Neoadjuvant Capecitabine and Oxaliplatin Before Concurrent Capecitabine and Radiation in Locally Advanced Rectal Cancers: Experience of a Cancer Hospital in Pakistan

Muhammad Atif Mansha, MBBS, MD1; Asmara Waheed, MBBS1; Tabinda Sadaf, MBBS1; Asma Rashid, MBBS1; Nabia Irfan, MBBS1; and Samreen Javed Chaudry, MBBS1

PURPOSE To report the toxicity and pathologic response rates after adding neoadjuvant capecitabine and oxaliplatin (CAPOX) followed by concurrent radiation and capecitabine (CAPRT) and surgery in patients with locally advanced rectal cancer.

MATERIALS AND METHODS We retrospectively analyzed medical records of 301 patients between January 2007 and December 2014. Patients were treated with four cycles of neoadjuvant chemotherapy comprising CAPOX, followed by radiotherapy at doses of 45-54 Gy in 25-30 fractions with concurrent capecitabine. A response assessment scan was performed at 4-6 weeks postradiation followed by surgical evaluation at 6-8 weeks. Pathologic tumor and nodal response rates as well as circumferential resection margin were assessed on surgical specimens.

RESULTS The median age of the patients was 43 years (range, 16-78). Overall, 227 (75.4%) patients were able to complete four cycles of CAPOX. Neoadjuvant chemotherapy was well-tolerated with no serious adverse effects. The most common toxicity was diarrhea (grade 2, n = 108; 35.8%; grade 3, n = 57; 18.9%; grade 4, n = 25; 8.3%) followed by neuropathy (grade 2, n = 132; 43.8%; grade 3, n = 54; 17.9%) and oral mucositis (grade 2, n = 108; 35.8%; grade 3, n = 47; 15.6%; grade 4, n = 9; 2.99%). A total of 229 (76.1%) patients underwent surgery. Pathologic complete response was seen in 52 (22.7%; 95% CI, 13 to 28), whereas 200 (87.3%; 95% CI, 82 to 99) patients had a negative circumferential resection margin on pathology.

CONCLUSION Neoadjuvant chemotherapy with CAPOX before CAPRT and planned total mesorectal excision surgery result in good tumor regression and substantial pathologic complete response rates with acceptable toxicity. With growing interest in organ preservation in rectal cancer, the strategy of completing all chemotherapy and chemoradiotherapy before planned surgery offers a favorable paradigm. However, further randomized clinical trials are needed to support this evidence.

INTRODUCTION Colorectal cancer is the third leading cause of cancer death in the world, and its incidence is steadily rising in developing countries. According to GLOBOCAN 2018 statistics, rectal cancer is the eighth most commonly diagnosed malignancy across the globe.1 In Pakistan, the prevalence of colorectal cancer ranges from approximately 4% to 6%.2 The standard treatment for locally advanced rectal cancers (LARC) is trimodality comprising total mesorectal excision (TME), radiation therapy, and chemotherapy. The basic advantage of such multimodal treatment, particularly total mesorectal surgical excision, is reduction in local recurrence rates to < 10%.3 The advantages of preoperative versus postoperative radiotherapy came from German randomized trial, which established the role of preoperative 5-fluorouracil–based chemoradiation in the treatment of rectal cancers.4 Subsequently, the practice of administering neoadjuvant chemoradiation before TME and adjuvant chemotherapy was established in North America.5

Although local recurrences are the main concern, another challenge for the patients who undergo the radical treatment of rectal adenocarcinomas is the risk of distant metastases. One of the major factors affecting the long-term survival of patients with rectal cancer is distant recurrences, and their frequency is estimated to be 22.5% at 5 years.6 Different strategies have been implemented to reduce the risk of distant metastases, which eventually increases the cure rate. One of them is to introduce systemic therapy before neoadjuvant concurrent chemoradiation in the treatment of LARC so that the dissemination of micrometastases is targeted early.
It is considered to be the most frequently explored attractive approach, as it not only addresses the risk of distant metastases by introduction of early systemic treatment but also reduces the risk of local recurrence. Many British and Spanish investigators have evaluated the role of neoadjuvant infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) before chemoradiation. These trials have demonstrated that increased chemotherapy exposures lead to high response rates and more favorable outcomes.6-8 Similarly, another well-known study has used the same strategy of using neoadjuvant CAPOX for around 12 weeks followed by radiation and capecitabine (CAPRT) for LARC and reported a pathologic complete response (pCR) rate of 20% and a rate of negative resection margin (R0) of about 88%.9 One study quoted the rate of sphincter preserving R0 resection of about 75% and a pCR rate of about 25% following preoperative four cycles of FOLFOX plus short-course radiation treatment.10

On the basis of the available scientific evidence, we started treating patients with rectal cancer at Shaukat Khanum Memorial Cancer Hospital and Research Centre with upfront chemotherapy in 2007. The purpose of this study is to report toxicity and pCR in patients treated at our institution. The relevant information acquired from this study will also enable us to compare our results with contemporary international literature and may also be used in the future as a part of evidence for changing treatment protocols to provide better local control and improved disease-free survival to our patients.

**MATERIALS AND METHODS**

After being granted of exempt status by institutional review board, records of all the patients’ treated for LARC between January 2007 and December 2014 with CAPOX followed by CAPRT and surgery were reviewed retrospectively. LARC was defined as tumor size T3-4 with or without nodal involvement or T2 with node-positive disease without any evidence of distant metastasis.11 All patients with histologically proven malignancy of rectum, age above 16 years, Eastern Cooperative Oncology Group performance status 0-2, and adequate renal and liver functions were included in the study. Patients with poor performance status, metastatic disease, and recurrent tumors were excluded. All patients had a full clinical history and physical examination including digital rectal examination, complete colonoscopy, magnetic resonance imaging (MRI) of pelvis, and computed tomography of chest and abdomen followed by multidisciplinary team discussion.

**Treatment**

Patients were planned for induction chemotherapy comprising four cycles of capecitabine 850 mg/m² given twice daily for 14 days and oxaliplatin 130 mg/m² given once on day 1 only, repeated every 3 weeks. Patients were assessed before each cycle of chemotherapy for local clinical response and adverse effects. Chemotherapy-induced toxicity was graded and documented using Common Terminology Criteria for Adverse Events Version 4.12

Three weeks after the last course of induction chemotherapy, patients were planned for concurrent CAPRT. Radiotherapy was delivered using conformal planning at a dose of 45-54 Gy using 6-15 MV photons. All patients underwent a planning computed tomography scan with 3 mm slices. The clinical target volume included the postchemotherapy gross primary tumor and entire mesorectum together with presacral, obturator, and internal iliac and external iliac lymph nodes.

Patients were treated with three-dimensional conformal radiation therapy using three to four coplanar fields. Weekly online imaging was performed to verify the treatment and planning positions. These patients received concurrent capecitabine at a dose of 825 mg/m² twice daily during the days of radiation.

Pelvic MRI was performed 6 weeks after the end of CAPRT to assess the local clinical response using response evaluation criteria in solid tumors version 1.1, and TME was performed at 7-12 weeks by specialist
Pathologic Assessments

TME specimens were evaluated using rectal cancer regression grading (RCRG) system. All lymph nodes were examined, and circumferential resection margin (CRM) was measured. A pCR was defined as no tumor cells in entire specimen, and involved CRM was defined when the tumor cells were located at 1 mm or less from the CRM.

RESULTS

A total of 301 patients were given CAPOX before CAPRT at Shaukat Khanum Memorial Cancer Hospital and Research Centre. The mean age of the patients at presentation was 43 years. Of 301, 227 (75.4%) patients had T3 disease. Most common histology was adenocarcinoma (n = 229 [76.1%]), and a majority of tumors were moderately differentiated (n = 134 [44.5%]). Regional lymph node metastasis was found in 282 (93.7%) patients, with N1 disease in 52 (17.3%) and N2 disease in 230 (76.4%) patients. One hundred seventy (56.5%) patients had lower rectal cancer starting within 5 cm of anal verge. Further details of disease are shown in Table 1.

Neoadjuvant CAPOX was offered to all patients, and most of them completed four cycles of chemotherapy (n = 227 [75.4%]). Most common toxicity was diarrhea, with grade 2 and grade 3 diarrhea observed in 108 (35.8%) and 57 (18.9%) patients. Grade 2 oral mucositis was found in 108 (35.8%) patients, whereas 47 (15.6%) developed grade 3 oral mucositis. Neuropathy was seen in 186 patients, with 132 (43.8%) and 54 (17.9%) developing grade 2 and grade 3 neuropathy. Only 98 (32.6%) patients had grade II hematologic toxicity. Hand-foot syndrome was found in 91 (29.5%) patients, with 65 (20.9%) and 26 (8.63%) developing grade 2 and grade 3 neuropathy. The only grade 4 toxicity observed was diarrhea (n = 25 [8.3%]) and oral mucositis (n = 9 [2.9%]). Details of the toxicity associated with neoadjuvant CAPOX are shown in Table 2. Toxicity during chemoradiation was not reviewed.

A radiation dose of 5,040 cGy in 28 fractions was given to 290 (96.3%) patients, whereas 9 (3%) received 4,500 cGy in 25 fractions. Doses of 5,400 cGy in 30 fractions were given in two (0.7%) patients. All the fractions were delivered as a part of once daily fractionation scheme, 5 days a week. Concurrent chemotherapy with capecitabine was given in all patients. The radiation treatment was completed in a mean duration of 45 days, with a range of 35-70 days.

TABLE 1. Patient and Disease Characteristics

| Characteristic          | No. (%)       |
|-------------------------|---------------|
| Age, years              |               |
| Mean ± SD (range)       | 43 ± 14.417 (16-78) |
| ≤ 50                    | 206 (68.4)    |
| > 50                    | 95 (31.6)     |
| Sex                     |               |
| Male                    | 204 (67.8)    |
| Female                  | 97 (32.2)     |
| Performance status (ECOG)|             |
| 0                       | 214 (71.1)    |
| 1                       | 84 (27.9)     |
| 2                       | 3 (1.00)      |
| T stage (pretreatment)  |               |
| T2                      | 8 (2.70)      |
| T3                      | 227 (75.4)    |
| T4                      | 66 (21.9)     |
| Lymph node status (pretreatment) |     |
| N0                      | 19 (6.30)     |
| N1                      | 52 (17.3)     |
| N2                      | 230 (76.4)    |
| Tumor histology         |               |
| Adenocarcinoma          | 229 (76.1)    |
| Signet-ring or mucinous carcinoma | 72 (23.9) |
| Tumor grade             |               |
| Well-differentated       | 58 (19.3)     |
| Moderately differentiated| 134 (44.5)   |
| Poor or undifferentiated | 101 (33.6)   |
| Unknown                 | 8 (2.70)      |
| Distance from anal verge|               |
| < 5 cm low              | 170 (56.5)    |
| > 5 cm high             | 129 (42.9)    |
| Unknown                 | 2 (0.70)      |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, nodal; SD, standard deviation; T, tumor.

TABLE 2. Severity and Frequency of Various Toxicities Associated With Neoadjuvant Capecitabine and Oxaliplatin

| Toxicity                | Grade 1, No. (%) | Grade 2, No. (%) | Grade 3, No. (%) | Grade 4, No. (%) | Grade 5, No. (%) |
|-------------------------|------------------|------------------|------------------|------------------|------------------|
| Hand-foot syndrome      | 210 (69.7)       | 65 (20.9)        | 26 (8.63)        | 0 (0)            | 0 (0)            |
| Neuropathy              | 115 (38.2)       | 132 (43.8)       | 54 (17.9)        | 0 (0)            | 0 (0)            |
| Hematologic             | 203 (67.4)       | 98 (32.6)        | 0 (0)            | 0 (0)            | 0 (0)            |
| Diarrhea                | 111 (36.8)       | 108 (35.8)       | 57 (18.9)        | 25 (8.30)        | 0 (0)            |
| Oral mucositis          | 137 (45.5)       | 108 (35.8)       | 47 (15.6)        | 9 (2.99)         | 0 (0)            |

792 © 2021 by American Society of Clinical Oncology
Treatment was interrupted in only seven patients. Following completion of CAPRT, a response assessment by MRI of pelvis was performed in 294 (97.7%) patients. The extent of response by digital rectal examination or endoscopy was not reviewed and could not be correlated with the radiologic or pathologic response. About 229 (76.1%) patients underwent surgery, with 137 (59.8%) undergoing lower abdominal resection and 92 undergoing abdominopерineal resection (40.2%). In 72 (23.9%) cases, TME was not performed as disease was technically unresectable (n = 52 [72.2%]) or because of medical comorbidities or extrapelvic metastases rendering patient inoperable (n = 9 [12.5%]) or either refused by patients (n = 11 [15.3%]). The details of various treatment-related characteristics are shown in Table 3. The frequency of various radiologic and pathologic responses is shown in Figure 1. For an easy comparison, RCRG 1 specimens with only microscopic foci of tumor are labeled as partial response. RCRG 2 and 3 specimens are labeled as stable disease and disease progression.

Tables 4 and 5 show pathologic tumor and nodal responses, respectively, in patients who underwent TME. In 4 (1.7%) patients, lymph nodes were not identified in the surgical specimen. A pCR (ypT0N0) was observed in 52 patients (22.7%; 95% CI, 13 to 28), whereas another 11 (4.8%) had near complete response (ypT1N0). CRMs turned out to be negative in 200 patients (87.3%; 95% CI, 82 to 99).

**DISCUSSION**

The concept of neoadjuvant chemotherapy before chemoradiation in LARC was initially explored by Chau et al in 2003 in which 5-fluorouracil and mitomycin were given before chemoradiation, and they reported R0 resection in 82% of patients. Another single-institution trial conducted at Memorial Sloan Kettering Cancer Center used neoadjuvant FOLFOX and bevacizumab without radiation for patients with stage 2 and 3 rectal cancer, which also reported a high rate of R0 resection and a pCR of 27%.

In our experience, a majority of patients who underwent surgery postinduction CAPOX and CAPRT achieved negative CRM and pCR. Furthermore, treatment was well-tolerated as 75.4% of the patients completed four cycles of CAPOX given initially. Although progression during initial CAPOX is rare, there remains a possibility as it has already

![FIG 1. Radiologic and pathologic responses after neoadjuvant chemotherapy followed by concurrent chemoradiation.](image-url)
been demonstrated by Chau et al, wherein 12% of the patients progressed on induction chemotherapy. Therefore, clinical response assessment was performed with the help of MRI and radiologic response was documented at the completion of CAPRT. One potential concern of using beforehand chemotherapy would be the possibility of excessive toxicity, which could make pelvic radiotherapy even more difficult for the patient to tolerate. Although it was expected, all patients managed to complete planned doses of CAPRT.

This treatment strategy has shown several potential benefits. With the use of modern surgical techniques along with improvements in preoperative chemoradiation through advancements in radiation treatment delivery technology, the risk of local failure has substantially decreased. Therefore, now, the main concern for the patients with LARC is micrometastasis and one of the possible ways for the eradication of this micrometastasis would be the start of early treatment with systemic therapy.

Although it is not specifically quantified in this retrospective analysis, most of the patients reported remarkable remission of symptoms, like rectal bleeding or pain, commonly after the first cycle of receiving neoadjuvant chemotherapy. This initial chemotherapy was found to be quicker in alleviating tumor-related symptoms than conventional chemoradiation. Theoretically, the delivery of systemic therapy before any surgical intervention or radiotherapy has proven to be more effective because the blood supply to the tumor bed has not been altered, which facilitates the optimal delivery of drug to the primary disease.

One of the mainly observed shortfalls of adjuvant chemotherapy in various clinical trials is that approximately 17%-28% of eligible patients do not start postoperative chemotherapy or nearly 37%-52% begin their treatment after a significant delay. One of the basic reasons of delay observed in the initiation of adjuvant chemotherapy is temporary diverting ileostomy or colostomy. Therefore, with the chemotherapy-first approach, this delay because of temporary ileostomy can be avoided. Furthermore, using this approach, time to temporary stoma reversal could be substantially reduced (3 v 9 months), resulting in improved quality of life. Another tangible benefit of giving neoadjuvant chemotherapy is that patients would be able to receive complete chemotherapy cycles, as compared with adjuvant chemotherapy where poor tolerance and high toxicities are observed after concurrent chemoradiation and surgery.

In this study, almost all patients were able to complete cycles of induction CAPOX, without any disruption or major toxicities.

Moreover, many studies have reported that final pathologic stage is more predictive of long-term survival outcomes than preclinical stage and patients with pCR have shown the overall survival rates ranging from 83% to 96%. There are certain shortcomings of our study. First, better outcome to pCR because of presurgical chemotherapy and chemoradiation can be an association rather than cause effect. Second, even a much larger number of patients analyzed retrospectively cannot remove the desirability of a randomized controlled clinical trial to support this analysis.

### TABLE 4. Pathologic Tumor Response

| Pretreatment T staging, No. (%) | ypT0 | ypT1 | ypT2 | ypT3 | ypT4 | Total |
|--------------------------------|------|------|------|------|------|-------|
| cT2                            | 2 (0.9) | 1 (0.4) | 4 (1.7) | 1 (0.4) | 0 (0) | 8 (3.5) |
| cT3                            | 45 (19.7) | 11 (4.8) | 41 (17.9) | 77 (33.6) | 8 (3.5) | 182 (79.5) |
| cT4                            | 6 (2.6) | 3 (1.3) | 7 (3.1) | 17 (7.4) | 6 (2.6) | 39 (17.0) |
| Total                           | 53 (23.1) | 15 (6.6) | 52 (22.7) | 95 (41.5) | 14 (6.1) | 229 (100) |

Abbreviations: c, clinical; p, pathologic; T, tumor; y, postneoadjuvant.

### TABLE 5. Pathologic Nodal Response

| Pretreatment N staging, No. (%) | ypNx* | ypN0 | ypN1 | ypN2 | Total |
|--------------------------------|-------|------|------|------|-------|
| cN0                            | 0 (0) | 14 (6.1) | 2 (0.9) | 0 (0) | 16 (7.0) |
| cN1                            | 0 (0) | 35 (15.3) | 6 (2.6) | 4 (1.7) | 45 (19.7) |
| cN2                            | 4 (1.7) | 95 (41.5) | 32 (14) | 37 (16.2) | 168 (73.4) |
| Total                           | 4 (1.7) | 144 (62.9) | 40 (17.5) | 41 (17.9) | 229 (100) |

Abbreviations: c, clinical; N, nodal; p, pathologic; y, postneoadjuvant.

*Lymph nodes were not identified in four patients.
It is the largest series to date of induction chemotherapy and complete delivery of all nonsurgical treatment before surgery in our experience and knowledge. We believe that it is a viable treatment option for LARC, and further studies depicting the role of induction chemotherapy with more effective systemic therapies are needed, so that increased pathologic response rates and long-term survival outcomes can be achieved.

**REFERENCES**

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Idrees R, Fallta S, Abdul-Ghafar J, et al: Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. World J Surg Oncol 16:129, 2018
3. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638-646, 2001
4. Sauer R, Liersch T, Merkel S, 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 30:1926-1933, 2012
5. Benson AB III, Bekaii-Saab T, Chan E, et al: Rectal cancer. J Natl Compr Canc Netw 10:1528-1564, 2012
6. Manfredi S, Benhamiche AM, Meny B, et al: Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer. Br J Surg 88:1221-1227, 2001
7. Chau I, Brown G, Cunningham D, et al: Neoadjuvant capcitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging–defined poor-risk rectal cancer. J Clin Oncol 24:668-674, 2006
8. Fernández-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capcitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: Grupo cáñcer de recto 3 study. J Clin Oncol 28:859-865, 2010
9. Chua YJ, Barbacano Y, Cunningham D, et al: Neoadjuvant capcitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: A phase 2 trial. Lancet Oncol 11:241-248, 2010
10. Myerson RJ, Tan B, Hunt S, et al: Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys 88:829-836, 2014
11. Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual (ed 6). New York, NY, Springer, 2002
12. Wheeler JM, Dodds E, Warren BF, et al: Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: Correlation with rectal cancer regression grade. Dis Colon Rectum 47:2025-2031, 2004
13. Hwang MR, Park JW, Park S, et al: Prognostic impact of circumferential resection margin in rectal cancer treated with preoperative chemoradiotherapy. Ann Surg Oncol 21:1345-1351, 2014

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.
15. Chau I, Allen M, Cunningham D, et al: Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 88:1017-1024, 2003
16. Poultsides GA, Servais EL, Saltz LB, et al: Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 27:3379, 2009
17. Schrag D, Weiser MR, Goodman KA, et al: Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: A pilot trial. J Clin Oncol 32:613-618, 2014
18. Gérard J-P, Conroy T, Bonnetain F, et al: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. J Clin Oncol 24:4620-4625, 2006
19. Bosset J-F, Collette L, Calais G, et al: Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114-1123, 2006
20. Capirci C, Valentini V, Cionini L, 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 72:99-107, 2008
21. Chang GJ, Rodriguez-Bigas MA, Eng C, et al: Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. Cancer 115:5432-5440, 2009
22. Das P, Skibber JM, Rodriguez-Bigas MA, et al: Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J Clin Oncol 29:219-224, 2006
23. Kuo L-J, Liu M-C, Jian JJ-M, et al: Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? Ann Surg Oncol 14:2766-2772, 2007
24. Quah HM, Chou JF, Gonen M, et al: Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation. Cancer 113:57-64, 2008
25. Stipa F, Chessin DB, Shia J, et al: A pathologic complete response of rectal cancer to preoperative combined-modality therapy results in improved oncological outcome compared with those who achieve no downstaging on the basis of preoperative endorectal ultrasonography. Ann Surg Oncol 13:1047-1053, 2006