Clinical and Translational Radiation Oncology 4 (2017) 8–14

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Time to surgery and pathologic complete response after neoadjuvant chemoradiation in rectal cancer: A population study on 2094 patients

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ARTICLE INFO

Article history:
Received 2 February 2017
Revised 22 March 2017
Accepted 20 April 2017

Keywords:
Rectal cancer
Time interval
Surgery
TME
Chemoradiation

ABSTRACT

Background: To retrospectively evaluate the difference in terms of pathologic complete response (pCR) according to time elapsed between chemoradiation (CRT) and total mesorectal excision (TME) on a large unselected real-life dataset of locally advanced rectal cancer (LARC) patients.
Methods: A multicentre retrospective cohort study of LARC patients from 21 Italian Radiotherapy Institutions was performed. Patients were stratified into 3 different time intervals from CRT. The 1st group included 300 patients who underwent TME within 6 weeks, the 2nd 1598 patients (TME within 7–12 weeks) and the 3rd 196 patients (TME within 13 or more weeks after CRT), respectively.
Results: Data on 2094 LARC patients treated between 1997 and 2016 were considered suitable for analysis. Overall, 578 patients had stage II while 1516 had stage III histological proven invasive rectal adenocarcinoma. A CRT schedule of one agent ($N = 1585$) or 2-drugs ($N = 509$) was administered. Overall, pCR was 22.3% ($N = 468$ patients). The proportion of patients achieving pCR with respect to time interval was, as follows: 12.6% (1st group), 23% (2nd group) and 31.1% (3rd group) ($p < 0.001$), respectively. The pCR relative risk comparison of 2nd to 1st group was 1.8, while 3rd to 2nd group was 1.3. Moreover, between the 3rd and 1st group, a pCR relative risk of 2.4 ($p < 0.01$) was noted. At univariate analysis, clinical stage III ($p < 0.001$), radiotherapy dose >5040 cGy ($p = 0.002$) and longer interval ($p < 0.001$) were significantly

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http://dx.doi.org/10.1016/j.ctro.2017.04.004

correlated to pCR. The positive impact of interval ($p < 0.001$) was confirmed at multivariate analysis as the only correlated factor.
Conclusion: We confirmed on a population-level that lengthening the interval (>13 weeks) from CRT to surgery improves the pathological response (pCR and pathologic partial response; pPR) in comparison to historic data. Furthermore, radiotherapy dose >5040 cGy and two drugs chemotherapy correlated with pPR rate.

Introduction

The current standard neoadjuvant treatment for locally advanced rectal cancer (LARC) is either the use of preoperative short-course radiotherapy (RT) or conventionally fractionated RT with continuous 5-FU infusion or oral capecitabine (chemoradiation or CRT), followed by total mesorectal excision (TME) surgery 6–8 weeks later. CRT is associated with improved local control (LC) rate, tolerable toxicity profile and high compliance rate, and tumor downsizing with a potentially increased sphincter preservation rate in patients with low-lying tumors [1,2].

Although response to CRT is variable, it has been recognized that LARC patients achieving a pathological complete response (pCR) have a better prognosis compared to non-responders. In fact, several series and meta-analyses have shown a clear correlation between the pCR and clinical outcomes in terms of LC, metastases free survival, disease free survival and overall survival [3–8]. Conversely, other two meta-analyses failed to show an improved outcome in patients with pCR [9–10].

In series of LARC patients treated with radiotherapy (RT) or 5-fluorouracil based-CRT, the pCR rates ranged from 11.4% to 15% [11–13]. This rate can be improved given the versatility of preoperative long course CRT, allowing drug and RT dose intensification as well as time interval (CRT-surgery) modulation.

Second generation phase II trials combining oxaliplatin or raltitrexed to neoadjuvant 5-FU/capecitabine-CRT suggested higher pCR rates range (11–42%) in comparison with preoperative 5-FU-CRT alone [14]. Subsequently, four randomized phase III trials (ACCORD 12, STAR-01, NSABP-R04 and PETACC-6) did not confirm a significant improvement of the pCR rate range (14–19.2%) with the addition of oxaliplatin to preoperative 5-FU-based CRT [15–18]. On the contrary, the recent phase III trial CAO/ARO/AIO-04 showed that addition of oxaliplatin to 5-FU-based CRT improved pCR rate and disease free-survival compared to 5-FU-CRT alone (13% versus 17%) [19]. Moreover treatment intensification was pursued through the RT dose escalation. A systematic review and meta-analysis on dose escalation showed an association between pCR and higher boost doses [20], while a model on dose-response relationship confirmed the correlation between total delivered dose and possibility to achieve pCR [21].

Finally, the so-called time factor, as a potential factor in pCR rate improvement, is a debated subject in literature. The Lyon R90-01 trial, published in 1999, was the first randomized trial evaluating the CRT-surgery time interval [22]. Two–hundred and ten LARC patients were randomized to surgery either after a short (less than 2 weeks) or long (6–8 weeks) interval from RT (total dose = 39 Gy/3 Gy per fraction). The longer interval was associated with a significantly higher proportion of patients with ypT0–1 disease but not pCR. This 6–8 weeks interval has become routine practice after CRT for rectal cancer. Subsequently, it was observed that waiting longer than 6 weeks after CRT is associated with an increased pCR and near pCR rates. This led to further retrospective analyses on the association between interval length and pCR rate. In these retrospective studies an interval beyond 10 weeks after CRT was found as an independent factor in improving pCR rate (between 18% and 24%), and disease-free survival [23–25].

Indeed, complete tumor regression may take months, as shown by a growing body of evidences [26–28]. In the past, the concern about delayed surgery beyond 6–8 weeks was due to theoretically increased risk of complications, more technical difficulty due to fibrosis, and risk of loco-regional progression of residual disease. To date, these issues are largely overcome by literature findings demonstrating similar morbidity regardless of waiting time [23–25,29,30].

A further emerging issue about lengthening the interval before surgery is that it permits administration of chemotherapy during the break. In the recent study of Garcia-Aguilar and colleagues [31], there was a statistically significant difference between the group which underwent surgery after 6–8 weeks without adjuvant chemotherapy (18% pCR) and the group receiving 6 cycles of chemotherapy (FOLFOX 6) in the pre-surgical interval (38% pCR). This result seems to suggest that not only the break improves the oncologic outcome, but also chemotherapy administered in this interval might contribute.

Based on the hypothesis that a considerable increase of time to surgery might itself justify the higher response rates, a proposal was presented by the Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology (AIRO-GI) to Italian centers treating LARC patients preoperatively, to combine their retrospective series. The aim was to perform a population based analysis to evaluate the difference in terms of pathologic response according to time of surgery on a large LARC population of patients treated with modern CRT techniques and TME.

Patients and methods

Study design and participants

We performed a multicenter retrospective cohort study on LARC patients treated in 21 Italian Radiotherapy Institutions. Patients' data were obtained from the historical database of gastrointestinal radiation oncologists who joined the study. Patients must have signed informed consent to the use of their clinical data for scientific purposes. Inclusion criteria were: age $\geq$18 years, clinical stage II (T3–4, N0) or III (any T, N1–2) invasive rectal adenocarcinoma, distal tumor border within 12 cm from the anal verge by proctoscopy. Local staging was performed by endorectal ultrasound or phased-array MRI. Before treatment, patients underwent a full colonoscopy, abdomino-pelvic CT scan and chest radiograph/CT. Patients were required to have an ECOG performance status score of 0/1 or a comparable Karnofsky score.

Procedures

The AIRO-GI asked participating centers for minimal data sets including: gender, age, clinical stage, type of treatment and pathological response. No information about workup staging procedures or acute and late toxicity was recorded, as well as about quality of surgical procedures or subsequent outcomes. Chemotherapy schedule and radiotherapy dose were according to the treating