Clinical Oncology 25 (2013) 321–327

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Quality of Life after Radical Radiotherapy for Prostate Cancer: Longitudinal Study from a Randomised Trial of External Beam Radiotherapy Alone or in Combination with High Dose Rate Brachytherapy

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Received 16 August 2012; received in revised form 2 January 2013; accepted 3 January 2013

Abstract

Aim: To compare prospective, long-term quality of life in patients randomised to external beam radiotherapy (EBRT) alone or with a boost of high dose rate (HDR) brachytherapy.

Materials and methods: In total, 216 patients participating in the UK randomised trial of EBRT ± HDR brachytherapy were included in this analysis. EBRT delivering 55 Gy in 20 fractions was compared with EBRT followed by HDR brachytherapy of 2 × 8.5 Gy. Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and FACT-G (General) questionnaires, administered before radiotherapy, at 6 months and bi-annually thereafter. Differences in mean FACT global scores and erectile function between treatment arms were compared using chi-squared tests.

Results: Over a 10.5 year follow-up, no difference in FACT-G, FACT-P or Trial Outcome Index (TOI) scores was seen between treatments and means were similar to their pretreatment values. Mean erectile function scores in arm 2 were similar to arm 1, but were significantly lower than the pretreatment mean ($P \leq 0.002$). There was no evidence that quality of life deteriorated with increasing follow-up time in any of the four FACT domains.

Conclusions: The improved biochemical control of disease seen in these patients with EBRT + HDR brachytherapy coupled with equitoxic early and late urinary and bowel morbidity, indicate a therapeutic advantage, which has now been confirmed by the results for general and prostate-related quality of life changes, despite a decline in erectile function.

Key words: High dose rate brachytherapy boost; hypofractionation; prostate cancer; quality of life; randomised trial

Introduction

Long-term survival is now achieved in a large proportion of patients with localised and locally advanced prostate cancer. A variety of treatment options, including watchful waiting, are available, but as most approaches seem to exert no perceptible impact on overall survival, other criteria must be used to identify the appropriate treatment option. There is increasing awareness that quality of life alongside objective measures of late adverse genitourinary and gastrointestinal toxicity are essential to this decision-making process in the management of patients with prostate cancer.

Brachytherapy is a well-established modality in the treatment of localised prostate cancer and can achieve excellent biochemical control of disease [1–3]. Three randomised controlled trials comparing external beam radiotherapy (EBRT) with EBRT and high dose rate (HDR) brachytherapy have evaluated treatment-related morbidity, only one of which has included an assessment of quality of life issues [4–7]. The Mount Vernon Hospital trial had relapse-free survival as the primary end point and overall survival, early and late genitourinary and gastrointestinal adverse events and quality of life as secondary end points [4,5]. The University of California trial, which mandated pelvic lymphadenectomy before iridium implantation, had the time to biochemical or clinical failure as the primary outcome. Secondary objectives included overall survival, genitourinary and gastrointestinal adverse events and sexual function [7]. Both trials showed a significant increase in biochemical/clinical control of disease for the experimental arm, but no difference in overall survival compared with EBRT alone [5,7].

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.01.001

In our study, the actuarial rate at 5 years of severe late genitourinary and gastrointestinal adverse events was similar in both arms, whereas the University of California trial showed a non-significant higher rate of gastrointestinal events for the combined schedule. The phase II Radiation Therapy Oncology Group 0321 trial was designed to evaluate genitourinary and gastrointestinal adverse events at $\geq$18 months after treatment. Secondary objectives included acute genitourinary and gastrointestinal adverse events and a variety of cancer-related events; only preliminary results for adverse events have been published [6].

An increasingly important outcome is quality of life, which in advanced disease has become the yardstick by which a new cancer treatment can be recommended (American Society of Clinical Oncology Guidelines, 1995 for metastatic disease). The present study compared long-term quality of life issues for patients enrolled in the Mount Vernon Hospital trial of EBRT $\pm$ HDR brachytherapy using a validated, self-administered quality of life questionnaire – Functional Assessment of Cancer Therapy (FACT). Long-term relapse-free and overall survival, early and late genitourinary and gastrointestinal adverse events and early quality of life events have been published previously [4,5].

Materials and Methods

Patients with a histological diagnosis of carcinoma of the prostate, stage T_1–T_3, with no evidence of metastatic disease, prostate-specific antigen (PSA) $<$50 μg/l, suitable for radical radiotherapy and fit for general anaesthesia were eligible. The single-centre trial was carried out in compliance with the Declaration of Helsinki and approved by the local research ethics committee. Written informed consent, before randomisation, was mandatory.

Patients were entered using a balanced one-to-one randomisation with stratification according to tumour stage, PSA, Gleason score and androgen deprivation therapy (ADT). No blinding was used for treatment delivery or follow-up assessments.

Radiotherapy

The techniques used have been described in detail previously [4,8]. Briefly, the external beam clinical target volume was defined to cover the prostate gland and the proximal seminal vesicles with a 1 cm margin reduced to 0.5 cm posteriorly. Patients randomised to EBRT alone (arm 1) received a total dose of 55 Gy in 20 daily fractions. The HDR group (arm 2) received EBRT to 35.75 Gy in 13 fractions and within 6 days a HDR brachytherapy boost. The clinical target volume was defined to cover the entire prostate gland and the seminal vesicles if involved. The dose per fraction to the brachytherapy clinical target volume was 8.5 Gy peripheral dose. The rectal dose constraint was $<$6.7 Gy to 2 cm^3 with no area receiving 8.5 Gy and the urethral constraint was $<$10 Gy to 10% of the urethra. A second fraction was given the following day to deliver a total dose of 17 Gy in two fractions in 24 h.

Androgen Deprivation Therapy

Neoadjuvant-adjuvant ADT was administered to 76% of patients after a policy of administration for 6 months in low/intermediate risk, and up to 3 years in high-risk patients.

Assessment of Quality of Life, End Points and Statistical Analyses

Version 3 of the FACT-P (Prostate) and FACT-G (General) measurement tools were self-administered before radiotherapy, during the first 12 weeks after treatment and then at 6 months and bi-annually thereafter. Follow-up intervals were calculated from the date of first EBRT dose and analyses were carried out as per protocol. Bin numbers 1–20 were assigned for each 6 monthly interval (i.e. bin #1 comprises data for questionnaires completed between 6 and 11.9 months; bin #2 for those completed between 12 and 17.9 months, etc. to bin #20 for those completed between 120 and 125.9 months). For clarity, only data for even bin numbers are presented in the figures.

Subscale scores for emotional (six items), functional (seven items), physical (seven items) and social (six items; question) wellbeing (EWB, FWB, PWB, SWB, respectively) and prostate cancer scale (12 items; PCS) were calculated using version 4 of the FACT scoring guidelines (www.facit.org). A FACT-P total score was obtained by adding EWB, FWB, PWB, SWB and PCS (range 0–152), FACT-G total score by adding EWB, FWB, PWB, SWB (range 0–104) and FACT-P Trial Outcome Index (TOI) by adding FWB, PWB and PCS subscale scores (range 0–104). Item 46 of the PCS subscale (ability to maintain an erection; range 0–4) was used to calculate an erectile function score. For all scales, the higher the score the better the quality of life.

Calculation of Subscale Scores

Negatively worded items were reversed by subtracting the score from 4. If there were missing items, prorating was carried out by multiplying the sum of the subscale score by the number of items in the subscale and then dividing by the number of items actually answered. Prorating was carried out only if more than 50% of the items were answered (e.g. a minimum of four of seven items for the FWB and PWB subscales, four of six items for the EWB and SWB subscales and seven of 12 items for the PCS subscale).

Calculation of Total Scores

FACT-P, FACT-G and FACT-P TOI scores were calculated as the sum of the unweighted subscale scores only if the overall item response rate was $>$80% (at least 31 of the 38 FACT-P items, 21 of 26 of the FACT-G and FACT-P TOI items were completed). Finally, a FACT total score for each domain was calculated only if all of the component subscales had valid scores.

Statistical comparisons were carried out using version 8.0.2 JMP™ (SAS Institute, Cary, NC, USA). Baseline demographics (age, tumour stage, Gleason score, PSA, risk group, ADT) of patients who contributed complete FACT