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Original Article

Predictive factors for tumour response after the neoadjuvant-treatment of rectal adenocarcinoma

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ABSTRACT

Purpose: Standard of care for locally advanced rectal cancer is neoadjuvant chemoradiotherapy followed by surgery. This study identified predictive factors for tumour response in our series.

Patients and methods: Between January 2005 and December 2018, 292 patients with locally advanced rectal cancer treated by preoperative chemo-radiation before surgery were retrospectively analyzed. The radiation dose was 50.4 Gy with fluoropyrimidine-based chemotherapy regimens. Patients-tumour and treatment-factors were tested for influence on tumour down staging and regression grade using Mandard scoring system on surgical specimens (TRG).

Results: Median age was 69 years (range 39–87); 33.9% of patients was Stage II and 54.5% Stage IIIB. Tumour down staging occurred in 211 patients (73%), including 63 patients (21.6%) with ypT0 (documented T0 at surgery) and 148 patients (50.7%) with a satisfactory tumour regression grade defined as TRG2–3. Upper rectal tumours were identified to predictive factors for pathologic complete response by univariate analysis ($p = 0.002$). TRG1–3 was associated with intervals from chemo-radiation to surgery ($p = 0.004$); TRG1–3 rates were higher with longer intervals: 1.71% in $\leq$ 5 weeks, 23.63% in 6–8 weeks and 46.9% in $\geq$ 9 weeks; and PTV 50.4 $\geq$ 800cc ($p = 0.06$); 3 and 5 years survivals were 85% and 90% for the group as a whole. Among ypT0 cases, the overall survival was 91.1% without significantly different ($p = 0.25$) compared with the remaining group, 87.2%. Among ypT0 cases, the relapse-free survival was 94.5%, with significantly different ($p = 0.03$) compared with the remaining group 78.2%. There were no treatment-associated fatalities. Thirty-two patients (10.96%) experienced Grade III/IV toxicities (proctitis, ephitelitis and neutropenia).

Conclusions: Tumour localization was identified as predictive factors of pathologic complete response for locally advanced rectal cancer treated with preoperative chemo-radiation. Upper rectal tumours are more likely to develop complete responses. Delay in surgery was identified as a favorable predictive factor for TRG1–3. The relapse-free survival in pathologic complete response group was higher compared with non-pathologic complete response.

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Fatores preditivos de resposta tumoral após tratamento neoadjuvante de adenocarcinoma retal

Palavras-chave:
Câncer retal
Tratamento neoadjuvante
Quimiorradioterapia

RESUMO

Objetivo: O tratamento padrão para o câncer retal localmente avançado é a quimiorradioterapia neoadjuvante, seguida de cirurgia. Este estudo identificou fatores preditivos de resposta tumoral em nossa série.

Pacientes e métodos: Entre janeiro de 2005 e dezembro de 2018, 292 pacientes com câncer retal localmente avançado, tratados com quimiorradiação pré-operatória, foram retrospectivamente analisados. O tratamento quimioterápico foi à base de fluoropirimidina e a dose de radiação foi de 50,4 Gy. Os tumores dos pacientes e os fatores do tratamento foram testados quanto à influência no estadiamento do tumor e no grau de regressão usando o sistema de classificação de Mandard em espécimes cirúrgicos (TRG).

Resultados: A mediana das idades foi 69 anos (variação de 39 a 87); 33,9% dos pacientes estavam no estágio II e 54,5% no estágio IIIB. O estadiamento do tumor ocorreu em 211 pacientes (73%), incluindo 63 pacientes (21,6%) com ypT0 (T0 documentado na cirurgia) e 148 pacientes (50,7%) com grau satisfatório de regressão do tumor, definido como TRG2–3. Os tumores retais superiores foram identificados como fatores preditivos de resposta patológica completa por análise univariada p = 0,002. TRG1–3 foi associado aos intervalos entre a quimioterapia e a cirurgia p = 0,004; As taxas de TRG1–3 foram maiores com intervalos mais longos: 1,71% em $\leq$ 5 semanas, 23,63% em 6–8 semanas e 46,9% em $\geq$ 9 semanas; e PTV 50,4 $\geq$ 800cc (p = 0,06); as sobrevidas de 3 e 5 anos foram de 85% e 90% para o grupo em geral. Entre os casos de ypT0, a sobrevida global foi de 91,1%, sem diferença significativa (p = 0,25) na comparação com o grupo restante (87,2%). Entre os casos de ypT0, a sobrevida livre de recidiva foi de 94,5%, com diferença significativa (p = 0,03) na comparação com o grupo restante (78,2%). Não houve fatalidades associadas ao tratamento. Trinta e dois pacientes (10,96%) apresentaram toxicidade de grau III/IV (proctite, efitelite e neutropenia).

Conclusões: A localização do tumor foi identificada como fator preditivo de resposta patológica completa para o câncer retal localmente avançado tratado com quimiorradiação pré-operatória. Os tumores retais superiores têm mais probabilidade de desenvolver respostas completas. O atraso da cirurgia foi identificado como um fator preditivo favorável para o TRG1–3. A sobrevida livre de recidiva no grupo com resposta patológica completa à quimiorradioterapia pré-operatória foi maior comparado ao grupo com resposta patológica incompleta.

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Introduction

In 2018, approximately 1,849,518 cases of rectal cancer were diagnosed in Europe.[1] The standard of care for locally advanced rectal cancer (Stage II-III) includes neoadjuvant chemoradiation, Total Mesorectal Excision (TME) and adjuvant chemotherapy.[2] Tumour response is determined at the time of surgical resection with histologic examination and it is quantified.[3] There are many Tumour Regression-Grading (TRG) systems, and one of the more commonly used is Mandard classification, which classified tumour regression into five subtypes: TRG1, non tumour cells; TRG2, residual cancer cells; TRG3, predominant fibrosis and residual cells; TRG4, predominant tumour cells and fibrosis; and TRG5, non tumour regression.[4] Multiple studies have correlated complete pathologic response with improved Disease-Free Survival (DFS) and Overall Survival (OS) for this there is different strategy to intent increase complete pathologic responses but it is no clear the clinical factors implicated.[5–7]

The aim our study was assesses the predictive clinical factors for regression grades or completes pathologic response in a series of 292 patients.

Materials and methods

Study patients

In this study, we enrolled patients with locally advanced rectal cancer (T3/4, N0/+, M0 according to the TNM Classification 7th Edition). They received neoadjuvant CRT followed by surgery at Ramón y Cajal Hospital from January 2005 to December 2018. Patients were selected from the Radiation Oncology Department's internal database based on diagnosis coding and total radiotherapy dose delivered. The Institutional Review Board approved this study's protocol.

Evaluation

Stage was determined by the TNM scoring system according to the American Joint Committee on Cancerś (AJCC). Clinical staging was with digital rectal examination and blood test with CEA level in all patients; 44.6% included colonoscopy and CT; 34.1% CT, MRI and transrectal ultrasound; 6.4% CT and MRI; 12.4% colonoscopy, CT and MRI; 0.8% CT; and 1.5% transrectal ultrasound, colonoscopy, MRI, CT and PET to determinate tumour and nodal staging. CT imaging of the thorax and abdomen excluded distant metastasis pre and post-CRT. We defined low rectal tumours, mid rectal tumours and high rectal tumours as those that were less than 5 cm, 5–10 cm and more than 10 cm from the anal verge, respectively.

Study treatment

Concomitant chemotherapy (5-fluorouracil – 5-FU, intravenously or capecitabine orally) was administered to all patients. All patients received pelvic radiation, and the whole pelvic field included the tumour volume with macroscopic lymph nodes, the presacral, internal iliac nodes, and the mesorectum and in some cases also the external iliac nodes and inguinal nodes, and the total dose administered was 45–50.4 Gy in 28 fractions in one or two phases. Radiotherapy was delivered as 3-Dimensional conformal radiotherapy with 6 MV or 15 MV photons; or Intensity Modulated Radiotherapy, IMRT. The beam arrangement consisted of one posterior beam and two lateral beams, and IMRT was developed with VMAT.

All patients underwent TME surgery, which included low anterior resection, ultra-low anterior resection, abdominoperineal resection or Hartmann's procedure. Surgery was planned 8–12 weeks after neoadjuvant CRT. Tumour size, nodal metastasis and margin status were identified from the patient's histology reports.

Mandard classification was used to analyze the different regression grades in the histological specimen.

After completion of neoadjuvant CRT and TME surgery, all patients were followed up postoperatively with history taking, examination and CEA blood test every 3 months for the first 2 years, every 6 months during years 3–5 and annually thereafter. CT of the chest, abdomen and pelvis were repeated annually to screen for local recurrence or distant metastasis. Postoperative colonoscopy was performed each one year.

Toxicities

Radiation toxicities were recorded weekly during treatment reviews and at subsequent follow-up visits. The toxicities were scored using Common Terminology Criteria for Adverse Events version v4.1.

Statistical analysis

Data were analyzed using SPSS version 21. Kaplan–Meier curves were plotted to provide an overview of the local recurrence, disease-free survival and overall survival rates of all patients. The differences between the curves were evaluated using the log Rank test. Factors for regression analyses were performed included age at diagnosis, gender, tumour location, TNM stage, chemotherapy regimen (intravenous 5-FU or oral capecitabine), tumour down staging and time to surgery. A p-value < 0.05 was considered to be statistically significant.

Results

Patientś characteristics

The stages was 2.4% of patients with T2N1; 0.7% of patients with T2N2; 33.7% of patients with T3N0; 39.9% of patients with T3N1; 11.8% of patients with T3N2; 3.8% of patients with T4N1; 1% of patients with T4N0 and 6.6% of patients with T4N2.

Median age was of 69 years (range 39–87 years); 62.3% were men and 37.7% women. Tumour location was 32.9% low rectal, 41.1% medium and 26% superior. Median CEA was 4.5 ng/mL (0.5–531) and Ca 19.9 pre-treatment was 7.75 IU/mL (2–467.8). In 94.4% of patients received 3D radiotherapy and 5.6% IMRT; 29.7% patients received concomitant chemotherapy with 5-FU continuous infusions 225 mg/m^2/day and 70.3% patients with oral capecitabine 825 mg/m^2/12 h; 89.2% received complete treatment without doses chemotherapy reduced or without interruptions. Median time to surgery was 63 days (10–230 days). There were 256/292 (87.7%) patients who received adjuvant chemotherapy.

Surgery and pathologic specimen

Type of surgery consisted of: 33.6% abdominal amputation, 60.3% low anterior resection, 1.7% pelvic exenteration, 1.3% others surgeries. Tumor down staging with good response occurred in 211 patients (73%), including 63 patients (21.6%) with ypT0 (documented T0 at surgery) and 148 patients (50.7%) with TRG2–3. The regression tumor grade in this series was TRG1 21.6%, TRG2 31.6%, TRG3 19.2%, TRG4 21.6%, and TRG5 6%.

Predictive factors of response

We analyzed clinical variables as gender, age, interval between radiotherapy and surgery, stage, positive lymph nodes, distance to anal verge, and good grade regression (Mandard 1, 2 or 3), and found distance to anal verge p = 0.002 as predictive factor for pathologic complete response. And TRG1-3 was associated with intervals from chemo-radiation to surgery (p = 0.004); 1.71% in $\leq$ 5 weeks, 23.63% in 6–8 weeks and 46.9% in $\geq$ 9 weeks; and PTV50.4 $\geq$ 800cc (p = 0.06) as predictive factors in univariate analysis (Table 1).

In multivariant analysis, upper location was the only predictive factor for pathological complete response.

Toxicity

Concurrent chemotherapy were stopped in 6.4% for digestive toxicity, in 2.8% for hematologic toxicity, in 0.8% was necessary dose reduced for age or comorbidities, in 0.4% for fever and 0.4% for epithelitis.

We analyzed digestive, hematologic, genitourinary and skin toxicities. Digestive toxicities included diarrhea and abdominal pain in 45% Grade 1, 12.8% Grade 2, 9% Grade

Table 1 – Predictive factors of complete or good pathological response (GR 1–3).

	pCR	Non pCR	p
Age	68.58	67	0.012
CEA	7.23	13.85	0.312
CA 19.9	7.13	25	0.078
Location	Sup 9.25% (27p) Medium 5.82% (17p) Inf 6.85% (20p)	Sup 16.78% (49p) Medium 34.93% (102p) Inf 26% (76p)	0.002
	GR1-3	GR4-5	P
Time to surgery	≤5w: 1.71% (5p) 6–8w: 23.63% (69p) ≥9w: 46.9% (137p)	≤5w: 1.71% (5p) 6–8w: 15% (38p) ≥9w: 11.64% (34p)	0.004
PTV50.4	≤800 41.7% (122p) >800cc 16.78% (49p)	≤800cc 13.7% (40p) >800cc 9.6% (28p)	0.062

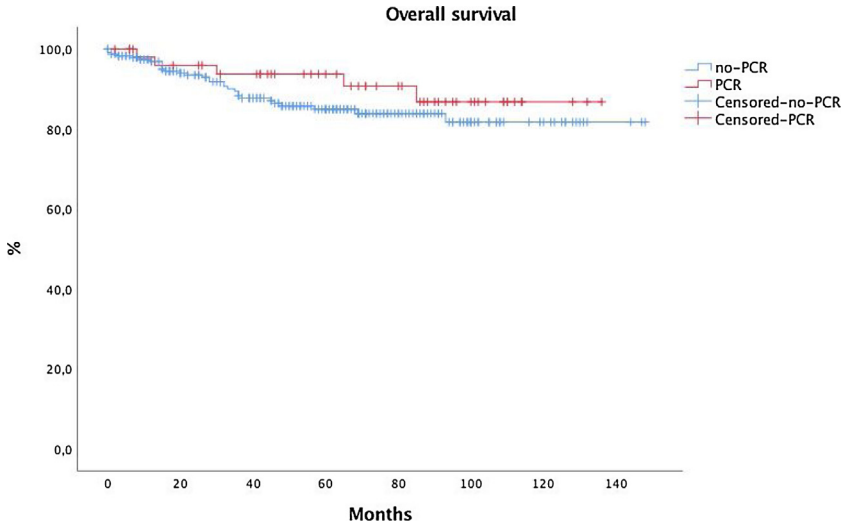

Fig. 1 – Differences in overall survival between groups.

3 and 0.7% Grade 4. Hematologic toxicities included neutropenia or anemia Grade 1 in 5.7%, Grade 2 in 3.2%, Grade 3 in 0.7% and Grade 4 in 0.4% of patients. Genitourinary toxicities included cistitis Grade 1 in 10.2% and Grade 2 in 0.7%. Ephitelitis was Grade 1 in 10.2%, Grade 2 in 7%, Grade 3 in 3.5% and Grade 4 in 0.4% of patients. There were no treatment-associated fatalities. Thirty-two patients (10.96%) experienced Grade III/IV toxicities (proctitis, ephitelitis and neutropenia).

Recurrence, overall survival and disease free survival

The mean follow-up was 55 months. There were only 6 (2.1%) local recurrences, 46 (15.8%) patients with distant relapses, and 2 patients with lymph node recurrence (0.7%).

Three and five years survivals were 85% and 90% for the group as a whole. Among ypT0N0 cases, the overall survival was 91.1% without significantly different ($p = 0.25$) compared with the remaining group, 87.2%. Among ypT0N0 cases, the relapse-free survival was 94.5%, with significantly different ($p = 0.03$) compared with the remaining group 78.2% (see survival curves: Figs. 1–4).

Discussion

In the last years, preoperative chemoradiotherapy followed by radical surgery with total mesorectal excision has been the standard approach for advanced rectal adenocarcinoma.[8] In the literature, about 10 %–30% patients will achieve a complete pathological response (ypT0N0), defined as the presence of fibrosis without tumour cells in the histologic specimen. In our series we found 21.6% patients with a pCR. Despite of acute toxicity Grade 3–4 occurs in 15 %–28% of patients with concomitant therapy,[9] the treatment was well tolerated in our patients, with only 32 patients (10.96%) having acute Grade 3–4 toxicities consisted of proctitis, ephitelitis and neutropenia. A pCR to preoperative treatment is an important outcome for rectal cancer. A pooled analysis of individual patient data showed that patients with LARC who achieved pCR after preoperative CRT had an improved five-year disease survival rate of 83.3% versus 65.6% for patients who did not achieve Pcr.[10] Our results are similar to other studies. We reported 5 year local recurrence, disease-free survival and overall survival rates of about 2.1 %, 83.5% and 85%, respectively. Preoperative CRT in rectal cancer assumes ranges for 5 year local recurrence

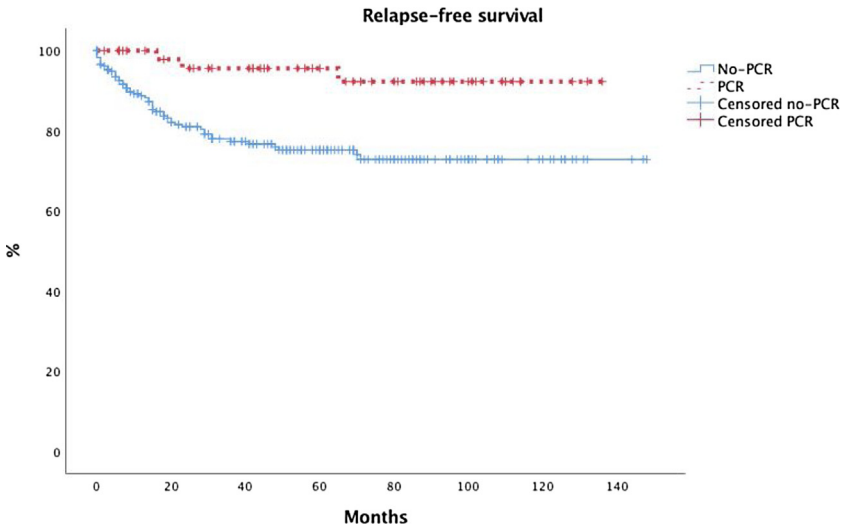

Fig. 2 – Differences in relapse-free survival between groups.

from 2% to 15%, disease-free survival from 70% to 86% and OS from 60% to 85%. pCR after preoperative CRT improve disease-free survival with significantly different (p = 0.03) compared with the remaining group (94.5% vs. 78.2%) without differences in overall survival. Importance in patients with pCR includes the possibility of non-surgery. Brazilian investigators initially described the "watch-and-wait" in 2004. After wait and see they described local recurrence of 4.6% with disease free survival at 5 years of 72% and overall survival of 96%.[11,12] Unfortunately, clinical or imaging evaluations are limited in their ability to distinguish post radiation changes from residual disease. Recently we are studied the predictive value of MRI in this approach.[13]

Predictive factors of pathological complete response after neoadjuvant treatment were tumor location to anal verge, CEA or Ca 19.9, histology, stage, time to surgery, type of surgery or tumour volume.

Das et al. demonstrated more response in lesions for more than 5 cm of the anal canal 16, in our study lesions located in the superior had more pCR rate (p = 0.001).[14] Huang et al. compared response in upper vs. middle and lower rectal tumours after CRT. They concluded that patients with upper rectal tumours had similar DFS and a trend toward longer OS compared middle/lower tumors without significant differences in tumour response (19% vs. 24.3%, p = 0.424).[15] Other series had investigated predictive factors of pathological response in LARC seems to level of CEA or Ca 19.9, non mucinous histology, type of surgery or time to surgery.

One of determinants in pathological down-staging is the interval from completion of CRT to surgery. The Lyon R90-01 trial demonstrated that patients undergoing surgery at 6 weeks had increased rates of tumour down-staging despite similar oncologic outcomes as compared to those who were operated on at 2 weeks after radiotherapy.[16] Further, evidence

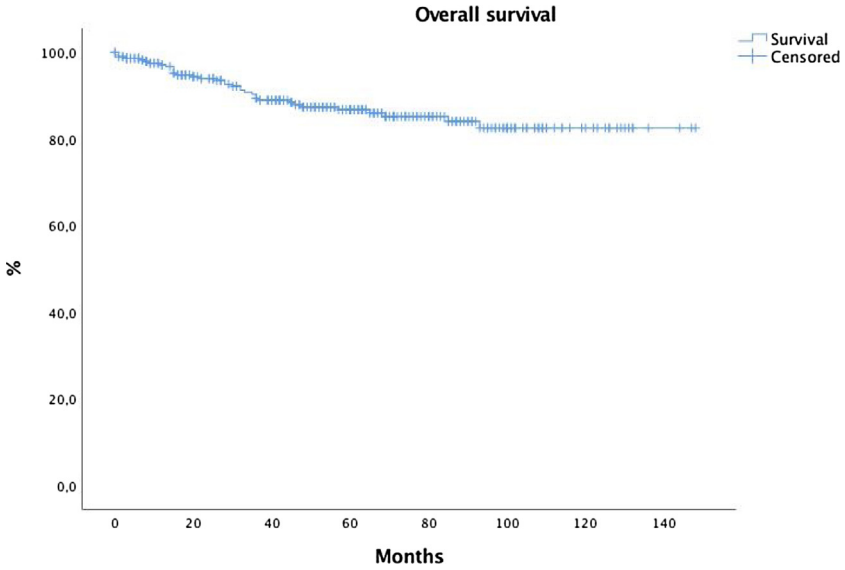

Fig. 3 – Overall survival.

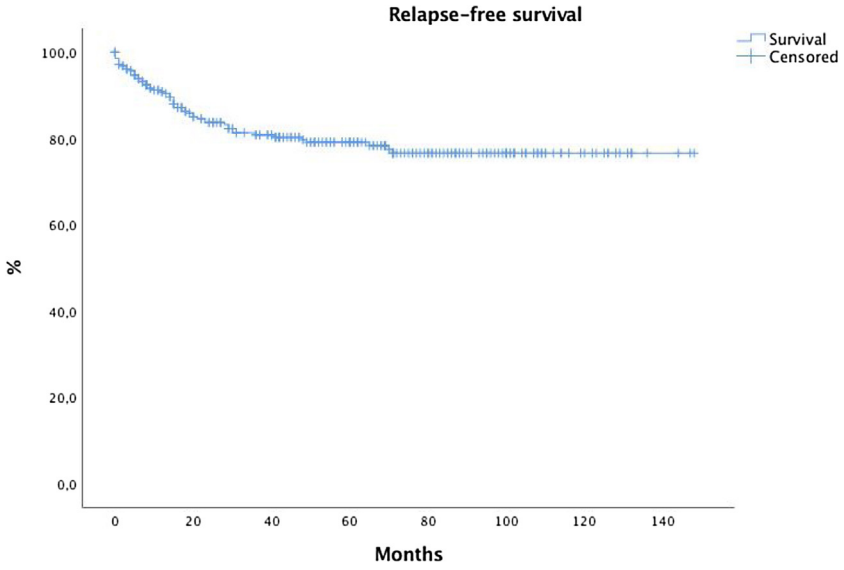

Fig. 4 – Relapse free survival.

suggests that tumour response to CRT is time-dependent and that tumour regression may take more than just 6 weeks. Tulchinsky et al. showed that an interval of more than seven weeks between completion of CRT and surgery improved pCR.[17] This was confirmed in a meta-analysis that showed that an interval to surgery of over eight weeks increased the pCR rate by 6%. A meta-analysis of 13 trials including 3584 patients evaluated whether a longer interval between the end of neoadjuvant CRT and surgery is associated with a higher pCR rate. Patients were divided into the following two groups: patients who underwent TME shorter than 6–8 after CRT and patients who underwent TME longer than 6–8 weeks after CRT. The longer interval from the end of CRT was found to be associated with a significantly improved pCR rate (19.5 vs. 13.7% in patients who waited > 6–8 weeks).[18] Other meta-analysis included 26 publications with 25,445 patients, it demonstrated a minimum 8 week interval increases pCR, and improves recurrence-free survival without more surgical morbidity.[19] In our study, 6/56 patients had pCR after ≤ 6 weeks and 50/56 patients > 6 weeks; 5.2% (15/292) of patients who had surgery 12 weeks after the completion of CRT achieved pCR. As response continues over time, it is possible that more patients with cCR can be captured with longer wait times. However, surgeons have been reluctant to delay surgery beyond 8 weeks because of concerns about increased radiation-induced pelvic fibrosis causing more surgical complications. Moreover, there has been apprehension that the longer interval may allow for disease progression. Huntington et al. demonstrated more positive resection margin in this cases.[20]

Third factor of favorable regression was to a greater volume that received the dose of 50.4 Gy. In the study of Liu et al.,[21] selected the tumour volume that receives the highest prescription dose, obtaining a significant association with the tumour response. So far, several clinical studies have confirmed that volume influences tumour response and prognosis in different types of tumours. This result is significant for patients with low rectal cancer in terms of organ preservation.[22–24]

In univariate analysis, we found distance to anal verge and time to surgery clinical factors of good grade regression according to Mandard Classification, PTV50.4 Gy was a trend that approached significance (p = 0.06). pCR was predictive factor for better disease free survival (p = 0.03).

There are several studies that have looked at strategies to improve pCR rates. Firstly, escalation of radiotherapy dose in the preoperative setting has been shown to increase pCR rates. Secondly, preoperative CRT with combination chemotherapy has shown promise in increasing pCR rates. Thirdly, researchers have investigated the delivery of chemotherapy in the interval period between completion of CRT and surgery. With the introduction of newer systemic agents, another approach to maximize pCR was the incorporation of oxaliplatin to standard 5-FU – based CRT with the intent of enhancing radio-sensitization of the tumour cells. This was investigated in 4 randomized controlled trials, such as STAR-01, ACCORD, NSABP R-04, and the German CAO/ARO/AIO-04 study. Aschele et al. and Gérard et al.[25–27] demonstrated that adding oxaliplatin to fluorouracil-based chemoradiotherapy increases toxicity without better tumour response. O'Connell et al. demonstrated that capecitabine with neoadjuvant radiotherapy achieved similar pCR, sphincter-sparing surgery and surgical downstaging compared with continuous infusion of 5-FU. However, Rödel et al.,[28] demonstrated that oxaliplatin and fluorouracil-based neoadjuvant chemoradiotherapy and adjuvant chemotherapy improved disease-free survival of patients with clinically staged LARC. The knowledge of predictive factors will increase the personalized treatment for tumour response. In the future we could increase radiotherapy or chemotherapy doses in poor responders and decreases doses or omitting concurrent chemotherapy in good responders.

Our study was limited because it is a retrospective analysis. We find predictive factors of pathologic response and we are thinking new lines of study.

Conclusion

In conclusion, we found that tumour localization was identified as predictive factors of pCR for LARC treated with preoperative chemo-radiation. Upper rectal tumours are more likely to develop complete responses. Delay in surgery was identified as a favorable predictive factor for TRG1–3.The relapse-free survival in pCR group was higher compared with non-pCR.

Conflicts of interest

The authors declare no conflicts of interest.

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