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CLINICAL INVESTIGATION **Prostate**

VOLUME AND HORMONAL EFFECTS FOR ACUTE SIDE EFFECTS OF RECTUM AND BLADDER DURING CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER

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Purpose: To identify dosimetric variables predictive of acute gastrointestinal (GI) and genitourinary (GU) toxicity and to determine whether hormonal therapy (HT) is independently associated with acute GI and GU toxicity in prostate cancer patients treated with conformal radiotherapy (RT).

Methods and Materials: This analysis was performed on 336 patients participating in a multicenter (four hospitals) randomized trial comparing 68 Gy and 78 Gy. The clinical target volume consisted of the prostate with or without the seminal vesicles, depending on the risk of seminal vesicle involvement. The margin from the clinical target volume to the planning target volume was 1 cm. For these patients, the treatment plan for a total dose of 68 Gy was used, because nearly all toxicity appeared before the onset of the 10-Gy boost. Acute toxicity (<120 days) was scored according to the Radiation Therapy Oncology Group criteria. The dosimetric parameters were obtained from the relative and absolute dose–volume/surface histograms derived from the rectal wall (rectal wall volume receiving ≥5–65 Gy) and the bladder surface (bladder surface receiving ≥5–65 Gy). Additionally, relative and absolute dose–length histograms of the rectum were created, and the lengths of rectum receiving more than a certain dose over the whole circumference (rectal length receiving ≥5–65 Gy) were computed. The clinical variables taken into account for GI toxicity were neoadjuvant HT, hospital, and dose–volume group; for GU toxicity, the variables pretreatment GU symptoms, neoadjuvant HT, and transurethral resection of the prostate were analyzed. The variable neoadjuvant HT was divided into three categories: no HT, short-term neoadjuvant HT (started ≤3 months before RT), and long-term neoadjuvant HT (started >3 months before RT).

Results: Acute GI toxicity Grade 2 or worse was seen in 46% of the patients. Patients with long-term neoadjuvant HT experienced less Grade 2 or worse toxicity (27%) compared with those receiving short-term neoadjuvant HT (50%) and no HT (50%). The volumes of the prostate and seminal vesicles were significantly smaller in both groups receiving neoadjuvant HT compared with those receiving no HT. In multivariate logistic regression analysis, including the two statistically significant clinical variables neoadjuvant HT and hospital, a volume effect was found for the relative, as well as absolute, rectal wall volumes exposed to intermediate and high doses. Of all the length parameters, the relative rectal length irradiated to doses of ≥5 Gy and ≥30 Gy and absolute lengths receiving ≥5–15 and 30 Gy were significant. Acute GU toxicity Grade 2 or worse was reported in 56% of cases. For patients with pretreatment GU symptoms, the rate was 93%. The use of short-term and long-term neoadjuvant HT resulted in more GU toxicity (73% and 71%) compared with no HT (50%). In multivariate analysis, containing the variables pretreatment symptoms and neoadjuvant HT, only the absolute dose–surface histogram parameters (absolute surface irradiated to ≥40, 45, and 65 Gy) were significantly associated with acute GU toxicity.

Conclusion: A volume effect was found for acute GI toxicity for relative, as well as absolute, volumes. With regard to acute GU toxicity, an area effect was found, but only for absolute dose–surface histogram parameters. Neoadjuvant HT appeared to be an independent prognostic factor for acute toxicity, resulting in less acute GI toxicity, but more acute GU toxicity. The presence of pretreatment GU symptoms was the most important prognostic factor for GU symptoms during RT.

Radiotherapy, Prostate cancer, Volume effect, Acute toxicity, Hormonal therapy.

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INTRODUCTION

To improve outcomes in prostate cancer patients treated with radiotherapy (RT), higher radiation doses to the prostate (and seminal vesicles [SVs]) have been examined in several randomized and nonrandomized trials. A major concern when using higher doses is the increased rate of complications, especially because of the often-protracted course of this disease and the potentially long survival. A greater complication rate can only be accepted if significantly better outcomes are achieved and if these complications are not too severe.

We performed a Phase III multicenter randomized trial, comparing two treatment arms: 68 Gy and 78 Gy. Previously, we reported the results of acute and late gastrointestinal (GI) and genitourinary (GU) complications with regard to general treatment factors and patient-related factors (1). In our previous report, no significant differences in acute toxicity were found between the randomization arms. In contrast, several clinical variables appeared to be important prognostic factors for GI and GU toxicity. For acute GI toxicity, a higher dose to the SVs and the presence of pretreatment GI symptoms were associated with a significantly greater complication rate, but patients who had received hormonal therapy (HT) experienced less acute GI toxicity. Conversely, HT yielded a significantly greater incidence of acute GU toxicity. The strongest prognostic factor for acute GU toxicity was the presence of pretreatment GU symptoms. Finally, patients treated with transurethral resection of the prostate before RT had fewer acute GU complaints.

In contrast to other studies (2–8) on dose–volume effects and acute toxicity in irradiated prostate cancer patients, we used dose–volume histograms (DVHs) based on the rectal wall and bladder surface, without including the contents of these organs. In addition to these DVH parameters, we also included a parameter in which the irradiated circumference was taken into account, and investigated whether an association exists between acute GI toxicity and the rectal length irradiated to a certain dose over the whole circumference of the rectum. Skwarchuk *et al.* (9) used a comparable approach and found a significant association between late rectal bleeding and the enclosure of the outer rectal contour by the 50% isodose surface.

The purpose of this analysis was to identify a possible volume effect for acute GI and GU toxicity, taking into account the above-mentioned clinical variables. We also wanted to assess whether the reduced GI toxicity after neoadjuvant HT was a result of downsizing the prostate and SVs.

METHODS AND MATERIALS

Inclusion criteria and stratification

Between June 1997 and February 2003, four Dutch centers participated in a Phase III trial in which prostate cancer patients were randomized to receive 68 or 78 Gy. The details of the study design have been previously published (1). TNM staging was scored according to the American Joint Committee on Cancer 1997 guidelines. At histologic evaluation, Gleason score and/or differentiation grade were assigned. Exclusion criteria were prostate-specific antigen (PSA) level $\geq$60 ng/mL, Stage T1a, well-differentiated (Grade 1 or Gleason score $<$5) T1b-T1c tumors with PSA level $<$4 ng/mL, positive regional lymph nodes, distant metastases, anticoagulant therapy, Karnofsky performance status $<$80, and previous radical prostatectomy or pelvic irradiation. HT was allowed and was commonly prescribed to high-risk patients. HT was usually started a few months before RT and was prescribed for a total duration of 3 years in Hospital A and for 6 months in Hospital B. Generally, a luteinizing hormone-releasing hormone agonist preceded by a short course of an antiandrogen was prescribed. In Hospitals C and D, no HT was given, except for 1 patient. Four dose–volume groups were defined according to the estimated risk of SV involvement, according to Partin *et al.* (10). Group 1 included Stage T1b, T1c, and T2a patients with an estimated risk of SV involvement of $<$10%. Group 2 included Stage T1b, T1c, and T2a patients with an estimated risk between 10% and 25%. Group 3 contained Stage T1b, T1c, and T2a patients with a risk $>$25% and all Stage T2b and T3a patients. Group 4 comprised all Stage T3b and T4 patients. Patients were stratified by hospital, HT (yes vs. no), age ($\leq$70 vs. $>$70 years), and dose–volume group.

Treatment planning

For each dose–volume group, specific planning target volumes (PTVs) were defined. Up to 68 Gy, margins of 1 cm were added to the clinical target volume (CTV) to obtain the PTV. For patients included in the high-dose treatment arm, the margins for the last 10 Gy were reduced to 5 mm to obtain the PTV, except for the interface between the CTV and rectal wall, where no margin was taken. In Group 1, the CTV was defined as the prostate only. In Group 2, for the first 50 Gy, the CTV was defined as the prostate and SVs; for the rest of the treatment, the CTV was the prostate only. In Group 3, the CTV consisted of the prostate and SVs until 68 Gy and was restricted to the prostate for the boost of 10 Gy. Finally, for Group 4, the CTV was defined as the prostate and SVs for the whole treatment and in both randomization arms.

The rectum was delineated from the level of the tuberosities to the level of the inferior border of the sacroiliacal joints or when the rectum was no longer adjacent to the sacrum. This definition resulted from a quality control study performed at the beginning of the trial (11). The anal canal was drawn separately and added to the rectum, if not already included in the rectum delineated according to the definition. Rescanning was advised when the rectal volume, including filling, was $>$150 cm^3. In Hospital A, patients were instructed to use laxatives the evening before the planning CT scan.

Selection of patients and treatment plans

Of the 669 patients randomized to receive 68 Gy (n = 332) or 78 Gy (n = 337), 336 patients were selected for this study for the following reasons. For both treatment arms, the evolution of toxicity during RT was similar (Fig. 1). Patients with GI or GU Grade 2 or worse had this toxicity in the first 7 weeks of treatment, except for 17 (2.6%) and 16 (2.4%) patients, respectively. This means that for nearly all patients in the high-dose treatment arm, the additional boost of 10 Gy (given in the eighth week of treatment) did not contribute to the greater incidence of acute GI and GU Grade