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CLINICAL INVESTIGATION **Rectum**

LATE PATIENT-REPORTED TOXICITY AFTER PREOPERATIVE RADIOTHERAPY OR CHEMORADIOTHERAPY IN NONRESECTABLE RECTAL CANCER: RESULTS FROM A RANDOMIZED PHASE III STUDY

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Purpose: Preoperative chemoradiotherapy (CRT) is superior to radiotherapy (RT) in locally advanced rectal cancer, but the survival gain is limited. Late toxicity is, therefore, important. The aim was to compare late bowel, urinary, and sexual functions after CRT or RT.

Methods and Materials: Patients ($N = 207$) with nonresectable rectal cancer were randomized to preoperative CRT or RT (2 Gy × 25 ± 5-fluorouracil/leucovorin). Extended surgery was often required. Self-reported late toxicity was scored according to the LENT SOMA criteria in a structured telephone interview and with questionnaires European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), International Index of Erectile Function (IIEF), and sexual function -vaginal changes questionnaire (SVQ).

Results: Of the 105 patients alive in Norway and Sweden after 4 to 12 years of follow-up, 78 (74%) responded. More patients in the CRT group had received a stoma (73% vs. 52%, $p = 0.09$). Most patients without a stoma (7 of 12 in CRT group and 9 of 16 in RT group) had incontinence for liquid stools or gas. No stoma and good anal function were seen in 5 patients (11%) in the CRT group and in 11 (30%) in the RT group ($p = 0.046$). Of 44 patients in the CRT group, 12 (28%) had had bowel obstruction compared with 5 of 33 (15%) in the RT group ($p = 0.27$). One-quarter of the patients reported urinary incontinence. The majority of men had severe erectile dysfunction. Few women reported sexual activity during the previous month. However, the majority did not have concerns about their sex life.

Conclusions: Fecal incontinence and erectile dysfunction are frequent after combined treatment for locally advanced rectal cancer. There was a clear tendency for the problems to be more common after CRT than after RT.

Chemoradiotherapy (CRT), Nonresectable, Radiotherapy (RT), Rectal cancer, Late toxicity.

INTRODUCTION

The superiority of preoperative chemoradiotherapy (CRT) over radiotherapy (RT) alone in locally advanced rectal cancer has been documented in three clinical trials (1–3). The improvements in reduced risk of local failure are rather limited, although they are sufficient to incorporate CRT into routine clinical use, despite the risk of increased acute toxicity (4). Because there was a limited gain (3) or no gain (1,2) in overall survival in the trials when chemotherapy was added to RT, late adverse effects and health-related quality-of-life issues (HRQoL) are very important. Descriptions of late adverse effects and long-term HRQoL after rectal cancer RT in the literature are mainly limited to trials of preoperative short-course RT (5), and no report has thus far compared preoperative long-course RT with CRT. Pietrzak *et al.* (6) compared short-course RT with long-course CRT and found no difference in HRQoL or late toxicity after 4 years of follow-up. Bruheim *et al.* (7) noticed considerable long-term effects on anorectal function and poorer social functioning in patients with locally advanced rectal cancer treated with long-course preoperative or postoperative RT/CRT when compared with rectal cancer patients treated with surgery alone.

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Improved tumor outcome after CRT relative to RT has been observed in numerous tumor sites. Increased early toxicity has been recognized in virtually all trials, but there is an almost complete lack of comprehensive data about late toxicity from the randomized trials (8). Recent meta-analyses/systematic overviews have concluded that there are insufficient data to assess whether late toxicity is affected by the addition of chemotherapy to RT (4, 9–11).

Patients in our study participated in a randomized multicenter trial during 1996–2003, comparing RT alone with CRT (3). Chemoradiotherapy improved local control and cancer-specific survival, but overall survival was not significantly influenced. Chemoradiotherapy led to more acute toxicity, but no differences were observed in the mean values for physician-reported late toxicity between the two groups. However, this registration was not well specified in the protocol written in 1996, the follow-up was not long enough for all patients for an optimal assessment (median, 61 months; range, 38–130 months), and the patient perspectives were not considered. Therefore we found it important to add a cross-sectional investigation with a longer follow-up, using more detailed questionnaires and a detailed interview. The aim of this report was to compare self-reported late morbidity and sexual function in the two groups, CRT and RT.

METHODS AND MATERIALS

Patients

Between 1996 and 2003, 207 patients with primary, nonresectable (clinical stage T4) or locally recurrent rectal adenocarcinoma were randomized to preoperative CRT (n = 98) or RT (n = 109). Tumors were considered to be nonresectable when digital examination and rigid rectoscopy showed a fixed tumor and when computed tomography or magnetic resonance imaging indicated overgrowth to the sacrum, pelvic side wall/floor, base of the bladder, or prostate gland. Many patients required extensive surgery, and the registration of long-term morbidity was an important part of their follow-up.

A cross-sectional registration of late morbidity, including fecal incontinence and urinary and sexual problems, was completed after a minimum of 4 years after treatment (median follow-up of 85 months [range, 59–135 months] in CRT group and 78 months [range, 57–148 months] in RT group). Patients still alive (n = 105) in Norway and Sweden were contacted in 2006–2008. Patients from Poland were excluded from further registration because of logistic difficulties concerning the telephone interview and questionnaires. The first contact was made by mail, and two reminders were sent to nonresponders. Of the patients, 78 (74%) responded: 78 were interviewed, 76 answered the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), and 71 (44 men and 27 women) answered the sexual questionnaires. There were no statistically significant differences between responders and nonresponders with regard to any of the patient characteristics as listed in Table 1. Of the 34 responders in the RT group, 1 patient was excluded from the analyses because of a previous local recurrence.

The ethical committees in the two countries approved the trial. All patients gave their written informed consent. The registration of late toxicity via telephone interviews and questionnaires about sexual problems were not included in the original protocol, and these amendments were approved separately by the ethical committees in Sweden and Norway. A user agreement with Mapi Research Trust (on behalf of Pfizer Lyon, France) to use the International Index of Erectile Function (IIEF) questionnaire was signed.

Treatment

A three- or four-beam technique (alternatively, two beams in special cases) was used. The patients were treated with daily fractions of 2.0 Gy 5 days a week. Clinical target volume (CTV) 1, defined as the gross tumor volume plus a 2-cm margin, received 46 Gy followed by a 4-Gy boost, with 50 Gy in total. Clinical target volume 2, defined as CTV 1 plus lymph node stations in the dorsal pelvis, received 46 Gy. Whether the external iliac lymph nodes were included in CTV 2 depended on the tumor extension. The anal canal was excluded when an abdominoperineal resection (APR) was unlikely.

Patients randomized to chemotherapy received bolus 5-fluorouracil (400 mg/m^2) concomitantly with RT preoperatively and 500 mg/m^2 postoperatively, followed by 100 mg of leucovorin on two consecutive days every second week (Nordic schedule). The 5-fluorouracil injection was given before the RT fractions on Days 1 to 2, 11 to 12, and 21 to 22. In the CRT group all patients were scheduled to receive adjuvant chemotherapy starting 4 to 6 weeks postoperatively and continuing for 8 cycles, irrespective of their pathologic stage. Surgery was performed 5 to 8 weeks after the last RT fraction. Total mesorectal excision was recommended, and pelvic organs or structures with cancer involvement at diagnosis were resected en bloc if possible, to achieve an R0 resection.

Of the responding patients in the CRT group, 20 (45%) received postoperative chemotherapy for 4 months (8 courses). In the CRT group the proportion starting postoperative chemotherapy did not differ between responders and nonresponders: 59% and 63%, respectively (Table 1).

Follow-up

Follow-up investigations were scheduled every 3 months during the first 2 years, then every 6 months the following 2 years, and thereafter, annually. Evaluation included patient history, clinical examination, rectoscopy, blood tests, quality-of-life questionnaire (EORTC QLQ-C30), and World Health Organization toxicity score. Imaging was performed when signs or symptoms indicated the presence of recurrent disease.

Late patient-reported toxicity

Patients who agreed to participate in this cross-sectional follow-up study were asked to fill out and return a questionnaire about sexual function and vaginal problems, the sexual function–vaginal changes questionnaire (12) for women and the IIEF questionnaire (13) for men. For both questionnaires, the time frame was the previous month. Whenever possible, the same four response categories as in the European Organisation for Research and Treatment of Cancer QLQ-C30 were used. In addition, patients answered a structured questionnaire in a telephone interview conducted by an oncology nurse. Symptoms were scored according to the LENT SOMA scale for late effects on normal tissue (14) and the St. Marks score for fecal incontinence (15). The questions focused on the parts of the LENT SOMA scale describing symptoms from the bowel (small intestine, large bowel, and rectum) and the urinary system. Questions about cardiovascular disease, other