Original Article

Determinants of Survival in Cancer Rectum: Our Experience at a Tertiary Care Center

Rashmi Singh, Anup Kumar, Manika Verma, Payal Raina
Department of Radiation Oncology, RIMS, Ranchi, Jharkhand, India

Abstract

Introduction: As per GLOBOCON 2018, colorectal cancer is the seventh leading cancer in India. Our primary aim was to look for various clinical, radiological, and pathological factors in the cancer rectum and their impact on overall survival (OS) and disease-free survival (DFS) at our tertiary care center. **Materials and Methods:** Nineteen patients' clinical and treatment details were compiled from the physical records stored in the department. Calculation of median survival (MS), mean OS, and DFS was done using the Kaplan–Meier method, and the Log-rank test was applied. **Results:** Bleeding per rectum (84.2%), increased serum carcinoembryonic antigen (63.2%), Grade 2 adenocarcinoma (95%), ulceroinfiltrating type (57.89%), and tumor length >5 cm (73.68%), and stage III (57.89%) were most common observation. Fifteen patients underwent upfront surgery, among them 66.6% of cases had ≤12 lymph node removal. 40% (6 / 15) of patients had either proximal ($n = 1$), distal ($n = 2$), or CRM positive ($n = 3$) (3 / 6). The MS was 45 months, and increased mean OS, as well as DFS, was observed in patients having younger age, female sex, stage II, N0, ulcer-infiltrating tumor, tumor length <5 cm, negative margin, abdominoperineal resection, LN resected <12 but *P* value were nonsignificant. **Conclusions:** We observed that increased nodal burden, margin positivity, and advanced T in histopathology are associated with locoregional and distant failure.

Keywords: Ca rectum, disease-free survival, overall survival, prognosis, prognostic factors

Introduction

Rectal cancer is the seventh leading cancer in India. Depth of tumor penetration, no of lymph nodes positive, lymphovascular invasion (LVI), residual tumor postchemoradiotherapy, margin status including circumferential resection margin (CRM), preoperative carcinoembryonic antigen (CEA) value, tumor grade, peripheral nerve invasion, type of histopathology, microsatellite instability (MSI)/high-MSI,[1] number of tumor deposits, and peritoneal disease status[2,3] are various clinic-pathological prognostic factors.

Total colonoscopy, endoscopic biopsy, magnetic resonance imaging of the pelvis, computed tomography (CT) scan of the thorax, CT scan of the abdomen, and serum CEA are standard investigations in a case of Ca rectum.

Multimodality treatment, including radiotherapy (RT), chemotherapy (CT), and surgery for most of the patients is recommended.

Total mesorectal excision (TME) is the standard for surgery with low anterior resection (LAR) and abdominoperineal resection (APR) with the lowest rate of local recurrence (LR).[4]

NACTRT is recommended for all newly diagnosed rectal cancer with T3N0, T3N1/N2, T4 N0/N2, threatened circumferential resection margin (CRM), and tumor abutting intersphincteric plane on imaging. NACTRT reduces the risk of LR, and increases pathological response but did not affect overall survival (OS), disease-free survival (DFS), sphincter preservation, and postoperative mortality than RT alone.[5,6] The total duration of perioperative therapy, including chemo-RT and CT should not exceed 6 months. The wait-and-watch approach for complete responders is also being evaluated.

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Address for correspondence: Dr. Rashmi Singh, Department of Radiation Oncology, RIMS, Ranchi - 834 009, Jharkhand, India.
E-mail: rashmisingh.noor@gmail.com

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We are presenting here our study of Ca rectum with clinical, radiological, pathological, and treatment details, and an assessment of factors affecting OS and DFS.

Materials and Methods

Study design

This retrospective study was conducted at our tertiary care center in the department of radiation oncology. Written informed consent and ethical committee clearance were exempted as it was a retrospective study. The study was conducted using the ethical guidelines outlined in the Declaration of Helsinki and ICMR guidelines.

Sample size

We included all patients as per the inclusion and exclusion criteria. There was no formal sample size calculation.

Study setting

Patients treated with RT in our department for rectal cancer from January 2015 to December 2019 were included for analysis. Patients' Eastern Cooperative Oncology Group (ECOG) performance scale, clinical complaints, staging, N status, imaging findings, serum CEA, type of histology, grade of the tumor, margin status, type of surgery, details of concurrent, adjuvant, and neo-adjuvant CT, RT details which included the position of the patient (supine/prone), technique, dose, fractionation all these were compiled from the physical records stored in the department.

Inclusion criteria

The following were the inclusion criteria: biopsy proved adenocarcinoma cases of cancer rectum, ECOG score of 1–4, age 18–75 years, no previous history of cancer, and having normal laboratory investigations.

Exclusion criteria

Cases with anal cancer, colon cancer, dual malignancy, metastatic, and HIV(+) disease were excluded. Patients' files with incomplete details and RT defaulters were also excluded from this study [Figure 1].

Study variables

Our primary aim was to look for various clinical, radiological, and pathological factors and analysis of OS and DFS.

OS was defined as the date of death from any cause or the date of the last follow-up since the date of registration. DFS was defined as the duration of recurrence-free survival either local or distant or both after completion of treatment.

Statistical analysis

Statistical analysis was done using SPSS software version 20 IBM SPSS Statistics for Windows, version 20 (IBM Corp; Armonk, N.Y, USA). The categorical variables were described as frequency or percentages, and mean/median were calculated using descriptive statistics. Kaplan–Meier survival analysis was done to calculate median survival (MS), mean OS, and DFS. The log-rank test was used to test the statistical significance of differences in the survival and control rates for assessing the different factors such as TNM staging, N status, CEA, type of surgery, type of treatment modality, margin status, tumor location, tumor length, type of tumor, and grade of the tumor. $P < 0.05$ was considered statistically significant.

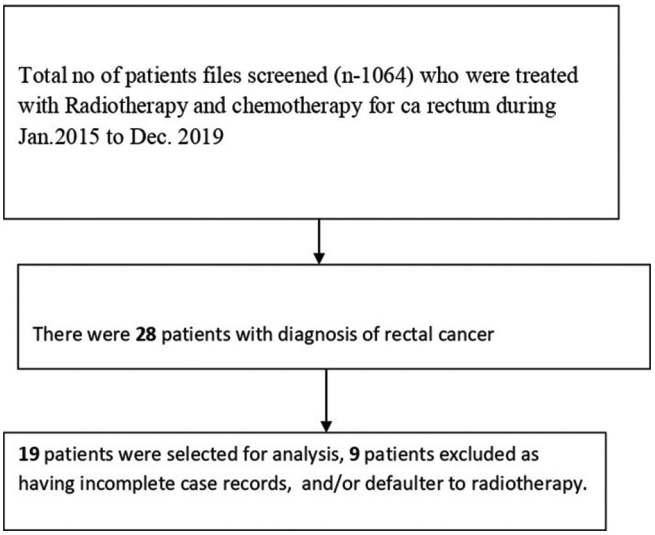

Figure 1: Schema of the study

Treatment modalities

Surgery

Patients were treated with upfront surgery in the majority using either APR or LAR.

Radiotherapy

We are having at our center one high-energy linear accelerator, named Elekta Synergy for RT. Three-dimensional (3-D) techniques and two-dimensional (2-D) techniques were used as decided by the radiation oncologists. Patients were treated supine with a dose of RT varying from 25 Gy/5# and 48–54 Gy with a fraction size of 1.8 Gy-2 Gy/# 5 fractions per week.

Chemotherapy

As per protocol, altogether, a total of six cycles of CAPOX were prescribed to patients combining neo-adjuvant, and adjuvant settings. FOLFOX was also prescribed to one patient in an adjuvant setting.

Results

The majority of the patients (68.47%) were males and the median age was 45 years (22–77). 18 (94.73%) of patients were in ECOG score 2. 84.2% ($n = 16$) patients presented with bleeding per rectum, while complaints of abdominal distension, difficulty, and pain during defecation were present in 16.7% (3) patients. CT scan was the main imaging modality done for staging in 83.3% (16) patients [Table 1].

Grade 2 adenocarcinoma was the most common (84.2%) histopathology; the other variants were mucinous ($n = 2$), and papillary ($n = 1$) serum CEA was raised in 63.2%

Table 1: Patients profile (median age, Eastern Cooperative Oncology Group, type of imaging, symptoms, and radiotherapy details)

	n (%)
Median age	45 (22–77)
ECOG PS	
2	17 (94.4)
4	2 (5.6)
Imaging	
CT	16 (83.3)
MRI	3 (16.7)
Colonoscopy	
Yes	10 (52.61)
NA	9 (47.36)
Symptoms	
BPR	16 (84.2)
Other symptoms	3 (15.78)
RT technique	19 (100)
3D	13 (68.42)
2D	6 (31.57)
RT dose	19 (100)
50.4 Gy/28#	14 (73.68)
45–54 Gy	4 (21.05); 1.8–2 Gy/#
25 Gy/5#	1 (5.2)

ECOG PS: Eastern Cooperative Oncology Group Performance Scale, NA: Nonavailable, BPR: Bleeding per rectal, RT: Radiotherapy, 3D: Three dimensional, 2D: Two dimensional, CT: Computed tomography, MRI: Magnetic resonance imaging

of patients with a mean value of 18.14 ± 18.24 ng/mL (2.51–67.00).

The majority of the patients were in stage III (57.89%) and 52.61% of cases were node-positive. About 47.36% of patients had a tumor in the mid-lower rectum, followed by the mid-upper rectum in 26.31%, and 31.5% had in and rectosigmoid region with the ulcero-infiltrating type of growth in 57.89% (11) patients, with a majority (73.68%) of patients had tumor length of >5 cm, with a mean value of 6.25 ± 1.9 cm.

Surgery

A total of 15/19 (78.94%) patients were treated with upfront surgery (APR-66.66%; and AR-35.11%) with ≥12 lymph node dissection was done in only 33.3% of patients. We observed a lack of standardization of practices of surgery as upfront surgery and not NACTRT was in practice in the majority, and the adequate number of lymph nodes (≥12) was not removed in them. This could be attributed to no functional surgical oncology department before 2019 [Table 2].

Radiotherapy

All 19 patients received RT (NACTRT [*n* = 4]; and adjuvant RT [*n* = 15] with 3-DCRT (68.42%) and 2-D RT (31.57%). Pre-RT diversion colostomy was advised in the NACTRT group as routine practice to avoid any obstruction during RT. Patients were treated in a supine position. RT dose details are shown in Table 1. One of our patients in the NACT-RT group received 25 Gy/5# as short-course RT (SCRT) due to poor KPS, and concurrent chemotherapy (CTRT) was avoided. For 3-D RT RTOG contouring guidelines were followed. A dose of 50.4 Gy/28# was prescribed to 95% PTV respecting doses to OARs. For 2D planning, treatment volumes were decided as per standard protocol with the anterior and posterior portals using bony landmarks. The upper border of the field was kept at L5–S1, the lower border at 3 cm below the lower extent of the growth, and lateral borders at 1 cm beyond lateral pelvic walls. In APR cases lower margin was kept at the perineum to cover all the scars. Inguinal regions were included where clinically confirmed nodes were present.

Colostomy stoma was usually kept out of the radiation field to prevent stoma stenosis. All patients were assessed weekly during RT.

Chemotherapy

Out of 15, 12 patients received concurrent capecitabine (825 mg/m^2/d twice a day 5 days a week) along with RT as adjuvant therapy. In the NACT-RT group, 3/4 of patients received concurrent capecitabine. Concurrent capecitabine was avoided in SCRT patients. Almost all of our patients received 2–3 cycles of CAPEOX before the start of RT, and the remaining cycles of CT were prescribed after the completion of RT. A total of six cycles of CT were administered.

Regarding margin positive status, we have included CRM, proximal as well distal margin. We observed that 6/15 (40%) of patients had a positive margin, and among those 50% had positive CRM.

Survival analysis

On survival analysis, the MS of 45 months was observed. We did not observe a significant impact of age, gender, nodal status, TNM stage, tumor characteristics (type, location, and length), margin status, serum CEA value, and treatment modality (NACT-RT/surgery; LAR/APR) on mean OS and DFS [Table 2]. However, we did observe a rising trend of the mean OS as well as DFS in patients having younger age, female sex, stage II [Figure 2], N0 [Figure 3], ulcero-infiltrating, tumor length <5 cm, negative margin [Figure 4], and in APR, LN resected <12. Pearson correlation tumor length showed a positive correlation with pretreatment CEA (P = 0.035, r = 0.486).

Treatment of local recurrence and distant metastasis

Locoregional recurrence was observed in three patients; they were treated with tegafur, irinotecan, and capecitabine, and one patient also received one course of pressurized intraperitoneal aerosol chemotherapy at another center.

Distant metastasis was observed in two patients (brain =1; bone =1), and they were treated with local palliative RT for the same.

Discussion

In a retrospective study of 79 patients, survival was unaffected by the grade of disease, type of primary tumor, stage of the disease, and time interval to surgery post-NACTRT.[7] In

Table 2: Association of overall survival and disease-free survival with different factors

Factors (% of patients)	OS (months)	*P*	DFS (months)	*P*
Pretreatment CEA (ng/mL)				
<10 (52.64)	*	0.450	49.01±0.00	0.673
>10 (47.36)	*		18.15±4.03	
N status				
N0 (47.36)	56.86±8.39	0.074	49.01±0.00	0.068
N+ (52.63)	20.84±2.96		10.95±2.33	
Stage				
II (42.10)	56.86±8.39	0.074	49.01±0.00	0.075
III (57.89)	20.84±2.96		11.06±2.3	
Growth type				
Ulcero-proliferating (31.57)	37.05±9.78	0.485	22.36±4.32	0.880
Ulcero-infiltrating (57)	50.78±10.68		35.75±10.22	
Tumor length (cm)				
3–3.5 (21.05)	48.78±9.68	0.135		0.028
5 (5.2)	35.05±6.78			
>5 (73.68)	15.35±2.16			
Adequate LN (≥12) removed				
Yes (>12) (33.33)	26.17±2.8	0.160	14.87±2.2	0.203
No (<12) (66.66)	41.91±10.99		27.45±10.2	
Type of surgery				
APR (66.66)	54.70±17.62	0.315	37.68±8.4	0.301
AR (33.33)	17.62±2.94		11.06±3.57	
Margin status				
Negative (60.0)	52.69±9.58	0.667	33.90±10.68	0.769
Positive (40.0)	21.82±3.66		12.5±2.7	

*OS could not be computed. OS: Overall survival, DFS: Disease-free survival, N0: Node negative, N+: Node positive, LN: Lymph node, APR: Abdominoperineal resection, AR: Anterior resection, CEA: Carcinoembryonic antigen

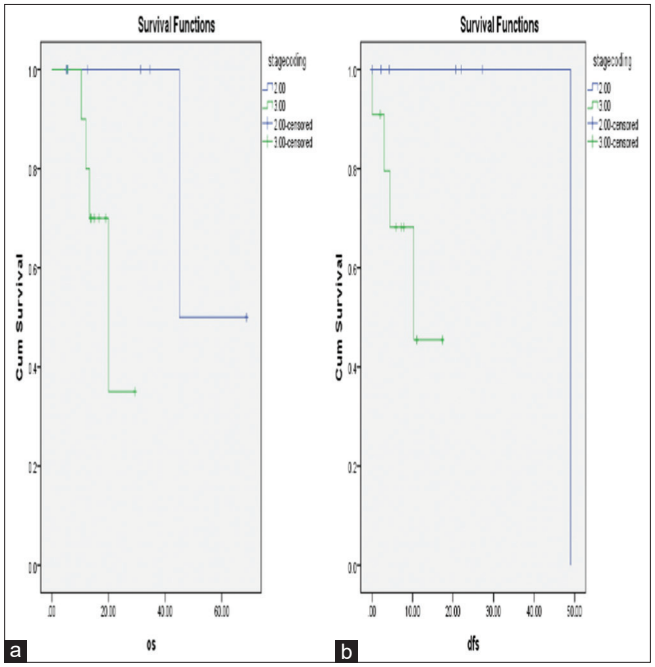

Figure 2: (a) Showing association of Overall Survival with staging, (b) showing association of disease free survival with staging

another retrospective study also, tumor size and type of growth have not been found to affect the prognosis of rectal cancer patients.[8] We observed increased mean OS as well DFS in

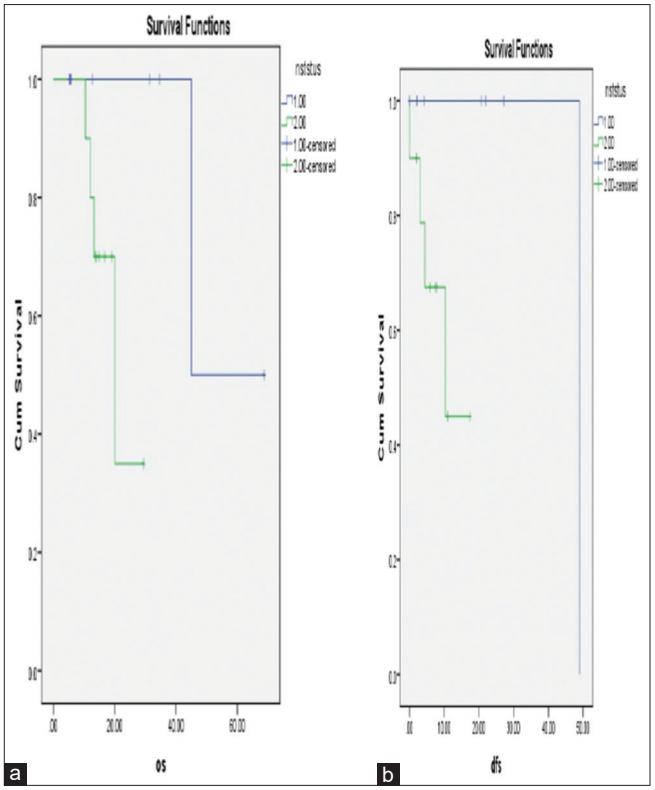

Figure 3: (a) Showing association of Overall Survival with nodal status, (b) showing association of disease free survival with nodal status

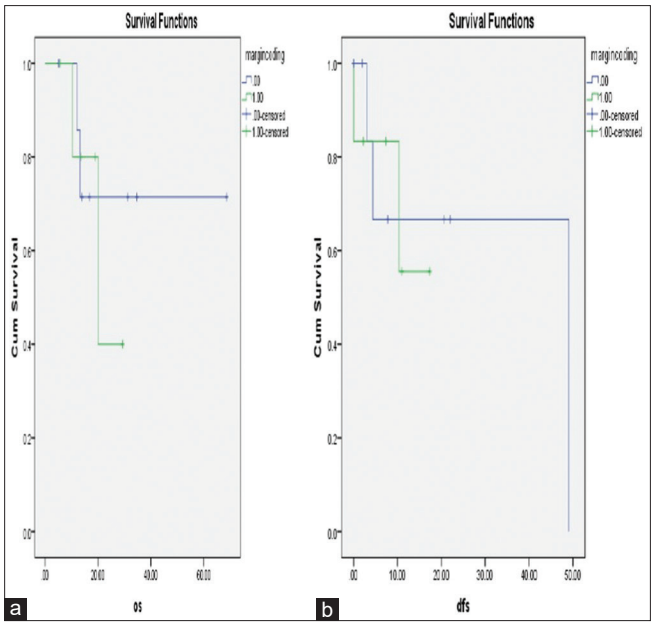

Figure 4: (a) Showing association of Overall Survival with margin status, (b) showing association of disease free survival with margin status

patients having female sex, stage II, N0, ulcero-infiltrating tumor, but the *P* value was nonsignificant. Mean OS and DFS were similar for both NACTRT and the surgery group.

Studies have revealed that high-volume operating centers, with surgeons specializing in colorectal surgeries (3,000,000 patients, $P = 0.002$)[9] have better OS in patients. A meta-analysis study observed improved 5-year OS with TME (5267 patients, $P \leq 0.00001$).[10] Adjuvant CT within 8 weeks following the curative resection[11] in a meta-analysis, complete histopathology response after RT + CT (1913, patients, $P = 0.002$)[12] in a prospective study are also associated with improved 5-year OS. The impact of the presence of anastomotic leaks[12] in a multicenter prospective study, increased serum CEA,[13] and peritoneal metastasis[14] in a phase III study showed poor OS. In a meta-analysis, lymph node ratio[15] has been observed to have a prognostic impact on OS and DFS in patients with <12 harvested LNs, as well as in those with ≥12 harvested LNs ($P < 0.05$). CRM is a strong predictor of both LR, and distant metastasis[16] in patients undergoing NACRT; in a retrospective study, however, the distal margin did not influence distant metastasis, but it impacted the LR as CRM.[17] We observed an increasing trend of mean OS (52 months vs. 21.82 months) as well DFS (33 months vs. 12.5 months) in patients with a negative margin ($P = 0.769$), also in cases with LN resected <12 in number.

In a retrospective study of 97 patients, LVI, and age older than 70 years were associated with decreased survival and less time to pelvic recurrence in patients treated with radical surgery alone for T2–T3 N0.[18] We observed increased mean OS (57 months vs. 33 months) as well as DFS (40 months vs. 18 months) in patients having younger ages in comparison to those aged >40 years (*P* = Nonsignificant).

Authors in a randomized study observed better OS and DFS with AR (68% and 57.6%) than APR (55% and 38.5%).[19] However, in our patients increased OS (66 months vs. 33 months; $P = 0.315$) as well as DFS (37 months vs. 11 months; $P = 0.30$) were observed with APR.

In a prospective study including 221 patients with rectal cancer, a pathological tumor size of >5 cm was observed as an independent prognostic factor for LR (1.40% and 23.00%, $P = 0.0001$) as well as 5 years OS (82.60% and 71.20%, $P = 0.0001$) after curative surgery following NACTRT.[20] We observed increased OS in patients with tumor size <5 cm (48 months vs. 15 months; $P = 0.135$).

Limitations of our study

It is a retrospective study with a small patient population. We could not assess pathological response, TME, postoperative anastomotic leaks remark on OS and DFS, as these details were not available for various reasons.

Conclusions

We observed nodal burden, margin positivity, advanced T in histopathology, and APR are associated with increased trend locoregional and distant failure (*P* = nonsignificant). The advanced stage (57.89%) at presentation in our patients suggests enforcement of screening protocols and standard workup plans, especially in patients having bleeding PR to help in early diagnosis and treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, *et al.* Prognostic factors in colorectal cancer. College of American pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124:979-94.
2. Fujita S, Shimoda T, Yoshimura K, Yamamoto S, Akasu T, Moriya Y. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. J Surg Oncol 2003;84:127-31.
3. Lo DS, Pollett A, Siu LL, Gallinger S, Burkes RL. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. Cancer 2008;112:50-4.
4. Liang YC, Qing SH, Ding WX, Chen PY, Huang YB, Yu HT. Total mesorectal excision versus conventional radical surgery for rectal cancer: A meta analysis. Zhonghua Wei Chang Wai Ke Za Zhi 2007;10:43-8.
5. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012;99:918-28.
6. De Caluwé L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev 2013;2013:CD006041.
7. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, *et al.* Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-33.
8. Venkatesan K, Anand V, Bajpai R, Kabre RS, Kapadia A, Almel S, *et al*. A single-institution retrospective analysis of outcomes for locally

advanced rectal cancer treated with neoadjuvant chemoradiotherapy. J Radiat Cancer Res 2020;11:81-9.
9. Archampong D, Borowski D, Wille-Jørgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev 2012;3:CD005391.
10. Des Guetz G, Nicolas P, Perret GY, Morere JF, Uzzan B. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer 2010;46:1049-55.
11. Bhangu A, Ali SM, Darzi A, Brown G, Tekkis P. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. Colorectal Dis 2012;14:1457-66.
12. den Dulk M, Marijnen CA, Collette L, Putter H, Påhlman L, Folkesson J, *et al.* Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 2009;96:1066-75.
13. Yang KM, Park IJ, Kim CW, Roh SA, Cho DH, Kim JC. The prognostic significance and treatment modality for elevated pre- and postoperative serum CEA in colorectal cancer patients. Ann Surg Treat Res 2016;91:165-71.
14. Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, *et al.* Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: A pooled analysis of North Central Cancer Treatment Group phase III trials N9741 and N9841. J Clin Oncol 2012;30:263-7.
15. Lee SD, Kim TH, Kim DY, Baek JY, Kim SY, Chang HJ, *et al.* Lymph node ratio is an independent prognostic factor in patients with rectal cancer treated with preoperative chemoradiotherapy and curative resection. Eur J Surg Oncol 2012;38:478-83.
16. Glynne-Jones R, Mawdsley S, Novell JR. The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: Why we need a common language. Colorectal Dis 2006;8:800-7.
17. Debove C, Maggiori L, Chau A, Kanso F, Ferron M, Panis Y. What happens after R1 resection in patients undergoing laparoscopic total mesorectal excision for rectal cancer? A study in 333 consecutive patients. Colorectal Dis 2015;17:197-204.
18. Nissan A, Stojadinovic A, Shia J, Hoos A, Guillem JG, Klimstra D, *et al.* Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol 2006;24:4078-84.
19. Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P, Dutch Colorectal Cancer Group, *et al.* Low rectal cancer: A call for a change of approach in abdominoperineal resection. J Clin Oncol 2005;23:9257-64.
20. Chen CH, Hsieh MC, Hsiao PK, Lin EK, Lu YJ, Wu SY. A critical reappraisal for the value of tumor size as a prognostic variable in rectal adenocarcinoma. J Cancer 2017;8:1927-34.