Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Neoadjuvant oral *vs.* infusional chemoradiotherapy on locally advanced rectal cancer: Prognostic factors

Sofia Conde[a,*], *Margarida Borrego*[a], *Tânia Teixeira*[a], *Rubina Teixeira*[a], *Anabela Sá*[b], *Paula Soares*[a]

[a] *Radiotherapy Department, Hospitais da Universidade de Coimbra, Portugal*
[b] *Oncology Department, Hospitais da Universidade de Coimbra, Portugal*

ARTICLE INFO

Article history:
Received 20 April 2011
Received in revised form
24 May 2012
Accepted 13 July 2012

Keywords:
Rectal cancer
Neoadjuvant oral chemoradiotherapy
Neoadjuvant infusional chemoradiotherapy
Prognostic factors
Adjuvant chemotherapy

ABSTRACT

Aim: To evaluate the prognostic factors and impact on survival of neoadjuvant oral and infusional chemoradiotherapy in patients with locally advanced rectal cancer.

Background: There is still no definitive consensus about the prognostic factors and the impact of neoadjuvant chemoradiotherapy on survival. Some studies have pointed to an improvement in overall survival (OS) and progression-free survival (PFS) in patients with tumor downstaging (TD) and nodal downstaging (ND).

Materials and methods: A set of 159 patients with LARC were treated preoperatively. Group A – 112 patients underwent concomitant oral chemoradiotherapy: capecitabine or UFT + folinic acid. Group B – 47 patients submitted to concomitant chemoradiation with 5-FU in continuous infusion. 63.6% of patients were submitted to adjuvant chemotherapy.

Results: Group A: pathologic complete response (pCR) – 18.7%; TD – 55.1%; ND – 76%; loco-regional response – 74.8%. Group B: pCR – 11.4%; TD – 50%; ND – 55.8%; LRR – 54.5%. The loco-regional control was 95.6%. There was no difference in survival between both groups. Those with loco-regional response had better PFS.

Conclusions: Tumor and nodal downstaging, loco-regional response and a normal CEA level turned out to be important prognostic factors in locally advanced rectal cancer. Nodal downstaging and loco-regional response were higher in Group A. Those with tumor downstaging and loco-regional response from Group A had better OS. Adjuvant chemotherapy had no impact on survival except in those patients with loco-regional response who achieved a higher PFS.

1. Background

Rectal adenocarcinoma is associated with a very high rate of local relapse after surgery alone. Some studies have demonstrated that adjuvant chemotherapy (CT) and radiotherapy (RT) reduce the rate of local relapse and prolong survival in patients whose tumors extend into the perirectal fat (T3) or who have mesorectal or pelvic lymph nodes involvement (N1–3).[1]

* *Corresponding author at*: Hospitais da Universidade de Coimbra; Praceta Prof. Mota Pinto, Portugal. Tel.: +351 919 212 230.
E-mail address: sofconde@hotmail.com (S. Conde).

1507-1367/$ – see front matter © 2012 Greater Poland Cancer Centre. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.
http://dx.doi.org/10.1016/j.rpor.2012.07.010

Preoperative chemoradiotherapy (CT + RT) offers some theoretical advantages over adjuvant therapy for patients with a tumor of the middle to lower rectum[2]: (i) micrometastases are treated early in the course of the disease; (ii) the risk of tumor seeding during surgery is reduced; (iii) RT toxicity is also reduced; (iv) the efficacy of CT and RT is higher in a tumor with an intact vasculature; (v) if the tumor shrinks, a sphincter preserving procedure can be performed. Nevertheless, this treatment also has some drawbacks: (i) definitive therapy is delayed, which may allow the growth and dissemination of the tumor; (ii) as preoperative staging is not very precise, patients on early stages (T1–2N0) of the disease, who do not need this therapy because of their very low risk of relapse, would be overtreated.

After the randomized trial CAO/ARO/AIO,[3] neoadjuvant CT + RT became the standard of care, since the 5-year local recurrence rate is reduced, adherence is better and it has fewer acute and long-term toxic effects than postoperative CT + RT. Neoadjuvant use of CT and RT allows a higher rate of resectability associated to a tumor and nodal downstaging.[4]

Concomitant neoadjuvant 5-FU CT + RT provides a pathologic complete response (pCR) in 8–27% of cases and is associated with an increased local control.[2–14] The single randomized trial that compared preoperative *vs.* postoperative CT + RT concluded that there was a lower 5-year local relapse (6% *vs.* 13%, $p = 0.006$) and a decrease in acute and late toxicity with preoperative CT + RT, although there was no difference in overall survival.[3] Theoretically, oral fluoropyrimidines are suitable to replace protracted infusion of 5-FU and avoid more invasive procedures.

Elevated preoperative serum carcinoembryonic antigen (CEA) levels, the most widely used tumor marker for the management of colorectal cancer, has been reported to be associated with a pathologic complete response, tumor downstaging and with an increased risk of relapse and poor patient outcome.[15–17]

The impact of neoadjuvant CT + RT on survival has been controversial. Some studies have pointed to an improvement in overall survival (OS) and progression-free survival (PFS) in patients with pathological response after neoadjuvant therapy.[9,18,19]

2. Aim

Since the standard schedule of preoperative CT + RT for rectal cancer remains to be established, and due to the convenience of oral drugs, we evaluate the therapeutic response to 5-FU and oral chemotherapy either with UFT and folinic acid or capecitabine combined with preoperative RT in patients with stages II–III rectal cancer in order to establish the best regimen for neoadjuvant treatment. Toxicity and survival were also analyzed for both groups, as well as the relationship between pathologic response, tumor downstaging, nodal downstaging and loco-regional response and survival. We analyze the impact of adjuvant chemotherapy in these patients, as this has also been a controversial issue.[20,21]

3. Materials and methods

3.1. *Patients*

We analyzed prospectively 159 patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy from December 2002 to September 2009. We included all patients with endoscopic and/or radiologic tumors staged as II–III rectal cancer from our Institution, without associated co-morbidities that preclude the proposed therapy and group selection was done according to the ability to adhere to oral therapy. Patients were divided into 2 groups. Group A: consisting of 112 patients who were treated with RT and concomitant oral CT. Group B: consisting of 47 patients, submitted to RT and concomitant CT with continuous infusion of 5-FU. Patients' characteristics corresponding to the different groups are described in Table 1.

3.2. *Neoadjuvant radiotherapy*

The patient's prone position was recommended, and a belly board immobilization device was used. A pelvic CT scan in the treatment position was performed in all patients, from L5-S1 to 2 cm distal to the anus. All patients underwent three-dimensional treatment planning. CT scan was used to define gross tumor volume (GTV). Clinical target volume (CTV) included the GTV + 2 cm in all directions, perirectal, internal iliac and presacral nodes up to the promontory; for T4 (seminal vesicles, prostate, vagina or uterus involvement) external iliac nodes were also included; the inguinal areas were irradiated in those patients who had invasion of the anal canal.[22,23]

The planning target volume (PTV) was defined as CTV + 1 cm margin. The treatment was delivered through three to four fields *via* the isocenter technique, shaped with multileaf collimator, and high-energy photons of 18 MV. The total dose administered was 50.4 Gy with conventional fractionation of 1.8 Gy/d, five days per week. The prescribed dose was specified at the International Commission on Radiation Units and Measurements point and isodose distribution to the PTV (95% to 107%).

3.3. *Neoadjuvant chemotherapy*

Group A was treated with oral CT concomitant to RT, including capecitabine or UFT. The capecitabine subgroup (61 patients) received an oral 825 mg/m^2 dose twice daily for the duration of RT (Monday–Sunday, including technical breaks). the UFT subgroup received a dose of 300 mg/m^2/d of UFT together with folinic acid 90 mg/d (51 patients), in three fractions/d, 5 days/week (Monday–Friday, with the weekend as a rest period). Group B was treated with RT concomitant to infusional CT and 5-FU was administered at a dose of 225 mg/m^2/d in a continuous infusion, 7 days/week.

3.4. *Surgery*

Patients were scheduled for surgery between the sixth and eighth week following the conclusion of the neoadjuvant therapy and were treated with a total mesorectum excision.