients (8.1 %) in the underweight group. On the basis of the WHO classification, 21 patients (3.9 %) were classified into class I obesity (BMI 30–34.9 kg/m^2), and four patients into class II/III (BMI >35 kg/m^2). Eight class I and three class II/III obese patients received right hemicolectomy for proximal colon cancer. The mean number of LNs examined in class I obese patients was 18.9 (min, 9; max, 36) which was below the mean number in normal and underweight groups (23.1 and 28.1). The four class II/III obese patients had higher mean numbers of LN recovery (mean 21, min 15, and max 30). LN harvest in both classes I and II/III obesity were lower than in normal and underweight patients, but there was no statistical significance when compared with normal BMI group (data not shown). The characteristics of the patients and tumours are outlined in Table 1. More females than males were found in the underweight group (p=0.011). In terms of tumour locations, patients who had proximal colon cancers were more frequently not overweight or obese (p=0.018). Patients who were overweight and obese were less likely to have anaemia and low albumin levels in our analysis (p=0.023 and p=0.002). We achieved adequate lymphadenectomy in 520 patients of this study. Significant difference between adequate and inadequate LN retrieval was demonstrated for different BMI groups by Pearson's chi-square test (p=0.013, Table 1). Only three underweight patients had inadequate LN retrieval (5.8 % of underweight group). Among these 520 patients, node recovery was more adequate in underweight patients than in obese and overweight patients when compared to patients with normal BMI (odds ratio=3.825; 95 % CI, 1.155–12.669; p=0.028). Mean number of LNs examined in normal and underweight groups was 23.1 and 28.1, respectively, and was higher than in overweight and obese groups (Table 1). The difference in mean number of LNs examined was −3.6 (−0.6 to −6.6; p=0.013) and 5.0 (9.8–0.2, p=0.04) when comparing overweight and underweight groups to the normal BMI group (95 % CI, p value), respectively. There was no significance in the difference between LNs examined in obese vs normal BMI group (p=0.129, Table 1). Different surgical methods and tumour locations also influenced the number of LNs examined in different BMI groups (Table 2); the mean harvested numbers were 26.9 (min, 6; max, 81), 16.5 (min, 5; max, 44) and 19.8 (min, 2; max, 75) with RH, LH and AR, respectively. Factors that were significantly associated with examination of 12 or more LNs were analysed using logistic regression (Table 3). Adequate LN retrievals were more in the underweight group, when compared to the normal BMI group, (odds ratio= 3.678; 95 % CI, 1.079–12.540; p=0.037), and in cases of proximal colon vs distal colon resection (odds ratio=3.015; 95 % CI, 1.800–5.052; p<0.001). In terms of tumour differentiation, well- and moderately differentiated adenocarcinoma showed greater recovery of more than 12 LNs, as compared to poorly differentiated adenocarcinoma (odds ratio=3.834, p=0.009; and odds ratio=3.235, p=0.005 for well- and moderately differentiated tumours, respectively). Stage IIIC patients had a higher chance of ≥12 LNs recovery. Cancer histology type (adenocarcinoma, signet ring cell and mucinous) and CEA level were not factors in adequate LN recovery. In this study, 462 patients had received adjuvant chemotherapy, and others had no further therapy. There was no difference in performance of adjuvant chemotherapy in the different BMI groups (p=0.116). The 5-year RFS rate in our analysis was 70.1, 65.9, 61.1 and 59.9 % in the normal, overweight, obese and underweight groups, respectively (p= 0.523). The 5-year OS rate was 66.1, 72.1, 64.6 and 53.3 % in the normal, overweight, obese and underweight groups, respectively (p=0.127) (Fig. 1). The 5-year OS and 5-year RFS adjusted for gender also showed no difference among different BMI groups (Figs. 2 and 3). Possible prognostic factors affecting survival, including BMI, age, sex, adjuvant chemotherapy, CEA level, histology type and grade, harvested LN number and TNM-T and TNM–N stages were processed with Cox regression for multivariate analysis to identify significant variables. Age >75 years, CEA level, adjuvant chemotherapy, histology type and TNM-N1 or N2 were found to be prognostic factors for patients' RFS and OS (Tables 4 and 5). In univariate analysis, hazard ratio for OS was 1.29 (95 % CI, 0.70–2.38) and 0.538 (95 % CI, 0.08–3.85) for WHO class I and class II/III obese individuals compared with normal BMI group; there was no statistical significance (data not shown).

Discussion

Many cohort studies support a relationship between obesity and colon cancer, with the number of total harvested LNs being an independent prognostic factor. A 1.5–1.8-fold increased risk of incidence of colon cancer has been reported for obese people, and this association is stronger in the colon, especially the proximal colon, relative to the rectum [17–20]. Obese males show stronger colon cancer risk than females [21]. A possible mechanism for the association of BMI and risk of colorectal cancer could be that elevated glucose and insulin levels promote the growth of adenomatous polyps, and in turn, malignant lesions in the colon. At a molecular level, insulin, IGFs and IGF-binding protein

Table 1 Characteristics of patients, tumours and lymph node retrieval

	Normal (n=332)	Overweight (n=173)	Obese (n=88)	Underweight (n=52)	Total (n=645)	p value
Gender, M/F	165/167	90/83	46/42	14/38	315/330	0.011
Age (year)						
Mean (SD)	61.3 (14.4)	61.8 (12.8)	61.8 (13.1)	60.2 (18)	61.4 (14.2)	0.114
>75 years (%)	58 (9.0)	26 (4.0)	13 (2.0)	13 (2.0)	110 (17.1)	
≤75 years, ≥40 years (%)	241 (37.4)	137 (21.2)	69 (10.7)	31 (4.8)	478 (74.1)	
<40 years (%)	33 (5.1)	10 (1.6)	6 (0.9)	8 (1.2)	57 (8.8)	
Operative method						0.032
RH* (%)	131 (20.3)	50 (7.8)	21 (3.3)	24 (3.7)	226 (35)	
LH* (%)	20 (3.1)	10 (1.6)	6 (0.9)	2 (0.3)	38 (5.9)	
AR* (%)	181 (28.1)	113 (17.5)	61 (9.5)	26 (4.0)	381 (59.1)	
Tumour location						0.018
Proximal colon	133	51	25	24	233	
Distal colon	199	122	63	28	412	
Histologic type						0.425
Adenocarcinoma (%)	294 (45.6)	147 (22.8)	83 (12.9)	46 (7.1)	570 (88.4)	
Signet ring cell (%)	3 (0.47)	2 (0.31)	1 (0.16)	–	6 (0.9)	
Mucinous (%)	35 (5.4)	24 (3.7)	4 (0.6)	6 (0.9)	69 (10.7)	
Histologic grade						0.899
WD* (%)	47 (7.3)	24 (3.7)	8 (1.2)	7(1.1)	86 (13.3)	
MD* (%)	265 (41.1)	140 (21.7)	74 (11.5)	43 (6.7)	522 (80.9)	
PD* (%)	20 (3.1)	9 (1.4)	6 (0.9)	2 (0.3)	37 (5.7)	
Mean examined LN number (SD)	23.1 (13.2)	19.5 (10.9)	19.8 (11.4)	28.1 (15)	22.1 (12.8)	<0.001
Difference of mean examined LNs (95 % CI, p value)*	Reference	−3.6 (−0.6–−6.6, p =0.013)	−3.3 (0.6–−7.2, p=0.129)	5.0 (9.8–0.2, p=0.04)		
ELNs* ≥12 (% in each group)	269 (81)	139 (80.3)	63 (71.6)	49 (94.2)	520	0.013
ELNs <12 (% in each group)	63 (19)	34 (19.7)	25 (28.4)	3 (5.8)	125	
ELNs ≥12, OR (95 % CI, p value)	Reference	0.957 (0.602–1.524, p=0.855)	0.590 (0.344–1.011, p=0.055)	3.825 (1.155–12.669, p=0.028)		
Mean pathologic lymph node number (SD)	3.4 (3.6)	3.2 (3.1)	3.4 (2.9)	3.3 (2.4)	3.35 (3.28)	0.973
TNM-N1* (n)	228	118	61	33	440	0.891
TNM-N2* (n)	104	55	27	19	205	
T stage						0.249
T1, 2 (n)	17	15	2	5	39	
T3, 4 (n)	315	158	86	47	606	
Stage III						0.520
IIIA	15	9	2	5	31	

Table 1 (continued)

	Normal (n=332)	Overweight (n=173)		Obese (n=88)	Underweight (n=52)	Total (n=645)	p value
IIIB	213	109		59	28	409	
IIIC	104	55		27	19	205	
CEA*							0.766
CEA ≥5	136	74		41	24	275	
CEA <5	185	95		45	26	351	
Hb* (SD)	10.9 (2.5)	11.6 (2.2)		11.8 (2.4)	10.7 (2.1)	11.2 (2.4)	0.023
Hb ≥10	217	132		69	35	453	
Hb <10	114	41		19	17	191	
Albumin (SD)	3.97 (0.51)	4.10 (0.43)		4.11 (0.38)	3.79 (0.6)	4.0 (0.49)	0.002
Alb ≥3.5	271	155		81	38	545	
Alb <3.5	52	14		5	12	83	

*Abbreviations: *RH* right hemicolectomy, *LH* left hemicolectomy, *AR* anterior resection, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *ELNs* examined lymph nodes, *TNM-N1* lymph nodes mets ≤3, *TNM-N2* lymph nodes mets >3, *CEA* carcinoembryonic antigen, *Hb* haemoglobin

could all possibly be involved in these interactions [22, 23]. Insulin and IGF-I promote cell proliferation and inhibit apoptosis in cells, and they may further promote progression of micrometastases [24]. However, the influence of BMI on the outcome of colon cancer treatment remains uncertain. In a prospective study of adjuvant therapy trial for stage III colon cancer patients between April 1999 and May 2001, Meyerhardt et al. [25] analysed 1,053 of 1,264 patients to evaluate the association between BMI and risk of cancer recurrence or death during a median follow-up period of 5.3 years. The multivariate hazard ratio for DFS was 1.00 (95 % CI, 0.72–1.40) and 1.24 (95 % CI, 0.84–1.83) for WHO class I and class II/III obese individuals, respectively, compared with normal weight individuals. There were no significant differences in disease-free survival (DFS) and OS with increasing BMI in their study. There were also no significant differences in number of LNs sampled, number of positive LNs, or LN ratio. The univariate hazard ratios for OS for WHO class I and class II/III obesity in our study were also not statistically significant. In 2010, Shibakita et al. [13] found worse 5-year disease-free survival rates in lower BMI (<21 kg/m^2) and higher BMI (≥24 kg/m^2) patients. In conclusion, advanced tumour stage and fewer number of lymph nodes dissected may contribute to a worse survival rate. However, the data base of Shibakita et al. [13] included stages I–III colorectal cancer; many factors, like neoadjuvant radiotherapy and different survival rates in different stages, may affect the long-term outcome. Sinicrope et al. [26] reviewed seven colon cancer adjuvant trials sponsored by the U.S. National Cancer Institute and conducted by Mayo Clinic, North Central Cancer Treatment Group, and the Southwest Oncology Group: 4,381 patients were included in this study. There were significant associations between BMI and gender (p<0.0001) and tumour site (p=0.0144). Females were more likely to be underweight, and proximal colon cancer tended to occur more frequently in the underweight group. Obese patients, compared with normal weight patients, tended to have distal colon tumour (p=0.0575) and have more metastatic LNs (p=0.0171). Obese patients had a trend toward worse DFS (p=0.0725) and OS (p=0.0805), and underweight patients had a significantly worse OS (p=0.0258). Overweight patients had a significantly better OS rate in multivariate analysis. In our analysis for stage III colon cancer, OS and RFS were not associated with BMI even though there was a significant difference in LN recovery among the different BMI groups. However, we also found a trend toward worse OS in the underweight group and worse RFS in underweight males. The highest 5-year OS, 72.1 %, was also observed in overweight patients. Being underweight may reflect underlying comorbidities or a preoperative deconditional status, which may increase mortality risk. On the other hand, being overweight may be adaptive to stress and may preserve immune

Table 2 Mean lymph node retrieval in different BMI groups and tumour locations

Mean ELN* (min, max) in different BMI groups					
	Normal (n=332)	Overweight (n=173)	Obese (n=88)	Underweight (n=52)	p value
Operations					
RH*	27.23 (6, 71)	22.10 (8, 53)	30.48 (7, 62)	32.29 (11, 81)	0.009
n=226	131	50	21	24	
LH*	17.50 (8, 44)	15.60 (5, 26)	15.50 (11, 19)	13.50 (13, 14)	0.849
n=38	20	10	6	2	
AR*	20.76 (2, 75)	18.73 (3, 65)	16.59 (2, 40)	25.35 (5, 54)	0.005
n=381	181	113	61	26	
Total=645					
Tumour locations					
PC*	27.15 (6, 71)	21.76 (7, 53)	28.72 (7, 62)	32.29 (11, 81)	0.009
n=233	133	51	25	24	
DC*	20.42 (2, 75)	18.59 (3, 65)	16.30 (2, 40)	24.50 (5, 54)	0.006
n=412	199	122	63	28	
Total=645					

*Abbreviations: *ELN* examined lymph node, *PC* proximal colon, *DC* distal colon, *RH* right hemicolectomy, *LH* left hemicolectomy, *AR* anterior resection

function. Being overweight may confer proactive effects, a phenomenon described as obesity paradox [27]. These relations of the obesity paradox and mortality have been observed and discussed in patients with congestive heart failure, hypertension, coronary heart disease and pulmonary embolism [28, 29]. Actually, BMI does not discriminate between the contribution of fat and muscle to body weight. In some studies examining the relationship between BMI and risk of death, overweight people without a history of cancer were found to have the lowest mortality [30, 31]. In terms of the association of BMI with colon cancer survival rate, our result was different from that of Sinicrope et al. [26]. This may be a result of a smaller population in our analysis (patient number, 645), case limitation in stage III colon cancer and different classification of obesity (based on recommendation of BMI at Department of Health Executive Yuan, R.O.C. Taiwan). However, our other findings were similar to those of Sinicrope et al. [26] in that females were overrepresented in the underweight group (p=0.011 in our study), and patients who had proximal colon cancers were more frequently not overweight or obese (p=0.018 in our study). Moreover, overweight and obese patients also had anaemia less frequently (p=0.023 in our study) and more frequently had normal albumin levels (p=0.002) in our analysis. Patients' symptoms can accurately predict the site of colon cancers. Changes in bowel motions such as diarrhoea or constipation (p<0.0024) and rectal bleeding (p< 0.0001) were significantly associated with distal colon cancer. Microanaemia was significantly associated with proximal colon cancer (p<0.0001) [32]. We speculated that patients with proximal colon cancer were easily underweight and therefore anaemia and low albuminaemia were significantly associated with different BMI. Deconditional status in different cancer locations may possibly explain, at

Table 3 Results of binary logistic regression model to identify significant variables of adequate lymph node recovery (≥12 LNs harvested)

Variable	Category	OR	95.0 % CI	p value
BMI groups	Overweight vs normal	0.995	0.613–1.615	0.984
	Obese vs normal	0.602	0.344–1.053	0.075
	Underweight vs normal	3.678	1.079–12.540	0.037
Tumour locations	Proximal vs distal	3.015	1.800–5.052	<0.001
CEA	<5 vs ≥5	1.004	0.660–1.528	0.985
Histologic grade	WD vs PD	3.834	1.395–10.541	0.009
	MD vs PD	3.235	1.414–7.401	0.005
Histology type	Signet ring cell vs adenocarcinoma	0.805	0.118–5.493	0.825
	Mucinous vs adenocarcinoma	1.158	0.533–2.519	0.711
Stage III	IIIA vs IIIC	0.368	0.144–0.942	0.037
	IIIB vs IIIC	0.573	0.354–0.929	0.024

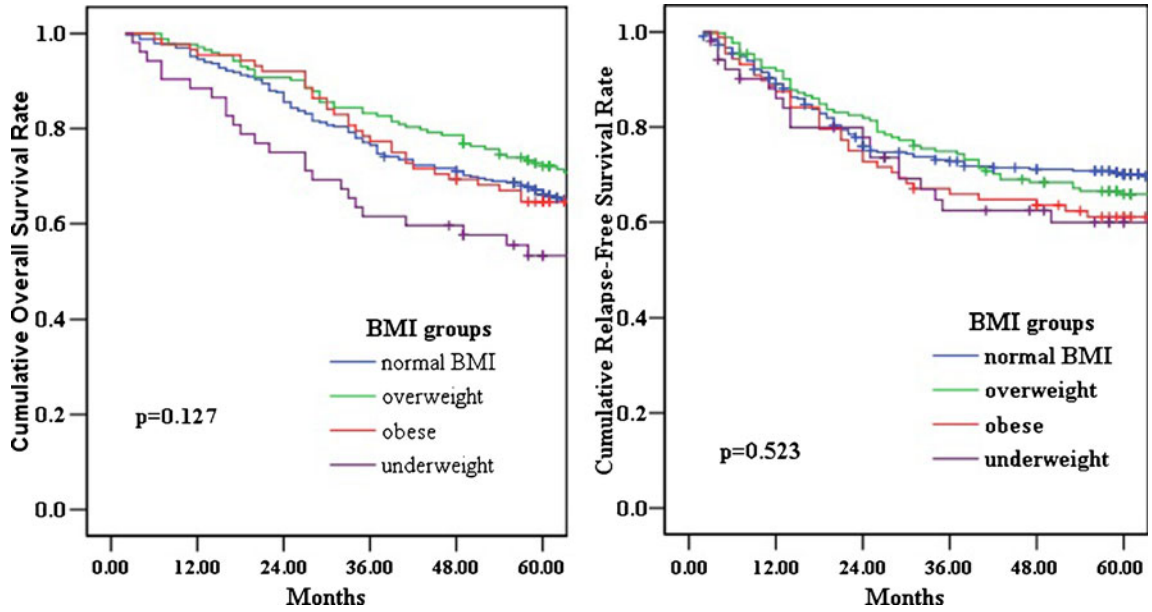

Fig. 1 Kaplan–Meier 5 year OS (*left*) and RFS (*right*) curve of stage III patients stratified by BMI. Comparisons between groups were performed by log-rank test

least in part, why patients with proximal colon cancer tend to be underweight and have anaemia and low albuminaemia in our study.

Furthermore, our findings are consistent with those of Shibakita et al. [13] and Laura et al. [33] who described a higher nodal yield in nonobese colon cancer patients compared with obese cancer patients. In our findings, LN harvest was significantly higher in underweight patients. Several studies have addressed the survival benefit of adequate nodal examination. The 5-year survival rates varied in stage II cancer patients based on the number of nodes harvested [34]. Le Voyer et al. [34] found that survival rates were 73, 80 and 87 % in patients with fewer than ten nodes harvested, 11–20 nodes harvested and over 20 nodes harvested, respectively. In another study including 2,056 patients from January 1998 to December 2003, Chen et al. [3] described that harvest of more than 12 LNs was associated with increased long-term survival in stages II and III colon cancer patients at a single institution. The effect of number of nodes examined on survival was significant in a multivariate Cox regression (odds ratio=1.58). However, even though higher LN harvest was proved in the underweight group, LN harvest in different BMI groups showed no influence on RFS or OS in our study. We reviewed other

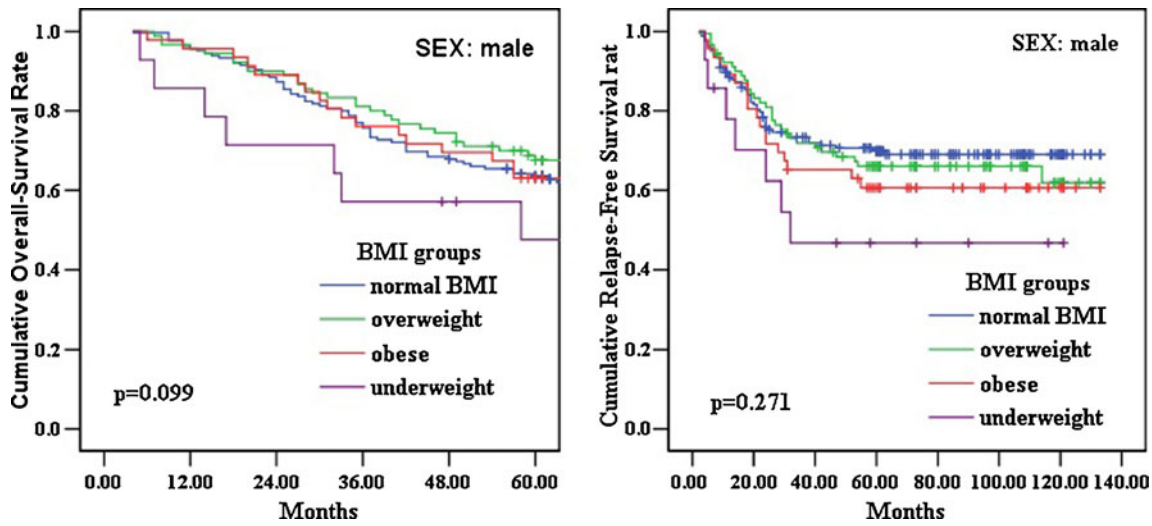

Fig. 2 Kaplan–Meier 5 year OS (*left*) and RFS (*right*) curve of male patients stratified by BMI. Comparisons between groups were performed by log-rank test

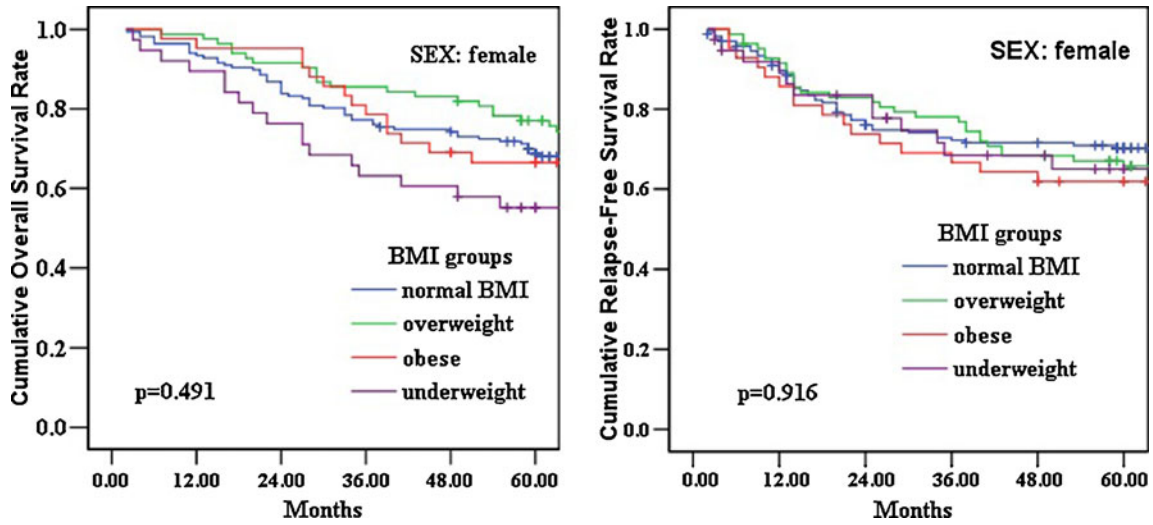

Fig. 3 Kaplan–Meier 5 year OS (*left*) and RFS (*right*) curve of female patients stratified by BMI. Comparisons between groups were performed by log-rank test

studies in stage III cancer patients and found contradictory results. The Italian National Intergroup Trial for Adjuvant Therapy on Colon Cancer study failed to find an association between number of LNs examined and survival in 1,613 stage III patients [35]. In a study of 738 stage III patients, there was also no difference in survival rates in patients with <6, 6–11 and ≥12 nodes harvested [36]. In our study, the number of harvested LNs ≥12 or <12 had no significant effect on 5-year RFS (odds ratio=1.20) or 5-year OS (odds ratio=1.16) of stage III colon cancer in a multivariate Cox model. Therefore, in stage III colon cancer, variation of LN harvest in different BMI cases probably contributed less to patient's survival even if a significant relation existed between BMI and LN harvested in our analysis. With regard to different colon cancer stage, the number of LNs harvested may not always be a predictive factor.

In our study, patients with proximal colon cancer were more likely to be underweight, and mean node recovery was different for proximal and distal colon cancer resections (26.9 and 19.5, respectively; $p<0.001$; data not shown). A significant difference in mean examined LNs was noted when the underweight group was compared to the normal

Table 4 Results of Cox regression hazard model to identify multivariate of RFS

Variable	Category	HR	95.0 % CI	*p* value
BMI groups				0.237
	Overweight vs normal	0.871	0.647–1.171	0.360
	Obese vs normal	0.989	0.691–1.414	0.950
	Underweight vs normal	1.420	0.924–2.180	0.109
Age				0.017
	≤75, ≥40 vs <40 years	1.403	0.848–2.322	0.188
	>75 vs <40 years	2.036	1.167–3.551	0.012
Sex	Female vs male	0.849	0.664–1.087	0.195
Adjuvant chemotherapy	Yes vs no	0.659	0.496–0.874	0.004
CEA	<5 vs ≥5	0.589	0.461–0.752	<0.001
Histology type				0.024
	Signet ring cell vs adenocarcinoma	3.090	1.156–8.261	0.025
	Mucinous vs adenocarcinoma	1.401	0.953–2.058	0.086
Histologic grade				0.156
	WD* vs PD*	0.576	0.319–1.039	0.067
	MD* vs PD*	0.636	0.389–1.042	0.073
Harvested LN	<12 vs ≥12	1.200	0.889–1.620	0.233
TNM-N	N1* vs N2*	0.562	0.435–0.726	<0.001
T stage	T1,T2 vs T3, T4	0.553	0.291–1.053	0.072

Table 5 Results of Cox regression hazard model to identify multivariate of OS

Variable	Category	HR	95.0 % CI	*p* value
BMI groups				0.125
	Overweight vs normal	0.836	0.616–1.135	0.251
	Obese vs normal	0.955	0.662–1.376	0.804
	Underweight vs normal	1.496	0.965–2.319	0.071
Age				0.005
	≤75, ≥40 vs <40 years	1.382	0.830–2.301	0.214
	>75 vs <40 years	2.175	1.239–3.817	0.007
Sex	Female vs male	0.867	0.673–1.116	0.267
Adjuvant chemotherapy	Yes vs no	0.610	0.457–0.814	0.001
CEA	<5 vs ≥5	0.638	0.497–0.819	<0.001
Histology type				0.026
	Signet ring cell vs adenocarcinoma	2.866	1.069–7.683	0.036
	Mucinous vs adenocarcinoma	1.456	0.985–2.151	0.059
Histologic grade				0.106
	WD* vs PD*	0.585	0.325–1.054	0.074
	MD* vs PD*	0.589	0.360–0.964	0.035
Harvested LN	<12 vs ≥12	1.159	0.849–1.581	0.353
TNM-N	N1* vs N2*	0.557	0.429–0.724	<0.001
T stage	T1,T2 vs T3, T4	0.444	0.217–0.907	0.026

BMI group (Table 1, $p=0.04$). In order to evaluate whether BMI or tumour location had a more significant influence on LN recovery, we used two-way ANOVA. Tumour location had a major influence on the number of LNs harvested. Consistent with other reports, we found that higher numbers of LNs were harvested in right side colon cancer [35, 37]. The fact that the number of class I–III obesity cases was limited and that 11 of these patients (11/25, 44 %) had proximal colon cancer may be why LN retrieval in WHO class I and II/III obesity in our study showed no significant difference when compared with the normal BMI group. Bilimoria et al. [38] presented an average of 12 nodes harvested in right side colectomy, compared to eight nodes in left side colectomy ($p<0.0001$). The length of the specimen is another possible factor affecting LN recovery. A significant difference was presented in LN recovery from specimens longer than and shorter than 23 cm [11]. Gorog et al. [10] found significantly lower node recovery in obese vs nonobese patients undergoing short segment rectal cancer surgery. Although we did not analyse the length of the specimen in different tumour locations, we found that cases of right hemicolectomy generally had longer specimens and included wider mesenteric tissue than cases of anterior resection. Patients who had proximal colon cancers were more frequently not overweight or obese in our study ($p=0.018$, Table 1); therefore, the underweight group had a higher rate of LN retrieval; this was probably the real cause for the differences in LN recovery in different BMI of stage III colon cancer observed in our study.

Additionally, pathologists identified the tumour and nodes by visual inspection and palpation in our institution. We supposed that more fat tissue in the mesocolon of obese patients may result in difficult palpation and inspection of lymph nodes from specimens. The pathologists and surgeons were bias factors in this study because we did not classify these by different pathologists and surgeons. The training or experience of pathologist or pathology assistant can dramatically affect lymph node harvests [40]. In that study, the mean number of harvested LNs increased to 18.4–20.7, and the percentage of specimens achieving 12 LNs was 83–87 %. Both of the improvements were statistically significant ($p<0.00001$, *t* test). In our institution, pathology work-up is conducted by a team of two pathologists who have been responsible for colorectal cancer for over 10 years. Also, the effect of surgeon volume in our study was not analysed because surgical procedures have been well defined in colorectal surgery. A higher number of curative colon cancer resections performed in a year by a surgeon is also not linked to a higher rate of node retrieval [41]. In univariate and multivariate analyses of this report, surgeon, pathologist and pathological technician were not statistically significant.

Conclusions

The results of our institutional study suggest that it is reasonable to expect a greater number of LNs to be harvested

from underweight patients undergoing colon cancer surgery. However, the differences in LN recovery across different BMI groups may be due to an association between BMI and tumour location. Patients who had proximal colon cancer were more likely to be underweight, and more LNs could be harvested with right hemicolectomy. BMI is a partial predictor of LN harvest but not a prognostic factor for the long-term survival of stage III colon cancer patients.

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