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Research Article

Complete Mesocolic Excision for Right Colon Cancer Treatment in Elderly Patients: Retrospective Analysis of Oncological Outcomes

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Abstract

Background: Complete Mesocolic Excision has emerged as the best therapeutic approach for right colon cancer in the adult population. This surgery is based on central vascular ligation and complete mesocolic excision with a large frame of mesocolon. However, despite the widespread of colon cancer in the elderly population, the safety and the benefits of CME in the elderly are poorly known. The frailty of these patients and their comorbidities add more complexity to this kind of surgery, that is demanding also in the adults.

Aim: Purpose of this study is to determine the correlation of CME with the oncological outcomes in the elderly patients.

Methods: We retrospectively analysed data of 152 elderly patients in stage I-III who underwent surgery for right colon cancer between 2011 and 2014 in a single general hospital. 94 patients were treated with CME surgery, while in 58 patients with non CME surgery. We considered as endpoints: 5-years Overall Survival, 5-years DFS, the relationship with local recurrence, the prognostic role of the number of harvested lymphnodes, and the correlation with postoperative complications. Statistical analysis was carried out with MEDCALC and we used Kaplan Meier curves, multivariate analysis with Cox regression, T-student for unpaired data and the Mann-Whitney test.

Results: Basing on the results, after statistical analysis, CME is related to a better oncological outcome in the treated patients. CME patients showed a better median survival (54, 5 vs 51, 2 months in non CME group). CME is independent predictive factor for 5 years survival. Analysing data of population by stage, CME was associated with a better median survival, especially in patients presenting with locally advanced stage (55, 71 vs 45, 88 months). CME is associated also with a better DFS (52, 63 vs 46, 0 months). CME is an independent predictive factor for 5-years DFS. CME surgery is also associated to a lower local recurrence rate compared to traditional surgery (0 % vs 5, 1 %). CME surgery allows also a better staging procedure, through an higher nodal harvest, meeting the concept of "stage migration". CME is a safe surgery compared to the traditional one (Clavien Dindo ≥3 5, 41 % vs 1, 72 % p>0.05).

Conclusion: CME in the elderly is a safe and feasible procedure for the treatment of right colon cancer; it offers better oncological outcomes than traditional lymphadenectomy and gives a more accurate staging.

Keywords: Colorectal cancer; Complete mesocolic excision; Lymphadenectomy; Right colon cancer

Introduction

Colo-rectal cancer is the third most common cancer in Europe and remains one of the major causes of morbility and mortality despite the significant improvements in its management. Hohenberg et al, following the oncologic principles of Total Mesorectal Excision [1,2], proposed Complete Mesocolic Excision (CME) with central vascular ligation, emphasizing the mesocolic plane dissection in the treatment of right colon cancer. The principles of this technique add more complexity to the surgery with the need of more comprehension of the applied vascular anatomy. CME is considered the "state of art" in locally advanced

right colon cancer treatment for its oncological outcomes in the adult population. However data about CME in the elderly patient are lacking in literature. Traditionally surgical treatment of colon cancer in the elderly patient is limited by patient's comorbilities and operative risk. The comorbilities of this population could make more demanding the management of a surgical complication. Therefore in the elderly open time-sparing surgery was performed with segmental resections and non standardized lymphadenectomy, avoiding vascular trauma and subsequent risks on tissue trophism. This work considers the long term oncological outcomes of two elderly (Age≥70 yrs) groups [3-5]. The rationale of this study stands on the increased life expectancy (in Italy 85 years for women and 82 years for men), fitness, cognitive abilities of the actual elderly population. We evaluate the feasibility, the advantages and the safety in the exposure of elderly population affected by right colon cancer to a more demanding surgery.

Study Design

Materials and Methods

We retrospectively analyzed data of 152 elderly patients (Tables 1 and 2) who underwent surgery for right colon cancer between 2011 and 2014. We defined as "elderly " patients over 70 years. Tumours' location was in ileocaecal valve, ascending colon, hepatic flexure, mid-transverse colon. Histological diagnosis was obtained with pancolonscopy and biopsy. All patients received an abdomino-pelvic CT scan with contrast for staging (in doubtful cases patients were studied by PET/CT scan). Chest CT scan was performed just in suspicious cases of lung metastases. Tumour's location was confirmed pairing endoscopic data with intraoperative assessment. Surgical treatments included :open or laparoscopical standard right hemicolectomy and extended right hemicolectomy. 94 patients (Group 1) were treated with the Complete Mesocolic Excision (CME), while in 58 patients (Group 2) with a standard lymphadenectomy. The criteria leading us to include patients in CME group were applied basing on the surgical procedure with right-antero-lateral dissection of fatty-lymphatic tissue around superior mesenteric vein, central vascular ligation and complete dissection of mesocolic root preserving Fredet's fascia. Lack of these criteria brought the inclusion in Group 2. Patients' comorbidities were stratified according to ASA score classification (ASA I : 23, 40% vs 20, 68% ; ASA II :29, 78% vs 43, 10%; ASA III 40, 42% vs 31, 03 ; ASA IV 6, 38 % vs 5, 17%). ASA score was considered a synthetic index to summarize patients' comorbilities and to stratify population. Patient's comorbilities are also shown in Table 3. Median age was 74, 47 years in Group 1 and 76, 18 years in Group 2. Median BMI was 25, 39 in Group 1 and 23, 81 in Group 2. We included patients in stage I, II, III (according to TNM VIII ed), who underwent radical elective surgery with diagnostic lymphadenectomy (harvested lymphnodes ≥12). We excluded patients in stage IV and patient presenting with obstruction or perforation. Elderly patients with good performance status followed an adjuvant chemotherapy (FOLFOX 4 or FLOX schedule), when indicated. Alternatively they took oral fluoropiridines if they had poor performance status or platinum intolerance. In Group 1 36 of 94 patients (38, 29 %) received adjuvant chemotherapy while in Group 2 18 of 58 patients (31, 03 %). The median follow up was 56, 72 ±22, 53 months. We considered as follow up the last instrumental restaging exam (CT-scan or PET-CT) in patients with impairing comorbidities preventing them from a regular follow up. In order to evaluate the time of local or distant recurrence we considered the first clearly diagnostic radiological exam. In doubtful cases this time was evaluated considering a second confirmatory radiological exam (both follow up or other radiological investigation). Mortality of all patients was cancer related . We excluded from our database patients who died prematurely despite the oncological stage because of their comorbilities . Basing on this assumption mortality has to be intended as completely cancer related. See also in Table 3 median 5 years OS stratified according the most common copathologies.

	GROUP 1 (CME +)	GROUP 2 (CME-)	OS (months)	P value
AGE	74,47 aa	76,18 aa		
SEX				
M	47/94 (50%)	29/58 (50%)	58,34±1,02 vs 50,34±2,99	P<0,01
F	47/94 (50%)	29/58 (50%)	51,85±2,48 vs 52,65±2,89	P<0,01
BMI (media)	25,39	23,81		
BMI< 25	56/94(59,57%)	42/58 (72,41%)	52,21±16,94 vs 51,80±15,03	P=0,90 P=0,61
BMI> 25	38/94(40,42%)	16/58 (27,58%)	57,44±7,83 vs 50,68±18,00	P=0,06 P<0,01
COMORBILITIES (ASA)				
ASA I	23,40% (22/94)	20,68% (12/58)	59±4,69 vs50,41±18,57	P=0,04
ASA II	29,78 % (28/94)	43,10% (25/58)	54,28±15,40 vs 55,56±9,81	P=0.72
ASA III	40,42% (38/94)	31,03% (18/58)	50,78±16,98 vs 49,44±17,88	P=0,78
ASA IV	6,38 % (6/94)	5,17% (3/58)	59,83±0,40 vs 34,33±24,58	P=0.02
STAGE				
I	14	10	58,42±1,57 vs 58,7±1,30	
II	49	22	52,61±2,37 vs 54,86±2,70	
III	31	26	55,71±2,18 vs 45,88±3,72	P<0,05
NODES				
Nodal Harvest	42,47±13,85	26,27±12,15		
GRADING				
G1	13/94 (13,82 %)	8/58 (13,79 %)	58,07±6,08 vs 55,75±12,02	P=0.53 P=0,17
G2	66/94 (70,21 %)	38/58 (65,51 %)	54,66±14,07 vs 51,76±15,50	P=0,33 P=0,06
G3	15/94 (15,95%)	12/58 (20,68 %)	49,60±18,60 vs 47,83±18,90	P=0,80 P=0,63
LOCAL RECURRENCE	0 %	5,1 %		P=0,02
COMPLICATIONS				
Clavien-Dindo 1	10,63 % (10/94)	6,89% (4/58)		
Clavien-Dindo 2	11,70 % (11/94)	12,06 % (7/58)	22,4 % vs 18,96 %	P=0,25
Clavien-Dindo 3	3,19 % (3/94)	1,72 % (1/58)		
Clavien-Dindo 4	2,12 % (2/94)	0% (0/58)	5,31 % vs 1,72 %	P=0,26
ADIUVANT CT	36/94 (38,29 %)	19/58 (32,75 %)	55,02±13,36 vs 53,00±14,86	P=0,60 P=0,21

Table 1: Analyzed data of 152 elderly patients.

	GROUP 1 (CME +)	GROUP 2 (CME-)	DFS(mo.)	P value
AGE	74,47 aa	76,18 aa		
SEX				
M	47/94 (50%)	29/58 (50%)	54,51±13,75 vs 45,58±21,71	P<0,01
F	47/94 (50%)	29/58 (50%)	51,66±17,72 vs 47,06±22,31	P<0,01
BMI (median)	25,39	23,81		
BMI<25	56/94(59,57%)	42/58 (72,41%)	49,33±19,90 vs 49,83±18,44	P=0,90 P=0,61
BMI>25	38/94(40,42%)	16/58 (27,58%)	56,63±9,92 vs 38,75±25,10	P=0,06 P<0,01
STAGE				
I	14	10	58,42±1,57 vs 58,7±1,3	
II	49	22	51±2,6 vs 48,31±4,1	
III	31	26	50,96±3,11 vs 41,0±4,49	P<0,05
NODAL HARVEST	42,47±13,85	26,27±12,15		
GRADING				
G1	13/94 (13,82%)	8/58 (13,79%)	58,07±6,08 vs 50,87±16,94	P=0,53 P=0,17
G2	66/94 (70,21%)	38/58 (65,51%)	54,06±15,14 vs 47,60±20,85	P=0,33 P=0,06
G3	15/94 (15,95%)	12/58 (20,68%)	45,80±22,37 vs 43,50±23,20	P=0,80 P=0,63
LOCAL RECURRENCE	0%	5,1%		P=0,02
ADJUVANT CT	36/94 (38,29%)	19/58 (32,75%)	51,47±17,71 vs 44,57±22,72	P=0,60 P=0,21

Table 2: Analyzed data of 152 elderly patients.

COMORBILITIES	CME + (94)	CME- (58)	5-years OS
Hypertension	39/94	31/58	54,02 Vs 53,77 months p>0,05
Diabetes	17/94	5/58	57,70 vs 46,6 months p=0,05
Chronic Kidney Disease	2/94	0	
Atrial Fibrillation	8/94	6/58	59,5 vs 40,16 months p<0,01
Ischemic heart disease	12/94	6/58	59,25 vs 47,08 months p>0,05
Pacemaker	3/94	4/58	
Obesity	6/94	2/58	
Stroke	2/94	2/58	
Osteoporosis	2/94	1/58	
HCV related Hepatopathy	6/94	6/58	32,16 vs 49,83 months p>0,05
Benign Prostatic Hyperplasia	4/94	3/58	
Tireopathy	3/94	1/58	
Chronic Obstructive Pulmonary Disease	3/94	2/58	48,66 vs 60 months p=0,05
Hematologic Diseases	1/94	2/58	

Table 3: Patient's comorbilities.

Statistical Analysis

Statistical analysis was carried on using MedCalc as software. We tested the data with Kaplan Meier curves, Chi squared test, Cox regression model for multivariate analysis, T student for unpaired data, Mann-Whitney test.

Endpoints

Endpoints included: 5-years Overall Survival (OS), 5-years Disease Free Survival, local recurrence rate, the prognostic role of the number of harvested lymphnodes, and the correlation between CME and postoperative complications (grouped by Clavien Dindo Score). Secondary endpoints were : relation between the number of harvested lymphnodes with Overall Survival and Disease Free Survival, the role of Lymph Node Ratio (LNR) as prognostic factor.

Results

5 years Overall Survival

In Group 1 (CME surgery) 72 of 94 patients were alive after 5 years (76, 6 %), while 22 (23, 4 %) died. In Group 2 (Conventional Lymphadenectomy) 35 of 58 patients were alive after 5 years (60, 3 %) while 23 (39, 7 %) died. According to Kaplan-Meier's curves Group 1 showed a median survival of 54, 5±1, 45 months, compared to 51, 2±2, 05 months, observed in Group 2. This difference was statisticaly significant (p=0, 025), HR 2, 14 for Group 2. (Figure 1). Applying multivariate analysis (Cox regression model with covariates staging, grading, lymph node harvest) CME was an independent predictive factor for 5-years overall survival (p=0, 04) (Figure 2). This data is confirmed also with ASA score, use of adjuvant chemotherapy, staging (p=0, 03) (Figure 3).

According subgroups based on clinical stage:

In Group 1 14 patients were in stage I (13 alive and 1 dead for cancer unrelated causes), 49 patients were in stage II (33 living after 5 years, 16 dead for cancer related causes), 31 patients were in stage III (26 living and 5 dead for cancer related causes after 5 years). In Group 2 10 patients were in stage I (9 living and 1 dead for cancer unrelated causes), 22 patients were in stage II (14 living after 5 years and 8 dead for cancer related causes), 26 patients were in stage III (13 alive and 13 dead for cancer related causes).

i. Comparing survival data of the two groups, according to stage, with Kaplan Meier's curve we observed that : 1.in stage I the median survival time in Group I was 58, 42±1, 57 months while it was 58, 7±1, 30 months in Group 2 (p=0.83) (Figure 5)

ii. in stage II the median survival time in Group 1 was 52, 61±2, 37 months vs 54, 86 ± 2, 70 months of Group 2 (p=0.97) (Figure 6).

iii. in stage III the median survival time in Group 1 was 55, 71±2, 18 mesi vs 45, 88±3, 72 months of Group 2. (p=0, 01, HR 0, 28 vs 3, 48) (Figure 7).

These data collected and analyzed cumulatively for stages I-III were statistically significant (p=0.025) (Figure 4). Complete Mesocolic Excision is associated with an increase of 5 years survival rate, especially in locally advanced stage.

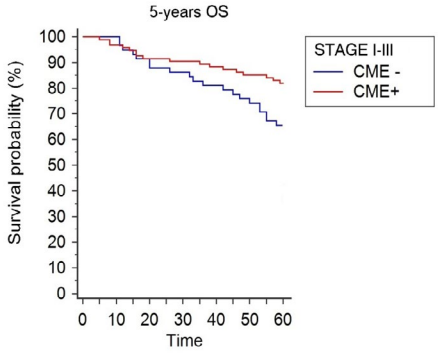

Figure 1: Correlation between CME and 5-years overall survival.

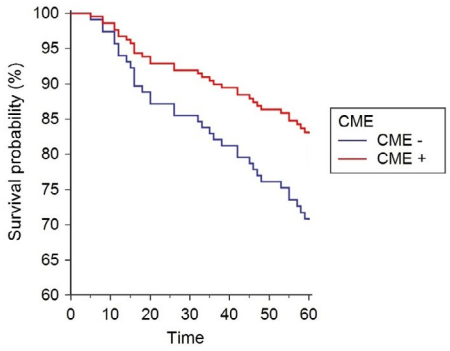

Figure 2: Multivariate analysis of CME group and non CME group (covariates : staging, grading, nodal harvest).

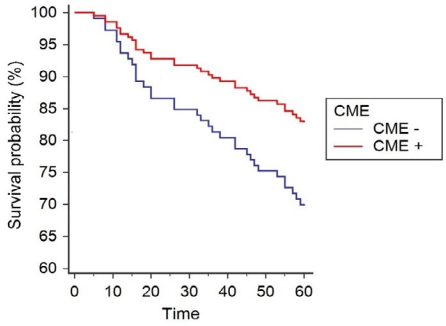

Figure 3: Multivariate analysis of CME group and non CME group (covariates : ASA score, adjuvant CT, stage).

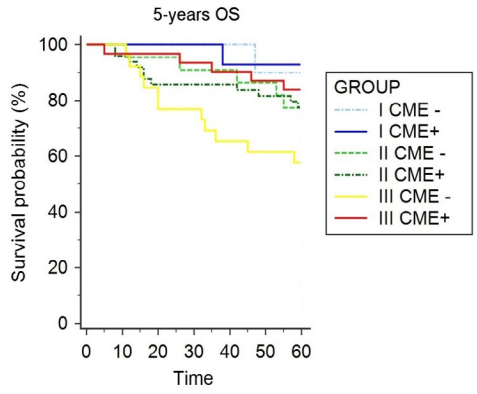

Figure 4: Correlation between CME and 5-years survival according by stage.

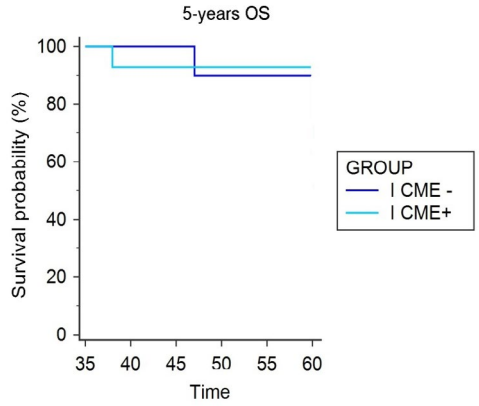

Figure 5: Correlation between CME and 5 years overall survival in stage I.

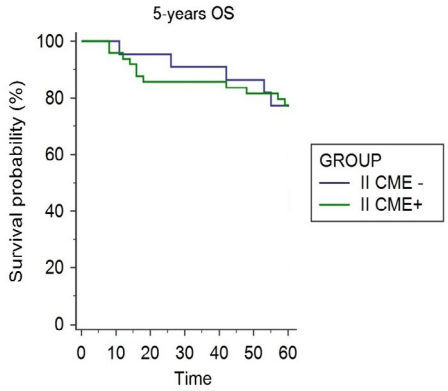

Figure 6: Correlation between CME and 5 years overall survival in stage II.

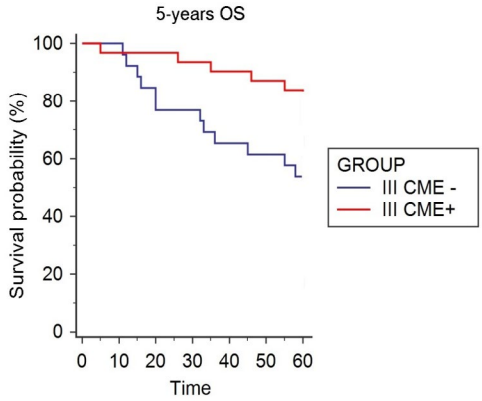

Figure 7: Correlation between CME and 5 years overall survival in stage III.

5-years Disease Free Survival

In Group 1 79 (84, 04 %) of 94 patients were disease-free after 5 years and 15 of 94 (15, 9%) relapsed during follow up (distant recurrence). In Group 2 45 (77, 58 %) of 58 patients were disease-free after 5 years, 13 of 58 (22, 4 %) relapsed (3 had local recurrence and 10 distant recurrence). In Group 1 the median 5yrs-DFS was 52, 63±1, 69 months, while in Group 2 it was 46, 0±2, 73 months (p=0, 03) (see Kaplan Meier's curves Figure 8). Analyzing data by stage we observed, in Group 1 : in stage I, 14 disease free patients after 5 years ;in stage II 49 patients, 41 (83, 67 %) disease free and 8 (16, 33 %) with distant recurrence ;in stage III 31 patients, 24 disease free (77, 42 %) and 7 (22, 58 %) with a distant recurrence. In Group 2 there were : in stage I 10 disease free patients after 5 years, in stage II 22 patients, 19 disease free (86, 36 %), 3 with distant recurrence (13, 64%), in stage III 26 patients, 16 disease free (61, 54%), 3 with local recurrence (11, 54%), 7 with distant recurrence (26, 92 %). Comparing by stage data on median 5 years disease-free survival, we observed better and statistically significant (p=0, 04) outcomes for patients in Group 1 : in stage I (58, 42±1, 57 in Group 1 vs 58, 7±1, 3 months in Group 2) ; in stage II (51±2, 6 vs 48, 31±4, 1 months in Group 2) ; in stage III (50, 96±3, 11 vs 41, 0±4, 49 months). (Figure 9). CME is thus associated with a longer disease free survival. After a multivariate analysis (covariates BMI, grading, nodes harvested, adjuvant chemotherapy), CME can be considered as an independent predictive factor for 5 yrs-DFS (p<0, 01) (Figure 10). The local recurrence rate in Group 1 was 0% while in Group 2 was 5, 1 % (p=0, 02, χ2-test).

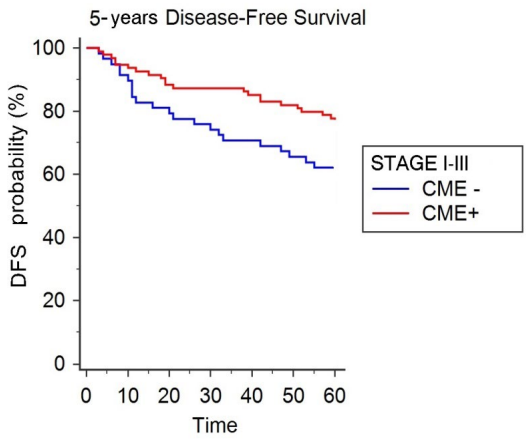

Figure 8: Correlation between CME and 5-years Disease Free Survival.

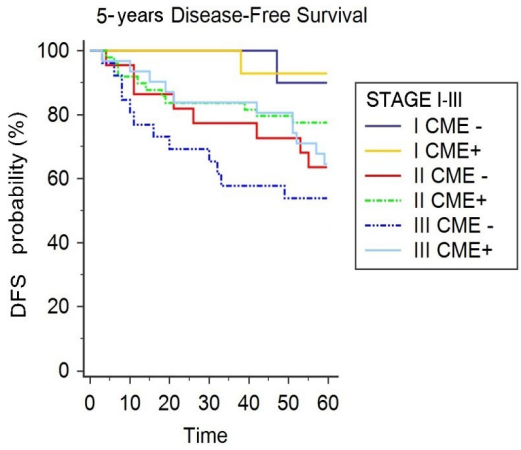

Figure 9: Correlation between CME and 5-years Disease-Free Survival according by stage.

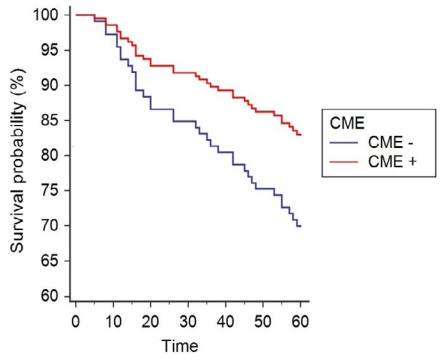

Figure 10: Multivariate analysis CME vs disease free survival (covariates :BMI, staging, nodal harvest, adjuvant CT).

Nodal Harvest

In CME group a median number of 42, 47±13, 85 nodes were isolated, while in "non CME" group the median number of harvested nodes was 26, 27±12, 15 (p<0, 0001, Mann-Whitney test) (Figure 11). The median number of pathologic harvested nodes was in Group 1 1, 50 ±3, 38 and in Group 2 1, 58±3, 06 (p=0.23). We also considered the metastatic Lymph Node Ratio (mLNR) and then regrouped the data into 4 categories, according mLNR interval (a : <0, 05 ;b: 0, 05-0, 19;c: 0, 20-0, 39;d:0, 40-1, 00). Median mLNR was 0, 11 in CME Group and 0, 20 in non CME Group. Basing on the categories, we reported above, Group 1 was made up of : 13 cases with mLNR< 0, 05, 12 cases with mLNR between 0, 05 and 0, 19, 5 cases with mLNR between 0, 20 and 0, 39 ; 1 case with mLNR between 0, 40 and 1, 00. In Group 2 we described : 7 cases with mLNR <0, 05 ; 8 cases with mLNR between 0, 05 and 0, 19; 3 cases with mLNR between 0, 20 and 0, 39 ; 3 cases between with 0, 40 and 1, 00.

We regrouped the cases in mLNR categories for each Group, adding patients in mLNR a subgroup with those in mLNR b (mLNR ≤0, 19), and patients in mLNRc subgroup with those in mLNR d subgroup (mLNR ≥0, 20). In CME Group patients with mLNR ≤0, 19 (25 cases) reported a median survival of 56, 8±8, 55 months compared to 52, 60±13, 97 months in patients with mLNR ≥0, 20 (15 cases)in non CME Group.(p=0, 03, t-Student) (Figure 12). We obtained the same impact on median survival, matching patients with mLNR ≥0, 20 in Group 1 and Group 2 respectively (49, 83±22, 09 vs 36, 33±24, 36 months) (Figure 13). We also tested the relashionship with the disease free survival. In Group 1 patients with mLNR≤0, 19 disease free survival was 52, 36±17, 07 months compared to 47, 46±22, 42 months in Group 2 (p=0, 002, T student for unpaired data) (Figure 14). In Group 1 disease free survival for patients with mLNR≥0, 20 was 50, 50±23, 27 months compared to 23, 50±17, 17 months of Group 2 (p=0, 04, T Student for unpaired data) (Figure 15). A greater lymphnode harvest has a key role for a more accurate staging and is a predictive factor for overall- and disease-free survival. The Lymph Node Ratio is related to long term overall - and disease-free survival. The greater number of harvested nodes thanks to CME allows to obtain lower mLNR, and this has a correlation with an increase of both overall- and disease free- survival.

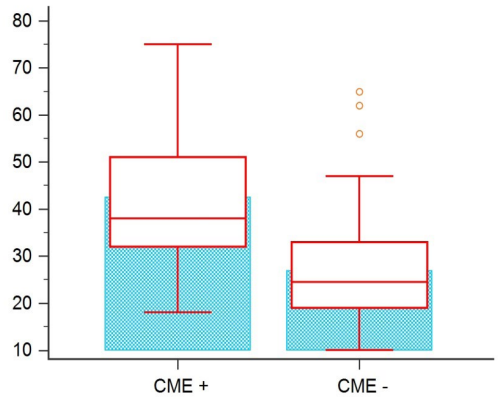

Figure 11: CME and nodal Harvest.

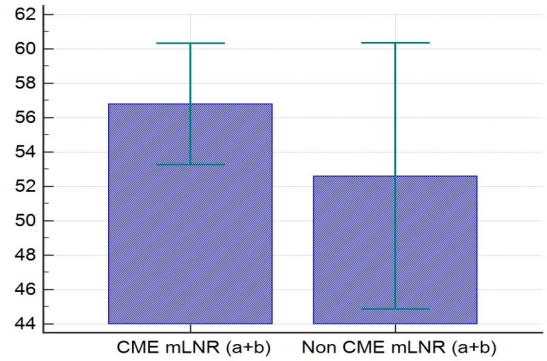

Figure 12: Lymph Node Ratio ≤ 0, 19 in Group CME + and CME -.

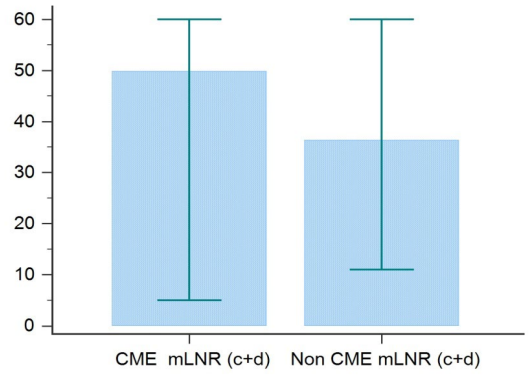

Figure 13: Lymph Node Ratio ≥ 0, 20 in Group CME + and CME -.

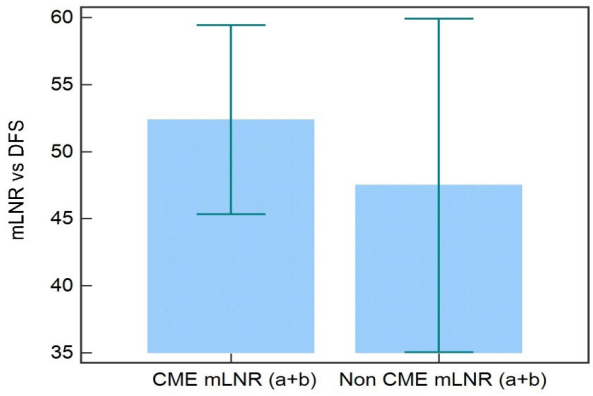

Figure 14: LNR≤0, 19 and its relation with DFS in CME and non CME group.

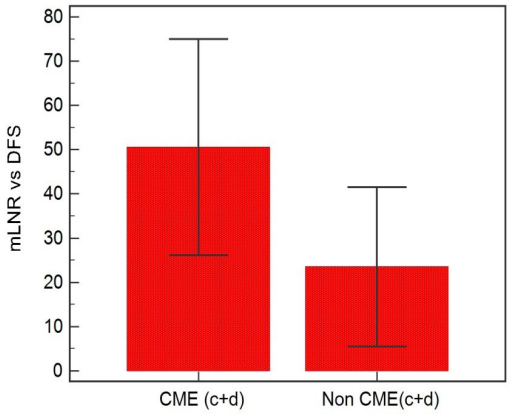

Figure 15: LNR≥0, 20 and its relation with DFS in CME and non CME group.

Discussion

Our series of 152 patients showed the role of CME as independent prognostic factor on 5 years -survival, disease-free survival (especially in III stage), and local recurrence rate. This technique leads to a more accurate staging, improving the pathologic lymphnode isolation on a greater number of harvested nodes. This concept takes to the "stage migration".

In our study LNR was considered to implement the prognostic benefit of the greater nodal harvest of CME and the better stratification of stage III's risk categories. There were no differences in postoperative complications of CME, evaluated with Clavien-Dindo score, compared to the traditional

lypmphadenectomy in elderly patients. We specify that elderly patients recruited in this coohort are homogeneus in comorbilities : ASA IV were 6, 38 % in Group 1 and 5, 18 % in Group 2. The majority of the patients of the two groups were subcategorized in ASA II / ASA III. Average age of the patients was 74, 47 years in Group 1 and 76, 18 in Group 2. The role of a more demolitive surgical treatment shows significance in patients unsuitable for adjuvant chemoterapy because of their comorbilities or incomplete compliance. This result is also confirmed by the statistically unsignificant difference in median overall survival and disease-free survival in patients who underwent to adjuvant CT after CME and traditional surgery respectively (OS: 55, 02 vs 53, 00 months and DFS: 51, 47 vs 44, 57 months). An important limit of our series is the lack of anatomo-pathological evaluation of the quality of mesocolon, with photographic documentation of its integrity, its distance from the central ligations, and its total area of excision. This limit is caused by the period of selection between (2011 and 2014)where those evaluations weren't performed by protocol. A homogeneus evaluation and lymphnode isolation in our series was ensured by a dedicated pathologist. The greatest part of the population in the groups examined has BMI < 25 (59, 57 % in Group 1 and 52, 21 % in Group 2). BMI doesn't significantly affect 5-years survival and disease free survival. Patients' comorbilities in our series aren't related with surgical and oncological outcomes of CME (see Table 3).

Detractors of CME, or Japanese D3 Lymphadenectomy, claimed that the complete lymphadenectomy of apical nodes was more feasible and safety in skinny patients and in a "standard " population, as the Asians, compared to the western population, where there is more heterogeneity and more incidence of obesity. In Group 1 overweight patients who underwent to CME were 40, 42 % compared to Group 2 of traditional lymphadenectomy (27, 58 %). However in our series lacked a clear subpopulation of elderly with obesity and/or severe obesity because of the small sample size. CME is a safe and feasible technique in the elderly with comorbilities and doesn't add an higher complication rate than traditional surgery and this is proved by the comparison of postoperative complications (major and minor, classified with Clavien-Dindo score) that showed no statistically significant differences. The evaluation of the comorbilities was considered using the ASA score, but it is a sinthetic anesthesiological index who lacks of the stratification of the other geriatric, cardiologic (NYHA) and pneumological (GOLD) scores that better enclose the most common geriatric pathologies. We have chosen ASA score because it gives the clear evaluation of the preoperative and intraoperative risk of the patient. The data and results, we obtained, were consistent with the literature.

Basing on the similar principles of embriological anatomy of TME [1], Hohenberger, et al. [2] introduced the concept of CME in 2009, where dissection is carried preserving the integrity of colon's visceral fascia, removing as more regional nodes as possible, with the ligation of vessels in the mesenteric root, thus reducing the pathways of the addominal spreading and improving patients'oncological outcomes. Since 2011 NCCN recommended CME for the treatment of the locally advanced colic cancer [6]. There are concerns about CME surgery in elderly patients because of its larger extension of the resection area compared to standard surgery, in association with the age-related physiopathological involution of the vital parameters (hepatorenal function, bone marrow reserve). Jin Li [7] shows that elderly patients achieve similar oncological outcomes to adult patients after laparoscopic CME. In that work intraoperative blood loss in elderlies was estimated greater than in adults [8-12]. That is related to a reduced vascular compliance, in addition to platelet aggregation disorders, despite of normal hemometry and clotting test. However, in Jin-Li's series [7] there were the similar rate of postoperative blood transfusions despite of the greater intraoperative blood loss [13-18]. In addition Jin-Li, et al. [7] recorded the same conversion rate (for laparoscopic surgery) in the two populations. Also elderlies' overall survival and disease free survival of were similar to adults'. The conclusion of the study was that age is not a limiting factor for CME surgery.

A minor number of lymphnodes is retrieved in elderly patients' specimens [19] and age-related changes are described in lymphnodes' morphology [19,20]. However the difference in the distribution of the pathological stage of elderly could be also the consequence of their different selection as candidate to surgery, and of a less demolitive surgery leading to a minor number of harvested lymphnodes. According to some works in literature, comorbility and mortality in the 30 days after surgery [21,22] are consistent in the elderly and 5 - year survival rate (either cancer -related or cancer-unrelated) is lower. In contrast, data about disease-free survival of the elderly are conflictual. Some studies showed a similar cancer-related - and disease-free survival in all the age groups undergoing surgery for colon cancer [23,24], while other authors stressed a lower survival in the elderly group [25]. However the results we obtained suggest that elderly patients should be treated with the same surgical strategy of the younger, almost in the absence of severe comorbility. An alternative way to evaluate the nodal status is to measure the lymphnode ratio LNR (pathologic nodes/total harvested nodes). Severe studies have directly compared LNR with the N staging of TNM and observed that LNR is more accurate in staging of colon cancer [26-30]. The application of the variations of LNR changes the prognostic stratification in patients with nodal metastases. Moug, et al. [31] have showed that important changing in prognostic stratification in relation to 5-year survival and clinical response after adjuvant chemotherapy with the application of LNR in stage III of colon cancer compared to the common use of the N-staging

alone. A result of LNR ≤0, 19 in a patient reflects the better surgical and pathological management with a complete primary tumour excision and extended lymphadenectomy followed by a pathological processing of all the nodes in the specimen. On the other side LNR>0, 19 shows a worse prognostic and pathologic behaviour of the tumour.

CME, as confirmed by our series, is associated with a better disease free survival. The hypothesis is that an important amount of patients in non-CME group are indirectly understaged from stage III to stage II with the lacking of lymphonodal dissection of the area in the central ligation (apical nodes). This could lead to a local recurrence [32]. Following CME 's principles there is no risk to leave potential regional micrometastases in the area of central ligation. An hallmark of surgical quality is the integrity of the mesocolic plane leading to a significant improvement of oncologic outcome [33]. The Japanese group has showed the prognostic influence of the localization of local metastases. The involvement of the lymphnodes around the main vessels leads to a worsening of the prognosis compared to the involvement of the pericolic nodes. Patients with high risk of nodal involvement could benefit from high ligation [34,35]. The number of lymph nodes has been proposed as a surrogate marker of the quality of surgery, but it depends on the quality of the pathologic exam and on patient /tumour related factors (ie. Age, microsatellite instabily, tumour dimension, stage) [36]. According to Perrakis, et al. [37] CME correlated to an higher nodal count.

Some author argued that similar oncological outcomes could be obtained without the dissection of the central nodes, but CME in right colectomy isn't associated with an increase of short term mortality and morbility [38-40]. The advantage of CME is the surgical landmark of the superior mesenteric vein leading to a complete and safe excision of the mesocolic lymphnodes. This procedure is easier in skinny patients, while in the obese patients the clear exposition of all the vascular anatomy is of paramount importance before the central ligation and section.Preoperative CT could difference T1/T2 tumours from T3/T4 with expert radiologist, but neither preoperative CT nor other methods could predict the pathological nodal status. Although the reduction of the recurrence risk is greater in stage III, the reduction of absolute risk can be stressed also in stage I and II [41-45]. The superior mesenteric artery is surrounded by the superior mesenteric nevous plexus that is a continuation of the celiac plexus and its ganglia [42,43]. Some detractors of CME argued that the central node dissection could implicate the risk of plexus injury leading to a neurogenic diarrhea [2], with a worsening of the quality of life. In contrast, according to Bertelsen, et al. [44] there is no risk of worsening the bowel movement because limphadenectomy of the superior mesenteric artery is carried preserving the surrounding nervous tissue while the lympathic tissue on the superior mesenteric vein is "peeled" on the periadventitial plane.

Limitations

The study is limited by numerosity of the series and by the monocentric experience. Lacks also the anatomopathological assessment of the quality of excised mesocolon.

Conclusion

Basing on the results of our retrospective study, CME is related to a better oncological outcome in the treated patients. Median survival in CME patients is 54, 5 months compared to 51, 2 months in patients of non CME Group. This is also confirmed by multivariate analysis, that identifies CME as independent predictive factor for 5 year survival [covariates : staging, grading, nodal harvest, comorbidities, adiuvant chemotherapy]. Analyzing data of population by stage, CME was associated with a better median survival, especially in patients presenting with locally advanced stage (55, 71 months in Group 1 vs 45, 88 months in Group 2). CME is associated also with a better DFS. In the series of Group 1 median DFS was 52, 63 months compared to 46, 0 months in Group 2. After the analysis by stage, this data is confirmed especially on stage II (51, 43 months in Group 1 vs 48, 31 months in Group 2) and stage III (50, 96 months in Group 1 vs 41, 0 months in Group 2). The multivariate analysis shows that CME is an independent predictive factor for 5-years disease free survival [covariates : BMI, staging, grading, nodal harvest, adjuvant CT]. CME surgery is also associated to a lower local recurrence rate compared to traditional surgery. In our series the local recurrence rate in Group 1 was 0 % while in Group 2 was 5, 1 %. CME surgery allows also a better staging procedure, through an higher nodal harvest, meeting the concept of "stage migration".

In Group 1 the mean nodal harvest was 42, 47 while it was 26, 27 in Group 2. Lymph Node Ratio (LNR) ≤0, 19 is related to a better median survival (Group 1 :56, 8 months vs 52, 60 months in Group 2) and to a better disease free survival (52, 36 months in Group 1 vs 47, 46 months in Group2). In contrast if LNR >0, 19 there is a worsening of median 5-year survival (49, 83 months in Group 1 vs 36, 33 in Group 2) and disease free survival (50, 50 months in Group 1 vs 23, 50 months in Group 2). LNR offers a better prognostic stratification in stage III patients and the greater nodal harvest obtained with CME contributes to lower LNR values. This could allow a more complete staging and the migration in staging III of patients that otherwise had been classified in stage II lacking a CME limphadenectomy. CME surgery is not burdened by postoperative minor and major complications compared to the traditional surgery. In Group 1 Clavien Dindo ≥3 was obtained in 5, 41 % of cases compared to 1, 72 % of Group 2, but this difference wasn't statistically significant. There is no statistically significant difference also in minor complications (22, 4 % in Group 1 vs 18, 95 % in Group 2). In conclusion, considering the prognostic effect in stage II-III population affected by right colon cancer and

the limits of CT in nodal staging, CME should be considered for tumours starting from stage T2N0 also in elderly population with the improvement of the oncological outcomes.

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