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Phase III randomised trial

Randomized non-inferiority trial of Bicalutamide and Dutasteride versus LHRH agonists for prostate volume reduction prior to I-125 permanent implant brachytherapy for prostate cancer ☆

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ABSTRACT

Objective: To determine the efficacy and toxicity of a 3-month regimen of Dutasteride and Bicalutamide compared to LHRH agonists for prostate volume (PV) reduction prior to permanent implant prostate brachytherapy (PIPB).

Material and methods: Patients with low-risk or low-tier intermediate risk prostate cancer eligible for PIPB with a prostate volume greater than 50 cc were randomized to either Dutasteride 0.5 mg Bicalutamide 50 mg daily and Tamoxifen 10 mg daily for 3 months (D + B group) or to a 3 month dose of an LHRH agonist and Bicalutamide daily for 1 month (LHRH group). Their PV was measured at baseline and at pre-implant. Non-inferiority analysis was completed for the relative (%) PV reduction. IPSS and EPIC questionnaires were completed at baseline, pre-implant and at 1, 3, 6, 12, 18 and 24 months post-treatment. IPSS and EPIC comparisons were based on superiority analysis

Results: 60 patients were randomized (31 to LHRH group and 29 to D + B group). Mean relative PV reduction (SD) was 35.5% (8.9) in the LHRH group and 31.7% (9.6) in the D + B group. The upper bound of the 95% confidence for the interval for the difference between groups favouring LHRH agonists for PV reduction was 8.6 which did not cross the 10% non-inferiority margin meaning D + B is non-inferior to LHRH agonist for PV reduction, although 5/29 (17%) of those in the D + B group required longer duration of D + B to achieve adequate volume reduction. There were no statistically significant differences in IPSS scores over the entire follow-up period. EPIC sexual summary score was significantly better in the D + B group at pre-implant, 1 month, 3 months post-implant.

Conclusion: Dutasteride and Bicalutamide is a regimen of non-inferior efficacy to LHRH agonist based regimens for prostate volume reduction prior to permanent implant prostate brachytherapy. D + B has less sexual toxicity compared to LHRH agonists prior to implant and for the first 6 months after implant. D + B is therefore an option to be considered for prostate volume reduction prior to PIPB.

Technical aspects of permanent implant prostate brachytherapy (PIPB) can render some men ineligible for this technique or make implantation significantly more challenging. One significant factor that can limit the successful completion of a brachytherapy procedure is a large prostate volume. Large prostate volume can result in pubic arch interference, poor dosimetry and a possible increase in both urinary obstructive symptoms and rates of urinary obstruction requiring catheterization [1–4]. For this reason both the American Brachytherapy Society (ABS) and the European Association of Urology (EAU) guidelines for permanent implant prostate brachytherapy suggest a maximal allowable volume to be eligible for a PIPB procedure. These guidelines suggest that men with prostates less than 50 cc (EAU) or less than 60 cc (ABS) would be best suited for treatment with PIPB [4,5].

This however does not mean that men with prostates larger than 50–60 cc should be ineligible for PIPB. Many studies have evaluated the use of LHRH agonists [6–12] or antiandrogens like Bicalutamide [8,13,14] to decrease prostate volume to a volume at which the brachytherapy technique is deemed technically feasible. LHRH agonists used for durations of 2–9 months have

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resulted in rates of prostate volume reduction varying from 21% to 48% [6,7,9–11,13–15]. However LHRH agonists can have significant side effects such as hot flashes, decreased libido, erectile dysfunction and decreased overall quality of life. Many have also hypothesized that short term LHRH agonists in association with PIPB could result in an increase in cardiovascular mortality [16,17]. In a significant proportion of PIPB cases where LHRH agonists are used, they are used solely for prostate volume reduction and not for oncological benefit. For this reason, this practice remains controversial; one study even showed an increase in all cause mortality in men who receive hormonal therapy with PIPB that could not be explained by cancer related risk factors (PSA, stage, etc.) [17].

Merrick et al. recently published results of a single institution experience of a regimen of Dutasteride 0.5 mg. daily and Bicalutamide 50 mg (D + B) daily for 3 months that resulted in a 34% reduction in prostate volume [18]. This regimen used a combination of both a 5-Alpha Reductase inhibitor (Dutasteride), and an anti-androgen (Bicalutamide). This combination should theoretically have much less effect on serum testosterone levels and thus would likely have less effect on erectile dysfunction and hormonal symptoms such as hot flashes than traditional use of LHRH agonists. However, to our knowledge no such information on toxicity has ever been published.

With these facts in mind, we designed a randomized trial based on 2 hypotheses. We believed that a combination of Dutasteride and Bicalutamide would be of similar (i.e. non-inferior) clinical efficacy as a traditional regimen of LHRH agonists for prostate volume reduction. We also hypothesized that a combination of Dutasteride and Bicalutamide would likely have less effect on both acute and late erectile dysfunction rates. To evaluate these hypotheses we designed a randomized controlled non-inferiority trial comparing Dutasteride and Bicalutamide with an LHRH agonist regimen that we judged to be standard of care. Expecting similar efficacy and less toxicity with D + B, we felt that a non-inferiority design was best suited to studying our hypotheses. The primary objective of the study was to show that prostate volume reduction with D + B was non-inferior to LHRH agonists. Secondary objectives were to determine acute and late effects on sexual function and urinary toxicity with both regimens.

Materials and methods

We designed randomized-controlled non-inferiority study comparing two regimens for prostate volume reduction prior to permanent implant prostate brachytherapy.

Recruitment

Patients were recruited from patients referred to one centre (Centre Hospitalier Universitaire de Québec-Hôtel-Dieu de Québec) for consideration of permanent implant prostate brachytherapy who had a prostate volume of greater than 50 cc at the time of initial consultation and pre-randomization trans-rectal ultrasound (TRUS) evaluation. Prostate volume was determined with TRUS based step-section planimetry. To be eligible for the study, patients had to have pathologically proven previously untreated adenocarcinoma of the prostate, clinical stage T1c, T2a or T2b, Gleason Score of 6 or 7(3 + 4), PSA of $\leqslant$15 ng/ml $\leqslant$ 30 days prior to study entry and a normal serum testosterone. Exclusion criteria included abnormal liver Function tests (>2$\times$ normal AST or ALT and/or >1.5$\times$ normal bilirubin), history of hormonal treatment including any of the following: LHRH agonists, antiandrogens or a 5 alpha reductase inhibitor during the year before study entry, history of prior pelvic irradiation, history of TURP and anticoagulation with warfarin.

Randomization

Patients were randomized in a 1:1 ratio within blocks of uneven size to one of two neoadjuvant regimens. Neither investigators nor patients were blinded to treatment allocation because of the nature of the medication given. The LHRH group received a 3-month dose of an LHRH agonist (either Luprolide 22.5 mg or Gosserelin 10.8 mg) and Bicalutamide 50 mg daily for one month starting at least 5 days prior to the administration of the LHRH agonist. The Dutasteride and Bicalutamide group (D + B) received Dutasteride 0.5 mg, Bicalutamide 50 mg and Tamoxifen 10 mg daily for 3 months. Tamoxifen was added to prevent gynecomastia with longer duration of Bicalutamide [19].

Research ethics board approval was obtained prior to initiating the study. The study was also registered with Health Canada (study No 112 661) and with the National institutes of Health (www.clinicaltrials.gov ID NCT00866554). Signed written consent was obtained from all study participants.

Treatment and follow-up

Patients had a TRUS at baseline and 3 months post-randomization (pre-implant). TRUS were completed by one of three qualified investigators. If their prostate size at time of the pre-implant ultrasound was less than 50 cc, they were deemed eligible for brachytherapy. Otherwise, investigators were free to either continue allocated medication or cross-over to the other group's regimen.

Permanent implant brachytherapy was done with I-125 real-time inverse planning with simulated annealing (IPSA) with a prescription dose of 144 Gy to the prostate. The technique used at the CHUQ-HDQ has been well described in the literature [20–22].

Patients had a clinical evaluation at baseline, immediately pre-implant as well as 1, 3, 6, 9, 12, 18 and 24 months after implant. Clinical evaluations involved history, digital rectal exam, PSA, serum testosterone, and French Canadian versions of both the International Prostate Symptom Score (IPSS) [23] and Expanded Prostate Index Composite (EPIC) [24] questionnaires. Symptomatic Gynecomastia was self-reported by patients as a dichotomous yes or no.

Statistical analysis

We estimated the sample size for the study using a primary hypothesis of non-inferiority. From previous studies, we estimated the SD for relative prostate volume reduction at 14.5%. Study members deemed that a clinically significant difference between groups would be approximately 10%. We surveyed multiple brachytherapy practitioners to determine which difference in prostate cytoreduction would be acceptable to them in lieu of lesser sexual toxicity. To achieve a desired power of 80% and a significance level of $\alpha = 0.05$ we determined that a non-inferiority analysis comparing these two approaches would require a sample size of 80. Allowing for a loss to follow-up rate of 10% we chose a sample size of 88, meaning 44 per group.

Baseline characteristics are presented without statistical analyses. Prostate volume reduction was defined as the relative reduction in prostate volume between the TRUS done at baseline and the TRUS done at 3 months after randomization. The relative reduction in PV was compared between groups with independent sample t-tests. This was designed as a non-inferiority hypothesis with non-inferiority threshold at -10% determined at the time of study design. Results of IPSS scores and EPIC scores for all measurement time points were compared with independent sample *t*-tests first with mean scores between groups and then for within patient difference (change from baseline) based on a