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Phase III randomised trial

Radiotherapy with rectangular fields is associated with fewer clinical failures than conformal fields in the high-risk prostate cancer subgroup: Results from a randomized trial

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ABSTRACT

Objective: High-risk prostate cancer patients are at risk for subclinical disease and micro-metastasis at the time of treatment. Nowadays, tight margins reduce dose to periprostatic areas compared to earlier techniques. We investigated whether rectangular fields were associated with fewer failures compared to conformal fields (with lower extraprostatic dose).

Methods: We selected 164 high-risk patients from the trial population of 266 T1-T4N0M0 patients, randomized between rectangular ($n = 79$) and conformal fields ($n = 85$). Prescribed dose was 66 Gy to the prostate and seminal vesicles plus 15 mm margin. We compared clinical failure rates (in- and excluding local failures), between both arms. Dose differences around the prostate were calculated based on an inter-patient mapping method.

Results: Median follow-up was 34 months. There were 9 clinical failures in the rectangular arm versus 24 in the conformal arm ($p = 0.012$). Number of failures outside the prostate was 7 and 19, respectively ($p = 0.025$). We observed average dose differences of 5–35 Gy between the arms in the regions around the prostate.

Conclusions: We found a significantly lower risk of early tumor progression for patients treated with rectangular fields. Treatment failure can probably in part be prevented by irradiation of areas suspected of subclinical disease in high-risk prostate cancer.

Patients treated with radiotherapy for localized prostate cancer have different risk profiles with regard to recurrence of the disease and prostate cancer-related death. Well established predictive factors are: pretreatment Prostate-Specific Antigen (PSA) level, T stage, and Gleason score/differentiation grade. These factors are broadly recognized and used to define low-, intermediate- and high-risk prostate cancer. The definition of Chism et al. [1] identifies low risk as PSA $\leqslant$ 10, T1B-T2a, and Gleason < 7, high-risk as PSA > 20 ug/L, and/or T3, and/or Gleason 8–10, and intermediate risk as all other patients.

High-risk patients show a much higher hazard rate for clinical failures during the first years after radiotherapy compared to low- and intermediate risk. This can be contributed to extracapsular cancer growth into surrounding tissues (e.g. invasion of rectum or bladder neck, perineural invasion), and micro-metastasis to lymph node areas already present at the time of radiotherapy [2–6]. Clinical failures after a longer period of time (e.g. 10 years) can be contributed to local failure of the treatment [2]. Risk estimations of subclinical disease outside the prostate vary from a few percent for low-risk patients to more than 30% for high-risk, depending on the risk profile [6,7].

Elective nodal irradiation in patients with unfavorable prostate cancer is a controversial topic; the presence of micro-metastasis in part of these patients suggests favorable outcomes for elective irradiation, but results from two randomized trials are inconclusive [8,9]. Therefore elective nodal irradiation has remained a point of discussion since the introduction of conformal therapy about 20 years ago [10].

In a previous study we found a dose–effect relationship for accidental dose delivered *outside* the prostate and freedom from failure [11]. This concerned a subgroup of high-risk patients from a randomized trial in which either 68 Gy or 78 Gy was described to the prostate and seminal vesicles with conformal techniques and a 1 cm margin. To validate the results of this explorative analysis, we investigated failure rates of high-risk prostate cancer patients in an independent data set. This concerned data of a previous randomized clinical trial [12] in which the original goal was to look

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into toxicity levels of conformal fields compared to rectangular fields. All patients in this trial were treated with modern three-dimensional (3D) treatment techniques and their setup was monitored and corrected when necessary during treatment. In this toxicity trial patient had been randomized between rectangular fields to treat the prostate and seminal vesicles, and conformal fields (with lower unintended dose to regional areas). Our hypothesis was that rectangular fields may be associated with a lower risk of clinical failure.

Material and methods

Study Population

We reviewed data from a randomized clinical trial performed at the Daniel den Hoed Clinic/Erasmus Medical Center in Rotterdam (The Netherlands). Patient recruitment took place in the period 1994–1996. A total of 266 patients entered this toxicity trial in which adverse toxicity event rates were compared between treatments with conformal fields versus the conventional (at that time) rectangular fields. More details of this study population are described elsewhere [12]. From this patient group, we selected 164 high-risk patients, using criteria described by Chism et al. [1]: PSA > 20 μg/L, or poor differentiation, or T3. Since no Gleason score was available for these patients diagnosed in 1994–1996, we used the differentiation grade to select high-risk patients. Characteristics of the selected high-risk patients are summarized in Table 1. Trial patients with T1B/C tumors were treated for the prostate only and therefore none of them were selected for the current analysis: this excluded 2 high-risk patients with a T1B tumor and poor differentiation.

Treatment

Patients were randomized to either rectangular or conformal radiation fields, stratifying for gross tumor volume. The prescribed dose was 66 Gy in 33 fractions. Patients were instructed to have a full bladder and empty rectum for the planning CT scan. The clinical target volume was the prostate and seminal vesicles plus a 3D expansion of 15 mm. A three-field technique was used with two lateral (oblique) fields and one anterior treatment field which was planned with a 3D planning system (CADPLAN). In the conformal arm, a multi leaf collimator was used to shape the treatment fields. Patient set-up was checked at regular intervals using an electronic portal imaging device. During treatment an Electronic Portal Imaging Device was used to check the patient setup. With "a set-up correction protocol" [13] the average systematic positioning accuracy of the bony anatomy could be limited to 1.5 mm (1 SD) with a average random error of 2.5 mm (1 SD).

Table 1
Patient and treatment data of selected high-risk patients (n = 164).

Characteristics	Rectangular fields (n = 79)	Conformal fields (n = 85)
Mean age in years (1 SD)	70 (6.5)	70 (6.4)
Tumor stage:		
T2A	2	1
T2B	9	7
T2C	22	19
T3A	15	27
T3B	29	22
PSA (μg/L)		
<10	13	15
10–20	19	24
>20	46	45
Unknown	1	1
Differentiation grade		
Good	17	21
Moderate	44	34
Poor	16	25
Unknown	2	5
Neo-adjuvant HT[a]:		
Yes	15	12
No	64	73

[a] HT, hormonal treatment.

Endpoint

No data on follow-up PSA measures or biochemical failure were available for this patient group. Therefore only clinical failure was the study endpoint. Failure could be local, regional, and/or distant metastasis. Procedures to investigate clinical failures were similar in both arms, and were performed according the clinical guidelines: physical exam and blood tests were performed at each follow-up, and if there was an indication for possible tumor progression, additional imaging (like bone scan, CT scan) was performed as decided by the treating physician. The clinical failures in this study were all identified within 3.6 years after treatment. Longer follow-up was not available from this randomized trial since it was designed as a toxicity study.

Dose distributions

We calculated dose maps for each patient, and constructed a dose difference map, by using a mapping procedure which is described by Witte et al. [11]. The dose mapping is based on the prostate contour delineated on the planning CT scan. From one patient to another, two points correspond if their distances to the prostate are equal, and their directions with respect to the center of mass of the prostate are the same. We also evaluated the dose in specific points on the dose map for each individual patient: 3.5 cm and 5 cm from the prostate edge, located in the obturator region. An example of the location of such a point is illustrated in Fig. 1 for two arbitrary patients.

Statistical analysis

We calculated time-to-event curves from the start of RT, using Kaplan Meier estimates. Log-Rank statistic was applied to test differences between groups. A Cox regression model was used to construct a multivariate model. IBM© SPSS© for Windows software was used for the analyses (release 20.0, IBM Corp.).

Results

Tumor progression & survival

Median follow-up was 34 months for patients alive (range 11–48). The number of patients with tumor progression was 9 in the rectangular arm and 24 in the conformal arm (total of 33). The first location of established tumor progression was "local" in 7 cases, "regional" in 2 cases, and "distant metastasis" in 24 cases (Table 2). Kaplan Meier estimates showed a significantly lower risk of the total number of clinical failures for rectangular fields (p = 0.012, Fig. 2). When we count only first failures outside the prostate (excluding first events of local failure), the number of events was 7 and 19, respectively (Log-Rank, p = 0.025). Within the limited follow-up of the study population 24 patients had died (12 in both arms); 6 of them died from prostate cancer (3 in both arms).

Dose differences

Using the dose mapping procedure, we found average dose differences in the range of 5–35 Gy between the arms in the regions