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ORIGINAL ARTICLE

Laparoscopic surgery after neoadjuvant therapy in elderly patients with rectal cancer

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Summary

Purpose: *The standard treatment for mid or low locally advanced rectal cancer is neoadjuvant therapy followed by surgical resection. Laparoscopic surgery has recently been applied for the treatment of rectal cancer. However, few studies have reported the outcomes of laparoscopic surgery for elderly patients with rectal cancer after neoadjuvant therapy. This study aimed to investigate the short- and long-term outcomes of laparoscopic surgery for elderly patients with rectal cancer after neoadjuvant therapy.*

Methods: *Patients received a total dose of 50.4 Gy over 5.5 weeks (45 Gy in 25 fractions to the pelvid and 5.4 Gy boost in 3 fractions to the primary tumor). Laparoscopic surgery for rectal cancer after neoadjuvant therapy was performed at our hospital on 89 elderly patients aged 75 years or older (the elderly group) from January 2008 to January 2016. Outcomes of the 89 patients were compared to those of 269 patients younger than 75 years enrolled during the same time period (the nonelderly group).*

Results: *Compared with the nonelderly group, the Charlson comorbidity index (CCI) and American Society of Anesthesiologists (ASA) scores were higher in the elderly group. For short-term outcomes, there were no statistically significant differences. Differences between the two groups in the 5-year overall survival (OS) rate and 5-year disease-free survival (DFS) rate were not statistically significant.*

Conclusion: *Although the CCI was higher in elderly patients than in the nonelderly patients, laparoscopic surgery after neoadjuvant therapy was safe and effective in elderly patients with rectal cancer. Therefore, in the absence of any contraindications, laparoscopic surgery after neoadjuvant therapy is an appropriate treatment approach for elderly patients with rectal cancer.*

Key words: *elderly patients, laparoscopic surgery, minimally invasive surgery, neoadjuvant therapy, rectal cancer*

Introduction

Improvements in the standards of living and medical care have resulted in an increase in the proportion of elderly people among the general population [1-3]. Improvements in cancer-screening techniques and the increase in human life span have contributed to an increased incidence of rectal cancer in the elderly [4]. Consequently, there has also been an increasing trend in the number of elderly patients (aged 75 years or older) with rectal cancer [4]. However, given that the elderly patients are more likely to develop impaired organ function, medical comorbidities, limited life expectancy, and are at higher risk of postoperative complications and higher mortality rate, some physicians believed that advanced age is a contraindication for radical surgery in patients with rectal cancer [5-7]. However, with the improvement of surgical operative techniques and intensive care in recent years, advanced age is no longer regarded as a limiting factor for surgery. As there are no obvious symptoms in early-stage rectal cancer, the majority of cases are in the locally advanced stage, when diagnosed [5-7]. For the treatment of mid or low locally advanced rec-

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tal cancer, the standard therapeutic treatment is to perform neoadjuvant therapy followed by surgical resection [8]. Large randomized controlled clinical trials have suggested that laparoscopic surgery for locally advanced rectal cancer after neoadjuvant therapy is characterized by minimal blood loss and short hospitalization, as well as oncological outcomes similar to those of traditional laparotomy [9-13]. However, elderly patients were excluded from the aforementioned trials to ensure trial success [14,15]. Few reports have been published on neoadjuvant therapy and laparoscopic surgery performed on elderly patients. This study aimed to compare the short- and long-term outcomes of neoadjuvant therapy and laparoscopic surgery among elderly and non-elderly patients diagnosed with rectal cancer.

Methods

This retrospective study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. The need for informed consent from all patients was waived because the study was retrospective.

A total of 489 patients with rectal cancer underwent laparoscopic surgery after neoadjuvant therapy at our hospital from January 2008 to January 2016. The inclusion criteria were as follows: pathological diagnosis of rectal adenocarcinoma; clinical stage T3N+; having undergone laparoscopic surgery after long-term neoadjuvant chemoradiotherapy; and no other visceral organs resected. Patients were excluded if they had a history of emergency surgery or incomplete clinical information. A total of 358 patients were eligible to participate in this study and were divided into the elderly group (aged 75 years or older, n=89) and the nonelderly group (aged younger than 75 years, n=269) according to their age at the time of surgery. Short- and long-term outcomes were compared between the elderly and the non-elderly group.

All enrolled patients underwent examinations such as endoscopy, pelvic magnetic resonance imaging (MRI), and thoracic and abdominal computed tomography (CT) before treatment in order to determine their clinical stages. Positron-emission tomography (PET)-CT or a bone scan was performed when necessary. Patients with clinical stage T3N+ were first subjected to neoadjuvant chemoradiotherapy. A total dose of 50.4 Gy was delivered which included 45 Gy in 25 fractions to the pelvis and 5.4 Gy boost in 3 fractions to the primary tumor over 5.5 weeks. Chemotherapy administered consisted of i.v. bolus 5-fluorouracil (400 mg/m^2/day) and racemic D L-leucovorin (20 mg/m^2/day) for 3 days in the first and fifth week of radiotherapy [9].

Laparoscopic surgery was performed after 6-8 weeks of neoadjuvant chemoradiotherapy [9-13]. The surgical techniques used have been previously described [9].

The severity of the 30-day postoperative complications was evaluated using the Clavien–Dindo classification. A mild complication was defined as Grade 1 and 2, and a severe complication was defined as Grade 3 to 5 [16-22]. Postoperative 30-day mortality was defined as death due to any cause 30 days after the operation.

Follow-up was realized with visits to surgery clinics, home visits, and physicians' correspondence with patients. Follow-up was conducted once every 3 months in the first postoperative year and once every 6 months in the second postoperative year. After that, the follow-up was conducted once a year. The final follow-up was conducted in October 2016.

Statistics

SPSS software 13.0 for Windows version (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Variables following a normal distribution were presented as mean±standard deviation, and were analyzed using the Student's *t*-test. Variables following a non-normal distribution were expressed as median and range, and were compared using the Wilcoxon test. Differences in the semiquantitative results were analyzed using the Mann-Whitney *U* test. Differences in the qualitative results were analyzed using the chi square (x^2) test or Fisher's exact test, as appropriate. Survival rates were analyzed using the Kaplan-Meier method, and differences between the two groups were analyzed using the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS. Univariate variables with $p< 0.05$ were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated and $p< 0.05$ was considered statistically significant.

Results

The baseline characteristics of study participants are listed in Table 1. The elderly group had significantly higher CCI and ASA scores than the nonelderly group. Additional baseline characteristics including sex, body mass index, tumor location, and clinical stage did not differ significantly between groups.

Short-term outcomes of the patients are shown in Tables 2 and 3. There were no statistically significant differences in operation time, intraoperative blood loss, conversion rate, days of hospitalization, and pathological results (TNM stages, tumor differentiation, circumferential resection margin and resection margin) between the two groups. Regarding the postoperative 30-day mortality rate and postoperative 30-day complications, no cases of mortality were observed after the postoperative day 30 in the two groups. No statistically significant differences in the incidence of complications and incidence of major complica-

Table 1. Baseline characteristics of the two groups

	Elderly (n=89) n	*Nonelderly (n=269)* n	*p value*
Age (y), n (range)	77 (75-81)	61 (54-74)	0.000
Gender (Male:Female)	51 : 38	168: 101	0.387
BMI (kg/m²), median (range)	21 (18-26)	23 (20-28)	0.230
ASA score			0.000
I	23	174	
II	38	63	
III	28	32	
Clinical TNM stage			0.911
II	21	59	
III	47	119	
Charlson comorbidity index			0.000
< 4	25	199	
≥ 4	64	103	
Tumor location (distance from anal verge, cm)			0.300
Middle rectum (5-10)	43	147	
Lower rectum (<5)	46	122	

BMI: body mass index

Table 2. Short-term outcomes of the two groups

	Elderly (n=89)	*Nonelderly (n=269)*	*p value*
Operative time, min (range)	170 (150-230)	160 (140-250)	0.250
Blood loss, ml (range)	180 (140-310)	170 (130-280)	0.109
Conversion to laparotomy, n	7	19	0.392
Hospitalization, days, median (range)	13 (10-29)	11 (8-24)	0.201
Type of resection, n			0.106
Low anterior	70	231	
Abdominoperineal	19	38	
Patients with post-operative complications, n	15	27	0.083
Patients with major complications, n	3	8	1.000
Postoperative 30-day death	0	0	-

tions between the two groups were noticed.

The median follow-up time for all recruited patients in this study was 42 months (38 months in the elderly group and 43 months in the nonelderly group). The difference was not statistically significant (p=0.352). At the time of the final follow-up, there were 18 (20.2%) deaths in the elderly group and 68 (25.2%) deaths in the nonelderly group (Table 4). Among them, most of the deceased patients died of tumor relapse, while a few in the elderly group died of non-tumor related diseases such as cerebral stroke and

Table 3. Pathological outcomes of the two groups

	Elderly (n=89) n	*Nonelderly (n=269)* n	*p value*
Pathological stage (pTNM)			0.753
pCR	5	14	
I	27	76	
II	31	99	
III	26	80	
Histologic differentiation			0.727
Good	29	81	
Moderate	33	104	
Poor	27	84	
Circumferential resection margin (mm)			0.851
Positive (≤1)	3	8	
Negative (>1)	86	261	
Residual tumor (R0/R1/R2)	88/1/0	267/2/0	0.733

pCR: pathological complete response after neoadjuvant therapy

Table 4. Follow-up data of the two groups

	Elderly (n=89) n	*Nonelderly (n=269)* n	*p value*
Tumor recurrence, n	19	71	0.342
Locoregional	7	21	0.544
Distant	8	26	0.661
Mixed	4	24	0.286
Time to recurrence, months, median, (range)	19 (10-65)	21 (9-49)	0.690
Mortality	18	68	0.333
Died of cancer	15	61	0.244
Died of non-cancer-related diseases	3	7	0.992

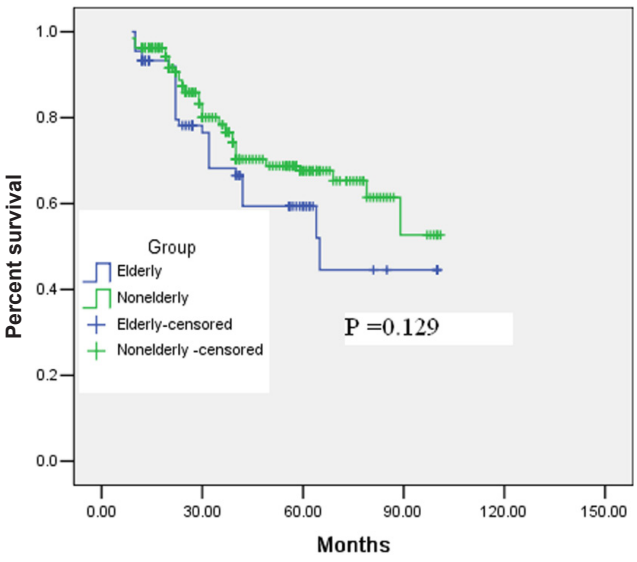

Figure 1. Comparison of overall survival shows no significant difference between elderly and nonelderly group.

myocardial infarction. The difference in mortality rates was not statistically significant (Table 4). The 5-year OS rate was 59% in the elderly group and 64% in the non-elderly group (p=0.129, Figure 1). Multivariate analysis suggested that stage T and N were two independent predictors for the OS rate (Table 5).

Five-year DFS rate was 57% in the elderly group and 61% in the non-elderly group, and this difference was not statistically significant (p=0.286, Figure 2). Multivariate analysis suggested that N stage and tumor differentiation were two independent predictors for the DFS rate (Table 6).

Table 5. Multivariate analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Pathological T stage			
T_0-T_2	1.00		
T_3-T_4	2.06	1.32–2.90	0.020
Pathological N stage			
N_0-N_1	1.00		
N_2	1.90	1.65–3.09	0.010

Table 6. Multivariate analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Pathological N stage			
N_0-N_1	1.00		
N_2	2.30	1.54–3.27	0.019
Differentiation grade			
Well–Moderate	1.00		
Poor	2.49	1.89–3.40	0.008

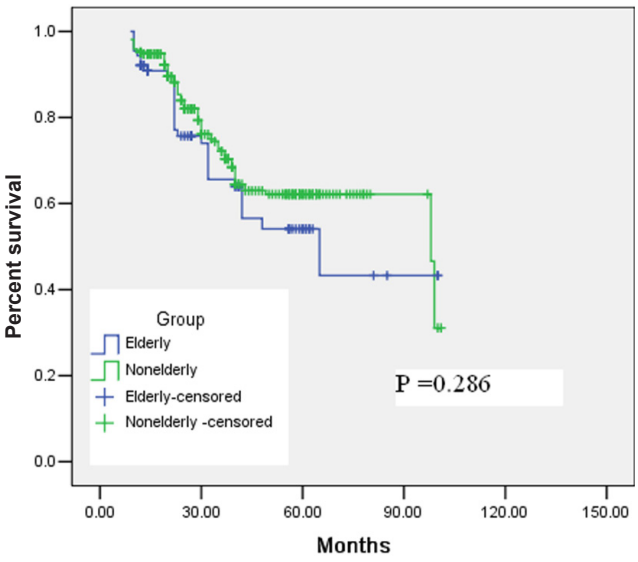

Figure 2. Comparison of disease-free survival between elderly and nonelderly group shows non significant difference.

Discussion

This study showed that elderly patients with rectal cancer who were subjected to laparoscopic surgery after neoadjuvant therapy were able to attain short- and long-term outcomes similar to nonelderly patients. Both the postoperative 30-day mortality rate and the incidence of postoperative 30-day complications in the elderly group were significantly lower than those in previously reported large-sample studies on laparotomy [1-4]. This fully demonstrates the minimally invasive characteristic of laparoscopic surgery. Moreover, this study also showed that approximately 30% of the patients in the elderly group had an ASA classification score, and despite this, their short-term outcomes were similar to those in the nonelderly group [23-26]. Long-term follow-up results indicated that only a few patients in the elderly group died of non-tumor diseases while most died of tumor relapse, which further potentiates the claim that active treatments for elderly patients with rectal cancer may increase their survival rate [27,28].

The standard treatment for mid or low locally advanced rectal cancer is neoadjuvant therapy followed by surgical resection [29]. Laparotomy for rectal cancer involves a large incision in the abdomen, which doesn't help to postoperative recovery [30]. In the past, some surgeons were reluctant to perform radical surgery on elderly patients with rectal cancer, largely due to the surgeons' concerns about postoperative complications [30-32]. However, laparoscopic surgery requires only 5 small incisions to access the abdominal cavity, and to resect and excise the tumors [33]. Some researchers believed that the pneumoperitoneum in laparoscopic surgery was likely to cause postoperative cardiopulmonary complications in elderly patients [28-30]. However, this study showed that no cardiac complications were observed in the elderly group, and only 4 cases showed pulmonary infections. All 4 patients were treated with intravenous administration of antibiotics, and the pulmonary infections belong to minor postoperative complications according to the Clavien–Dindo classification.

Some surgeons believed that most elderly patients with rectal cancer would die of non-tumor diseases owing to their limited life expectancy [30-32]. Therefore, resection was considered to have limited value for the treatment of rectal cancer. In this study, however, most of the deceased patients in the elderly group died of tumor relapse while only a few died of non-tumor diseases. Moreover, the two groups of patients in this study had simi-

lar OS and DFS rates. The observed survival rate in this study was also similar to that in previous large-sample studies [9-12]. The life expectancy of elderly patients in China has recently shown an increasing trend, thereby indicating that age is no longer a limiting factor for radical surgery for rectal cancer [37-40].

A limitation of this study is that it is a retrospective single-center study with a small sample size. However, to the best of our knowledge, this study has the largest sample size among studies on laparoscopic surgery after neoadjuvant therapy for elderly patients with rectal cancer. Hence, we claim that it has laid the foundations for future large-sample multicenter studies. A randomized controlled trial with longer follow-up and a larger sample size is required to further validate the results reported in this study.

In summary, the findings in this study indicated that compared to non-elderly patients, the incidence of postoperative complications and the postoperative mortality rate were not increased in elderly patients with rectal cancer who underwent laparoscopic surgery after neoadjuvant therapy. Moreover, they could achieve long-term outcomes similar to those of non-elderly patients. Therefore, age is not a contraindication for surgical resection in elderly patients with rectal cancer.

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Conflict of interests

The authors declare no confict of interests.

References

1. Cavic M, Krivokuca A, Boljevic I et al. Pharmacogenetics in cancer therapy - 8 years of experience at the Institute for Oncology and Radiology of Serbia. J BUON 2016;21:1287-1295.
2. Mahsuni Sevinc M, Riza Gunduz U, Kinaci E et al. Preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as new prognostic factors for patients with colorectal cancer. J BUON 2016;21:1153-1157.
3. Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P. Screening for Colorectal Cancer: A Systematic Review and Meta-Analysis. Clin Colorectal Cancer 2016;15:298-313.
4. Zullig LL, Smith VA, Jackson GL et al. Colorectal Cancer Statistics From the Veterans Affairs Central Cancer Registry. Clin Colorectal Cancer 2016;15:e199-e204.
5. Biondi A, Vacante M, Ambrosino I, Cristaldi E, Pietrapertosa G, Basile F. Role of surgery for colorectal cancer in the elderly. World J Gastrointest Surg 2016;8:606-613.
6. Hubbard JM. Management of Colorectal Cancer in Older Adults. Clin Geriatr Med 2016;32:97-111.
7. Millan M, Merino S, Caro A, Feliu F, Escuder J, Francesch T. Treatment of colorectal cancer in the elderly. World J Gastrointest Oncol 2015;7:204-220.
8. Wrafter PF, Connelly TM, Khan J, Devane L, Kelly J, Joyce WP. The 100 most influential manuscripts in colorectal cancer: A bibliometric analysis. Surgeon 2016;14:327-336.
9. Jeong SY, Park JW, Nam BH et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:767-774.
10. Ng SS, Lee JF, Yiu RY et al. Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial. Surg Endosc 2014;28:297-306.
11. Penninckx F, Kartheuser A, Van de Stadt J et al; and PROCARE. Outcome following laparoscopic and open total mesorectal excision for rectal cancer. Br J Surg 2013;100:1368-1375.
12. van der Pas MH, Haglind E, Cuesta MA et al; and COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-218.
13. Guillou PJ, Quirke P, Thorpe H et al; and MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): Multicentre, randomised controlled trial. Lancet 2005;365:1718-1726.
14. Aparicio T, Pamoukdjian F, Quero L, Manfredi S, Wind P, Paillaud E. Colorectal cancer care in elderly patients: Unsolved issues. Dig Liver Dis 2016;48:1112-1128.
15. Liang J, Fazio V, Lavery I et al. Primacy of surgery for colorectal cancer. Br J Surg 2015;102:847-852.
16. Xiao H, Xie P, Zhou K et al. Clavien-Dindo classification and risk factors of gastrectomy-related complications: an analysis of 1049 patients. Int J Clin Exp Med 2015;8:8262-8268.
17. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications:

five-year experience. Ann Surg 2009;250:187-196.

18. Zhou X, Su M, Hu K et al. Applications of computed tomography pelvimetry and clinical-pathological parameters in sphincter preservation of mid-low rectal cancer. Int J Clin Exp Med 2015;8:2174-2181.
19. Guo C, Zhang Z, Ren B, Men X. Comparison of the long-term outcomes of patients who underwent laparoscopic versus open surgery for rectal cancer. J BUON 2015;20:1440-1446.
20. Dong J, Wang W, Yu K et al. Outcomes of laparoscopic surgery for rectal cancer in elderly patients. J BUON 2016;21:80-86.
21. Sheng W, Zhang B, Chen W, Gu D, Gao W. Laparoscopic colectomy for transverse colon cancer: comparative analysis of short- and long-term outcomes. Int J Clin Exp Med 2015;8:16029-16035.
22. Zeng Y, Tian M. Laparoscopic versus open hepatectomy for elderly patients with liver metastases from colorectal cancer. J BUON 2016;21:1146-1152.
23. Lieffers JR, Baracos VE, Winget M, Fassbender K. A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer 2011;117:1957-1965.
24. Marventano S, Grosso G, Mistretta A et al. Evaluation of four comorbidity indices and Charlson comorbidity index adjustment for colorectal cancer patients. Int J Colorectal Dis 2014;29:1159-1169.
25. Wu CC, Hsu TW, Chang CM, Yu CH, Lee CC. Age-adjusted Charlson comorbidity index scores as predictor of survival in colorectal cancer patients who underwent surgical resection and chemoradiation. Medicine (Baltimore) 2015;94:e431
26. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-1251.
27. Wang CL, Qu G, Xu HW. The short- and long-term outcomes of laparoscopic versus open surgery for colorectal cancer: a meta-analysis. Int J Colorectal Dis 2014;29:309-320.
28. Bissolati M, Orsenigo E, Staudacher C. Minimally invasive approach to colorectal cancer: an evidence-based analysis. Updates Surg 2016;68:37-46.
29. van de Velde CJ, Boelens PG, Tanis PJ et al. Experts reviews of the multidisciplinary consensus conference colon and rectal cancer 2012: science, opinions and experiences from the experts of surgery. Eur J Surg Oncol 2014;40:454-468.
30. Vlad C, Kubelac P, Vlad D, Irimie A, Achimas-Cadariu P. Evaluation of clinical, morphopathological and therapeutic prognostic factors in rectal cancer. Experience of a tertiary oncology center. J BUON 2015;20:92-99.
31. Zhan S, Wang X, Huang X, Zhu H. Magnetic resonance imaging in restaging rectal cancer after neoadjuvant chemoradiotherapy. J BUON 2015;20:62-67.
32. Breugom AJ, Boelens PG, van den Broek CB et al. Quality assurance in the treatment of colorectal cancer: the EURECCA initiative. Ann Oncol 2014;25:1485-1492.
33. Zeng WG, Zhou ZX, Hou HR et al. Outcome of laparoscopic versus open resection for rectal cancer in elderly patients. J Surg Res 2015;193:613-618.
34. Feroci F, Baraghini M, Lenzi E et al. Laparoscopic surgery improves postoperative outcomes in high-risk patients with colorectal cancer. Surg Endosc 2013;27:1130-1137.
35. Vallribera Valls F, Landi F, Espín Basany E et al. Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. Surg Endosc 2014;28:3373-3378.
36. Hu JJ, Liang JW, Wang Z et al. Short-term outcomes of laparoscopically assisted surgery for rectal cancer following neoadjuvant chemoradiotherapy: a single-center experience. J Surg Res 2014;187:438-444.
37. Schiphorst AH, Verweij NM, Pronk A, Borel Rinkes IH, Hamaker ME. Non-surgical complications after laparoscopic and open surgery for colorectal cancer - A systematic review of randomised controlled trials. Eur J Surg Oncol 2015;41:1118-1127.
38. Yiu AJ, Yiu CY. Biomarkers in Colorectal Cancer. Anticancer Res 2016;36:1093-1102.
39. Zaharie F, Ciorogar G, Zaharie R et al. Laparoscopic rectal resection versus conventional open approach for rectal cancer - a 4-year experience of a single center. J BUON 2015;20:1447-1455.
40. Caglar Bilgin B, Kahramanca S, Akin T, Emre Gokce I, Akin M, Kucukpinar T. Factors influencing cost, length of hospital stay and mortality in colorectal cancer. J BUON 2015;20:1023-1029.