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The Impact of Body Mass Index on Pathological Response and Survival Outcome after Neoadjuvant Chemotherapy in Localized Bladder Cancer

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Abstract

Background: Neoadjuvant chemotherapy (NAC) grants a modest survival benefit in localized muscle-invasive bladder cancer (MIBC). We evaluated the pathological response and survival outcome after NAC in stage II and IIIA MIBC and their correlation with body mass index (BMI).

Method: Our retrospective study included stage II (T2 N0) and IIIA (T3 N0, T4 N0, T1-4 N1) MIBC. They received NAC followed by radical cystectomy. The patients were categorized into level I: a BMI of 18.5 – 24.9 kg/m^2, level II: a BMI of 25-29.9 kg/m^2, and level III: a BMI of ≥ 30 kg/m^2.

Results: 103 patients with localized MIBC were included. The median age was 63 years; 35 patients (34.0%) belonged to level I, 40 patients (38.8%) belonged to level II, and 28 patients (27.2%) belonged to level III. Smoking status was more common in level II (51.0%) and level III (36.7%) ($P < 0.001$). Only 18 patients had ECOG PS 2, all belonging to level III ($P < 0.001$). After NAC, the pCR was 34.3%, 25%, and 10.7% of level I, level II, and level III ($P = 0.03$), respectively. Of 19 patients who passed away, 10 patients belonged to level III and 6 patients belonged to level II ($P = 0.007$). For level I, level II, and level III, the disease-free survival was 23.2 months, 12.7 months, and 10.7 months and the overall survival was 61.9, 52.3, and 28.7 months, respectively.

Conclusion: Obesity and overweight could be predictive and prognostic markers in localized MIBC. These factors are associated with low pCR after NAC, poor disease-free survival, and overall survival.

Keywords: Urinary bladder neoplasms, Body mass index, Neoadjuvant chemotherapy

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Introduction

Obesity, an increasing epidemic, is a prevalent public health problem worldwide. Various diseases, including cancer, may be driven by subclinical chronic inflammation.[1] Obesity is now a recognized cause of subclinical chronic inflammation. Multiple pathways mediate the pleiotropic effects and increases the risk of cancer promotion.[2]

The Quetelet index or body mass index (BMI) is used to measure the amount of tissue mass; they categorize people into normal weight:18.5 to 24.9, kg/m^2: overweight, 25 to 29 kg/m^2, and obese: ≥ 30 kg/m^2.[3] Representing approximately 15% of all preventable malignancies, obesity is the third most common risk factor for cancer after tobacco and food.[4] It is a risk factor for many tumour developments such as prostate, endometrial, and breast and is linked to a poor outcome.[5-7]

A meta-analysis of cohort studies conducted by Chinese researchers demonstrated the association between BMI and the risk of 23 cancer types.[8]

Due to the higher rate of distant metastases compared with local recurrence following radical cystectomy (RC), the use of NAC has been the standard of care in localized MIBC. Furthermore, tumour down-staging is used in many pieces of literature as a surrogate marker for better survival outcomes.[9-11] It is also considered as an in vivo sensitivity test for chemotherapy efficacy based on pathology and radiology evaluation. Additionally, the choice of urinary diversion may depend on the response of the primary tumour to NAC.[12]

Although meta-analysis and randomized studies have approved the survival benefit of NAC, it is of limited value (only 5% improvement in 5-year overall survival (OS)), and lately, there has been a debate about NAC in UBC patients with low-risk features; owing to the absence of survival benefit in those subsets of patients, the authors advised limiting the NAC to high-risk

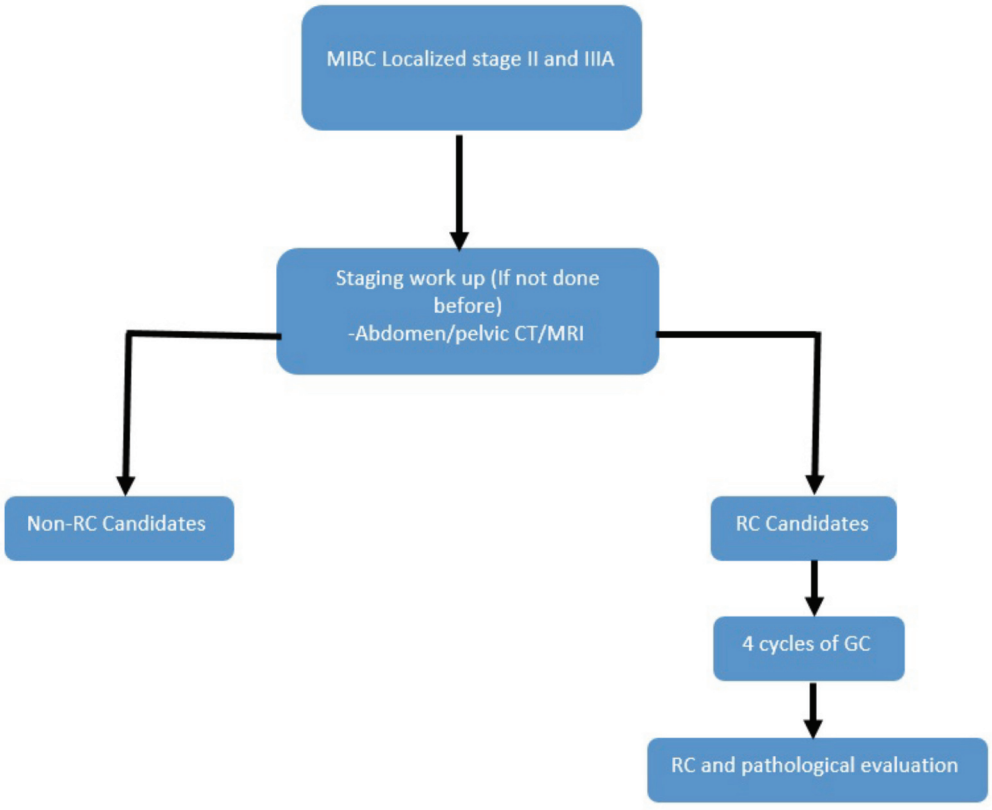

Figure1. This figure illustrates the flow treatment chart of our patients
MIBC: Muscle invasive bladder cancer; CT: Computed tomography; MRI: Magnetic resonance imaging; RC: Radical cystectomy; GC: Gemcitabine/ cisplatin

patients only.[13]

The current work aimed to assess the value of BMI with the pathological response and survival outcome after NAC in stage II and IIIA MIBCRC candidates.

Patients and Methods

Eligibility criteria

We retrospectively reviewed the medical file of 112 patients with stage II (T2 N0) and IIIA (T3 N0, T4 N0, T1-4 N1) MIBC who were RC

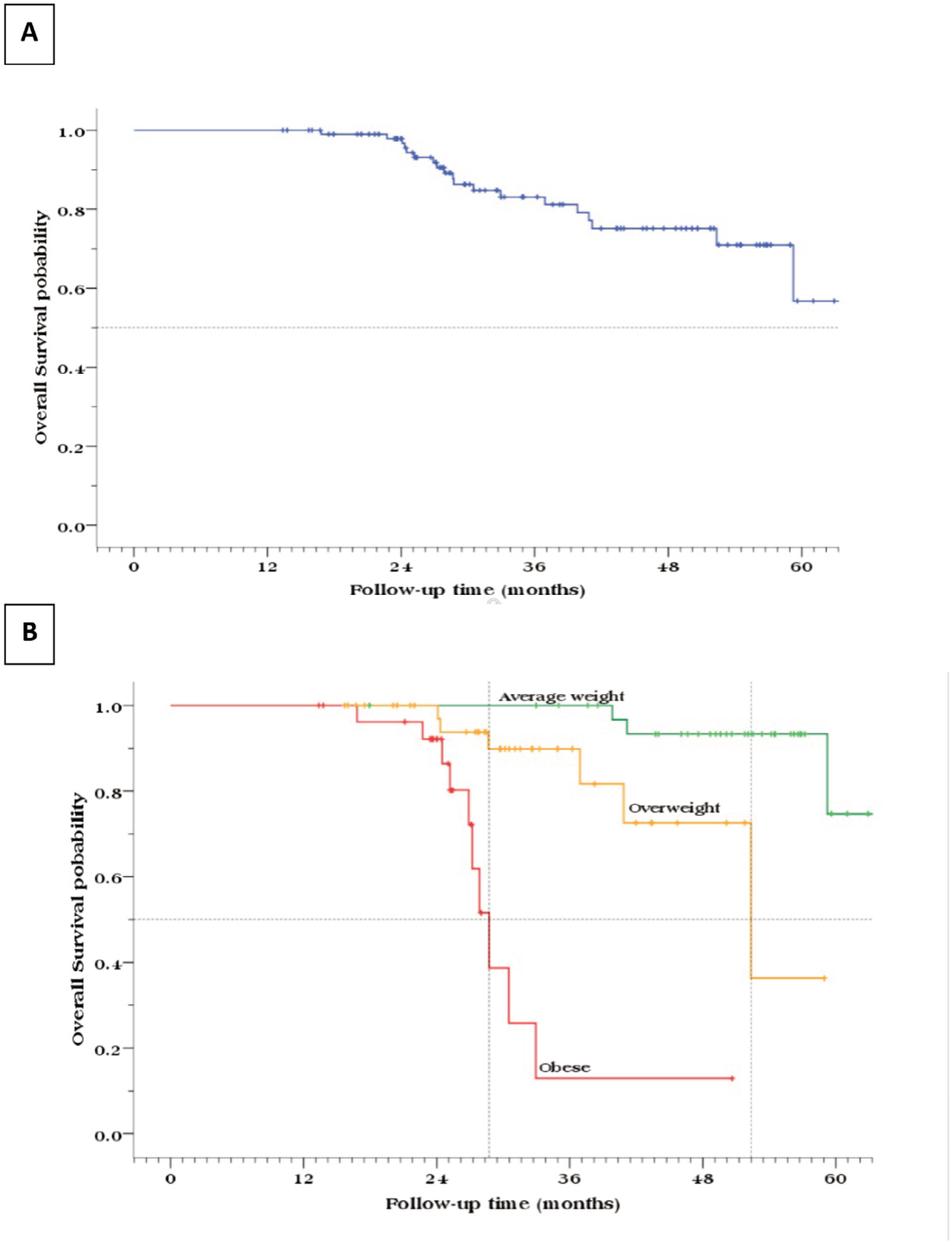

Figure 2. This figure represents A: Kaplan-Meier survival curve of all patient and B: Kaplan-Meier survival curve based on BMI.
BMI: Body mass index; $P < 0.001$

Table 1. The main features of patients

Parameters	Total number (103)	Percentage (%)
Age (years)		
Mean± Std. Deviation	62.7 ± 6.6	
Median (Range)	63 (46-77)	
Sex		
Male	61	59.2
Female	42	40.8
Smoking history		
No	54	52.4
Yes	49	47.6
Body mass index		
Mean± Std. Deviation	27.2 ± 4.8	
Median (Range)	26.1 (18.5-38.3)	
Body mass index		
Level I	35	34
Level II	40	38.8
Level III	28	27.2
ECOG PS		
0	56	54.4
1	29	28.2
2	18	17.5
Primary tumor		
T2	51	49.5
T3	34	33.0
T4	18	17.5
Lymph node (N1)		
Negative	38	36.9
Positive	65	63.1
Pathological response		
Non-pCR	78	75.7
pCR	25	24.3
Follow-up (months)		
Mean± Std. Deviation	36.3 ± 13.6	
Median (Range)	32.7 (13.4-64.5)	
Outcome		
Alive	84	81.6
Died	19	14.4

ECOG PS: Eastern Cooperative Oncology Group Performance state; Std: Standard; T: Tumor size; pCR: Complete pathological response

candidates, age > 18 years old, had histopathologically confirmed transitional cell carcinoma (TCC), were chemotherapy/ radiotherapy naïve, had Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 and adequate organs reservoir, and completed 4 cycles of NAC between March 2013 and November 2016 at the Medical Oncology Department Faculty of Medicine Zagazig University, Egypt and King Abdullah Medical City, KSA.

The BMI is calculated through dividing body weight (kg) by height (m2). The patients are categorized intolevel I: a BMI of 18.5 – 24.9 kg/m^2, level II: a BMI of 25-29.9 kg/m^2, and level III: a BMI of ≥ 30 kg/m^2.[4]

Patients with locally advanced (stage IIIB, IVA), and non-TCC were excluded. Figure 1 showed the flow chart and staging workup. The study has been performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) (Ethics code: ZU-IRB#6971-2-6-2020).

Data collection

Clinicopathological features were collected through medical chart review. The staging was based on the Joint Committee on Cancer (AJCC), 7th edition (2010) staging system. Being a retrospective study, there was no need for informed consent.

Treatment protocol

All the eligible patients received 4 cycles of gemcitabine (1250 mg/m^2 /day on days 1 and 8

(total dose per cycle = 2500 mg/m^2) IV in 250 mL normal saline (NS) over 30 minute and cisplatin (70 mg/m^2 /day on day 1). Pre-hydration for cisplatin with 1000 mL NS over 1 hour, then

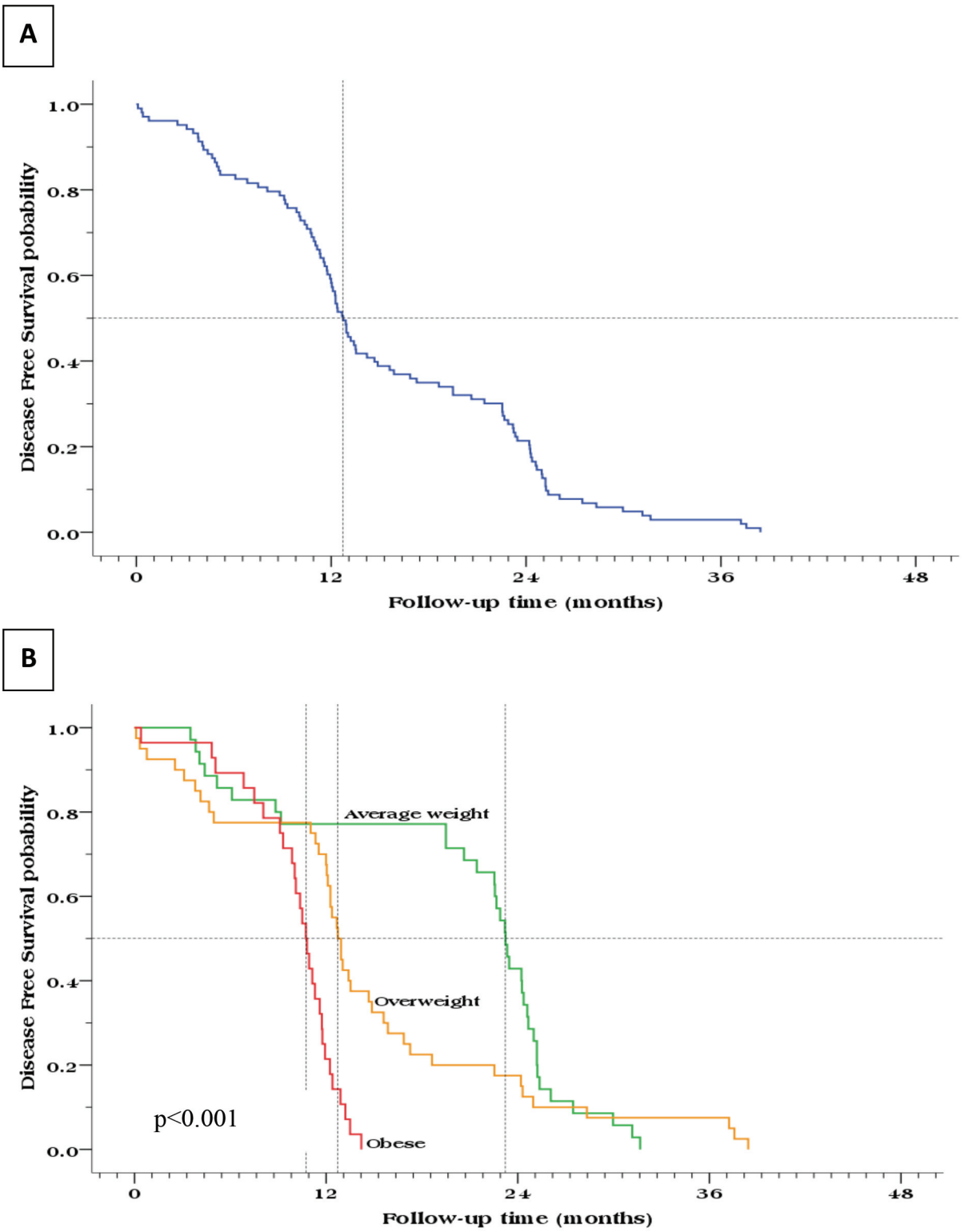

Figure 3. This figure represents A: Kaplan-Meier survival curve for disease-free survival of all patient and B: Kaplan-Meier survival curve for disease-free survival based on BMI.
BMI: Body mass index; $P < 0.001$

Table 2. The body mass index distributed through the clinicopathological features.

Parameter	Body mass index (kg/m^2)			*P* value
	Level I N (%) 35 (34.0)	level II N (%) 40 (38.8)	level III N (%) 28 (27.2)	
Mean age (years)±SD	63.2 ±7.5	62.6 ± 5.6	62.0 ± 6.9	0.4
Sex				
Male	22 (36.1)	27 (44.3)	12 (19.7)	
Female	13 (31.0)	13 (31.0)	16 (38.0)	0.1
Smoking history				
No	29 (57.7)	15 (27.8)	10 (18.5)	< 0.001
Yes	6 (12.2)	25 (51.0)	18 (36.7)	
ECOG PS				
0	30 (85.7)	24 (60.0)	2 (7.1)	< 0.001
1	5 (14.3)	16 (40.0)	8 (28.6)	
2	0 (0.0)	0 (0.0)	18 (64.3)	
Primary tumor				
T2	14 (40.0)	21 (52.5)	16 (57.1)	0.3
T3	14 (40.0)	12 (30.0)	8 (28.6)	
T4	7 (20.0)	7 (17.5)	4 (14.3)	
Lymph node metastasis				
Absent	12 (34.3)	25 (62.5)	1 (3.6)	0.03
Present	23 (65.7)	15 (37.5)	27 (96.4)	
Pathological response				
Non-pCR	23 (65.7)	30 (75.0)	25 (89.3)	0.03
pCR	12 (34.3)	10 (25.0)	3 (10.7)	
Outcome				
Alive	32 (91.4)	34 (85.0)	18 (64.3)	0.007
Died	3 (8.6)	6 (15.0)	10 (35.7)	

SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group; T: Tumor size; pCR: Complete pathological response; $P < 0.05$ was considered statistical significance

cisplatin IV in 500mL NS with 20 mEq potassium chloride and 1 g magnesium sulfate over 1 hour followed by 30 g mannitol over 30 minute as forced diuresis repeated every 21 days. The patients were followed by RC and pathological response evaluation (in cases without progression).

Pathological evaluation

Complete pathological response (pCR) referred to the absence of residual in BCa and lymph node (LN). The presence of residual in the specimens was considered as non-pCR.

Statistical analysis

Continuous variables were expressed as the mean ± SD and median (range), and the categorical variables were expressed as a number (percentage). Continuous variables were checked for normality using the Shapiro-Wilk test. Kruskal Wallis H was used to compare more than two groups of non-normally distributed variables. The percentage of categorical variables was compared using Pearson's chi-square test or Fisher's exact test when necessary. The trend of change in the distribution of relative frequencies between ordinal data was compared using the chi-square test for trend. Disease-free survival (DFS) was calculated as the time from the start of NAC to relapse or the most recent follow-up contact where the patient was relapse-free (censored). OS was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). These time-to-event distributions were estimated using the method of Kaplan-Meier plot and compared using a two-sided exact log-rank test. All tests were two-sided. A *P*-value <0.05 was considered as significant. All statistics were performed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

103 patients were eligible, thus included in the analysis. The median age was 63 years old, ranging from 46 to 77 years with a male to female ratio of 1.5:1. The smoking history was detected in 47.6% with a median BMI of 26.1 kg/m^2. The

majority of our patients had ECOG PS < 2 (PS0 = 54.4% and PS1 = 28.2%). According to the TNM staging system, T2 was found in 49.5% of patients and T3 in 33.0% as well as lymph node (N1) involvement in 63.1%. 35 patients (34.0%) belonged to level I, 40 patients (38.8%) belonged to level II, and 28 patients (27.2%) belonged to level III. After NAC, the pCR was detected in 25 patients (24.3%). The median follow-up was 32.7 months and 19 patients (14.4%) had disease-related mortality. Table1 shows the main features of the patients.

Smoking status was more common in level II (51.0%) and level III (36.7%) ($P < 0.001$). Only 18 patients had PS 2, all belonging to level III ($P < 0.001$). Lymph node metastasis was detected in 96.4% of level III and 37.5% of level II ($P = 0.03$) patients. After NAC, the pCR was 34.3%, 25%, and 10.7% in level I, level II, and level III ($P = 0.03$), respectively.

Of 19 patients who died, 10 patients belonged to level III and 6 patients belonged to level II ($P = 0.007$) (Table 2).

Regarding survival analysis, the median DFS was 12.7 months and the median OS was 54.9 months for all patients. For level I, level II, and level III, the DFS was 23.2 months, 12.7 months, and 10.7 months ($P < 0.001$), and for OS, it was 61.9 months, 52.3 months, and 28.7 months ($P < 0.001$), respectively (Figures 2 and 3).

Discussion

In the current work, poor prognostic clinico-pathological features were more common in level II and level III patients (overweight and obese patients) with localized MIBC. Smoking was found in 51.0% and 36.7% of level II and level III patients, respectively, compared with 12.2% in level I. After NAC, the pCR was 34.3%, 25%, and 10.7%, DFS was 23.2 months, 12.7 months, and 10.7 months, and OS was 61.9 months, 52.3 months, and 28.7 months of level I, level II, and level III ($P = 0.03$), respectively.

The association of obesity and smoking reported in our study is in line with a cross-section study done by Dare et al. on 499-504 adults to assess the relationship between obesity and smoking status. They reported that the risk of obesity proportionally correlated with the smoking amount more in former heavy smokers compared with former light smokers.[14] Moreover, a population-based study on Korean patients showed that MIBC correlated with BMI ($P < 0.01$, for trend).[15] Opposite results were reported in a previous epidemiological study which included 23,106 Japanese adults[16] based on a trial carried out using the Lung Health Study data.[17]

The differences in results may be attributed to the study population, demographic features, and/or smoking stratification (e.g. former smokers' vs. current smokers and heavy vs. light smokers).

All of our patients with ECOG PS 2 belonged to level III, indicating the association between poor PS and obesity, which is compatible with many previous studies.[18-20]

In the current study, the pCR rate was 24.3% which is close to the range of pCR rate reported previously (25%-29.2%). DFS was 12.7 months and OS was 54.9 months, which were worse in level II and level III than in level I. A prospective study included 72 patients with localized MIBC who received NAC; the pCR was detected in 29.2%, which correlated with survival outcome in both OS and DFS.[21] Also, Galsky et al. reported the same rate of pCR (29% and 31%) after NAC using either MVAC or GC regimens in patients with localized MIBC.[22] Moreover, Yuh et al. carried out a pooled analysis involving seven studies which showed that pCR was 25.6% after NAC.[23]

There are a lot of controversies regarding the impact of BMI on MIBC. A retrospective multicentre review study including 12 centres worldwide using the data of 4118 patients treated with NAC followed by RC revealed that obesity was associated with worse survival outcomes.[24] In another study done by Ferro et al., both obesity and overweight were correlated with local tumour recurrence and progression.[25] Moreover, Batty et al. conducted a prospective study on 18,000 adults, indicating the increased risk of MIBC-related death.[26] A meta-analysis conducted by Lin et al. on 11 studies reported that MIBC recurrence rate was statistically higher in obese compared with

average weight patients.[27]

On the contrary, Kwon and colleagues reported that obesity and overweight were associated with favourable clinicopathological features and better survival outcomes compared with average BMI.[28]

Of note, other studies failed to demonstrate a significant relationship between obesity and BMI.[29,30] In a large prospective trial by Calle et al. on 900,000 patients, a non-significant association was observed between obesity and MIBC recurrence.[7]

The link between high BMI and poor outcome could be related to several reasons. Obesity may accelerate tumour development via delivering more than enough substrate, which is necessary for the propagation of lipid membrane and ATP production. Although most of the tumour cells depend on glycolysis for energy production, other cells could use beta-oxidation in that location.[31-34]

Referring to the ovarian model, Nieman et al. reported that tumour cells might be fed fatty acids which are produced from nearby adipose depots.[35] Therefore, excess lipid store intraperitoneal in obese patients may support cancer progression.[36] Thus, using agents that regulate β-oxidation, because they work on fatty acids' passage to the mitochondria, may be a promising therapy, particularly in cancer cells depending on beta-oxidation.[32- 34]

Although BMI is the classic method for evaluating adiposity, it does not consider the other component elements of weight. In the case of cancer patients, it is quite different, as many cancers-related factors affect body weight. Recently, the skeletal muscle and adipose contents can be measured through image-processing software from computed tomography images. Via this software, the research workers can follow up cancer progression as well as obtain the exact measures of both skeletal muscle and adiposity instead of depending on BMI as the only surrogate marker.[37]

Under certain conditions such as pregnancy a body building, BMI is less accurate in the assessment of fat in the body building they may have little fat despite having a high BMI.[38]

There is a lack of data on the impact of overweight and obesity on drug pharmacokinetics. This is because most of the trials excluded obese patients due to the common associations between obesity and multiple co-morbidities.[39]

Generally, obesity impacts the pharmacokinetics of some chemotherapy through alternating the clearance and/or volume of distribution. In a pharmacokinetic study including 1,206 cancer patients, Sparreboom et al. divided patients into two groups based on BMI: obese ($\geq$ 30 kg/m^2) and lean ($\leq$25 kg/m^2). They reported a statistically significant increased clearance for paclitaxel, cisplatin, and troxacitabine (P = 0.023), while for it was reduced for doxorubicin (P = 0.013). Furthermore, they found a higher volume distribution for carboplatin, doxorubicin, and paclitaxel in obese patients. Due to this difference in pharmacokinetics in obesity, establishing a proper dose in obese patients is a challenge.[40]

Collectively, we believe that obesity could affect patient care due to multiple co-morbidities and lack of investigations related to technical difficulties as well as the association with aggressive disease behaviour because obesity is the most preventable disease. Thus, more efforts are needed in obesity prevention to control and improve the outcome of many diseases.

Limitations

Our study had some drawbacks. The retrospective nature of the study is usually accused of bias. BMI is not an ideal surrogate marker for obesity as it does not reflect the internal fat distribution, be it visceral or subcutaneous. Moreover, smoking intensity and duration were not involved in the evaluation of smoking history.

Conclusion

Obesity and overweight could be predictive and prognostic markers in localized MIBC. They are associated with low pCR after NAC, poor DFS, and OS. These findings may be of value regarding the evolution of risk-adapted therapy and clarification of serious obesity effects, which may assist in developing a relevant healthcare policy. Owing to the rising rate of obesity, more effort is required to ensure the biological

mechanisms attributed to obesity-associated carcinogens.

Conflict of Interest

None declared.

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