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Phase III randomised trial

The effect of short term neo-adjuvant androgen deprivation on erectile function in patients treated with external beam radiotherapy for localised prostate cancer: An analysis of the 4- versus 8-month randomised trial (Irish Clinical Oncology Research Group 97-01)

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ABSTRACT

Background and purpose: Erectile dysfunction is a common consequence of external beam radiotherapy (EBRT) for prostate cancer. The addition of neo-adjuvant androgen deprivation (NAD) has an indeterminate additive effect. We examined the long-term effect on erectile function (EF) of two durations (4 months: arm 1 and 8 months: arm 2) of NAD prior to radiation (RT) for patients with localised prostate cancer from the Irish Clinical Oncology Research Group (ICORG 97-01) 4- versus 8-month trial. In this study we aimed to (1) analyse the overall effect on EF of NAD in an EBRT population, (2) compare the probability of retained EF over time in an EBRT population treated with either 4 or 8 months of NAD and (3) identify any variables such as risk group and age which may have an additive detrimental effect. This analysis provides unique long term follow up data.

Materials and methods: From 1997 to 2001, 276 patients with adenocarcinoma of the prostate were randomised to 4 or 8 months of NAD before RT. EF data were recorded at baseline and at each follow-up visit by physician directed questions, using a 4-point grading system.

Results: Two hundred and thirty patients were included in the analysis of EF and were followed for a median of 80 months. One hundred and forty-one patients had EF at baseline. Neo-adjuvant androgen deprivation in addition to radiation therapy caused a significant reduction in EF. The most significant reduction in EF happens within the first year. The median time to grade 3–4 EF toxicity was 14.6 months, 17.6 months in arm 1 and 13.7 in arm 2. Freedom from late EF toxicity did not differ significantly between arms, overall or at 5 years ($n = 141$). The cumulative probability of EF preservation at 5 years was 28% (22–34) in arm 1 and 24% (19–30) in arm 2. Age was a significant predictor of post-treatment EF.

Conclusions: The first year post ADT and EBRT poses the greatest risk to sexual function and a continued decline may be expected. However, 26% of men can expect to retain sexual function at 5 years.

In 1997, the Irish Clinical Oncology Research Group initiated a randomised clinical trial (ICORG 97-01) investigating the effectiveness of different durations of neo-adjuvant androgen deprivation (NAD) using a combination of LHRH agonist triptorelin (Decapeptyl®) and oral flutamide (Drogenil®) anti-androgen tablets prior to definitive external beam radiation therapy (EBRT) for locally advanced prostate carcinoma. The primary endpoint was freedom from biochemical relapse. One of the secondary objectives was to evaluate toxicities including erectile function (EF). In this study we aimed to (1) analyse the overall effect on EF of NAD in an EBRT population, (2) compare the probability of retained EF over time in an EBRT population treated with either 4 or 8 months of NAD and (3) identify any variables such as risk group and age which may have an additive detrimental effect.

Erectile dysfunction (ED) after definitive RT for prostate cancer has been previously described. In one study by Turner et al. [1] it was reported that 38% of men whose EF was adequate before treatment had ED at 12 months, and this percentage increased to 59% at 24 months. Published studies report a wide degree of variation in the incidence of ED post EBRT. A review by Incrocci et al. [2] noted published rates of ED varying from 6% to 84% post EBRT alone. A meta-analysis of 54 studies where the pre-treatment functioning of subjects was known suggests that maintenance of EF varies widely [3].

Additionally, we know that androgen deprivation therapy (ADT) alone causes erectile dysfunction. For example, Potosky reported an incidence of ED of 80% in men receiving androgen deprivation

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therapy alone after 1 year compared with an incidence of 30% in men receiving no treatment [4].

Despite the increasing use of bimodality treatment, the effect of the combination NAD and EBRT on erectile function is less well reported in the literature than the effects of either modality alone. The need for further studies with "primary outcomes of overall and disease specific survival, disease progression and adverse effects including long term consequences of prolonged androgen deprivation including quality of life" was recognised by Shelley et al. during a review of randomised trials using neo-adjuvant androgen deprivation [5]. The impact of NAD on ultimate recovery of sexual function after the combined treatment is not known nor is the specific effect of duration of NAD on EF. Age, diabetes, coronary artery disease, etc. are other confounding factors. In addition long term follow up data are not widely available and there are few studies following patients who have detailed pre-treatment EF data. The possibility of ED frequently causes a high level of anxiety for the patient and given the variability of published data it is difficult to adequately counsel an individual about his particular risk. This paper attempts to address some of these previously unanswered questions and to examine other pre-treatment factors for their association with the development of ED.

Methods

The 4- versus 8-month trial (ICORG 97-01) was a randomised trial that accrued 276 patients with clinically localised prostate cancer between February 1997 and December 2001. This trial compared the effectiveness of two durations of NAD before radical external beam RT (70 Gy) in subjects with T1 to T4 N0 M0 prostate cancer. Patients were randomly assigned to receive 4 or 8 months of NAD consisting of a combination of LHRH agonist triptorelin (Decapeptyl®) and oral flutamide (Drogenil®) anti-androgen tablets. The primary endpoint was freedom from biochemical relapse. The design, objectives, patient eligibility criteria, treatment methods and statistical considerations have been reported previously [6].

Eligible patients were node negative and had no metastases with one or more of: PSA >20 ng/mL, Gleason score $\geqslant 7$, and stage T3 or more. The intermediate-risk stratum had one risk factor and the high-risk stratum had 2 or more risk factors (protocol risk stratification) [7].

The patients were required to have a performance status of $\geqslant 60$ on the Karnofsky scale. Evaluation for distant metastases included history and physical examination, FBC, screening profile including liver function tests, CXR, and bone scan. Any abnormalities on bone scan were investigated. A CT pelvis described nodal status on all patients. Suspicious nodes were histologically proven to be benign.

Patients were excluded if they had prior treatment for prostate cancer other than by transurethral resection of the prostate. Patients with a bilateral orchidectomy or prior hormone therapy were excluded. Other criteria for exclusion included previous malignancies (other than non-melanoma skin cancer) or medical illnesses severe enough to preclude a radical approach to treatment.

Radiation therapy

Three-dimensional conformal RT (3-DCRT) was used in 97% of patients (70 Gy in 35 fractions). Only these patients are analysed for EF in this paper.

Patients were positioned supine and underwent CT planning using 0.5 cm slices. The rectum and bladder were delineated with an external contour only. The target volume was generated by placing a 1 cm margin around the entire prostate and seminal vesicles. This margin was reduced to 0.5 cm in the region of the anterior rectal wall. Treatment was prescribed to an isodose that completely encompassed the target. The maximum permitted hot spot within the target volume was 110%. Dose volume constraints were as follows; no part of the rectum should receive >74 Gy, not more than 30% of the rectum should receive 100% of the dose, not more than 50% of the bladder should receive 100% of the dose. Multiple fields with customised blocking were used. If necessary a cone down was performed after 50 Gy (excluding the superior portions of the seminal vesicles from the target volume) to limit the dose to small bowel to 50 Gy.

Neo-adjuvant androgen deprivation therapy

Patients were randomised according to protocol risk stratification to receive either 4 or 8 months of NAD prior to external beam RT (EBRT). NAD consisted of monthly intra muscular injections of the LHRH agonist triptorelin (Decapeptyl®) 3.75 mg once monthly and oral flutamide (Drogenil®) anti-androgen tablets (250 mg 3 times daily). The RT was to begin within 1 month of the end of ADT.

Evaluation during study and follow-up

A pre-inclusion evaluation took place at Visit 1 after which the patient was randomised according to disease stratification to receive either 4 or 8 injections of the LHRH agonist Triptorelin ("Decapeptyl 1-month"). Baseline toxicity/assessment sheets were completed. Acute and chronic toxicity was graded according to the criteria of the RTOG–EORTC criteria [8] by way of physician directed questionnaire. Patients were evaluated for toxicity every week during RT. Follow-up was three-monthly and included history, rectal examination, PSA, and toxicity assessment. Treatment failure was noted if there was clinical evidence of local or distant recurrence, if salvage ADT was started, or if there was a biochemical failure (BF).

EF was similarly recorded at baseline and at each follow-up visit, using a 4-point grading system (1 – fully potent/ejaculates, 2 – able to have an erection but not able to ejaculate, 3 – able to have a partial erection, 4 – none). These grades were applied regardless of whether or not a patient used ED aids (Sildenafil citrate (Viagra®), Tadalafil (Cialis®) or Vardenafil (Levitra®)). ED included any patient who noted a decrease in EF from grades 1–2 to grades 3–4 after treatment. For most of the analyses, EF grades were collapsed into two categories i.e. grades 1–2 (sufficient for penetration) and grades 3–4 (insufficient for penetration).

Statistical analysis

Of the 276 patients, 46 were excluded from this analysis, leaving 230 evaluable patients. Five patients were excluded because they received NAD but no RT; 12 were treated in another centre and no ED data were available for them; 1 patient refused all treatment; 2 patients from the 4-month arm were excluded as they continued to receive AD after 4-months and RT was delayed; 1 patient died shortly after the end of RT; 2 patient had no initial EF assessment recorded, 3 patients were prescribed salvage hormones just before or soon after the end of RT; 16 more patients were either lost to follow-up or EF data were not recorded and 4 patients were excluded because they received 66 Gy. One patient randomised to receive 8 months of NAD received 4 months but was analysed on an intention to treat basis (Fig. 1).

Late complications, including ED, were defined as those documented at least 90 days after the last radiation treatment [9]. The worst severity toxicity documented was considered the final toxicity, even if the complication later resolved [9]. Pre-treatment clinical characteristics were compared between subjects treated with 4 versus 8 months of NAD using the Mann–Whitney test and the