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CLINICAL INVESTIGATION **Rectum**

PREDICTIVE FACTORS OF TUMOR RESPONSE AFTER NEOADJUVANT CHEMORADIATION FOR LOCALLY ADVANCED RECTAL CANCER

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Purpose: **Neoadjuvant chemoradiation followed by surgery is the standard of care for locally advanced rectal cancer. The aim of this study was to correlate tumor response to survival and to identify predictive factors for tumor response after chemoradiation.**

Methods and Materials: **From 1998 to 2008, 168 patients with histologically proven locally advanced adenocarcinoma treated by preoperative chemoradiation before total mesorectal excision were retrospectively studied. They received a radiation dose of 45 Gy with a concomitant 5-fluorouracil (5-FU)-based chemotherapy. Analysis of tumor response was based on lowering of the T stage between pretreatment endorectal ultrasound and pathologic specimens. Overall and progression-free survival rates were correlated with tumor response. Tumor response was analyzed with predictive factors.**

Results: **The median follow-up was 34 months. Five-year disease-free survival and overall survival rates were, of 44.4% and 74.5% in the whole population, 83.4% and 83.4%, respectively, in patients with pathological complete response, 38.6% and 71.9%, respectively, in patients with tumor downstaging, and 29.1and 58.9% respectively, in patients with absence of response. A pretreatment carcinoembryonic antigen (CEA) level of <5 ng/ml was significantly independently associated with pathologic complete tumor response ($p = 0.019$). Pretreatment small tumor size ($p = 0.04$), pretreatment CEA level of <5 ng/ml ($p = 0.008$), and chemotherapy with capecitabine (vs. 5-FU) ($p = 0.04$) were significantly associated with tumor downstaging.**

Conclusions: **Downstaging and complete response after CRT improved progression-free survival and overall survival of locally advanced rectal adenocarcinoma. In multivariate analysis, a pretreatment CEA level of <5 ng/ml was associated with complete tumor response. Thus, small tumor size, a pretreatment CEA level of < 5ng/ml, and use of capecitabine were associated with tumor downstaging.** **© 2011 Elsevier Inc.**

Rectal cancer, Neoadjuvant chemoradiation, Predictive factors, Tumor response.

INTRODUCTION

Chemoradiation (CRT) followed by surgery (proctectomy with total mesorectal excision [1]) is the standard of care for locally advanced stages (T3 and T4) of rectal cancer, to increase local control rates and ensures negative margin at surgery (2–6).

The challenge for clinicians is to determine the best therapeutic strategies adjusted to the patient's characteristics. Indeed, selection of patients is necessary in order to adapt the type and dose of neoadjuvant chemoradiation. Many factors may predict tumor response to CRT (7–11), but until now, there has been no way to propose a model that would predict clinically or pathology complete or partial tumor response after CRT.

Knowledge of such factors might be useful to clinicians for predicting treatment outcomes and take part in therapeutic decisions allowing development of risk-adapted treatment strategies. For example, more aggressive preoperative regimens may be considered in patients who are less likely to respond to standard preoperative therapy. As well, tumor-localized resection or nonoperative management of rectal cancer after neoadjuvant chemoradiation may be considered for patients with pathologic complete response (pCR) (12). A better knowledge of predictive factors also may help in

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the design of clinical trials for newer preoperative regimens, including targeted therapies.

In this setting, we performed a single-center retrospective analysis of 168 patients treated for locally advanced rectal adenocarcinoma with standard neoadjuvant chemoradiation. Our first objective was to correlate final pathologic stage (complete response, downstaging or absence of response) with survival (progression-free survival [PFS] and overall survival [OS]). The second objective was to identify parameters predicting tumor response (complete response or downstaging).

METHODS AND MATERIALS

Patients

From January 1998 to January 2008, 417 patients with histologically confirmed distal rectal adenocarcinoma were consecutively treated at Paoli-Calmettes Institute, Marseilles, France, by radiotherapy with or without chemotherapy, followed by carcinologic surgery. A total of 168 patients were included in our study and treated by preoperative concomitant chemoradiotherapy followed by proctectomy with total mesorectal excision for a T3/T4 or low T2, N0 to N+, M0 carcinoma. All others patients were excluded from this study.

Treatment consisted of whole-pelvis radiotherapy: mean dose of 45 Gy (range, 38–50 Gy), 1.8 Gy per fraction, 5 fractions by week over 5 weeks, using 18- MV photons beams and a three-field technique (one posterior field and two lateral fields). Concomitant chemotherapy was administered on the first day of pelvic radiation with either 5-fluorouracil (5-FU) intravenous continuous infusion (200 mg/m^2/day, Monday through Friday, over 5 weeks) in 71 patients (43%) or oral capecitabine (1600 mg/m^2 per day, given Monday through Friday, over 5 weeks) in 95 patients (57%).

At about 4 weeks after completion of preoperative CRT, all patients underwent an evaluation in order to appreciate tumor response. This evaluation included digital rectal examination, rigid proctoscopy, flexible endoscopy, and magnetic resonance imaging (MRI). Digital rectal examination and/or flexible endoscopy were performed in order to determine tumor size, based on the length of the tumor, distance of the inferior aspect of the tumor from the anal verge, and tumor circumference. Thoracoabdominal and pelvic computed tomography (CT) scans were obtained to determine possible distant disease. Carcinoembryonic antigen (CEA) levels were determined using the same technical processes.

Local extent of disease and evaluation of T and N stages were determined before and after CRT, using both pelvic MRI and endorectal ultrasonography (ERUS). Posttreatment ERUS was executed by the same medical team. The sixth edition of the American Joint Committee on Cancer TNM system was used for staging (13).

The surgical treatment was a proctectomy with total mesorectal excision, with or without sphincter preservation, in a median delay of 40.5 days (range, 16–228 days) after the end of CRT. Histological examination of the operative specimen was performed according to the technique originally described by Quirke *et al.* (14).

TNM, stage, number of invaded nodes, circumferential and distal margins, and venous or perineural invasion were recorded.

pCR was defined as the absence of any tumor cells in the operative pathology specimen defined by ypT0. Downstaging was defined as the lowering of the T stage between pretreatment ERUS and histological stage. PFS and the OS rates were studied according to pCR and downstaging.

The following parameters were evaluated as potential predictive factors of tumor response: age, sex, clinical T stage, clinical lymph node (N) classification, tumor size, distance from the anal verge, circumferential extent of tumor, fixed tumor, site of tumor, aspect of the tumor, pretreatment CEA level of less or more than 5 ng/ml, presence of mucinous features, pretreatment tumor differentiation, type of chemotherapy (5-FU vs. capecitabine), and delay between chemoradiotherapy and surgery.

Statistical analysis

Data were summarized by frequencies and percentages for categorical variables. For continuous variables, medians and ranges were computed.

To determine the association between response and covariates, univariate analysis was performed using the nonparametric chi square test or Wilcoxon rank sum test when appropriate. Statistical tests were two-sided.

Survival rates were estimated by the Kaplan-Meier method (15) and compared with the log-rank test. OS was defined by the time interval from the date of diagnosis to death, regardless of the cause. PFS was defined by the time from the date of diagnosis to locoregional relapse, metastasis, or death, whichever occurred first. Patients without events were censored at the time of last follow-up.

Changes of response probability according to predictive factors were assessed using a logistic model in multivariate analyses. A regression model was built only with factors presenting en effect in univariate analysis ($p < 0.15$). Statistical analysis was performed using R version 2.9.2. (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.1 software (SAS Institute Inc., Cary, NC).

RESULTS

Median age of the population was 60 years (range, 24–80 years). Clinical and pathological characteristics of population are described in Table 1.

Among 168 patients, 10 patients were excluded because tumor response could not be assessed. Evaluation of tumor response showed that 31 patients (19%) had a pCR at surgery on pathologic specimen analysis (ypT0). Downstaging occurred in 89 patients (56%). Sixty nine patients (44%) had no tumor response.

There was a significant lowering of the T classification from pretreatment clinical staging by ERUS to posttreatment staging on pathologic specimen.

The pathologic ypT classification was ypT0 in 31 patients (19%), ypT1 in 16 patients (10%), ypT2 in 36 patients (22%), ypT3 in 73 patients (45%), and ypT4 in 6 patients (4%). We found there was a difference between posttreatment ERUS T stage and the final pathology status (Table 2). Existing techniques of imagery do not allow correct assessment of the response rate and downstaging of the nodes.

Tumor response and survival

With a median follow-up of 34 months, five-year disease-free survival and OS rates of the whole population were, respectively, 44.4% (range, 34.8–56.7%) and 74.5% (range, 65.6–84.7%). Five-year disease-free survival rate was 83.4% (range, 69.5–100%) in case of complete response vs. 38.6% (range, 28.2–52.8%) in case of residual disease