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CLINICAL INVESTIGATION **Rectum**

PROGNOSTIC VALUE OF PATHOLOGIC COMPLETE RESPONSE AFTER NEOADJUVANT THERAPY IN LOCALLY ADVANCED RECTAL CANCER: LONG-TERM ANALYSIS OF 566 ypCR Patients

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Purpose: In the literature, a favorable prognosis was observed for complete pathologic response after preoperative therapy (ypCR) in patients with locally advanced rectal cancer. The aim of this study is to verify whether ypCR predicts a favorable outcome in a large series of patients.

Methods and Materials: The Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology collected clinical data for 566 patients with ypCR (ypT0N0) after neoadjuvant therapy. Eligibility criteria included locally advanced rectal cancer with no evidence of metastases at the time of diagnosis, evidence of ypCR after preoperative radiotherapy ± chemotherapy (CT).

Results: Median radiation dose was 50 Gy. A total of 527 patients (93%) received one of 12 different neoadjuvant CT schedules. Sphincter preservation, anteroposterior resection, and endoscopic surgery were performed in 73%, 22%, and 5% of patients, respectively. Adjuvant CT was administered to 22% of patients. Median follow-up was 46.4 months. Locoregional recurrence occurred in 7 patients (1.6%). Distant metastases occurred in 49 patients (8.9%). Overall, 5-year rates of disease-free survival, overall survival, and cancer-specific survival were 85%, 90%, and 94%, respectively. In multivariate analysis, only age and clinical stage statistically correlated with survival outcome. Adjuvant CT was still of borderline significance (worse for adjuvant CT). No relation was found between survival and neoadjuvant CT schedules.

Conclusion: A ypCR after neoadjuvant therapy identified a favorable group of patients, even in this large series of 566 patients collected in 61 centers. Locoregional recurrence occurred only in 1.6% patients. © 2008 Elsevier Inc.

Rectal cancer, Neoadjuvant chemoradiotherapy, Pathologic response, Prognostic factors.

INTRODUCTION

Recent European randomized trials of patients with locally advanced rectal cancer (RC) showed a lower risk of local recurrence when neoadjuvant 5-fluorouracil (5-FU)–based chemoradiation (CRT) was compared with neoadjuvant radiotherapy (RT) alone (1, 2) or postoperative CRT (3, 4).

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Moreover, a significant greater rate of complete pathologic response after preoperative therapy (ypCR), defined as the complete absence of intact tumor cells in the resected specimen, was observed in the preoperative CRT arms of these studies. However, this did not translate into improvements in disease-free (DFS) or overall survival (OS). Conversely, several nonrandomized studies suggested that ypCR was associated with improvement in DFS (5–19). The attempt to attribute prognostic value to ypCR is subject to multiple confounding factors related to interstudy variability (20, 21). In a recent systematic review, Hartley *et al*. (22) collected information for 3,157 patients enrolled in seven randomized trials and 45 Phase II trials. A total of 428 patients had a documented ypCR, resulting in a 13.5% ypCR rate; no survival information was referred to this group. To date, the prognostic value of ypCR after neoadjuvant therapy for patients with locally advanced RC remains uncertain.

Some recent reports addressed the role of local excision in patients who achieved a complete response in the primary tumor, opening the question of whether it is safe to perform organ preservation if ypCR is observed (23–25).

A survey was proposed by the Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology (AIRO-GI) to Italian centers that treated patients preoperatively, aimed to explore whether patients who achieve ypCR represent a favorable population within patients with RC.

METHODS AND MATERIALS

Eligibility

Eligibility criteria included locally advanced RC with no evidence of metastases at the time of diagnosis; evidence of ypCR response, defined as no viable tumor cells at both the T and N levels; any combination of neoadjuvant treatment, at least including RT; any surgical procedure; and adequate information for treatment and subsequent outcome. A group of 30 patients assigned ypT0 and no clinical evidence of lymph node metastases treated by local excision, either as a result of patient choice or medical reasons, was also included in the present analysis. Patients assigned ypT0N+ were excluded from the study.

In the absence of standardized criteria to analyze the surgical specimen, local practice was accepted, and no attempt was made to review pathologic findings centrally. The AIRO-GI asked participating centers for the following data for each patient: age, gender, Union Internationale Contre le Cancer (UICC) clinical stage (cStage), RT parameters, chemotherapy (CT) schedule, delay between RT and surgery, type of surgery, number of detected lymph nodes in the pathologic specimen, whether postoperative adjuvant CT was administered, and last follow-up information. No information about workup staging procedures or acute and late toxicity was recorded, as well as about the quality of the surgical technique.

The AIRO-GI invited all Italian RT centers to include patients assigned ypT0N0 into the database retrospectively; 34 centers participated, including 499 patients. Two non-Italian groups were also invited: the Mount Vernon Cancer Center, Northwood, UK, and the German CAO/ARO/AIO-94 study (Table 1).

Statistical analysis

Receiver operating characteristic analysis was performed to search cutoff values to categorize continuous variables. For dichotomous variables, the ordinary chi-square test was used.

Relative risks were calculated as the ratio between the incidence rate in patients exposed to a certain risk factor and the incidence rate in patients not exposed. These incidence rates were calculated according to the person-time method.

Survival was measured from the start of the neoadjuvant treatment. Patients alive and free of recurrence were censored for the DFS analysis. Patients who died of any cause and patients who died of RC were censored at the time of the last follow-up. The DFS, OS, and cancer-specific survival (CSS) analyses were carried out by using the Kaplan-Meier method, and analysis of differences was performed using the log-rank test for trend with equally spaced metric for ordered prognostic factors with more than two. For dichotomous variables, the ordinary log-rank test was used. Multivariate analysis was performed according to the Cox proportional hazards model by backward elimination of factors found with

Table 1. Accrual by Center

Radiotherapy center	Number of patients	Radiotherapy center	Number of patients	Radiotherapy center	Number of patients
Rome, Univ.UCSC*	103	Firenze, Careggi	15	Belluno	3
Aviano, CRO†	52	Udine	15	Cuneo	3
Rovigo	42	Perugia	14	Taranto	3
CAO/ARO/AIO-94 trial	36	Vicenza	14	Terni	3
Verona	34	Modena	13	Aquila	2
Mount Vernon H. Northwood, UK	31	Trento	9	Arezzo	2
Ancona	27	Bologna, Univ. S.Orsola§	8	Mestre	2
Ravenna	23	Pisa, Univ. S.Chiara¶	7	MI INT‖	2
Rome Univ. La Sapienza‡	23	Monza	6	Torino	2
Padova	20	S.Giovanni Rotondo	6	Viterbo	2
Chieti	18	Bologna, Bellaria	5	Lecco	1
Trieste	16	Ivrea	4		

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‡ Univ. Sapienza = ''La Sapienza'' University.
§ Univ. S.Orsola = University Hospital of St. Orsola.
¶ Univ. S.Chiara = University Hospital of St. Chiara.
‖ MI INT = Istituto Nazionale Tumori, Milano.