The Effect of Body Mass Index on Oncological and Surgical Outcomes in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Multicenter Study of the Association of Urooncology, Turkey

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August 28, 2020

Abstract

Objective: We aimed to evaluate the effect of body mass index (BMI) on oncological and surgical outcomes in patients who underwent radical cystectomy (RC) for bladder cancer (BC). Materials and Methods We retrospectively assessed data from patients who underwent RC with pelvic lymphadenectomy and urinary diversion for BC recorded in the bladder cancer database of the Urooncology Association, Turkey between 2007 and 2019. Patients were stratified into three groups according to the BMI cut-off values recommended by the WHO; Group 1 (normal weight, <25 kg/m2), Group 2 (overweight, 25.0–29.9 kg/m2) and Group 3 (obese, [?]30 kg/m2) Results In all, 494 patients were included, of them 429 (86.8%) were male and 65 (13.2%) were female. The median follow-up was 24 months (12-132 months). At the time of surgery, the number of patients in groups 1, 2 and 3 were 202 (40.9%), 215 (43.5%) and 77 (15.6%), respectively. The mean operation time and time to postoperative oral feeding were longer and major complications were statistically higher in Group 3 compared to Groups 1 and 2 (p=0.019, p<0.001 and p=0.025 respectively). Although the mean overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS) and metastasis-free survival (MFS) was shorter in cases with BMI [?]30 kg/m2 compared with other BMI groups, differences were not statistically significant (p=0.532, p=0.309, p=0.751 and p=0.213 respectively). Conclusion Our study showed that, although major complications are more common in obese patients, the increase in BMI does not reveal a significant negative effect on OS, CSS, RFS, and MFS.

Materials and Methods

We retrospectively assessed data from patients who underwent RC with pelvic lymphadenectomy and urinary diversion for BC recorded in the bladder cancer database of the Urooncology Association, Turkey between 2007 and 2019. Patients were stratified into three groups according to the BMI cut-off values recommended by the WHO; Group 1 (normal weight, <25 kg/m^2), Group 2 (overweight, 25.0–29.9 kg/m^2) and Group 3 (obese, [?]30 kg/m^2)

Results

In all, 494 patients were included, of them 429 (86.8%) were male and 65 (13.2%) were female. The median

follow-up was 24 months (12-132 months). At the time of surgery, the number of patients in groups 1, 2 and 3 were 202 (40.9%), 215 (43.5%) and 77 (15.6%), respectively. The mean operation time and time to postoperative oral feeding were longer and major complications were statistically higher in Group 3 compared to Groups 1 and 2 (p=0.019, p<0.001 and p=0.025 respectively).

Although the mean overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS) and metastasis-free survival (MFS) was shorter in cases with BMI [?]30 kg/m^2 compared with other BMI groups, differences were not statistically significant (p=0.532, p=0.309, p=0.751 and p=0.213 respectively).

Conclusion

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Keywords: Bladder cancer, radical cystectomy, body mass index, obesity

Introduction

Bladder cancer (BC) is the eleventh most diagnosed cancer in both sexes. The worldwide age-standardized incidence rate is 9.0 cases per 100,000 per year for men and 2.2 for women [1]. Approximately 75% of patients diagnosed with BC have mucosal disease and 15-25% have muscle invasive BC [2]. EAU Guidelines report that radical cystectomy (RC) is the standard treatment for localized MIBC and suggests for non-invasive tumors with the highest risk of progression[1].

Complications related to RC may be directly related to surgery, intestinal anastomosis or urinary diversion, other than previously existing comorbidity [3]. Early complications such as perioperative blood transfusion and gastrointestinal complications occur in 55–78% and major complications in 32% of the patients[4]. Late complications include urinary tract infection, kidney dysfunction, stone formation, metabolic complications, and relapse of the disease. Peri-operative mortality for RC and urinary diversion was reported as 2.3-8.0% at 90 days [1]. Increased BMI, High American Society of Anesthesiologists (ASA) score, bleeding, and Charlson Comorbidity Index (CCI) are among the known causes of perioperative complications [5]. Patients undergoing RC for BC, the 5-year recurrence-free survival (RFS) rate was 58%, cancer-specific survival (CSS) was 66% and overall survival (OS) was 66% [6,7]. Some of the most significant predictors of OS of RC with urinary diversion are age, ASA, smoking habits, stage, grade, nodal status, neoadjuvant chemotherapy, general condition status and delay from the first symptoms to surgery [8].

The effect of body mass index (BMI) on oncological and surgical outcomes of RC with urinary diversion is controversial. A number of studies examining the role of BMI in patients with BC report that high BMI is associated with a high risk of BC development and disease recurrence, negatively affecting cancer-specific mortality and surgical morbidity[2,9,10]. However, conflicting findings have also been reported which showed that BMI does not affect disease-specific survival after RC, and the complication, transfusion rates, and length of hospital stay are similar [11-14]. In this multicenter study, we tried to evaluate the effect of increased BMI on surgical and oncological outcomes of BC patients treated with RC, using the BC database of the Urooncology Association, Turkey

Materials and Methods

Patient selection

We retrospectively assessed data from patients who underwent RC with pelvic lymphadenectomy and urinary diversion for BC recorded in the BC database of the Urooncology Association, Turkey between 2007 and 2019. All procedures were performed by 8 experienced surgeons from six different institutions. RC with pelvic lymphadenectomy and urinary diversion was performed for localized MIBC or non-muscle-invasive tumors who \soutare were at highest risk of progression. The extensiveness of pelvic lymphadenectomy and the type of urinary diversion was at surgeons' discretion. Patients with concurrent presence of upper urinary tract carcinoma or/and the history of cancer other than bladder cancer or/and patients underwent robotic assisted RC due to low number or/and missing variables were excluded.

Data Collection

Patients were stratified into three groups according to WHO guidelines; Group 1 (normal weight, <25 kg/m^2), Group 2 (overweight, 25.0–29.9 kg/m^2) and Group 3 (obese, [?]30 kg/m^2) [15]. Data items included demographic characteristics such as age, gender, presence of diabetes, coronary artery disease, hypertension, ASA score, ECOG performance status score, operative data including surgical approach, type of diversion and lymph node dissection were recorded and analyzed. The complications were classified according to the modified Clavien system and were retrospectively analyzed [16]. Pathological specimens were evaluated at each institution's pathology department using Tumor Node Metastasis classification for staging and the 2004 World Health Organization classification for grading. Ethics committee approval for the study was obtained from the ethics committee of the University of Çukurova (approval number- September 4,2019;91/60).

Follow up

Similar follow-up protocol was used at each center. The patients were seen initially 1 month after surgery, then every 3 months for the first year, every 6 months for the second year and annually thereafter. The follow-up visits consisted of a physical examination and laboratory studies. Imaging modalities including chest radiography, abdominal CT or ultrasonography were applied at least every 6 months or when clinically indicated.

The primary outcome measures in this study were overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), metastasis-free survival (MFS) and disease free survival (DFS). Duration of follow-up was the time from surgery to the date of death or last clinic visit.

Statistical Analysis

All analyzes were done with IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, while continuous variables were summarized as mean and standard deviation as well as median and minimum-maximum if necessary. The chi-square test was used to compare categorical variables between the groups. For non-normal distributed data, Kruskal Wallis test was used to compare more than two groups. For univariate analysis event free survival was calculated by Kaplan-Meier method and log rank test was performed. Cox regression analysis was performed to determine significant predictors of OS and CSS variable. In univariate analysis, variables significant at the P <0.1 level were entered in Cox regression analysis. The statistical level of significance for all tests was considered to be 0.05.

Results

A total of 494 patients were eligible for final analyses, of them 429 (86.8%) were male and 65 (13.2%) were female. The mean age of the patients was 64.3±9.2 years (range 59.0-70.0 years).

The open RC 419(85.3%) was performed more frequently compared with laparoscopic approach 72(14.7%) (p=0.008). The median follow-up time was 24 months (12-132 months).

Among 494 patients, 202 (40.9%) had normal BMI (Group 1), 215 (43.5%) were over-weighted (Group 2) and 77 (15.6%) were obese (Group 3) at the time of surgery. Demographic and clinical characteristics of these groups are presented in **Table 1** . These BMI groups were similar in terms of characteristics in **Table 1** , except gender and ECOG performance status (p=0.002 and p<0.001 respectively). We found that ECOG performance status 0 and 1 was statistically significantly higher in Group 1 and Group 3, respectively (p=<0.001)

Operative Outcomes

Operative characteristics of the patients are listed in **Table 2.** There were no statistically significant differences in urinary diversion type, drain and nasogastric tube withdrawal time, intestinal motility, mobilization and length of stay between the groups. Open RC was performed in 419 (84.8 %) patients and 75 (15.2 %) patients underwent laparoscopic RC (p=0.008). The mean operative time was 317.1±92.1, 339.2±112.1, and

360.6±120.2, in Group 1, 2 and 3, respectively. Among the groups, more convenient inferences were obtained in Group 3, including longer operation time and oral feeding start (p=0.019, p<0.001). Patients' readmission to hospital within 30 and 90 days of surgery were 13.2% and 16.2%, respectively, and there was no difference between the groups (p=0.710, and p=0.275 respectively). The mean number of removed lymph nodes was 19.5±14.9, 20.1±12.8 and 19.3±10.4 in Group 1, 2 and 3, respectively. There was no difference between the 3 groups in terms of lymph node positivity (p=0.210). Groups were also similar in terms of surgical margin positivity (p=078).

Perioperative complication was seen in 17(8.4%), 4(1.9%) and 5(6.5%) patients in Group 1, 2 and 3, respectively and Group 2 had significantly fewer complication rate\souts compared with Group 1 and 3 (p=0.01). Statistically significant major complication rate was observed in Group 3 compared to Group 1 and 2 (p=**0.025**). There was no significant difference between groups in terms of transfusion (perioperative, postoperative) and readmission rates (30-day, 90-day) (**Table 3**). All of the pathological characteristics of the patients were found to be similar among the groups (**Table 4**).

Survival Outcome

Although the mean OS and CSS was shorter in cases with BMI>29.9kg/m2 compared with other BMI groups (74.2 vs. 84.4 and 94.2 months for OS, 97.5 vs. 105.1 and 101.0 months for CSS, respectively), the differences were not statistically significant (p=0.532 and p=0.309, respectively) **(Figure 1).** A Cox proportional hazards model was used to evaluate the potential predictors for OS and CSS and the results are shown in **Table 5** . Analysis revealed that OS and CSS was significantly associated with "Lymphovascular invasion" (HR: 2.17, 95% CI: (1.30-3.60); p=0.003 (OS), HR: 2.55, 95% CI: (1.30-4.98); p=0.006 (CSS)). In multivariate analysis, "pN+: N2" (HR: 4.80, 95% CI: (2.79-8.24); p<0.001 (OS), HR: 4.11, 95% CI: (1.90-8.90); p<0.001 (CSS)) was found to be the independent prognostic factor for OS and CSS. The association between increased BMI and mortality was not statistically significant in analysis (p>0.05). Although the mean RFS and MFS was shorter in cases with BMI>29.9kg/m2 compared with other BMI groups, there was no statistically significant difference between BMI groups in terms of RFS and MFS (p=0.751 and p=0.213 respectively)

(Figure 2).

Discussion

The prevalence of being overweight or obese has increased by 27.5% for adults, and obesity continues to be a major health problem worldwide[17]. The risk for multiple medical problems that can adversely affect surgical outcomes is increased in obese patients[18]. The relationship of BMI with bladder cancer and radical cystectomy has been the subject of scientific research in the past decade. However, in the literature, the results regarding the effect of obesity on the surgical and oncological outcomes of patients after RC for BC are still contradictory [2,9-12]. In this study, we evaluated the effect of BMI on oncologic and surgical outcomes in patients who underwent radical RC for BC. We found that the operation time and oral feeding start were longer and major complications were more common in obese patients. The results revealed that the mean OS, CSS, RFS, and MFS was shorter in cases with BMI>29.9kg/m2 compared with other BMI groups, however, the differences were not statistically significant.

Due to greater technical challenges, many studies reported that increased BMI is independently associated with perioperative and postoperative risks after RC. In a study on 1293 patients who underwent radical cystectomy, Tyson MD et al., by comparing patients with BMI<30 and patients with BMI [?]30, found that obese patients had longer operation time and more renal failure and \soutthey noted no differences in 30-day mortality after RC [19]. In another study, Maurer \soutand T et al, by comparing normal weight, and overweight patients who underwent RC, revealed that there was no significant difference according to intraoperative blood transfusion rate, postoperative TNM stage, and postoperative complications. They noted that the time of surgery was significantly prolonged and postoperative bleeding was more common in overweight patients[13]. After analyzing the data of 671 patients who underwent radical cystectomy, Gierth M et al reported that, there was no significant relationship between obesity and tumor stage, grade, lymph

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node metastasis, blood loss, urinary diversion type, and 90-day mortality. Severe complications within 30 days after RC, blood transfusion rates were higher and the mean operation time was longer in patients with BMI [?]30 kg/m^2 compared to the other BMI groups [20]. Another study by Lee et al showed that number of complications is higher in obese patients, but complication severity was similar between BMI groups [21]. In our study, statistically significant major complication rate was observed in Group 3 compared to Group 1 and 2 (p=**0.025**).

Increased BMI is associated with risk for many cancers, including urological cancers. It is also thought that cancer is associated with poor prognoses [22-24]. Many studies \soutevaluating examined the relationship between obesity and oncological outcomes of RC[2,11,12,20,25]. In multivariable analysis of 4118 RC patients due to BC, Chromecki et al found that patients with BMI> 30 had higher disease recurrence (HR 1.67, 95% CI 1.46 − 1.91, P < 0.001), lower CSS (HR 1.43, 95% CI 1.24 − 1.66, P < 0.001), and lower OS (HR 1.81, CI 1.60 − 2.05, P < 0.001). They thought that, this finding might be related to the metabolic syndrome seen in obese patients [25]. In another study, Dabi et al. found that the risk of disease recurrence or cancer-specific mortality increased by 1.5 fold for obese patients. They reported that increased BMI is an independent prognostic factor for oncological results of BC patients who underwent RC [2]. In literature, conflicting findings have also been reported. In a retrospective study, which analyzed the data of 300 patients who underwent cystectomy (radical or partial) due to BC and whose median follow-up was 39 months, Hafron J et al showed that the increase in BMI has no effect on OS or disease-specific survival in univariate or multivariate analysis. In addition, they found that age over 65 years, tumor stage, smoking, and the positive tissue margin were significant factors affecting OS [11]. Also, Gierth et al. found that increased BMI had no effect on survival and not associated with more aggressive tumor biology [20]. On the other hand, Kwon et al reported that overweight and obesity were associated with favorable pathological features and prognosis in patients with bladder cancer undergoing radical cystectomy [12]. Our study showed that the increase in BMI does not have a statistically significant negative effect on DSS and OS

The surgical approach is another point of discussion. The guidelines have recommended that none of the surgical approaches (open-, laparoscopic- or robotic RC) has clearly shown superiority in terms of functional or oncological results. In the CORAL study, a prospective study by Khan et al, the authors found no difference in 5-yr RFS, CSS, and OS rates of patients who underwent open, laparoscopic and robotic radical cystectomy for management of bladder cancer. Minimally invasive techniques achieved equivalent oncological outcomes to the gold standard of ORC [26]. After analyzing robot-assisted radical cystectomy (RARC) cases, Butt et al found that, overweight and obese patients had similar complication rates, operative times and estimated blood loss compared with patients with normal BMI [27]. Ahmadi et al showed that, BMI was not associated with significant differences in peri-operative, pathological or early oncological outcomes in patients undergoing RARC [28]. In our study, we did not include the RARC cases, as the number of those patients was very low. We found no statistically significant effect of surgical approach (open or laporoscopic) in terms of OS and CSS.

The present study has some limitations. Data collection and analysis was retrospective and non-randomized. Therefore, unidentified confounding variables may have an effect on the results. Another limitation was the performance of procedures by 8 high-volume surgeons in 6 different centers. However, this limitation is always present in such multicenter studies. Moreover, lack of central pathologic assessment is also a limitation.

Conclusion

We conclude that, although major complications are more common in obese patients, the increase in BMI does not reveal a significant negative effect on OS, CSS, RFS and MFS.

Across the spe ctrum of obese patients undergoing RARC with intracorporeal diversion, quality of surgery, postoperative data, pathological outcomes, complications and readmission rates were similar. Early onco-logical outcomes were also similar amongst patients in all four BMI categories. We conclude that, given an experienced robot-assisted surgery team, RARC with intracorporeal diversion is an effective option for over-weight, obese and morbidly obese patients with bladder cancer who are considering RC. Across the spectrum

of obese patients undergoing RARC with intracorporeal diversion, quality of surgery, postoperative data, pathological outcomes, complicationsand readmission rates were similar. Early oncological outcomes were also similar amongst patients in all four BMI categories. We conclude that, given an experienced robot-assisted surgery team, RARC with intracorporeal diversion is an effective option for overweight, obese and morbidly obese patients with bladder cancer who are considering RC.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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