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Original Article

Clinico-epidemiologic criteria and predictors of survival of rectal cancer among Egyptians in Delta region

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ABSTRACT

Background: Colorectal cancer represents a global health problem. Rectal cancer in particular is increasing and is believed to carry a unique epidemiologic and prognostic criteria.
Method: We herein study retrospectively the data of 245 patients from a tertiary center in Egypt. Clinico-epidemiologic criteria and predictors of survival are analyzed.
Results: The disease affects younger population without sex predilection. Prognosis is affected by age, nodal status, metastasis, and bowel obstruction.
Conclusion: Rectal cancer has unique criteria in the Egyptian population. A national population based registry is recommended to delineate the nature of the disease in Egypt.

Critérios clínico-epidemiológicos e preditores de sobrevida do câncer retal entre egípcios na região do Delta

Palavras-chave:
Câncer retal
Registro
Metástase
Sobrevida
Recorrência

RESUMO

Introdução: O câncer colorretal é um problema de saúde global. A incidência de câncer retal, em particular, está aumentando; acredita-se que esta neoplasia apresente critérios epidemiológicos e prognósticos únicos.
Métodos: O presente estudo avaliou retrospectivamente os dados de 245 pacientes de um centro terciário no Egito. Critérios clínico-epidemiológicos e preditores de sobrevida foram analisados.
Resultados: A doença afeta a população mais jovem, sem predileção por sexo. O prognóstico é afetado pela idade, estado nodal, metástase e obstrução intestinal.

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Conclusão: O câncer retal apresenta critérios únicos na população egípcia. Recomenda-se um registro nacional de base populacional para delinear a natureza da doença no Egito.

Introduction

Colorectal cancer (CRC) is the 3rd commonest cancer worldwide, as well as, a leading cause of cancer death.[1] In the Egyptian population, it ranks 7th among both genders with estimated 1070 rectal cancer cases in 2020 (excluding colon cancer).[2]

Colorectal cancer is typically a disease of the elderly (>50 years); however, an increasing incidence of young CRC in USA has been recently reported.[3]

The current standard of care for rectal cancer is total mesorectal excision in the holy plane of Heald, with partial mesorectal excision reserved for high rectal and rectosigmoid cancers excising 5 cm of mesorectum below the tumour.[4]

In addition, long course radiotherapy with 5-Fluorouracil/Capecitabine sensitization is a common protocol in use in locally advanced rectal cancer patients. Neoadjuvant therapy is generally indicated for T3 tumours, especially those in which clear circumferential margin cannot be attained, and for node positive patients. Debates about these indications do exist, especially in high rectal cancer and on the criterion definition of node positive in magnetic resonance imaging.[5]

CRC survival is highly dependent upon disease stage at diagnosis, ranging from a 90% 5 year survival rate for those detected at localized stage; 70% for regional disease; to 10% for patients diagnosed for distant metastasis.[6] Overall 5 year survival is slightly higher for rectal (66.5%) than for colon (64.2%) cancer; however, this is probably attributed to the higher percentage of rectal tumours diagnosed at a localized stage (44% vs. 38%) because stage-specific survival is similar.[7]

Studies on epidemiology of CRC in Egypt are limited, of which the most important are Abouzid et al. multicenter study in 2002, El-bolkainy et al. hospital based study in 2006, and Veruttipong et al. population based study using Gharbia governorate registry in 2012. They showed increased incidence of CRC in younger age and increased prevalence of rectal cancer.[8–10]

The limitations of the previous colorectal studies are that most of them did not study colon and rectal cancers separately. Moreover, there is lack in studies demonstrating survival of rectal cancer in Egypt. Thus, this study aimed at highlighting the epidemiology of rectal cancer in one of the high popularized regions of Egypt (Nile Delta), together with detecting the factors affecting survival in our patients.

Materials and methods

This is a retrospective study, where the institutional registry at the Oncology Center, Mansoura University (OCMU) was thoroughly revised for rectal cancer cases that attended the hospital from January 2006 to December 2017. Patients with pathologically proven rectal cancer were included, while patients without adequate data registry were excluded. Searching with diagnosis items; rectal cancer and rectum, four hundred and thirty six patients were found in the hospital electronic registry. After exclusion of those with wrong diagnosis, patients without pathologic confirmation documents available, 245 patients fulfilled the inclusion criteria and were included in the study. The objectives were assessment of disease epidemiology, methods of management and recurrence rate. The primary endpoints were overall and disease free survival. Patients were followed up till October 2018.

The data of these patients were analyzed using SPSS version 22 (Inc, Chicago, IL). Continuous variables are presented as mean when symmetrical or median and range when asymmetrical. Categorical variables are presented as proportions. Survival analysis was done using Kaplan–Meier curve and significance determined by log rank test. Significant factors affecting survival were then processed in multivariate analysis using Cox's regression test. P-value <0.05 was considered significant.

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study protocol was approved by Faculty of Medicine, Mansoura University Institutional Review Board (IRB). The IRB number is R/19.01.365.

Results

Demographics (Table 1)

Mean age at diagnosis was 47.2 with the youngest patient diagnosed at 15 and the oldest at 83 years old, age distribution is displayed (Fig. 1). Distribution of cancer in low (up to 6 cm from verge) middle (from 7 to 10 cm) and upper rectum including recto-sigmoid (11 cm or more) is displayed (Fig. 2). Pre-therapy stage distribution is displayed (Fig. 3A). The median follow up period after diagnosis was 18 months, ranging from 3 months to 16 years.

Operative details

Most of the studied patients (83.3%) underwent surgery. Eight cases only presented with acute intestinal obstruction necessitating urgent surgery. Metastasectomy was employed in only 4 cases, three underwent hepatic resection, while one underwent endoscopic inguinal node dissection as previously reported.[11] In the reported cases 78.8% underwent open surgery, laparoscopy was successfully employed in 17.5% with Transanal Total Mesorectal Excision (taTME) attempted in 4 cases with technique and results previously described.[12] Further, in 5.3% of patients the operation started laparoscopic

Table 1 – Showing basic clinico-epidemiologic and pathologic data.

Variable	Patients
Age at diagnosis	Mean 47.2 (SD = 14.5)
Sex	124 females and 121 males.
BMI	Mean 32.2 (SD = 7.5)
Distance from anal verge by proctoscopy	Median 5 cm
Radiologic Tumour size	Median 4 cm (maximum 13 cm)
Tumour form	35.5% polypoid, 26.5% ulcer and 20.8% stenosis.
Nodal status at diagnosis radiologically	38.8% node positive
Metastases at diagnosis	21.3% metastatic at diagnosis with this order of frequency (liver, peritoneal, lung, multivisceral, bone and finally non-regional nodes).
Preoperative therapy	34.7% received NART while 43.3% received NACT.
Operation	LAR in 25.7%, APR in 21.2%, ultraLAR in 9.4%, Exploration in 7.3%, ISR in 6.1%, pelvic exenteration in 2.8% and local excision in 2.7%.
Anastomosis	Commonest end to end in 62.7%. 56% were hand-sewn and 28.6% single stapling technique
Ostomy	76.6% of operated cases Commonest type loop ileostomy in 35.4% followed by terminal colostomy in 27.2% then loop transverse colostomy in 22.4%.
Operative time	Mean 270 minute (SD = 113).
Operative blood loss	Median 350 ml (range 150–3000).
Hospital stay	Median 9 days (range 1–45).
Oral intake	Median 3 days (range 1–17).
Pathology	Conventional adenocarcinoma in 66% followed by mucinous carcinoma in 25.9% then signet ring in 6.6%.
Lymph node harvest	Median 8 (range 0–26), with 70% have less than 12 node resected.
Number of positive lymph nodes	Median 1 with maximum of 22 infiltrated.

NART: neoadjuvant radiotherapy, NACT: neoadjuvant chemotherapy, LAR: low anterior resection, APR: abdominoperineal resection, ISR: inter-sphincteric resection.

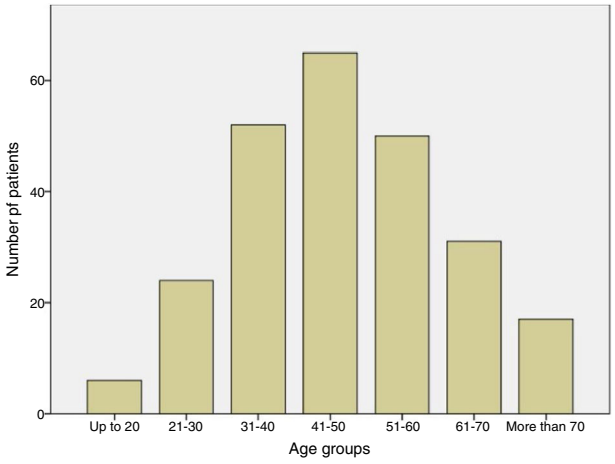

Fig. 1 – Age groups.

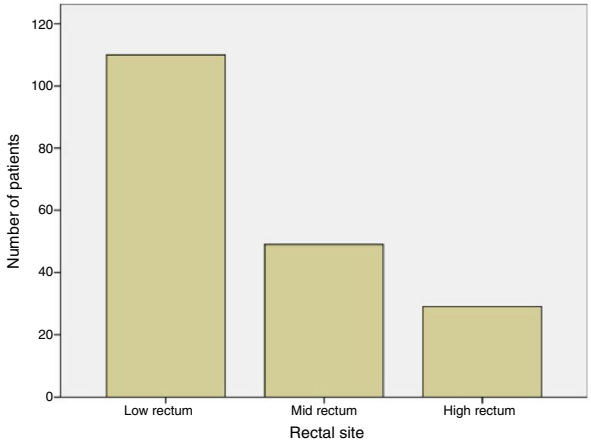

Fig. 2 – Tumour site.

then shifted to open due to locally advanced tumours and left ureter injury as the commonest conversion causes. Only 50% of patient with temporary ostomies underwent stoma closure. Blood transfusion was under recorded, but a valid percentage was 52.2%. Intra-operative complications occurred in 6.1% of patients, the commonest was bleeding.

Pathology

Pathologic stage is displayed (Fig. 3B). Circumferential Radial Margin (CRM) is under reported but was infiltrated in at least 13.3% of cases. Distal margin was infiltrated in 6.8% of cases, while proximal in 0.6%. Data on quality of TME is lacking in most cases, so a conclusion could not be drawn.

Pattern of recurrence and mortality

Local recurrence was reported in 15.8% of operated cases, while distant recurrence in 14.8% of operated cases. The distribution of distant recurrence was; 25% in the lung, in another 25% peritoneal, then liver in 21.4%, bone in 14.3%, multivisceral in 10.7% and one case with inguinal node recurrence. Only 7 cases died within one month from the operation, while a total of 29 cases were recorded dead in the hospital registry.

Predictors of survival (Tables 2 and 3)

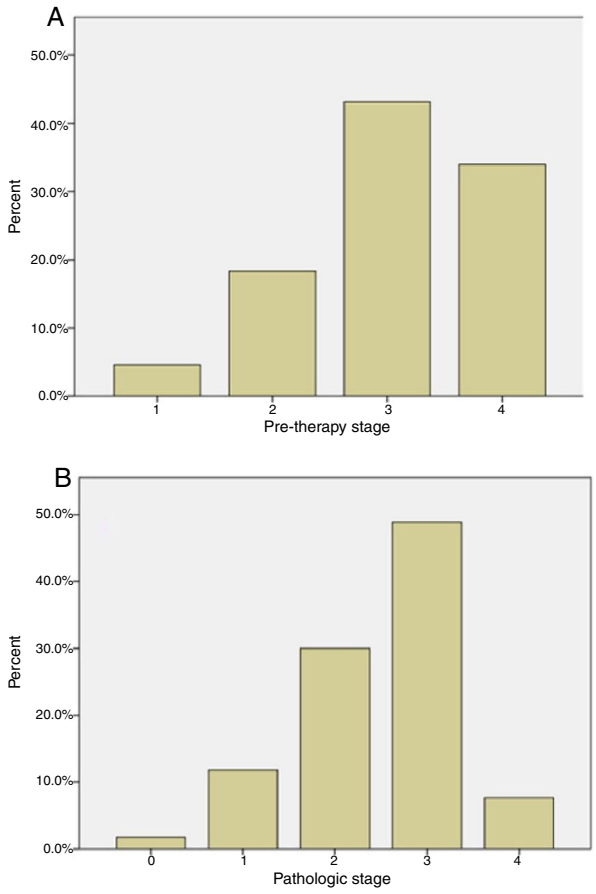

Fig. 3 – Stage groups (A) Initial radiologic pre-therapy staging (B) Pathologic staging.

Table 2 – Showing significant factors predicting overall and disease free survival in univariate analysis.

Factor	Estimated mean survival (months)	p-value
Overall Survival		
Age at diagnosis		0.047
Young (<40)	179.6	
Old (>40)	136.6	
Treatment goal		0.045
Curative	156.2	
Palliative	50.4	
3º day morbidity		0.001
Not encountered	104	
Encountered	48	
Disease Free Survival		
Sex		0.02
Male	49.7	
Female	111	
Metastasis at diagnosis		0.00
Present	8.3	
Absent	69.9	
Metastasis site		0.02
Liver	16.5	
Other	1.7	
Intestinal obstruction		0.00
Presentation with IO	0.5	
Without IO	90.5	
Pathologic T		0.032
Pathologic N		0.001
N0	76	
N1	60	
N2	41	
Longitudinal margin		0.028
Free	71.9	
Infiltrated	39.3	

Estimated mean Overall Survival (OAS) was 153 months, while estimated mean Disease Free Survival (DFS) was 88 months. The OAS was significantly directly related to younger age and to treatment with curative intent, while inversely related to 30 day morbidity (Fig. 4). On the other hand, the DFS was significantly directly affected by female sex, absence of metastasis at diagnosis and metastasis to the liver in comparison to other sites. However, DFS was inversely affected by bowel obstruction, advancing pathologic T stage, advancing pathologic nodal stage and infiltrated longitudinal margin (Fig. 5).

In multivariate Cox analysis, old age, patients treated with palliative measures, and those who suffered from morbidity within 30 days of operation significantly worsened the OAS. On the other hand, distant metastasis, advanced pathologic N stage and bowel obstruction significantly worsened the DFS.

Table 3 – Showing Cox multivariate analysis of different survival determinants.

Factor	Hazard ratio (95% CI)	p-value
Overall Survival		
Old age at diagnosis (>40)	10.8 (1.3–91.9)	0.03
Palliative treatment goal	7.2 (1.4–36.2)	0.017
Presence of 3º day postoperative morbidity	5.4 (1.7–17.2)	0.004
Disease Free Survival		
Male sex	1.5 (0.7–2.9)	0.26
Metastasis at diagnosis	5.5 (2.2–13.4)	0.00
Metastasis to sites other than liver	6.1 (0.7–51.8)	0.095
Presentation with intestinal obstruction	32.9 (4.4–248.1)	0.001
Pathologic T stage		0.124
Pathologic N stage		0.049
N1	1.1 (0.4–2.8)	0.84
N2	2.4 (1.1–5.1)	0.023
Infiltrated longitudinal margin	1.4 (0.4–4.7)	0.63

95% CI, Confidence Interval 95%.

Discussion

Rectal cancer is known to have a tendency toward male preponderance and toward younger population in comparison to colon cancer.[13,14] In our study; however, both males and females were nearly equally affected by the disease, and the disease affected obese patients (mean BMI 32) and relatively young age (mean 47 years old).

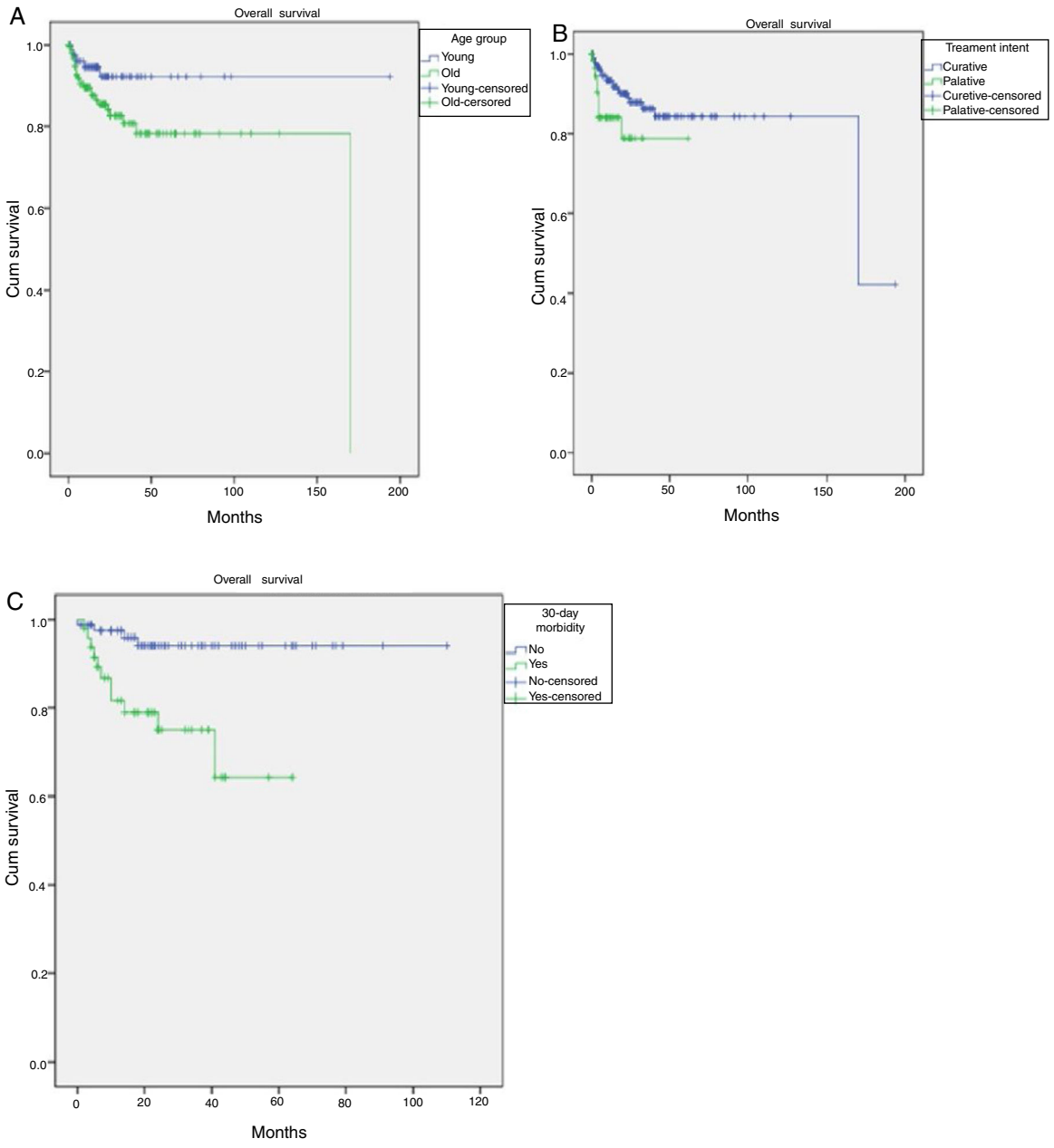

Fig. 4 – Kaplan–Meier curve for overall survival (A) Age group (B) Treatment intent (C) 3° day operative morbidity.

In this study, tumours were most common in the low rectum (nearly 45% of the patients) with median size 4 cm, which is much smaller than the size of colon cancer cases in our hospital (mean 9.3) as previously reported.[15]

Thirty eight percent of our patients were radiologically node positive and 21% were metastatic at diagnosis, a figure similar to data from UK where 35% of cases were Duke stage C and 19% were stage D at diagnosis.[16]

About half of our patients (54.4%) received initial chemo and/or radiotherapy. Furthermore, three quarters (76.6%) of operated patients in this series underwent stoma formation. 36% had permanent ostomy (terminal colostomy or ileostomy), while the rest had temporary stoma. Unfortunately, 50% of patients with temporary stomas have never had their stoma closed, a figure which is much higher than reported in other studies.[17]

Minimally invasive surgery was initially used in 22.8% of our cases with conversion rate kept at 23.2%, which is slightly higher than reported in a recent meta-analysis.[18]

In Gharbia based study on colorectal cancer, the median OAS and PFS were 23 and 25 months, respectively. They also found that elderly patients were more likely to have rectal tumors, non-adenocarcinoma histology, non-metastatic disease, more co-morbidities and were less likely to receive adjuvant chemotherapy. However, they stated that the OAS and PFS of elderly patients were not statistically different from the non-elderly.[19] In our patients, the OAS and the DFS figures were much better 153 and 88 months, respectively, with young

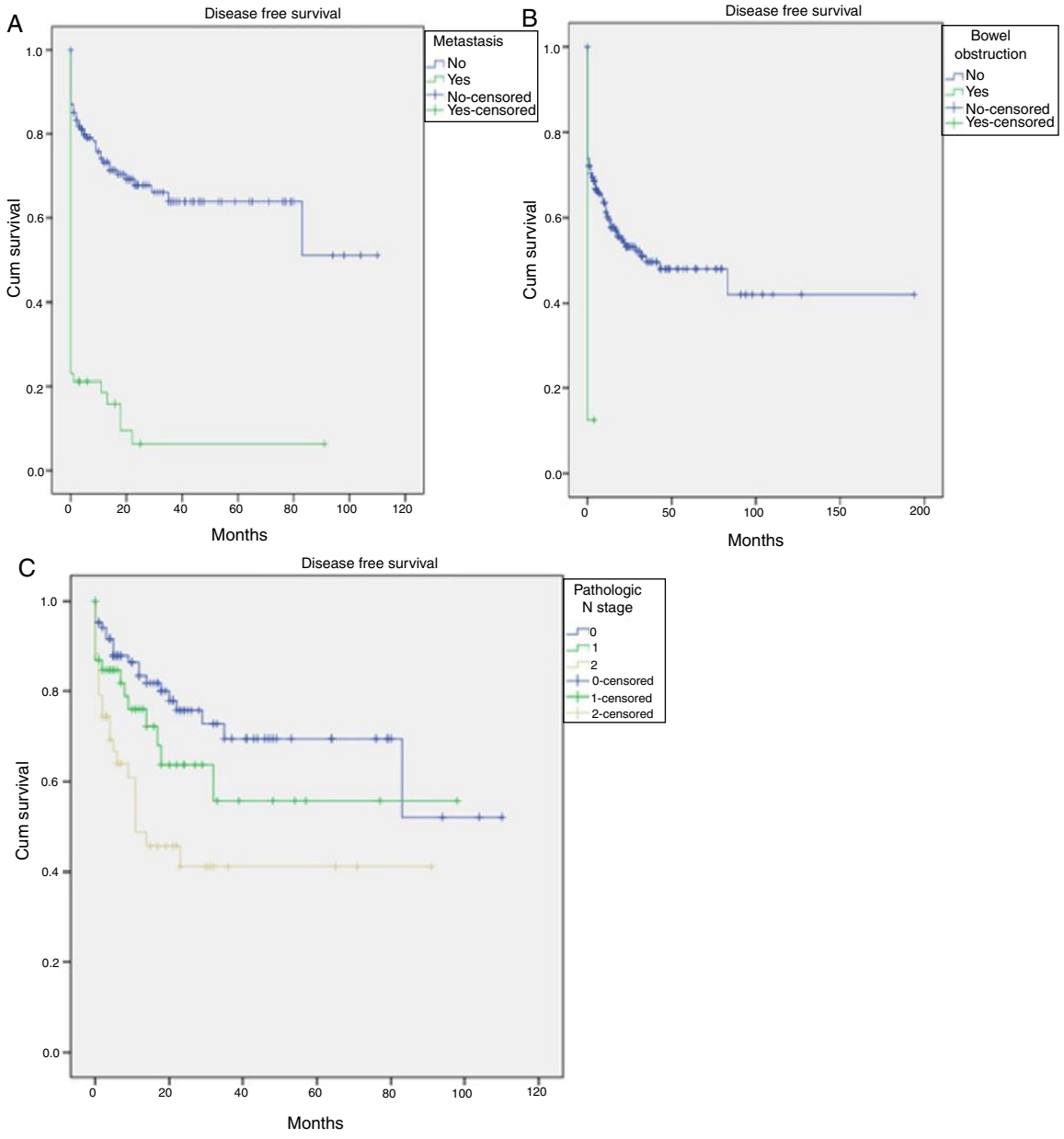

Fig. 5 – Kaplan–Meier curve for disease free survival (A) Distant Metastasis (B) Bowel obstruction (C) Pathologic N stage.

age being significantly associated with better OAS but not DFS in comparison to elder group.

Scholars showed that suboptimal lymph node yield was independently associated with worse OAS regardless of neoadjuvant therapy, pathological staging and patient factors in rectal cancer. This finding highlights the importance and challenge of an optimal lymph node evaluation for prognostication, especially for patients receiving neoadjuvant therapy.[20] Unfortunately the number of resected lymph nodes was suboptimal in 70% of our patients. This may be reasoned by the large number of cases receiving preoperative therapy which is known to decrease nodal count, plus the uncommon use of lipolysing techniques during pathologic assessment for cost issues. Furthermore, node yield did not affect either overall or disease free survival in this series.

Although the 8th edition of the AJCC staging of colorectal cancer only stratifies peritoneal metastasis as a worse prognosis, further studies had shown a better prognosis of liver and lung metastasis in comparison to other visceral metastasis.[21] The European treatment group of colorectal liver metastasis had suggested the reclassification of metastases into stage IV with hepatic metastasis and stage V with extra-hepatic disease.[22] This is in compliance with our data where patients with liver metastases carried a better disease free survival in comparison to other sites of spread.

Bowel obstruction as a first presentation of the rectal cancer was uncommon occurring in only 3.3% of our cases, however, it was significantly a bad prognostic sign associated with shorter DFS. This is similar to results of another study signifying obstruction as a negative predictor.[23]

Finally, in our multivariate analysis elder patients, those treated with palliative measures and those who suffered from morbidity within 30 days of operation had a shorter OAS. While, DFS was worsened by distant metastasis, pathologically positive nodes (especially if more than 3 nodes infiltrated), and operating on patients presenting with intestinal obstruction.

Conclusion

Rectal cancer in the Delta region affects younger, obese patients with equal sex distribution. It carries a good prognosis that is affected by age, surgical morbidity, distant metastasis, node positive disease, and bowel obstruction. However, the increased low rectal disease warrants an increasing demand for radiotherapy and sphincter sparing approaches including trans-anal procedures. Also, further employment of metastasectomy for liver/lung metastasis is needed.

Conflicts of interest

The authors declare no conflicts of interest.

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