Five-year outcomes of preoperative chemoradiation for rectal carcinoma in Saudi population: single-institutional experience

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OBJECTIVES: Preoperative chemoradiation (CRT) followed by surgery is the standard treatment for locally advanced rectal cancer (LARC). The outcomes of preoperative CRT in Saudi patients with LARC have not been widely studied. The study reports long-term outcomes after preoperative CRT followed by curative surgery in Saudi patients with LARC.

DESIGN AND SETTINGS: A retrospective, single-institutional study performed in the tertiary care oncology center in Saudi Arabia.

MATERIALS AND METHODS: A total of 154 out of 204 patients with LARC were treated with preoperative CRT followed by surgery at the oncology center between September 2005 and November 2012. Data regarding the response rates, toxicity profile, locoregional control (LRC), distant metastasis control (DMC), overall survival (OS), and disease-free survival (DFS) rates were analyzed.

RESULTS: The median age of the study population was 56.6 years (range: 26-89). Predominant clinical stages were IIA (70 patients; 45.4%) and IIIB (49 patients; 31.8%). Majority of patients (79.8%) underwent a complete total mesorectal excision (TME). Complete pathological response (ypT0N0) was seen in 26 patients (16.8%). At 5 years, locoregional recurrence (LR) was reported in 12 patients (7.8%), and distant metastases were noted in 33 patients (21.4%). The 5-year cumulative LRC, DMC, OS, and DFS rates were 91%, 71.3%, 78%, and 64.8%, respectively. Stage, nodal status, circumferential margins, ypT0N0, and adjuvant chemotherapy were found to be important prognostic factors for DFS.

CONCLUSION: The results of preoperative CRT followed by surgery and adjuvant chemotherapy in Saudi population are comparable with international data.

In Saudi Arabia, the incidence of colorectal cancer (CRC) has increased steadily. Colorectal cancer in Saudi Arabia has a predilection for the rectum and rectosigmoid. Majority of Saudi patients are diagnosed with locally advanced rectal cancer (LARC)—the predominant clinical stages being American Joint Committee on Cancer (AJCC) stage IIA-IIIC. Surgery alone is not a curative option due to mesorectal fascia invasion or regional lymphadenopathy. Such stages of rectal cancer are treated with preoperative chemoradiation (CRT) followed up with curative radical surgery and adjuvant chemotherapy. This is based on recommendations from the European randomized trials that reported a reduction in the locoregional recurrence (LR) rate by 40% to 50%.

The long-term outcomes for preoperative CRT in Saudi patients with LARC have not been studied widely. A retrospective study from King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia, that included 196 Saudi patients with LARC who were treated with preoperative CRT reported a 5-year survival rate of 84.3% and 79.8% for clinical stages II and III of LARC, respectively. Later, Bazarbashi S et al reported the long-term outcome of
preoperative CRT in 31 Saudi patients with LARC using concurrent oral capecitabine 825 mg/m² twice daily in a phase II trial.⁹ The study reported complete pathological response (ypT0N0) in 6.5% of patients. Tumor and lymph node downstaging were reported in 53.9% and 50% of patients, respectively. Sphincter preservation was achieved in 15% of low-lying rectal cancers. The 3-year overall survival (OS) and disease-free survival (DFS) rates were 76.6% and 59.8%, respectively.⁹ Another Study by Soudy H, et al reported a sphincter preservation rate of 73.3% and a ypT0N0 of 13.3% in 15 patients with LARC after preoperative CRT using concurrent oral capecitabine and cetuximab.¹⁰

The aim of the present study was to evaluate the treatment outcomes including downstaging, pathologic response rates, locoregional control (LRC), distant metastasis control (DMC), DFS rate, and OS rate after preoperative CRT followed by curative radical surgery in Saudi patients with LARC.

**MATERIALS AND METHODS**

An approval from the institutional Review Committee was obtained for the study. The medical records of 204 patients with LARC, who were treated at our hospital between September 2005 and November 2012, were reviewed and analyzed. The eligibility criteria included the following (1) histopathologically proven rectal and rectosigmoid adenocarcinoma, (2) tumors located within 15 cm from the anal verge on colonoscopy and radiologic imaging, (3) confirmed clinical and radiologic AJCC 7th Edition stage IIA-IIIC (mesorectal fascia invasion or presence of metastatic pelvic lymphadenopathy), with no evidence for distant metastasis outside the pelvis,⁷ (4) Eastern Co-operative Oncology Group performance status 0 to 2, (5) received preoperative CRT, (6) underwent curative radical surgery (anterior resection [AR], low anterior resection [LAR], or abdominoperineal resection [APR]), and (7) received adjuvant chemotherapy.

The following patients were excluded from the study: (1) with distant metastasis, (2) with positive para-aortic, external iliac or inguinal lymph nodes, (3) with a history of prior chemotherapy and (4) deemed inoperable after preoperative CRT. Pretreatment evaluation included: detailed medical history; physical examination; hematologic tests; renal and hepatic function tests; carcinoembryonic antigen (CEA) level; colonoscopy and radiologic imaging, (3) confirmed clinical and radiologic AJCC 7th Edition stage IIA-IIIC (mesorectal fascia invasion or presence of metastatic pelvic lymphadenopathy), with no evidence for distant metastasis outside the pelvis,⁷ (4) Eastern Co-operative Oncology Group performance status 0 to 2, (5) received preoperative CRT, (6) underwent curative radical surgery (anterior resection [AR], low anterior resection [LAR], or abdominoperineal resection [APR]), and (7) received adjuvant chemotherapy.

Preoperative pelvic irradiation

All the patients underwent CT simulation and were scanned from the level of the epigastrium to the mid-thighs in a prone position using belly boards, and in the supine position for patients with a diverting colostomy. After acquisition of CT images, 3D conformal radiotherapy (3D-CRT) planning was performed. During the initial phase, the gross tumor volume (GTV), clinical target volume (CTV-1) including GTV, peri-rectal lymph nodes, pre-sacral lymph nodes, internal iliac lymph nodes, obturator lymph nodes, lower common iliac lymph nodes, external iliac lymph nodes for T4b cases with prostate, cervix or vaginal invasion, posterior bladder (1 cm), ischio-rectal fossae for low-lying rectal cancers, and planning target volume-1 (PTV-1; CTV-1 + 1-1.5 cm margins) were delineated according to the Radiation Therapy Oncology Group (RTOG) contouring guidelines.¹¹ Four equally spaced, coplanar 3D-CRT field plans were generated for the pelvis. The prescribed radiation dose to PTV-1 was 45 Gy/25 fractions, 5 days per week, and up to 7% variation was considered acceptable. Additional boost dose of 5.4 Gy/3 fractions was given to CTV-2 (GTV + mesorectum), and a complete dose of 50.4 Gy was given to PTV-2 (CTV-2 + 0.5 cm margins). Organs at risk including small bowel, large bowel, urinary bladder, and femoral heads were delineated. During planning, the mean dose to the small bowel was constrained to <45 Gy.

Preoperative chemotherapy

Preoperative chemotherapy either (1) oral capecitabine: 825 mg/m² 7 days/wk or (2) 5-fluorouracil (5-FU): 225 mg/(m² . d) as a continuous venous infusion (CIV) 5 days/wk via a Port-a-Cath (Grosheing NXT ClearVue Silicone PICC Lines by Bard Access Systems, 4 French Single Lumen, Salt Lake City, Utah USA) was given concurrently with pelvic irradiation. Dose modifications were made if any patient experienced grade 2 or greater hematologic toxicities, and capecitabine/5-FU was stopped until these toxicities resolved. For grade 2 or greater non-hematologic toxicities, the drugs were reduced to 50% of the initial dose. If toxicities recurred, capecitabine/5-FU was stopped until they resolved.
Surgery
Surgery was performed 6 to 8 weeks after the completion of CRT. For AR/LAR, a 2-cm margin distal to the lower limit of the tumor was considered satisfactory. APR was reserved for low-lying rectal cancers in which a distal margin of 2 cm was not feasible. Following surgery, the quality of the total mesorectal excision (TME) specimen was graded according to the study by Quirke.12

Pathologic response rates
The pathologic stage was determined according to the Tumor, Node, and Metastasis classification system by the AJCC 7th edition.7 Downstaging was applied for “T” and “N” stage and was defined as “yp,” where “y” referred to after chemoradiation and “p” referred to postoperative pathologic examination. All resected specimens were evaluated for pathologic response to chemoradiation with careful inspection of the primary tumor, lymph nodes, mesorectal fat, and circumferential margins. A ypT0N0 stage was defined as the absence of cancer cells in the resected specimen.

Toxicity scoring
The National Cancer Institute Common Toxicity Criteria version 2.0 was used to score acute radiation and chemotherapy toxicity. During CRT, weekly weight, performance status, pelvic examination findings, hematologic, and blood chemistry results were determined. The RTOG Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity persisting beyond 90 days from the completion of radiotherapy.

Follow-up
After completion of CRT and surgery, all patients were evaluated every 3 months for the first 2 years, followed by every 6 months for the first 2 years, and then annually thereafter at radiation oncology and gastrointestinal oncology clinics. Evaluation consisted of a physical examination; hematologic, hepatic, and renal function tests; and CEA levels. Colonoscopy; chest, abdomen, and pelvis CT, and pelvic MRI were performed on an annual basis.

Statistical analysis
The primary endpoint was DFS. The secondary points were: LR, LRC, DMC, and OS rates. LR was defined as clinically or radiologically detectable recurrence in the surgical bed alone or in conjunction with radiologically metastatic pelvic lymph nodes. Distant metastasis (DM) was defined as clinically or radiologically detectable disease outside the pelvis. LRC was defined as the duration between the initiation of therapy and the date of documented LR (censored). DMC was defined as the duration between the initiation of therapy and the date of documented DM. DFS was defined as the duration between the initiation of therapy, and the date of documented disease recurrence, death resulting from the cancer, and/or last follow-up visit (censored). Overall survival (OS) was defined as the duration between the initiation of treatment, and the date of patient death or the last follow-up visit (censored).

The probabilities of LRC, DMC, DFS, and OS were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using the log-rank test. A P value of <.05 was considered statistically significant. Univariate and multivariate analyses were performed to evaluate the effect of the potential prognostic factors affecting DFS. Statistical analysis was carried out on the basis of intention-to-treat concept. Statistical analyses were performed using the computer program SPSS, version 17.0 (SPSS Inc, Chicago, IL, USA).

RESULTS
A total of 154/204 (75.5%) patients who completed preoperative CRT followed by radical curative surgery were considered eligible for analysis. Reasons for excluding the remaining 50 patients (24.5%) were as follows: (a) no concurrent chemotherapy (3 patients), (b) treatment interruption secondary to intestinal obstruction during CRT (2 patients), (c) missing surgical and histopathological data (18 patients), and (d) no follow-up in the hospital (27 patients). Patient characteristics are described in Tables 1 and 2.

The median age for the cohort was 56.6 (13.7) years. The male gender predominated the study cohort (118 patients; 76.6%). Mesorectal involvement on radiologic imaging was noted in 102 patients (66.3%). Metastatic pelvic lymph nodes were visualized radiologically in 68 patients (44.2%). All 154 patients (100%) tolerated preoperative CRT. After the completion of CRT, all patients underwent open curative radical surgery. The median time from surgery to completion of CRT was 8.2 weeks (range: 6.8-16.6). Social issues were reasons for delayed surgery in 5 patients (3.3%). Complete TME was performed in 79.8% patient, while 31 patients (20.2%) had either near-complete or incomplete TME. Patients with near-complete or incomplete TME were not operated on by a dedicated colorectal surgeon.

Toxicity profile
Acute grade 3 nausea and vomiting were observed in 27 patients (17.5%), grade 3 diarrhea was observed in
32 patients (20.8%), and grade 3 proctitis was observed in 26 patients (16.8%). Severe hand-foot syndrome was observed in 5 patients who received capecitabine (2.3%).

Acute grade 3 hematological toxicities noted were as follows: leucopenia (10 patients; 6.5%), neutropenia (6 patients 3.9%), and thrombocytopenia (8 patients; 5.2%). The wound complications were observed in 23 patients (14.9%). No treatment-related deaths or life-threatening events were observed. Late toxicities in the cohort were mild, and no grade 3 late toxicities were observed.

**Pathologic response**

Data regarding pathological response were available for all patients who underwent surgery. Complete pathological response (ypT0N0) was documented in 26 patients (16.8%). In these patients, the median from surgery to completion of CRT was 7.6 weeks (range: 6.8-9.7). Sphincter preservation was reported in 37/93 low-lying rectal cancer patients (39.8%). Downstaging for the depth of invasion, T3/T4 stages, was achieved in 74/137 patients (54.0%). Downstaging of metastatic lymph nodes was achieved in 37/68 patients (54.4%).

**Locoregional and distant control, disease-specific and overall survival rates**

The median follow-up was 5.7 years (range: 1.8-6.5). The 5-year cumulative LRC and DMC rates were 91%, and 71.3%, respectively.

At the time of the last follow-up, 12 patients (7.8%) developed LR. The pattern of LR was as follows: (a) pre-sacral in 5 patients (41.7%), (b) pelvic lymph nodes in 2 patients (16.7%), and (c) perineal scar in 1 patient (8.3%).

### Table 1. Clinical and treatment characteristics of cohort.

| Variable                        | N (%)          |
|---------------------------------|----------------|
| **Age** (mean)                  | 56.6 (26-89) SD (13.7) |
| **Gender**                      |                |
| Male                            | 118.0 (76.6)   |
| Female                          | 36.0 (23.4)    |
| **ECOG performance status**     |                |
| 0-1                             | 125.0 (81.2)   |
| 2                               | 29.0 (18.8)    |
| **Baseline CEA level (ng/mL)**  |                |
| 0-5                             | 58.0 (37.6)    |
| 5-7.5                           | 60.0 (39.0)    |
| Above 7.5                       | 36.0 (23.4)    |
| **Distance from anal verge (cm)**|             |
| 0-5 (lower third)               | 61.0 (39.6)    |
| 6-10 (middle third)             | 44.0 (28.8)    |
| 11-15 (upper third)             | 49.0 (31.8)    |
| **Baseline clinical AJcc stage**|                |
| IIA (T3N0M0)                    | 70.0 (45.4)    |
| IIB (T4aN0M0)                   | 9.0 (5.8)      |
| IIIA (T2N+M0)                   | 7.0 (4.5)      |
| IIB (T2N+M0, T3-T4aN+M0)        | 8 (5.2)        |
| IIIIC (T3-T4aN+M0 or T4N+M0)    | 49.0 (31.8)    |
| **Clinical lymph node status**  |                |
| cN0                             | 86.0 (55.8)    |
| cN+                             | 68.0 (44.2)    |
| **Radiological mesorectal involvement** |         |
| Yes                             | 102.0 (66.3)   |
| No                              | 52.0 (33.7)    |
| **Pre-CRT diverting colostomy** |                |
| Yes                             | 17.0 (11.3)    |
| No                              | 137.0 (88.7)   |
| **Radiotherapy dose**           |                |
| 45 Gy/25 fractions (%)          | 52.0 (33.7)    |
| 50.4 Gy/28 fractions (%)        | 102.0 (66.3)   |
| **Concurrent chemotherapy**     |                |
| Oral capecitabine               | 87.0 (56.5)    |
| CIV 5-flourouracil              | 67.0 (43.5)    |
| **Type of surgery**             |                |
| AR/LAR                          | 102.0 (66.3)   |
| APR                             | 52.0 (33.7)    |
| TME (LAR/APR)                   | 123.0 (79.8)   |
| **Adjuvant chemotherapy**       |                |
| Yes                             | 107.0 (69.5)   |
| No                              | 47.0 (30.5)    |

SD: Standard deviation; AJCC (7th Edition); American Joint Committee on Cancer; ECOG: Eastern Co-operative Oncology Group; CEA: carcinoembryonic antigen; CRT: chemoradiation; CTV: continuous intravenous; LAR: low anterior resection; APR: abdomino-perineal resection; TME: total mesorectal excision.

### Table 2. Post-chemoradiation histopathological characteristics of cohort.

| Variables | N (%)          |
|-----------|----------------|
| yp T stage|                |
| ypT0      | 26.0 (16.8)    |
| ypT1      | 47.0 (30.2)    |
| ypT2      | 32.0 (20.3)    |
| ypT3      | 40.0 (25.9)    |
| ypT4      | 9.0 (5.8)      |
| ypN stage (68 patients) |         |
| ypN0      | 14.0 (20.6)    |
| ypN1      | 28.0 (41.2)    |
| ypN2      | 26.0 (38.2)    |
| CRM (+)   |                |
| Yes       | 49.0 (31.8)    |
| No        | 105.0 (68.2)   |
| LVSI      |                |
| Yes       | 33.0 (21.4)    |
| No        | 121.0 (78.5)   |
| PNI       |                |
| Yes       | 28.0 (18.2)    |
| No        | 126.0 (81.8)   |

SD: Standard deviation; CRT: chemoradiation; T: tumor; N: lymph node; CRM: circumferential margins; LVSI: lymphovascular space invasion; PNI: perineural invasion.
A total of 33 patients (21.4%) had DM. The common sites for distant metastasis were the liver in 16 patients (48.5%), para-aortic lymph nodes in 5 patients (15.2%), lungs in 7 patients (21.2%), bones in 3 patients (9.0%), and brain in 2 patients (6.1%). The median time from initial LR to distant metastasis was 3.2 years (range: 2.8-4.2). At the time of analysis, OS and DFS were 78% and 64.8%, respectively (Figures 1A and 1B).

In a subgroup analysis, the 5-year DFS rate was significantly better in patients with early AJCC stage II-IIIA and patients with ypT0N0 (Table 3 and Figures 2A and 2B).

Univariate and multivariate analyses showed AJCC staging, nodal status, ypT0N0 stage, circumferential resection margins (CRM), and adjuvant chemothera-py as important prognostic factors for LRC and DFS (Table 4).

**DISCUSSION**

Preoperative CRT, followed by curative radical surgery is the standard treatment for LARC. This has resulted in LR rates below 10% and high sphincter preservation rates (41%-65%), without any obvious gain in OS rates. Preoperative CRT in LARC offers some theoretical advantage over adjuvant CRT: (i) It treats micrometastases early in the course of the disease, (ii) reduces the risk of tumor contamination during surgery, (iii) allows a reduction in radiation-induced toxicity, (iv) improves the efficacy of CRT to a tumor with an intact vasculature, and (v) allows a sphincter-preserving procedure if the tumor shrunk. However, the outcomes of preoperative CRT in the Saudi population have not been widely studied. In this retrospective study from a single institution, the 5-year long-term outcomes have been shown to be similar to previously reported data in published reports. Furthermore, hematological and non-hematological toxicities were similar to or less than those reported in other trials. A possible explanation for a lower toxicity profile in this study is the preponderance of cancers localized at middle and upper regions of the rectum and the use of 3D conformal radiotherapy.

The rate of complete pathological response (ypT0N0) was in agreement with previously published data, and higher than that reported by Bazarbashi S et al and Soudy H, et al. A possible explanation is the higher percentage of more advanced and low-lying rectal cancers in the study populations of Bazarbashi S et al and Soudy H, et al. This study showed lower sphincter preservation rates in the presence of high downstaging rates; this may be explained by the fact that a substantial proportion of the patients were not operated on by colorectal surgeons. This warrants a recommendation that all rectal cancers must be handled by dedicated colorectal surgeons. Recent data suggest that the achievement of ypT0N0 is associated with an improved local control, and further adjuvant chemotherapy is debatable. Apart from the complete pathological response, DFS depended on the following prognostic factors: primary T stage, nodal status, CRM, and adjuvant chemotherapy; this was in agreement with published reports. Other prognostic factors reported in published reports like age, gender, grade, location, lymphovascular space involvement, radiotherapy dose, and surgery type were not found to have any impact on the DFS in the cohort of this study.

Strengths of the study were as follows: reason-
Table 3. Disease-free survival and overall survival rates in the cohort.

| Characteristics                  | 5-yr DFS rate | P value | 5-yr OS rate | P value |
|----------------------------------|---------------|---------|--------------|---------|
| Age                              |               |         |              |         |
| >55 yr                           | 75.6%         | .6      | 79.1%        | .6      |
| <55 yr                           | 61.4%         |         | 76.3%        |         |
| Gender                           |               |         |              |         |
| Male                             | 66.2%         | .4      | 77.2%        | .3      |
| Female                           | 71.1%         |         | 80.8%        |         |
| Baseline CEA level (ng/mL)       |               |         |              |         |
| ≤5                               | 65.8%         | .7      | 77.8%        | .4      |
| >5                               | 63.5%         |         | 75.4%        |         |
| Tumor grade                      |               |         |              |         |
| Grade 1                          | 73.4%         | .06     | 78.3%        | .07     |
| Grade II                         | 69.2%         |         | 74.4%        |         |
| Grade III                        | 64.5%         |         | 71.2%        |         |
| Distance from anal verge (cm)    |               |         |              |         |
| ≤5                               | 65.3%         | .3      | 75.0%        | .7      |
| >5                               | 73.4%         |         | 80.1%        |         |
| Lymph node status                |               |         |              |         |
| N0                               | 73.4%         | .002    | 82.6%        | .001    |
| N+                               | 54.7%         |         | 65.8%        |         |
| Pathological CRM (+)             |               |         |              |         |
| Yes                              | 68.5%         | .001    | 70.2%        | .6      |
| No                               | 62.3%         |         | 72.5%        |         |
| LVSI/PNI                         |               |         |              |         |
| Yes                              | 69.7%         | .6      | 79.6%        | .7      |
| No                               | 63.5%         |         | 74.4%        |         |
| Radiotherapy dose                |               |         |              |         |
| 45 Gy/25 fractions               | 67.7%         | .3      | 79.1%        | .6      |
| 50.4 Gy/28 fractions             | 69.2%         |         | 83.8%        |         |
| Type of Surgery                  |               |         |              |         |
| LAR                              | 70.2%         | .6      | 79.4%        | .6      |
| APR                              | 67.7%         |         | 77.6%        |         |
| Adjuvant chemotherapy            |               |         |              |         |
| Yes                              | 71.3%         | .04     | 78.6%        | .5      |
| No                               | 60.7%         |         | 75.8%        |         |

CEA: Carcinoembryonic antigen; LAR: low anterior resection; APR: abdominoperineal resection; TME: total mesorectal excision; CRM: circumferential resection margins; LVSI: lymphovascular space invasion; PNI: perineural invasion; DFS: disease-free survival; OS: overall survival

Figure 2. Kaplan-Meier curves of disease-free survival (DFS) according to (A) complete pathological response (ypT0N0) and (B) clinical AJCC staging.
able sample size of Saudi patients with LARC, the use of modern radiation therapy techniques during preoperative CRT, and the longer follow-up period. Limitations of the study were as follows: (a) use of retrospective data; (b) lack of complete TME in 20.2% of the studied sample; (c) use of a colonoscope instead of a rigid proctosigmoidoscope to localize the cancer. It is well known that bowing of the colonoscope may falsely increase the measured distance between the anal verge and the tumor.27

In conclusion, the long-term outcomes after preoperative CRT followed by curative radical surgery in Saudi patients who have LARC are consistent with the international data. The low sphincter preservation rate in our series warrants a recommendation that all rectal cancer surgeries be performed by a dedicated colorectal surgeon.

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Table 4. Univariate and multivariate analysis of the effects of different prognostic factors on the disease-specific survival in our cohort.

| Variable                           | Univariate analysis |    | Multivariate analysis |    |
|------------------------------------|---------------------|--|--|-----------------------|--|--|
|                                    | HR (95% CI)         | P  | HR (95% CI)           | P |
| Age (yr)                           |                     |    |                        |    |
| (< 55 vs > 55)                     | 1.8 (0.8-3.0)       | .7 | 1.6 (0.7-3.0)         | .7 |
| Gender                             |                     |    |                        |    |
| (M vs F)                           | 1.0 (0.6-1.7)       | .4 | 1.5 (0.6-1.7)         | .6 |
| Distance from anal verge (cm)      |                     |    |                        |    |
| (≤ 5 vs ≥ 5)                       | 1.4 (0.9-2.5)       | .3 | 1.6 (0.8-2.7)         | .4 |
| AJCC staging                       |                     |    |                        |    |
| (II-IIIA vs. IIIB/C)               | 2.6 (1.6-4.3)       | .001 | 5.6 (1.8-13.5) | .001 |
| ypNo                               |                     |    |                        |    |
| (No vs Yes)                        | 2.2 (1.4-4.0)       | .001 | 3.4 (1.9-10.3) | .001 |
| Radiotherapy dose (45 Gy vs 50.4 Gy) |                  |    |                        |    |
|                                   | 1.4 (1.9-2.5)       | .09 | 1.1 (0.8-2.4)         | .1 |
| Type of Surgery                    |                     |    |                        |    |
| (LAR vs APR)                       | 1.7 (1.0-2.1)       | .5  | 1.6 (0.8-2.0)         | .4 |
| ypTo                              |                     |    |                        |    |
| (No vs Yes)                        | 2.5 (1.6-6.0)       | .001 | 4.6 (1.9-11.3) | .001 |
| Pathological CRM (+)               |                     |    |                        |    |
| (Yes vs No)                        | 2.4 (1.6-5.7)       | .001 | 3.2 (1.7-9.9) | .001 |
| LVS/PNI                            |                     |    |                        |    |
| (Yes vs No)                        | 1.3 (1.0-2.5)       | .7  | 1.10 (0.8-1.9)        | .8 |
| Adjuvant chemotherapy              |                     |    |                        |    |
| (Yes vs No)                        | 0.8 (0.4-1.1)       | .04 | 0.9 (0.7-1.0)         | .03 |

HR: Hazard ratio; 95% CI: 95% confidence intervals; AJCC: American Joint Committee on Cancer; LAR: low anterior resection; APR: abdominoperineal resection; ypTo: complete primary tumor pathologic response; ypNo: complete nodal response; LVS: lymphovascular space invasion; PNI: perineural invasion.
REFERENCES

1. Saudi Cancer Incidence Report (2012). Kingdom of Saudi Arabia Ministry of Health, Saudi Cancer Registry. www.scr.org.sa/files/file/2009.pdf.
2. Al-Saeed EF, Tunio MA, Al-Obaidi O, Abdulla M, Al-Anazi A, Al-Shanfili J, et al. Correlation of pretreatment hemoglobin and platelet counts with clinicopathological features in colorectal cancer in Saudi population. Saudi J Gastroenterol 2014;20:134-8.
3. Elsamany SA, Alzahrani AS, Mohamed MM, Elmorsy SA, Zakri JE, Al-Shehri AS, et al. Clinicopathological patterns and survival outcome of colorectal cancer in young patients: western Saudi Arabia experience. Asian Pac J Cancer Prev 2014;15:5233-43.
4. Aljebreen AM, Azam NA, Alzubaidi AM, Alsharqawi MS, Attalik TA, Alharbi OR, et al. The accuracy of multi-detector row computerized tomography in staging rectal cancer compared to endoscopic ultrasound. Saudi J Gastroenterol 2013;19:108-12.
5. van Gin W, Marjinen CA, Nagtegaal ID, Kranenburg EM, Putter H, Wiggers T, et al. Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre randomised controlled TIME trial. Lancet Oncol 2011;12:575-82.
6. Sauer R, Becker H, Hohenberger W, Rodel C, Wiltfang C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
7. Hoffmeister RD, Wenz F, Post S, Matzdorf F, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine, external beam radiation and cetuximab followed by definitive surgery in patients with localized (non-metastatic) rectal cancer. 39th ESMO Congress 2010. Abstract: 700 date accessed 06/09/2014.
8. Myerson RJ, Garofalo MC, Ennaq I, Abrams AE, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:S24-30.
9. Quirke P. The pathologist, the surgeon and colorectal cancer: get it right because it matters. Prog Pathol 1998;21:201-213.
10. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosjevic-Jelic L, et al.; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-23.
11. Bukjo K, Nasierowska-Guttmejer A, Wynicz L, Malinowska M, Krynski J, Kosakowska E, et al.; Polish Colorectal Study Group. Neoadjuvant treatment for unresectable rectal cancer: an interim analysis of a multicentre randomized study. Radiother Oncol 2013;107:171-7.
12. Tiv M, Puyraveau M, Mineur L, Calais G, Maingon P, Bardet E, et al. Long-term quality of life in patients with rectal cancer treated with preoperative (chemo-)radiotherapy within a randomised trial. Cancer Radiother 2010;14:530-4.
13. Felix J, Calvillo J, Escrivan A, Neoadjuvant therapy of rectal carcinoma with UFT-leucovorin plus radiotherapy. Ann Oncol 2002;13:730-6.
14. El-Sayed ME, El-Taher ZH. Prospective Phase II study of brachytherapy boost as a component of neo-adjuvant chemotherapy and external beam radiation therapy in locally advanced rectal cancer. J Egypt Natl Canc Inst 2008;20:10-6.
15. Rengan R, Paty P, Wong WD, Guillem J, Weiser M, Temple L, et al. Distal cT2N0 rectal cancer: is there an alternative to abdominopereineal resection. J Clin Oncol 2005;23:4805-12.
16. Tulchinsky H, Rabau M, Shacham-Shemueli E, Goldman G, Geva R, Inbar M, et al. Can rectal cancers with pathologic T0 after neoadjuvant chemoradiation (ypT0) be treated by transanal excision alone? Ann Surg Oncol 2006;13:347-52.
17. Fernandez-Martos C, Aparicio J, Bosch C. Preoperative uracil, tegafur, and concomitant radiation therapy in operable rectal cancer: a phase II multicenter study with 3 years’ follow-up. J Clin Oncol 2004;22:3016-22.
18. Capricci C, Valentini V, Cioni L, De Paoli A, Rodol C, Gloyn-Jones R, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys 2008;72:99-107.
19. Zhu J, Liu F, Ou W, Lian P, Sheng W, Xu J, et al. Concomitant boost IMRT-based neoadjuvant chemoradiation for clinical stage II/III rectal adenocarcinoma: results of a phase II study. Radiat Oncol 2014;9:70.
20. Yeo KH, Kim HH, Kim DY, Kim YJ, Ju JK. A distribution weighted prognostic scoring model for node status in advanced rectal cancer. Cancer Res Treat 2014;46:41-7.
21. Lee JH, Chie EK, Kim KJ, Jeong SY, Park KJ, Park JG, et al. The influence of the treatment response on the impact of resection margin status after preoperative chemoradiotherapy in locally advanced rectal cancer. BMC Cancer 2013;13:576.
22. Merkel S, Weber K, Schellerer V, Goel H, Fietkau R, Aagay A, et al. Prognostic subdivision of ypT3 rectal tumours according to extent beyond the muscularis propria. Br J Surg 2014;101:566-72.
23. Wolff HA, Conradi LC, Beissbarth T, Leh a, Hohenberger W, Merkel S, et al. Gender affects acute organ toxicity during radiochemotherapy for rectal cancer: long-term results of the German CAO/AIO/AO-98 phase III trial. Radiother Oncol 2013;108:49-54.
24. Schoelhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA. How important is rigid proctosigmoidoscopy in localizing rectal cancer? Ann J Surg 2008;196(6):904-8.