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Neoadjuvant chemotherapy without radiotherapy for patients with locally advanced rectal cancer. Oncologic outcomes

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ABSTRACT

Background: the standard treatment for locally advanced rectal cancer is neoadjuvant chemo-radiotherapy, surgery and adjuvant chemotherapy. Only 50% of patients receive the adjuvant treatment due to the surgical complications and toxicity of radiotherapy. Recently, neoadjuvant chemotherapy has been investigated in the locally advanced rectal cancer setting, with the aim of guaranteeing an uninterrupted systemic treatment. The objective of the present study was to assess the safety and efficacy of neoadjuvant chemotherapy in locally advanced rectal cancer.

Methods and patients: patients treated with neoadjuvant chemotherapy and surgery were identified from a prospective database of patients with rectal cancer (cII-III). The

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primary outcomes were the assessment of the number of R0 resections, the degree of pathologic response, patterns of recurrence and overall and disease-free survival. Treatment schedule: patients received 6-8 cycles of oxaliplatin and fluoropyrimides based chemotherapy.

Results: twenty-seven patients who received neoadjuvant chemotherapy were identified. Twenty-six anterior resections and one Hartmann intervention were performed. An R0 resection was performed in 27 (100%) patients and no involvement of the circumferential margin was observed. Complete pathologic response (ypT0N0) was confirmed in four (14.8%) patients. The median follow-up was 35 months (range: 10-81) and four distant recurrences were recorded. Overall and disease-free survival at five years was 85% and 84.7%, respectively. Twenty-seven (100%) patients received all the cycles of chemotherapy, with a mean of six cycles (range 5-8) per patient.

Conclusions: neoadjuvant chemotherapy is a promising alternative in the locally advanced rectal cancer setting and further phase III clinical trials are clearly warranted.

Key words: Locally advanced rectal carcinoma. Neoadjuvant chemotherapy. Response. Outcomes.

INTRODUCTION

The standard treatment for locally advanced rectal cancer (LARC) (cT2-3 and/or N1) is neoadjuvant chemo-radiotherapy (NCRT) followed by surgery, based on total mesorectal excision (TME) and adjuvant chemotherapy (ACT) (1,2). In spite of improvements in local disease control, disease-free survival at five and ten years has remained stable due to distant recurrences that occur in 25-30% of patients (1). It has been estimated that 20-25% of these patients have micrometastases at the time of diagnosis (3). Furthermore, 40% of patients do not receive systemic adjuvant chemotherapy and less than 50% receive the appropriate dose of oxaliplatin due to surgical complications and acute toxicity of the radiotherapy (wound complications and abnormal sphincter, sexual and urinary function) (4-6). A Cochrane review estimated that the benefit of radiotherapy for survival was 2%, with a modest improvement in the local control of disease (7).

For these reasons, several authors have investigated the safety and efficacy of neoadjuvant chemotherapy (NCT) (omitting the radiotherapy) in the treatment of LARC. In addition, clinical trials comparing neoadjuvant chemotherapy with neoadjuvant chemo-radiotherapy are currently underway (9-17). This study presents the results obtained in a series of patients with LARC, treated only with neoadjuvant chemotherapy and surgery, based on total mesorectal excision.

MATERIAL AND METHODS

Patients with LARC (cT2-3 and/or N+) who were only treated with neoadjuvant chemotherapy and surgery were identified from a prospective database of patients treated for rectal cancer. These patients refused radiotherapy and had a low expected risk of local relapse. This risk was assessed by taking into account factors such as invasion of the mesorectal fascia with circumferential resection margins (CRM) of less than 1 mm, the presence of four or more pelvic lymph nodes larger than 10 mm (bulky nodal disease) and tumors located in the distal rectum.

The study was approved by the Ethics Committee of the center and was performed according to the principles of the Declaration of Helsinki. All patients provided informed consent to participate in the study.

Patient selection and inclusion criteria

Patients over 18 years of age with a histologic confirmation of adenocarcinoma of the rectum, stages cT2-3 and/or N+, located within 14-15 cm of the anal verge as determined by colonoscopy were included in the study. Tumors were considered as N+ if one or more lymph nodes were larger than 5 mm. The tumors were staged using endoscopic ultrasound, magnetic resonance imaging of the pelvis and computed tomography of the thorax and abdomen. A prior full colonoscopy was performed in all patients to rule out synchronous tumors.

The patients included had a World Health Organization (WHO) performance status score of 0 to 1, or an Eastern Cooperative Group Performance score of 0 to 2 or comparable Karnofsky score. Furthermore, they also had appropriate hematologic, liver and kidney function parameters, i.e., leucocytes > 3,000/ml, platelets > 100,000

ml, creatinine clearance > 30 ml/min, total bilirubin 2 mg/dl and liver transaminase or alkaline phosphatase levels that were no more than three times the upper normal limit.

Treatment plan

Preoperative chemotherapy consisted of a standard combination of oxaliplatin and fluoropyrimidines, either capecitabine or 5-fluorouracil. All patients received 4-6 cycles of oxaliplatin (85 mg/m^2) infused over two hours on day 1, plus oral capecitabine (100 mg/m^2) twice a day on days 1-7, on a biweekly basis. Furthermore, they also received a bolus of 5-fluorouracil (400 mg/m^2) over 5-15 minutes, then 2,400 mg/m^2 continuously over 46-48 hours. Both combinations were considered due to the overlapping results achieved with both strategies in the adjuvant setting. Patients received 4-6 cycles before surgical assessment, according to the treating physician criteria.

Hematologic toxicity and adverse events (nausea, vomiting, mucositis, diarrhea, fever, motor and sensory neuropathy) during treatment were evaluated using the National Cancer Institute Common Terminology for Adverse Events scale (version 4.0). Evaluations were performed for every treatment cycle, during the on-study period and up to the first month after the last treatment administration.

Restaging

Prior to surgery, all patients were restaged using endorectal ultrasound (ERUS), computed tomography and nuclear magnetic resonance imaging of the pelvis. Surgery was performed three to four weeks later via a total mesorectal excision. A temporary ileostomy or laparoscopic resection was performed based on the judgement of the surgeon. Postoperative chemotherapy (FOLFOX) was administered, depending on the lead oncologist and the pathologic findings.

Patients were monitored every three months after surgery during the first two years and subsequently every six months, according to the norms of the Spanish Society of Medical Oncology (SEOM) (17). Recurrence was defined as histologic, radiologic or proctoscopic confirmation of an image compatible with recurrence.

Study endpoints and variables

The primary outcomes of the study were the number of R0 resections (defined as no evidence of tumor within 1 mm of the radial, proximal or distal margins), the degree of pathologic response of the tumor to chemotherapy, overall and disease-free survival and recurrence patterns. The secondary outcomes were tolerance to treatment and the incidence and severity of surgical complications, according to the Clavien-Dindo classification (18).

Overall survival was defined as the time from surgery to the last follow-up or death. Disease-free survival was defined as the time from surgery to tumor recurrence, including the development of a second primary colorectal cancer, or death from any cause. Follow-up data were updated in May 2019 and cases were censored on the date of the last follow-up.

Histologic analysis

Surgical specimens were analyzed according to the guidelines of the American College of Pathologists (19). Tumors were staged using the TNM classification of the American Joint Committee on Cancer (AJCC, 7th edition (20), and the degree of differentiation was evaluated using the WHO criteria (21). The circumferential resection margin (CRM) was assessed and was considered to be positive when the distance was less than 1 mm. The number of lymph nodes isolated, the number of lymph nodes affected and the lymph node ratio were recorded. All R0 resections were reviewed by the study pathologist (MA). An R1 resection was defined as microscopic evidence of residual disease or a CRM < 1 mm.

The presence of isolated tumor cells or clusters of up to four cells (tumor budding) in the tumor front or the presence of tumor buds within the tumor were analyzed using the criteria of the International Tumor Budding Consensus Conference (ITBCC) (22). Pathologic response was classified into five categories using the criteria of Ruo and Shia (23). This classification takes into account the percentage of tumor cells that remain visible in the surgical specimen as follows: grade 0 (no response to treatment) to grade 4 (no viable tumor identified, pathological complete response [pCR]). The degree of perineural and lymphovascular invasion were documented.

Statistical analysis

Categorical data are expressed as numbers and percentages and continuous variables, as the mean ± standard deviation (SD). Overall and disease-free survival were estimated according to the Kaplan-Meier method. Clinical histories were reviewed in May 2019 and were censored on the date of the last follow-up. All statistical analyses were performed using SPSS/PC version 15 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Twenty-seven patients were treated with NCT between January 2010 and June 2018, with a median number of 5.5 cycles (range 4-7) per patient (Fig. 1). Nineteen (70.4%) were male and the mean age was 62 years (SD; 12.8). Most patients had clinical stage cT3N1 and the most frequent location of the tumor was the upper third of the rectum (n = 19, 70.4%) (Table 1).

The most frequent maximal toxicities during the on-study period were as follows. Grade 1 to 2 neutropenia: nine (33.3%); grade 1 to 2 diarrhea: six (22.2%); grade 1 to 2 mucositis: three (11%); grade 1 to 3 nausea and vomiting: nine (33.3%); and grade 1 to 2 neurotoxicity: 62.9%. No mortality occurred during NCT. No grade 4 toxicities were reported and all patients underwent surgery between the third and fourth week after completing treatment. The mean time interval between starting chemotherapy and surgery was 89.2 days.

Twenty-six anterior rectal resections and one Hartman intervention were performed (Table 1). There were three postoperative complications; one was an anastomosis leak, which was severe (Clavien-Dindo > IIIb). No temporary ileostomies were performed and the mean hospital stay was 6.5 days (SD 2).

Pathological response and oncologic outcomes

R0 resections were performed in 27 (100%) patients and no involvement of the circumferential margin was observed. Table 2 summarizes the pathologic findings. A median of 16 (range 10-50) lymph nodes were isolated and perineural and lymphovascular invasion were observed in four (14.8%) and two (7.4%) cases,

respectively. A complete pathologic response was observed in four (14.8%) patients and a near complete response in six (> 95%, grade 3+).

The median follow-up was 35 months (range: 10-81), three (11%) patients developed distant metastases (lung, liver), one peritoneal metastases and three died of the disease. Overall and disease-free survival at five years was 85% and 84.7%, respectively (Fig. 2).

DISCUSSION

The standard treatment for LARC (cT2-3 and /or N+) is neoadjuvant chemoradiotherapy, followed by surgery based on total mesorectal excision (TME) and adjuvant chemotherapy (1,2,24). In spite of improvements in local control, overall and disease-free survival have remained stable as 25-30% of patients develop distant recurrence (2,3). A recent analysis by the Dutch Colorectal Cancer Group Trial reported an overall ten-year survival in patients who had received preoperative radiotherapy, which was similar to that of patients treated only with surgery (TME) (48% *vs* 49%) (24).

Several studies have reported that 20-25% of patients with LARC have microscopic metastatic disease at the time of diagnosis (3). Furthermore, 40% of patients do not receive adjuvant chemotherapy and less than 50% receive the appropriate doses of oxaliplatin due to the acute toxicity (wound complications, abnormal bowel sphincter, sexual and urinary function) of the radiotherapy and the surgical complications (4,5).

Based on these premises and the acceptable tolerance to preoperative chemotherapy, several authors have reported the isolated use of neoadjuvant chemotherapy. This aims to guarantee the early systemic treatment of micrometastases, assess the degree of response of the tumor to chemotherapy and increase the number of R0 resections in LARC (3,12). Despite the small number of cases and the lack of prolonged follow-up, these studies have reported an R0 resection rate between 95 and 100%, the absence of local recurrence and a complete pathologic response (pCR) rate between 15% and 25%. These figures are similar to those obtained with conventional neoadjuvant chemo-radiotherapy and the more recent total neoadjuvant therapy (TNT) approach, which all include RT and CT delivered in the preoperative setting (25). Thus, we

decided to analyze the oncologic outcomes in a selected group of patients with LARC, who had been treated exclusively with NCT and TME surgery.

In our series, all resections were R0. This figure is similar to that reported in other studies following similar protocols (12) and slightly higher than that reported by Uehara and Deng (14). The degree of complete pathologic response was 14.8%, which is slightly lower than that reported in the above-mentioned studies and similar to the incidence of 16% reported in a pooled analysis of 3,100 patients treated with conventional NACRT (26). The pathologic response was greater than 95% in 42% of cases, which is similar to that reported by Schrag (12).

The oncologic outcomes obtained in our series of a 100% R0 resection rate, a local recurrence rate of 0% and a five-year DFS of 84.7% are similar to that reported by Schrag and slightly higher than those reported by Bossé et al. These series have the same inclusion criteria and patients were treated with preoperative chemoradiotherapy. This served as the basis for a multi-center intentional phase II/III clinical trial comparing preoperative chemoradiotherapy with neoadjuvant chemotherapy (FOLFOX) and the selective use of radiotherapy in patients that do not respond to CT, followed by surgery (12,27). A British multi-center randomized phase II trial (NCT01650428) of patients with T3 tumors in the middle third were randomized to 12 weeks of NCT, with either FOLFOX with bevacizumab or FOLFOXIRI. However, the trial was stopped due to a lack of recruitment. A recent French trial (NCT 01333709) investigated the tumor response of induction chemotherapy (FOLFIRINOX). However, the trial was prematurely terminated due to low accrual (28).

The incidence of pCR in several studies using the so-called total neoadjuvant therapy (TNT) ranged from 14% to 36%. The pCR and R0 resection rates in a recent meta-analysis of 648 patients treated with TNT were 21.8% (range 10-40) and 94.9% (range 88-100), respectively. The five-year overall and disease-free survival rates were 74.4% and 65.4%, respectively (29).

In our series, three complications were recorded and one (3.2%) was severe (Clavien-Dindo > IIIb) due to a fistula. Other studies have reported similar complication rates (3.9% or more 7.6%), although comparisons are complex due to the variability in tumor location and the multi-center nature of the studies and variable dates (13,15).

In our series, a local recurrence rate of 0% was observed, which is lower than that reported by other studies following the standard guidelines with neoadjuvant radiochemotherapy. Overall survival, disease-free survival and recurrence patterns were similar to those observed in other studies (Table 3). Although they are higher than in some other studies, perhaps due to the variability in treatment protocols. With the caveats already mentioned, it is worth highlighting that pathologic response, local recurrence rate and DFS were similar to those reported in recent studies with TNT.

Limitations

We are well aware of the limitations of the study due to its retrospective nature with a small but homogeneous number of patients, a low risk of local recurrence and limited follow-up. However, the data were collected prospectively as part of an institutional cancer database and additional audits were performed to ensure the accuracy of the patient data included. All recurrences occurred during the first 15 months and since the median follow-up was 29 months, we are confident that the majority of relapses were diagnosed.

CONCLUSIONS

Neoadjuvant chemotherapy is a feasible, safe and effective alternative in the multimodal treatment of locally advanced rectal cancer. These preliminary findings confirm those reported in previous studies and highlight the need for further phase II/III trials.

REFERENCES

1. 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 2012;30(16):1926-33. Cited: Jan 18th, 2019. Available from: http://ascopubs.org/doi/10.1200/JCO.2011.40.1836

2. Yu Y, Li Y, Xu C, et al. Comparison of long course and short course preoperative radiotherapy in the treatment of locally advanced rectal cancer: a systematic review

and meta-analysis. Rev Esp Enferm Dig 2019;111(1):17-27. Cited: Jun 19th, 2019. Available from: https://online.reed.es/fichaArticulo.aspx?iarf=685767743235-414279198168

3. Glynne-Jones R. Neoadjuvant treatment in rectal cancer: do we always need radiotherapy-or can we risk assess locally advanced rectal cancer better? Recent Results Cancer Res 2012;196:21-36. Cited: April 18th, 2018. Available from: http://link.springer.com/10.1007/978-3-642-31629-6_2

4. Merkow RP, Bentrem DJ, Mulcahy MF, et al. Effect of postoperative complications on adjuvant chemotherapy use for stage III colon cancer. Ann Surg 2013;258(6):847-53. DOI: 10.1097/SLA.0000000000000312

5. Haynes AB, You YN, Hu C-Y, et al. Postoperative chemotherapy use after neoadjuvant chemoradiotherapy for rectal cancer: analysis of surveillance, epidemiology and end results - Medicare data, 1998-2007. Cancer 2014;120(8):1162-70. DOI: 10.1002/cncr.28545

6. Jamnagerwalla M, Tay R, Steel M, et al. Impact of surgical complications following resection of locally advanced rectal adenocarcinoma on adjuvant chemotherapy delivery and survival outcomes. Dis Colon Rectum 2016;59(10):916-24. Cited: Jul 26th, 2018. Available from: http://insights.ovid.com/crossref?an=00003453-201610000-00003

7. Wong RKS, Tandan V, De Silva S, et al. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database Syst Rev 2007;(2):CD002102. Cited: Apr 18th, 2018.

8. Colorectal Cancer Chemotherapy Study Group of Japan - The 2nd Trial. Results of a randomized trial with or without 5-FU-based preoperative chemotherapy followed by postoperative chemotherapy in resected colon and rectal carcinoma. Jpn J Clin Oncol 2003;33(6):288-96. Cited: Jul 20th, 2018.

9. Ohwada S, Sato Y, Izumi M, et al. Preoperative tegafur suppositories for resectable rectal cancer: phase II trial. Dis Colon Rectum 2006;49(10):1602-10. Cited: Jul 20th, 2018.

10. Ishii Y, Hasegawa H, Endo T, et al. Medium-term results of neoadjuvant systemic chemotherapy using irinotecan, 5-fluorouracil, and leucovorin in patients

with locally advanced rectal cancer. Eur J Surg Oncol 2010;36(11):1061-5. Cited Jul 20th, 2018.

11. Fernández-Martos C, Brown G, Estevan R, et al. Preoperative chemotherapy in patients with intermediate-risk rectal adenocarcinoma selected by high-resolution magnetic resonance imaging: the GEMCAD 0801 phase ii multicenter trial. Oncologist 2014;19(10):1042-3. Cited: May 22nd, 2019. Available from: http://theoncologist.alphamedpress.org/cgi/doi/10.1634/theoncologist.2014-0233

12. 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 2014;32(6):513-8. Cited: Jul 20th, 2018. DOI: 1200/JCO.2013.51.7904

13. Deng Y, Chi P, Lan P, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol 2016;34(27):3300-7. Cited: Jul 20th, 2018. Available from: http://ascopubs.org/doi/10.1200/JCO.2016.66.6198

14. Koike J, Funahashi K, Yoshimatsu K, et al. Efficacy and safety of neoadjuvant chemotherapy with oxaliplatin, 5-fluorouracil, and levofolinate for T3 or T4 stage II/III rectal cancer: the FACT trial. Cancer Chemother Pharmacol 2017;79(3):519-25. Cited: May 23rd, 2019.

15. Hasegawa S, Goto S, Matsumoto T, et al. A multicenter phase 2 study on the feasibility and efficacy of neoadjuvant chemotherapy without radiotherapy for locally advanced rectal cancer. Ann Surg Oncol 2017;24(12):3587-95. Cited: Jul 20th, 2018.

16. Tomida A, Uehara K, Hiramatsu K, et al. Neoadjuvant CAPOX and bevacizumab alone for locally advanced rectal cancer: long-term results from the N-SOG 03 trial. Int J Clin Oncol 2019;24(4):403-10. Cited: May 22nd, 2019.

17. González-Flores E, Losa F, Pericay C, et al. SEOM Clinical Guideline of localized rectal cancer (2016). Clin Transl Oncol 2016;18(12):1163-71. Cited: May 29th, 2019.

18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205-13. DOI: 10.1097/01.sla.0000133083.54934.ae

19. Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133(10):1539-51.

20. Compton CC, Byrd DR, García-Aguilar J, et al. AJCC Cancer Staging Atlas 2, 2013. Springer eBooks. New York: Springer New York; 2012. p. 637.

21. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban R, eds. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. pp. 134-46.

22. Ueno H, Murphy J, Jass JR, et al. Tumour "budding" as an index to estimate the potential of aggressiveness in rectal cancer. Histopathology 2002;40(2):127-32. Cited: Jul 25th, 2018.

23. Ruo L, Tickoo S, Klimstra DS, et al. Long-term prognostic significance of extent of rectal cancer response to preoperative radiation and chemotherapy. Ann Surg 2002;236(1):75-81. DOI: 10.1097/00000658-200207000-00012

24. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12(6):575-82. DOI: 10.1016/S1470-2045(11)70097-3

25. Franke AJ, Parekh H, Starr JS, et al. Total neoadjuvant therapy: a shifting paradigm in locally advanced rectal cancer management. Clin Colorectal Cancer 2018;17(1):1-12. Cited: Jul 26th, 2018.

26. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11(9):835-44. Cited: Jul 27th, 2018.

27. Bossé D, Mercer J, Raissouni S, et al. PROSPECT eligibility and clinical outcomes: results from the Pan-Canadian Rectal Cancer Consortium. Clin Colorectal Cancer 2016;15(3):243-9. Cited: Jan 18th, 2019.

28. Rouanet P, Rullier E, Lelong B, et al. Tailored treatment strategy for locally advanced rectal carcinoma based on the tumor response to induction chemotherapy. Dis Colon Rectum 2017;60(7):653-63. Cited: Jan 18th, 2019. Available from:

http://insights.ovid.com/crossref?an=00003453-201707000-00003

29. Zaborowski A, Stakelum A, Winter DC. Systematic review of outcomes after total neoadjuvant therapy for locally advanced rectal cancer. Br J Surg 2019;bjs.11171. Cited: May 23rd, 2019.

Table 1. Baseline characteristics of 27 patients with LARC after NCT and total mesorectal excision

Baseline characteristics	*n (%)*
Male	19 (70.4)
BMI (mean, SD)	25 (2.9)
Age (mean, SD)	62 (12.8)
ASA	
–II (mild disturbance)	12 (44.4)
–III (severe disturbance)	15 (55.5)
Distal tumor margin from anal verge (cm) (X, SD)	10.3 (3.5)
–Mid rectum	8 (29.6)
–Upper rectum	19 (70.4)
Surgical procedure	
–Low anterior resection	26 (96.2)
–Hartmann procedure	1 (3.7)
LOS, mean (SD)	6.5 (2.3)
Complications	
–Severe complications (≥ IIIb)*	1 (3.2)
Clinical stage†	
– T2 N+	1 (3.7%)
– T3 N+	16 (59.3)
– T3 N0	7 (25.9)
– T4 N+	2 (7.4)
– T4 N0	1 (3.7)

ASA: American Society of Anesthesiologists, physical status classification; BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); LOS: length of hospital stay; LAR: locally advanced rectal cancer; NCT: neoadjuvant chemotherapy; SD: standard deviation. *According to the Clavien-Dindo classification (ref. 20). †According to the 7th edition of the American Joint Committee on Cancer TNM staging system.

Table 2. Pathologic findings after NCT and total mesorectal excision in patients with LARC. Post-treatment pathological feature and TRG score

	n (%)
T stage	
–μpT0	4 (14.8)
–ypT1	4 (14.8)
–ypT2	11 (40.7)
–ypT3	7 (25.9)
–ypT4	1 (3.7)
N stage	
–yN0	20 (74.1)
–yN1	6 (22.2)
–yN2	1 (3.7)
Isolated nodes, median (range)	16 (10-50)
Perineural invasion	4 (14.8)
Lymphovascular invasion	2 (7.4)
Mucinous areas < 50%	8 (25.8)
TRG	
–0	1 (3.2)
–1	4 (12.9)
–2	6 (19.4)
–3	6 (19.4)
–3+	6 (19.4)
–4	4 (14.8)
Complete pathologic response	4 (14.8)
Circumferential resection margin	
–Margin negative	27 (100)
Final TNM* stage	
–0 (pCR, ypT0N0)	4 (14.8)
–I (ypT1-2, N0)	11 (40.7))
–II (ypT3-4, N0)	5 (18.5)

–III (ypT1-4, N1-2)	7 (25.9)
Differentiation	
–Well	5 (18.5)
–Medium	21 (77.8)
–Poor	1 (3.7)
Vital/disease status	
–Dead as result of CA	3 (11.1)
–Alive metCA	1 (3.7)
–Alive NED	23 (85.2)

TRG: tumor regression grade (ref. 25); pCR: pathologic response. metCA: metastatic cancer; NED: no evidence of disease; NCT: neoadjuvant chemotherapy; LARC: locally advanced rectal cancer. *According to the 7th edition of the American Joint Committee on Cancer TNM staging system.

Table 3. Studies of neoadjuvant chemotherapy without radiation in locally advanced rectal cancer

	Year	*n*	*Eligibility*	*End point*	*R0 resection rate (%)*	*pCR (%)*	*LR (%)*	*Fistula (%)*	*DFS (%)*	*Induction chemotherapy*
Colorectal cancer chemotherapy Study group of Japan (8)	2003	257	Duke's B,C	5-y OS 5-y DFS	NR		13.3 %		60.5 at 5-y	5-FU (continuous infusion for 5 days)
Ohwada S (9)	2006	129	c II-III	c&pR	100%	3.9	6.2%	9%	67.6 at 4-y	Tegafur supp.
Ishii Y (10)	2010	26	c II-III	R0 DFS	100%	3.8	11.5 %	7.6%	74 at 5-y	IFL
Fdez. Martos (11)	2014/2017	46	T3 middle third	R0, LR, DFS, ORR	100%	14.3	6%	13%	75 at 2-y	CAPOX
Schrag D (12)	2014	32	c II-III (but not T4)	R0, pCR, LR, DFS	100%	25	0%		92 at 4-y	mFOLFOX Bevacizumab
Deng Y (13)	2016	152	c II-III (upper/middle/distal)	R0, pCR, DFS	89.4%	6.6	NR	7.9%	NR	mFOLFOX6
Koike J (14)	2017	53	c II-III	Clinical response R0, pCR, DFS, complication rate	92.9%	11.9	NR	7.6%	NR	mFOLFOX6

Hasegawa S (15)	2017	53	c II-III	R0, pCR, complication rate	98.3%	16.7	NR	11.6%	NR	mFOLFOX Cetuximab Bevacizumab
Tomida A (16)	2019	32	c T4 any TN2	Compliance R0, DFS, LR, pCR, adverse effect	90%	13.8	13.9 %	13.9%	72 at 5-y	CAPOX
Present series	2019	27	c II-III (upper/distal)	R0, pCR, DFS	100%	14.8	0%	3.2%	84.7 at 5-y	mFOLFOX6

pCR: pathologic complete response; CAPOX: capecitabine, oxaliplatin and bevacizumab; IFL: leucovorin, 5-fluorouracil and irinotecan; FOLFOX: bolus 5-fluorouracil: infusional 5-fluorouracil: folinic acid and oxaliplatin; DFS: disease-free survival; ORR: overall response rate; LR: local recurrence; NR: not reported; c&pR: clinical and pathological response.

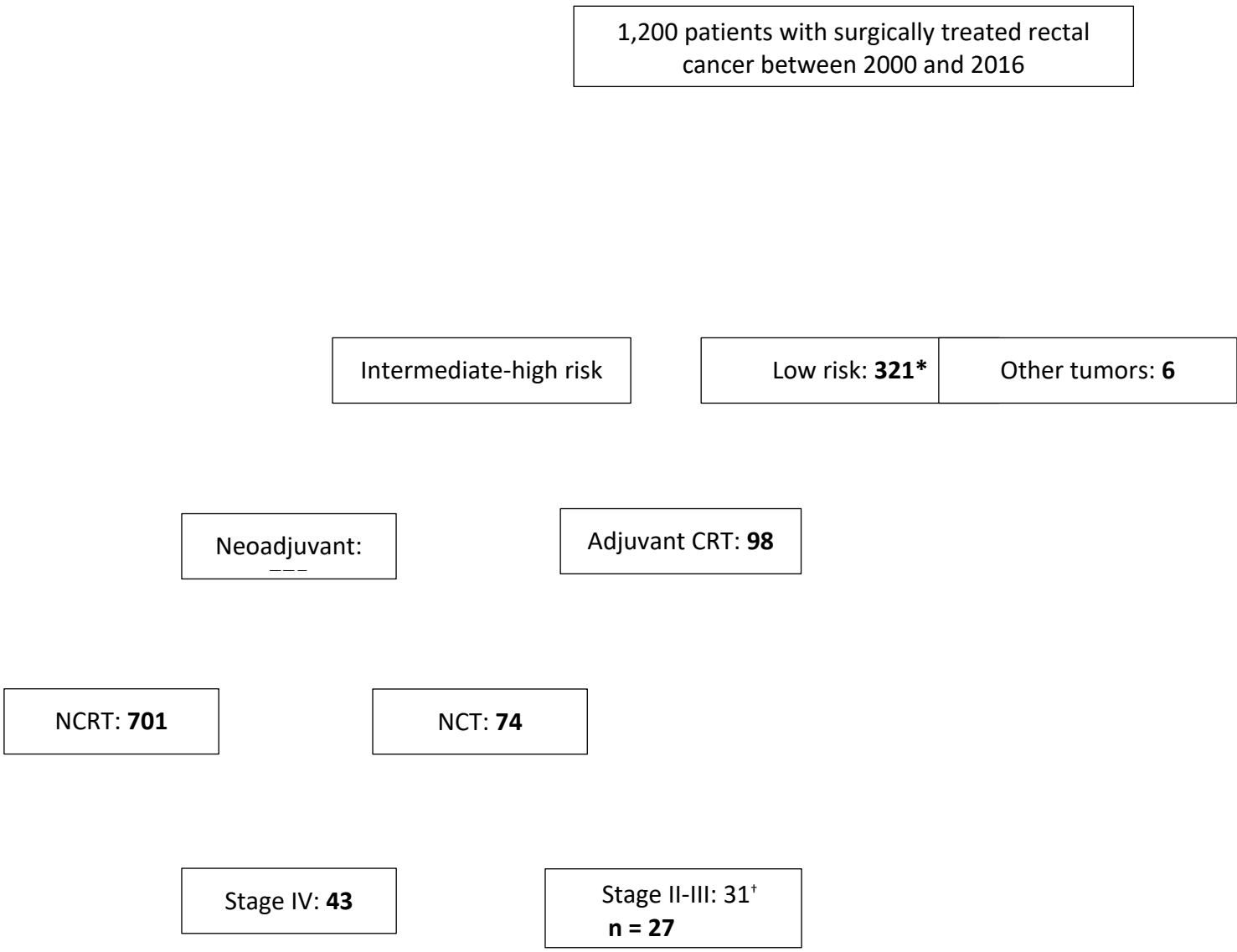

Fig. 1. A schematic diagram of the study patients. CRT: chemo-radiotherapy; NCRT: neoadjuvant chemo-radiotherapy; NCT: neoadjuvant chemotherapy. *No adjuvant/neoadjuvant treatment. †Four excluded by incomplete treatment.

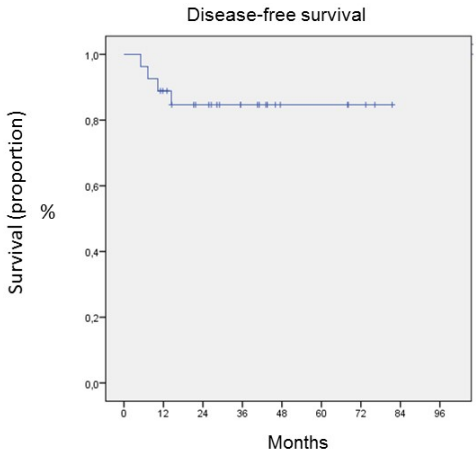

Fig. 2. Disease-free survival (DFS). Kaplan-Meier curve for patients with LARC treated with neoadjuvant chemotherapy.