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RESEARCH ARTICLE

Mid-term oncologic outcome of a novel approach for locally advanced colon cancer with neoadjuvant chemotherapy and surgery

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Abstract

Purpose Neoadjuvant chemotherapy is being actively tested as an emerging alternative for the treatment of locally advanced colon cancer (LACC) patients, resembling its use in other gastrointestinal tumors. This study assesses the mid-term oncologic outcome of LACC patients treated with oxaliplatin and fluoropyrimidines-based preoperative chemotherapy followed by surgery.

Methods and patients Patients with radiologically resectable LACC treated with neoadjuvant therapy between 2009 and 2014 were retrospectively analyzed. Radiological, metabolic, and pathological tumor response was assessed. Both postoperative complications, relapse-free survival (RFS), and overall survival (OS) were studied.

Results Sixty-five LACC patients who received treatment were included. Planned treatment was completed by 93.8 % of patients. All patients underwent surgery without delay. The median time between the start of chemotherapy and surgery was 71 days (65–82). No progressive disease was observed during preoperative treatment. A statistically significant tumor volume reduction of 62.5 % was achieved by CT scan (39.8–79.8) ($p < 0.001$). It was also observed a median reduction of 40.5 % (24.2–63.7 %) ($p < 0.005$) of SUV_{max} (Standard Uptake Value) by PET-CT scan. Complete pathologic response was achieved in 4.6 % of patients. Postoperative complications were observed in 15.4 % of patients, with no cases of mortality. After a median follow-up of 40.1 months, (p_{25}–p_{75}: 27.3–57.8) 3–5 year actuarial RFS was 88.9–85.6 %, respectively. Five-year actuarial OS was 95.3 %.

Conclusion Preoperative chemotherapy in LACC patients is safe and able to induce major tumor regression. Survival times are encouraging, and further research seems warranted.

Keywords Preoperative chemotherapy · Oxaliplatin · Fluoropyrimidines · Tumor response · Survival

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Introduction

Colon cancer (CC) is a public health problem due to its high prevalence, being the fourth most common cause of cancer death [1]. Management of stage I disease relies on surgical resection, whereas systemic therapy, either chemotherapy or targeted therapies, remains the cornerstone of treatment in the metastatic setting. The accepted standard of care for stage III CC patients is based on oncologic surgery followed by adjuvant chemotherapy. Clinical guidelines also recommend

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adjuvant chemotherapy in high-risk stage II CC, defined as clinical presentation with bowel obstruction or bowel perforation, T4 stage, peritumoral/lymphovascular involvement, poorly differentiated tumors, or inadequate lymphadenectomy [2]. Although both stage III and high-risk stage II CC patients are currently homogenously treated with a combination of oxaliplatin and fluoropyrimidines, prognosis greatly varies among this subset of patients. Indeed, 5 year overall survival (OS) for locally advanced CC (LACC) ranges from 66 % in stage IIA patients to 28 % in stage IIIC [3]. Moreover, a survival paradox has been observed between different subgroups, possibly due to a higher biologic aggressiveness [4]. These data highlight the need for more effective and patients' tailored therapeutic approaches. Unfortunately, the use of Irinotecan, epithelial growth factor receptor (EGFR), or vascular endothelial growth factor (VEGF) monoclonal antibodies (MoAbs) in the adjuvant setting has proved useless [5, 6].

In recent years, a growing amount of data has consistently suggested the potential benefits of preoperative chemotherapy [7, 8] as is the case in other locally advanced gastrointestinal tumors [9]. The rationale for this approach includes an expected better compliance rate—independently from surgical complications—compared to postoperative chemotherapy [10]; a tumor volume shrinkage may translate into a higher likelihood of achieving a complete resection, less surgical tumor cell shedding, and the possibility of an in vivo chemosensitivity test. There are, however, two major potential drawbacks for a neoadjuvant strategy; first, it may be challenging to preoperatively identify which patients are most likely to benefit with the currently available imaging techniques, thus avoiding overtreatment. In addition, disease progression during preoperative treatment may preclude a curative surgery. Preoperative chemotherapy may also cause an eventual higher incidence of surgical morbidity. Several groups have assessed the role of neoadjuvant treatment in LACC patients, showing that this approach is feasible and safe [7, 8]. Our preliminary data showed among 22 LACC patients, an R0 resection rate of 100 %, with 55 % of patients achieving major tumor regressions and at the expense of an acceptable rate of post surgical complications [11].

As a follow-up of that pilot study, we evaluated in the present work the mid-term oncologic outcome, in terms of survival times and patterns of relapse, of LACC patients treated in our institution with preoperative chemotherapy and surgery.

Method

This retrospective analysis includes consecutive patients with radiologically resectable LACC who were treated with preoperative chemotherapy and surgery in a tertiary center between July 1, 2009 and July 1, 2014. Patients were identified through a prospectively collected tumor registry database from our institution. The clinical staging was based on colonoscopy and thoracoabdominopelvic CT scan. In some patients, a whole-body ^{18}Fluorodesoxiglucose (^{18}FDG) positron emission tomography-computed tomography (PET-CT) scan was also performed. Eligibility criteria included a histologically confirmed the diagnosis of adenocarcinoma, being over 18 years of age with good performance status, correct analytical levels, absence of important comorbidities, and the ability to provide written informed consent [11]. Radiological signs of suspicious lymph nodes and/or extramural tumor invasion >5 mm by CT scan were required. Rectal tumors, complete colonic obstruction, distant metastases, or peritoneal carcinomatosis were considered exclusion criteria.

Study protocol

Preoperative chemotherapy consisted of a standard combination of oxaliplatin and fluoropyrimidines, either capecitabine or 5-Fluorouracil, and was administered at the standard dose and schedule used in daily clinical practice. Both combinations were considered, given the overlapping results achieved with both of them in the adjuvant setting. Patients were explained the specific toxicity profile of each combination, the differences in the incidence of some side effects, and the need for a central venous catheter with the use of FOLFOX. Decision was thus made taking into account patients' and physicians' preferences. Patients received 4–6 cycles before surgical assessment according to the treating physician criteria. Patients who received anti–EGFR or anti-VEGF MoAbs were excluded from the analysis. A CT scan or PET-CT scan was performed three to 4 weeks after the end of neoadjuvant chemotherapy to assess tumor response and to confirm resectability. Changes in tumor volume, T and N classification during preoperative chemotherapy were assessed by CT scan. Metabolic response was assessed according to EORTC criteria [12]. The histological tumor stage (pTNM) and grade of differentiation were determined according to guidelines established by the AJCC [3]. Lymphovascular and perineural involvement, as well as distal and circumferential margins were also recorded. Tumor regression grade (TRG) was reported according to the scale proposed by Shia et al. for rectal cancer [13]. Postoperative complications were defined as any clinical condition that required a prolonged hospital stay or any deviation from the normal postoperative course. The use of postoperative adjuvant chemotherapy was discussed on an individual basis, taking into account the pathological stage and grade of response in the surgical specimen, patients' preferences, and prior tolerance to preoperative chemotherapy. Follow-

up included physical examination, CEA-level measurement, CT scan every 4 months, and colonoscopy after 1 year. Additional tests were performed if considered necessary. Diagnosis of recurrence was based on two consecutive CT scans within 4–6 weeks. Pathological verification was performed when feasible.

Statistical analysis

Statistical analysis was done using SPSS/PC v.15 for windows statistical package (SPSS, Chicago, IL, USA). Results were expressed as mean (standard deviation) or median (P_{25}–P_{75}) for continuous variables depending on whether normal distribution was followed or not. Proportion was used for qualitative variables. Wilcoxon test was also employed for paired samples. Relapse-free survival (RFS) and OS were studied by the Kaplan–Meier method analysis and described as the percentage of cumulative survival.

Results

Patients

Sixty-five LACC patients treated with preoperative chemotherapy were retrospectively analyzed. The clinical and tumor characteristics of the patients are summarized in Table 1. The mean age was 64.8 years (SD 10.9), and most of them were male. Tumors were mostly allocated into sigmoid-descendent colon. All but four patients (93.8 %) completed the planned neoadjuvant treatment. Forty-six (70.8 %) patients received oxaliplatin in combination with capecitabine (XELOX), and 19 patients (29.2 %) received FOLFOX. Both chemotherapy regimens were administered on a biweekly basis. Toxicity was managed in an outpatient setting, with no delays in the planned surgery date. At the end of neoadjuvant chemotherapy, the mean haemoglobin and platelet levels were 11.9 g/dL (SD 1.5) and 205 × 10^9/L (SD 64.9), respectively, and the mean white blood cell count was 5.9 × 10^9/L (SD 2.2). The median time between the start of chemotherapy and surgery was 71 days (65–82), and the median time between the end of preoperative chemotherapy and surgery was 24 days (21–30). No distant relapses were observed, neither by CT scan nor by PET, during the preoperative treatment.

Median baseline tumor volume, assessed by CT scan, was 46.5 cc (26.4–75.5) compared to 18.2 cc (8.7–27.5) after chemotherapy. This translates into a statistically significant tumor volume reduction of 62.5 % (39.8–79.8) ($p < 0.001$; Wilcoxon test). Sixty-five percent of patients achieved a tumor volume reduction greater than 50 %. Among the 50 patients with baseline nodal involvement,

Table 1 Baseline demographic and clinical characteristics

	N (%)
Age[a]	64.8 (10.9)
Sex	
Female	20 (30.8)
Male	45 (69.2)
ASA	
II	35 (53.8)
III	30 (46.2)
BMI[b]	26.5 (24.2–29.2)
Comorbidity	36 (55.3)
Location	
Descending-sigmoid	42 (64.6)
Ascending	21 (32.3)
Transverse	2 (3.1)
T stage by CT at diagnosis	
T2	5 (7.7)
T3	48 (73.8)
T4	12 (18.5)
N stage by CT at diagnosis	
N −	15 (23.1)
N +	50 (76.9)
Circumferential involvement by endoscopy[b]	80 (61.5–100)
Chemotherapy schedule	
XELOX	46 (70.8)
FOLFOX	19 (29.2)

ASA American Society of Anesthesiologists, BMI Body mass index

[a] Mean (standard deviation)

[b] Median (p25–p75)

60 % achieved a complete nodal radiological response after chemotherapy. PET-CT scan was performed in 13 patients. Median baseline SUV was 18.4 (13.3–23.8) in comparison with 10.7 (5.7–15.5) after chemotherapy, with a median reduction of 40.5 % (24.2–63.7 %) ($p < 0.005$; Wilcoxon test). Stable, partial, and complete metabolic responses were observed in four patients, eight patients, and one patient, respectively.

Surgical aspects

All patients underwent surgery after preoperative chemotherapy, most of them (58.4 %) by a laparoscopic approach and with only one patient requiring conversion to open surgery. The left hemicolectomy/sigmoidectomy and right hemicolectomy were performed in 43 (66.1 %) and 22 (33.9 %) patients, respectively. Four patients (6.1 %) required a red blood cell transfusion. Postoperative complications included anastomotic leakage (four patients; 6.1 %), postoperative ileus (three patients; 4.6 %), abdominal bleeding, intestinal perforation, and urinary tract infection

(one patient each; 1.5 %). Five patients (7.7 %) required a second surgery. The median hospital stay was 6 days (5–8), and there were no cases of mortality.

Histopathology

The pathological characteristics of the operative specimen are summarized in Table 2. AJCC stages 0, I, II, and III were found in 3, 16, 29, and 17 patients, respectively, after neoadjuvant treatment. Disease free resection margins were obtained in all the cases. Three patients (4.6 %) achieved a complete pathologic response.

Postoperative outcome

Postoperative adjuvant chemotherapy was administered to 60 % of the patients. Three patients could not receive the treatment because of surgical complications (anastomotic leakages) and one due to an osteoporotic vertebral fracture. After a median follow-up of 40.1 months, (p_{25}–p_{75}:

Table 2 Pathologic characteristics of the surgical specimens

	N (%)
Differentiation grade	
High	7 (10.8)
Moderate	55 (84.6)
Low	3 (4.6)
ypT	
T0	3 (4.6)
T1	4 (6.2)
T2	20 (30.8)
T3	34 (52.3)
T4	4 (6.2)
ypN	
N0	48 (73.8)
N1	8 (12.3)
N2	9 (13.8)
ypStage	
0	3 (4.6)
I	16 (24.6)
II	29 (44.6)
III	17 (26.2)
TRG	
0,1,2	41 (63.1)
3	15 (23.1)
3+, 4	9 (13.8)
Lymphovascular invasion	7 (10.8)
Perineural invasion	6 (9.2)
Resected nodes[a]	20 (15–29)

TRG Tumour regression grade

[a] Expressed as median ($p25$–$p75$)

27.3–57.8) 3–5 year actuarial RFS was 88.9–85.6 %, respectively (Fig. 1a). Five-year actuarial OS was 95.3 %. (Fig. 1b). Seven patients have so far relapsed. A detailed analysis of the observed relapses is shown in Table 3. Two patients have died during the follow-up period. One patient, with a pT3N0, TRG: 0, and no other adverse prognostic factors died due to progressive disease (liver and lung relapse) 34 months after surgery of the primary tumor. Another patient died from a myocardial infarction after 32 months, without evidence of disease.

Discussion

The present study suggests that neoadjuvant chemotherapy followed by surgery in LACC patients is feasible, with no apparent impact on the rate of postoperative morbidity. This strategy induces measurable radiologic and metabolic changes as well as a pathologic tumor regression that translates into promising survival times. Nearly, 95 % of patients completed all cycles of preoperative chemotherapy with good tolerance, and all of them underwent surgery. A tumor reduction was achieved in all patients, and none of them developed tumor progression during neoadjuvant treatment. With the neoadjuvant protocol employed in this study, patients received chemotherapy and underwent surgery in a period of time around two and a half months. The median number of retrieved nodes fulfills the current higher standards of quality, which recommend more than 20 lymph nodes to achieve a better prognosis [14].

The global complication rate is comparable to another series [10] with no cases of perioperative mortality being registered. This fact supports that neoadjuvant chemotherapy in colon cancer does not associate with a high postoperative complication risk [15]. Fifty-five percent of our patients had some important copathology, which is a risk factor of surgical complications and hospital stay, but the hospital admission period was within the same range as other colorectal surgery series.

To our knowledge, this retrospective analysis is one of the first to report on the impact of a preoperative systemic approach on the mid-term outcome of LACC patients. The 5 year actuarial OS of 95 % seems provocative, specially taking into account that at baseline CT assessment, 76.9 % of patients were N+, and 18.5 % had T4 tumors. The observed actuarial survival times compare slightly favorable with those reported by Jakobsen et al. That study achieved a similar pathologic complete response, and did not find any benefit in adding panitumumab to a chemotherapy backbone in terms of survival [8]. No patients with 3+/4 TRG in our cohort developed metastases. Cancer-related death observed in our cohort occurred in a patient with a poor TRG, a known adverse prognostic
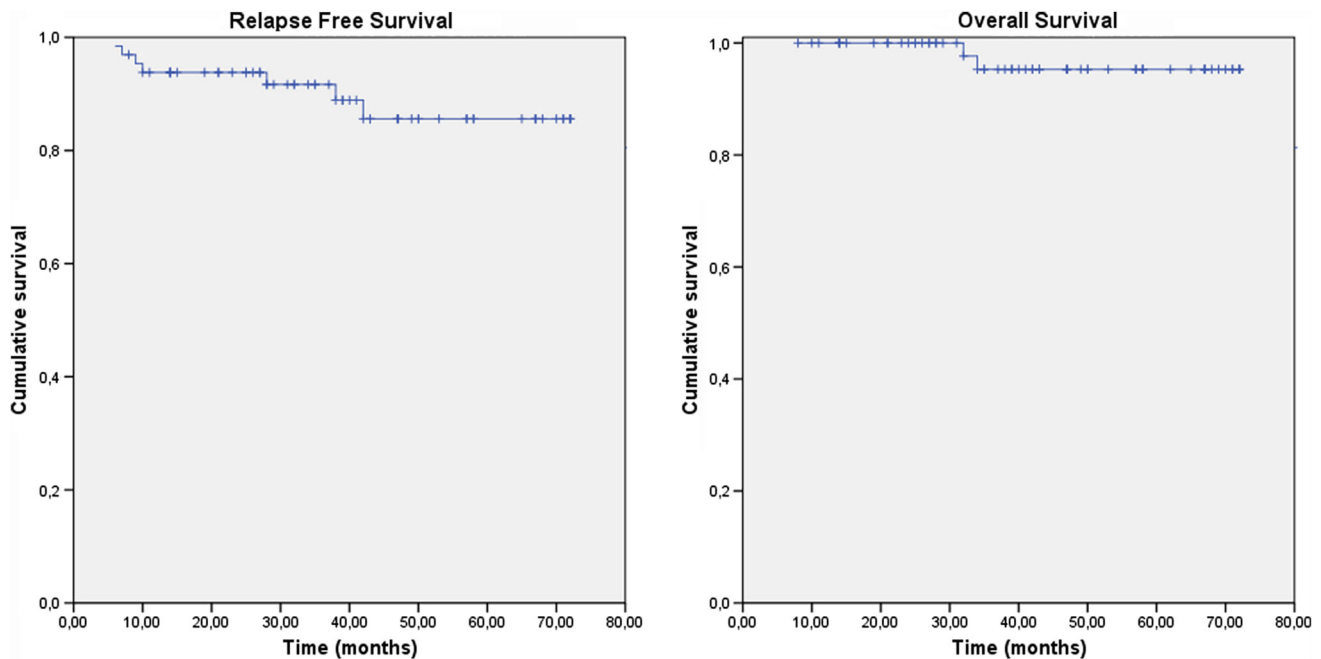
Fig. 1 a Relapse-free survival. b Overall survival

factor in other locally advanced gastrointestinal tumors [16]. Therefore, poor TRG could be a warning sign that could alert about the necessity of modifying adjuvant chemotherapy scheme. Five out of six patients with perineural invasion developed metastases, suggesting that the prognostic importance of this factor warrants further research [17]. After a median follow-up of 40 months, seven distant relapses were observed (10.7 %). It must be highlighted that three were lung metastases. Although this pattern of metastases is typically seen more in the low rectal third, two out of three lung metastases were from primary tumors allocated in the right sided colon. Four out of seven patients who developed distant recurrence metastases could be surgically removed. This finding highlights the importance of identifying potential adverse prognostic factors to tailor the intensity and type of the follow-up program. This fact might achieve an early diagnosis of relapse that would allow patients to benefit from a curative surgery.

One of the main concerns with preoperative chemotherapy is the appropriate selection of patients to avoid overtreatment. This selection is currently based on CT-scan images, whose accuracy has improved due to the use of oral and rectal contrast agents, and with the availability of multidetector CT scan. Several studies have shown that CT scan is able to identify high-risk colon cancer (T3–4) with minimal overstaging [18, 19]. We have previously observed the accuracy of CT scan for the preoperative staging of LACC patients. A nine percent overstaging was identified for TN stage and suggests that patient selection for neoadjuvant chemotherapy is

promising [20]. It should be taken into account that preoperative radiologic staging has been depicted as an independent predictor for survival [21]. PET-CT scans provide fused functional and morphological imaging and there is an increasing interest in its role for diagnoses, follow-up, monitoring treatment response, and the prediction of tumor response to therapy. It remains uncertain, however, whether the employment of PET-CT will provide determinant information in LACC patients [22].

Although preliminary, our data show that preoperative chemotherapy for LACC is an emergent therapeutic alternative, which is attracting an increasing scientific interest [23–25]. Indeed, it is currently being actively tested in several phase II and III clinical trials (NCT00647530-Birmingham; NCT01918527-Vejle; NCT02415829-Shanghai; NCT01675999-Paris). The analysis of these trials consistently suggests that this approach is well tolerated and capable of increasing the likelihood of achieving a macroscopic complete surgical resection and major histological regressions.

Limitations

This study has some limitations that deserve consideration. This is a retrospective analysis, with all the known bias inherent to this type of analysis. It is a single institutional experience, where a control group is lacking and the sample size is small. Moreover, the neoadjuvant chemotherapy regimen used is not homogeneous, although both of them were based on the standard oxaliplatin plus fluoropyrimidines, without the use of MoAbs.

Table 3 Tumour relapses during follow-up

Age	Sex	Primary location	Relapse location	Initial volume	% Volume modification	PreQth NI	PostQth NI	Neoadj cycles	Adj cycles	pTN	Nodal retrieval	NI	LNR	LVI	PNI	TRG	RFS	Management
58	M	Sigmoid	Lung	171	−77	Yes	Yes	3	4	T3N2	36	6	0.2	Yes	Yes	2	40	Qth
61	F	Sigmoid	Liver	32	−22	Yes	Yes	4	4	T3N2	16	11	0.7	Yes	Yes	3	10	R0 HS
56	F	Descendent	Paraaortic	13	−63	Yes	Yes	4	4	T4N2	18	6	0.3	Yes	Yes	1	39	Qth
56	F	Ascendent	Lung	100	−68	Yes	No	4	4	T3N1	14	3	0.2	Yes	No	1	9	R0 PS
71	F	Ascendent	Lung and liver	41	−62	Yes	Yes	4	0	T3N0	27	0	0	No	No	0	7	R0 HS and PS.
57	M	Transverse	Peritoneum	15	−70	No	No	4	4	T3N0	18	0	0	No	Yes	2	28	Qth
73	F	Ascendent	Liver	26	−4	Yes	No	4	4	T4N2	13	7	0.6	No	Yes	2	8	R0 HS

M Male, *F* Female, *V NI* nodal involvement by TAC before neoadjuvant chemotherapy, *PostQth NI* nodal involvement by TAC after neoadjuvant chemotherapy, *Neoadj cycles* number of neoadjuvant cycles, *Adj cycles* number of adjuvant cycles, *Nodal retrieval* number of retrieved lymph nodes, *NI* number of involved lymph nodes, *LNR* lymph node ratio, *LVI* lymphovascular involvement, *PNI* perineural involvement, *TRG* tumour regression grade, *Qth* chemotherapy, *R0* R0 surgery, *HS* hepatic surgery, *PS* pulmonary surgery, *RFS* relapse-free survival, in months

Nevertheless, the data add to the growing body of evidence suggesting the feasibility and efficacy of neoadjuvant chemotherapy for selected LACC patients. Longer follow-up and further studies in larger series of patients are warranted to validate these results.

Conclusions

Preoperative chemotherapy in LACC patients is safe and able to induce a major tumour regression. Mature results from ongoing randomized trials will shed light into the real impact of this novel strategy.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
2. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22:3408–19.
3. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual (7th ed). New York: Springer; 2010.
4. Kim MJ, Jeong SY, Choi SJ, Ryoo SB, Park JW, Park KJ, et al. Survival paradox between stage IIB/C (T4N0) and stage IIIA (T1-2N1) colon cancer. Ann Surg Oncol. 2015;22:505–12.
5. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2011;29:11–6.
6. Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307:1383–93.
7. Foxtrot Collaborative G. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. Lancet Oncol. 2012;13:1152–60.
8. Jakobsen A, Andersen F, Fischer A, Jensen LH, Jørgensen JC, Larsen O, et al. Neoadjuvant chemotherapy in locally advanced colon cancer. A phase II trial. Acta Oncol. 2015;29:1–7.
9. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
10. Hendren S, Birkmeyer JD, Yin H, Banerjee M, Sonnenday C, Morris AM. Surgical complications are associated with omission of chemotherapy for stage III colorectal cancer. Dis Colon Rectum. 2010;53:1587–93.
11. Arredondo J, Pastor C, Baixauli J, Rodríguez J, González I, Vigil C, et al. Preliminary outcome of a treatment strategy based on perioperative chemotherapy and surgery in patients with locally advanced colon cancer. Colorectal Dis. 2013;15:552–7.
12. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer. 1999;35:1773–82.
13. Shia J, Guillem JG, Moore HG, Tickoo SK, Qin J, Ruo L, et al. Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome. Am J Surg Pathol. 2004;28:215–23.

14. Iachetta F, Reggiani Bonetti L, Marcheselli L, Di Gregorio C, Crilli C, Messinese S, et al. Lymph node evaluation in stage IIA colorectal cancer and its impact on patient prognosis: a population-based study. Acta Oncol. 2013;52:1682–90.

15. Arredondo J, Martínez P, Baixauli J, Pastor C, Rodríguez J, Pardo F, et al. Analysis of surgical complications of primary tumor resection after neoadjuvant treatment in stage IV colon cancer. J Gastrointest Oncol. 2014;5:148–53.

16. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, 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;11:835–44.

17. Cienfuegos JA, Rotellar F, Baixauli J, Beorlegui C, Sola JJ, Arbea L, et al. Impact of perineural and lymphovascular invasion on oncological outcomes in rectal cancer treated with neoadjuvant chemoradiotherapy and surgery. Ann Surg Oncol. 2015;22:916–23.

18. Dighe S, Swift I, Magill L, Handley K, Gray R, Quirke P, et al. Accuracy of radiological staging in identifying high-risk colon cancer patients suitable for neoadjuvant chemotherapy: a multicentre experience. Colorectal Dis. 2012;14:438–44.

19. Smith NJ, Bees N, Barbachano Y, Norman AR, Swift RI, Brown G, et al. Preoperative computed tomography staging of nonmetastatic colon cancer predicts outcome: implications for clinical trials. Br J Cancer. 2007;96:1030–6.

20. Arredondo J, González I, Baixauli J, et al. Tumor response assessment in locally advanced colon cancer after neoadjuvant chemotherapy. J Gastrointest Oncol. 2014;5:104–11.

21. Huh JW, Jeong YY, Kim HR, Kim YJ. Prognostic value of preoperative radiological staging assessed by computed tomography in patients with non-metastatic colon cancer. Ann Oncol. 2012;23:1198–206.

22. Hendlisz A, Golfinopoulos V, Deleporte A, Paesmans M, El Mansy H, Garcia C, et al. Preoperative chemosensitivity testing as predictor of treatment benefit in adjuvant stage III colon cancer (PePiTA): protocol of a prospective BGDO (Belgian Group for Digestive Oncology) multicentric study. BMC Cancer. 2013;13:190.

23. Cervantes A. Preoperative chemotherapy for colon cancer is getting closer. Lancet Oncol. 2012;13:1073–4.

24. Zhou Z, Nimeiri HS, Benson AB 3rd. Preoperative chemotherapy for locally advanced resectable colon cancer—a new treatment paradigm in colon cancer? Ann Transl Med. 2013;1:11.

25. Mayor S. Chemotherapy before surgery for colon cancer may improve survival, study shows. BMJ. 2012;345:e7487.