



# Optimal prophylactic and definitive therapy for bicalutamide-induced gynecomastia: results of a meta-analysis

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## ABSTRACT

### Objective

Bicalutamide is approved as an adjuvant to primary treatments (radical prostatectomy or radiotherapy) or as monotherapy in men with locally advanced, nonmetastatic prostate cancer (pca). However, this treatment induces gynecomastia in most patients, which often results in treatment discontinuation. Optimal therapy for these breast events is not known so far. We undertook a meta-analysis to assess the efficacy of various treatment options for bicalutamide-induced gynecomastia.

### Methods

The MEDLINE, CANCERLIT, and Cochrane library databases were searched and the Google search engine was used to identify prospective and retrospective controlled studies published in English from January 2000 to December 2010 comparing prophylactic or curative treatment options with a control group (no treatment) for pca patients who developed bicalutamide-induced gynecomastia. Radiotherapy-induced cardiotoxicity was also evaluated.

### Results

The search identified nine controlled trials with a total patient population of 1573. Pooled results from prophylactic trials showed a significant reduction of gynecomastia in pca patients treated with prophylactic tamoxifen 20 mg daily (odds ratio: 0.06; 95% confidence interval: 0.05 to 0.09;  $p = 0.09$ ), and pooled results from treatment trials showed a significant response of gynecomastia to definitive radiotherapy (odds ratio: 0.06; 95% confidence interval: 0.01 to 0.24;  $p < 0.0001$ ). Aromatase inhibitors and weekly tamoxifen were not found to be effective as prophylactic and curative options. For the radiotherapy, skin-to-heart distance was found to be an

important risk factor for cardiotoxicity ( $p = 0.006$ ). A funnel plot of the meta-analysis showed significant heterogeneity (Egger test  $p < 0.00001$ ) because of low sample size.

### Conclusions

Our meta-analysis suggests using prophylactic tamoxifen 20 mg daily as the first-line preventive measure and radiotherapy as the first-line treatment option for bicalutamide-induced gynecomastia. Aromatase inhibitors and weekly tamoxifen are not recommended.

### KEY WORDS

Meta-analysis, bicalutamide-induced gynecomastia, prostate cancer

## 1. INTRODUCTION

In patients with locally advanced nonmetastatic prostate cancer (pca), bicalutamide 150 mg (Casodex: AstraZeneca Pharmaceuticals, Wilmington, DE, U.S.A.) is increasingly being used to reduce the risk of disease progression. Bicalutamide has not been approved as monotherapy by the U.S. Food and Drug Administration, but it has been licensed in some European countries as adjuvant treatment for early pca. Compared with other androgen deprivation therapy options (such surgical or pharmaceutical castration), this nonsteroidal antiandrogen leads to fewer adverse events in terms of sexual dysfunction and loss of bone mineral density<sup>1,2</sup>. However, because of its hypergonadotropic action, bicalutamide is associated with adverse breast events such as gynecomastia that arise from an increase in the estrogen:androgen ratio in the male breast<sup>3</sup>. Despite the reduced toxicity profile of bicalutamide, one meta-analysis of 8 trials involving 2717 patients suggested that nonsteroidal antiandrogen is associated with lower overall survival in metastatic pca<sup>4</sup>.

In the Early Prostate Cancer program, the incidence of gynecomastia was 68.3%–73.6%, with symptoms developing within the first 6–9 months of bicalutamide use in most cases. Development of this side effect resulted in treatment discontinuation in 16.7% of patients, with the risk of compromising their treatment outcome<sup>5</sup>. Several interventions have been used in an attempt to prevent or alleviate bicalutamide-induced gynecomastia, including radiation therapy, surgery and radiation, and surgery and hormonal therapy (tamoxifen and anastrozole). Results have been promising<sup>6</sup>, but controversy about the optimal therapy for bicalutamide-induced gynecomastia remains<sup>7</sup>.

We undertook the present meta-analysis with the aim of determining the optimal treatment for bicalutamide-induced gynecomastia and the potential risk factors for prophylactic radiotherapy-induced gynecomastia.

## 2. METHODS

### 2.1 Studies and Study Population

To be included in the meta-analysis, studies had to be either full publications of prospective controlled trials or retrospective analyses if well-controlled.

Studies were eligible for inclusion if

- patients had histologically confirmed localized or locally advanced nonmetastatic PCA.
- patients had received bicalutamide as monotherapy.
- gynecomastia was the primary outcome.
- prevention and treatment for bicalutamide-induced gynecomastia was mentioned.

Studies were excluded if they were

- pre-clinical studies,
- reviews or editorials, or
- single-arm studies.

Abstracts with complete details were included. The MEDLINE, CANCERLIT, and Cochrane library databases were searched using the terms “prostate,” “cancer or carcinoma,” “bicalutamide,” “bicalutamide related gynecomastia, breast pain or breast events,” “treatment for bicalutamide associated breast events,” “prophylactic or definitive radiotherapy or radiation,” “hormonal therapy tamoxifen and anastrozole,” and “surgery” (for bicalutamide-induced breast events). These terms were then combined with a search for controlled reviews and meta-analyses. Relevant articles were selected by 2 methodologists. The inclusion and exclusion criteria were then applied. Any discrepancy between the methodologists was settled by the remaining co-authors of the present meta-analysis.

### 2.2 Outcome Measures

The outcome measures were response rates, breast event-free survival, and cardiotoxicity by prophylactic or definitive radiation therapy.

### 2.3 Review Analysis

All analyses took an intention-to-treat perspective. For categorical variables, weighted risk ratios and their 95% confidence intervals (CIs) were calculated using the Review Manager (RevMan) software application, version 5.0, provided by the Cochrane Collaboration (part of the meta-analytic software program Metaview: Update Software, Oxford, U.K.). The results were tested for heterogeneity at a significance level of  $p < 0.05$ . If there was evidence of heterogeneity, a random effects model was used for the meta-analysis; otherwise, a fixed effects model was used. The odds ratio and 99% CIs were calculated for each trial and presented in a forest plot.

We determined response rates and breast event-free survival using the follow-up period mentioned in each trial. We also determined the risk factors for patients who underwent prophylactic or definitive radiation therapy.

Publication bias was evaluated using funnel plots, the Begg–Mazumdar adjusted rank correlation test<sup>8</sup>, and the Egger test<sup>9</sup>. The Cochran Q-test was used to determine the homogeneity of the studies.

## 3. RESULTS

### 3.1 Yield of Search Strategy and Characteristics of Eligible Studies

The electronic search located 1007 relevant citations published in English from January 2000 to December 2010. After screening, sixty-six full-text articles were retrieved for further assessment. Finally, nine studies were identified that met the inclusion and exclusion criteria (Figure 1). The total population was 1573 patients. Tables I and II outline the characteristics and analytical approaches of the included studies.

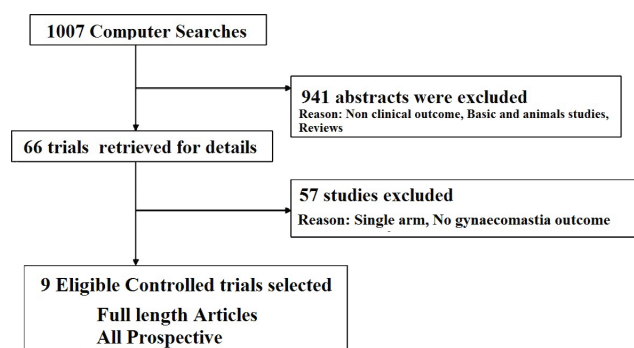


FIGURE 1 Flow chart of the literature search strategy.

TABLE 1 Characteristics of the included studies

| Reference                                                                                     | Period    | Country                         | Inclusion criteria                                  | Study design                                                           | Treatment type                                                           | Duration of treatment                                  | Endpoints                             | Follow-up |
|-----------------------------------------------------------------------------------------------|-----------|---------------------------------|-----------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------|-----------|
| Widmark <i>et al.</i> , 2003 <sup>16</sup>                                                    | 2000–2003 | Sweden                          | Locally advanced, non-metastatic pca (T1b–T4/Nx/M0) | Prospective, randomized, controlled Scandinavian trial (SPCG-7/SFUO-3) | Arm A: Prophylactic RT, single-fraction (12–15 Gy)<br>Arm B: Control     | Arm A: 12–15 Gy, two and three fractions               | Gynecomastia and mastalgia incidence  | 1 Year    |
| Boccardo <i>et al.</i> , 2005 <sup>10</sup>                                                   | 2004–2005 | Italy                           | Localized, locally advanced, and recurrent pca      | Double-blind, placebo-controlled trial                                 | Arm A: Tamoxifen 20 mg daily or anastrozole 1 mg daily<br>Arm B: Control | Arm A: 48 weeks<br>Arm B: 48 weeks                     | Gynecomastia, mastalgia incidence     | 1 Year    |
| Perdonà <i>et al.</i> , 2005 <sup>12</sup> ,<br>Di Lorenzo <i>et al.</i> , 2005 <sup>19</sup> | 2002–2004 | Italy                           | Localized, locally advanced pca (T1b–T4/Nx/M0)      | Prospective, controlled trial                                          | Arm A: Tamoxifen 10 mg daily<br>Arm B: Prophylactic RT<br>Arm C: Control | Arm A: 24 weeks<br>Arm B: 12 Gy, single fraction daily | Gynecomastia and mastalgia incidence  | 2 Years   |
| Saltzein <i>et al.</i> , 2005 <sup>13</sup>                                                   | 2004–2005 | United States                   | Locally advanced, non-metastatic pca (T1b–T4/Nx/M0) | Double-blind, placebo-controlled, multicentre trial                    | Arm A: Tamoxifen 20 mg daily or anastrozole 1 mg daily<br>Arm B: placebo | Arm A: 48 weeks<br>Arm B: 48 week                      | Gynaecomastia and mastalgia incidence | 1 Year    |
| Van Poppel <i>et al.</i> , 2005 <sup>18</sup>                                                 | 2000–2002 | United Kingdom, Belgium, France | Nonmetastatic pca (T1b–T4, Nx, M0)                  | Open-label, noncomparative multicentre study                           | Arm A: Definitive RT<br>Arm B: Control                                   | Arm A: 6 Gy, two fractions                             | Gynaecomastia and mastalgia incidence | 1 Year    |
| Fradet <i>et al.</i> , 2007 <sup>11</sup>                                                     | 2006–2007 | Canada                          | Locally advanced, nonmetastatic pca                 | Double-blind, parallel-group, multicentre trial                        | Arm A: Tamoxifen (1, 2.5, 5, 10, or 20 mg daily)<br>Arm B: Placebo       | 12 Months                                              | Gynecomastia and mastalgia incidence  | 1 Year    |
| Tyrrell <i>et al.</i> , 2007 <sup>15</sup>                                                    | 2003–2004 | United Kingdom                  | Localized, locally advanced pca (T1b–T4/Nx/M0)      | Multicentre trial, randomized, sham-controlled, double-blind           | Arm A: Prophylactic RT<br>Arm B: Sham RT                                 | Arm A: 10 Gy, single-fraction                          | Gynecomastia and mastalgia incidence  | 1 Year    |

TABLE I  
*Continued*

| Reference                                     | Period    | Country | Inclusion criteria                                          | Study design                                       | Treatment type                                                | Duration of treatment         | Endpoints                             | Follow-up |
|-----------------------------------------------|-----------|---------|-------------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------------|-------------------------------|---------------------------------------|-----------|
| Bedognetti <i>et al.</i> , 2010 <sup>17</sup> | 2003–2006 | Italy   | Localized, locally advanced, or biochemically recurrent pca | Prospective, controlled, non-inferiority trial     | Arm A: Tamoxifen 20 mg daily<br>Arm B: Tamoxifen 20 mg weekly | 12 Months                     | Gynecomastia and mastalgia incidence  | 2 Years   |
| Ozen <i>et al.</i> , 2010 <sup>14</sup>       | 2008–2009 | Turkey  | Localized pca                                               | Prospective, randomized, multi-institutional trial | Arm A: Prophylactic RT<br>Arm B: Control                      | Arm A: 12 Gy, single-fraction | Gynaecomastia and mastalgia incidence | 1 Year    |

pca = prostate cancer; RT = radiotherapy.

The studies were conducted in several countries. Five were multicentric studies; the rest were single-centre studies. All studies included patients with localized, locally advanced, or recurrent nonmetastatic pca. All studies reported on gynecomastia outcomes.

### 3.2 Meta-analysis

A random effects model meta-analysis of the full cohort resulted in a pooled odds ratio (OR) of 0.20 (95% CI: 0.16 to 0.26), suggesting a lower incidence of gynecomastia favouring prophylactic or definitive treatment (Figure 2). These are the pooled ORs for each treatment group: prophylactic tamoxifen OR, 0.06 (95% CI: 0.05 to 0.09); prophylactic radiotherapy OR, 0.25 (95% CI: 0.18 to 0.35); prophylactic anastrozole OR, 1.44 (95% CI: 0.78 to 2.64); definitive tamoxifen OR, 0.14 (95% CI: 0.07 to 0.30); prophylactic weekly tamoxifen OR, 4.51 (95% CI: 1.88 to 10.84); and definitive radiotherapy OR, 0.06 (95% CI: 0.16 to 0.24).

The resultant funnel plot shows evidence of significant asymmetry, with statistical significance by Egger test of  $p < 0.00001$  (Figure 3). The asymmetry in the funnel plot was caused mainly by one small study (left side, negative) and may indicate publication bias. However, other explanations are also possible. The small study may be of lesser or poor quality, especially failure to conceal allocation, which often results in exaggerated treatment effect sizes. Alternatively, this small study may have been performed in a particularly high-risk population in which the effect was large. (The  $p$  values from the Begg–Mazumdar test and the Egger test were 0.02 and 0.01 respectively.)

Tables I and II also summarize the varying levels of study quality. The included studies varied in cohort representativeness (hormonal or radiotherapy, prophylactic or definitive treatment, and blinded or not blinded). Among the nine study cohorts, four studies used blinded outcome assessment; the remaining studies assessed their cohorts after multiple adjustments for confounders. No study showed selection bias for the treatment and control cohorts, and all had follow-up adequate for outcome assessment.

### 3.3 Treatment-Related Side Effects

Prophylactic radiotherapy and tamoxifen were generally well tolerated, with minimal and manageable side effects (Table III). No grade 3 or 4 toxicities were seen in any prophylaxis or treatment group. No treatment-related deaths were reported. All studies of radiotherapy techniques used conventional electron-beam radiotherapy, without computed tomography data (Table IV).

## 4. DISCUSSION

The results of our meta-analysis of prophylaxis and treatment studies suggest that daily tamoxifen

TABLE II Analytical approach of included studies

| Reference                                                                                     | Sample size |           |              | Follow-up      | Outcome assessment                                                                                      |                                                      | OR<br>(95% CI)         |
|-----------------------------------------------------------------------------------------------|-------------|-----------|--------------|----------------|---------------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------|
|                                                                                               | Overall     | Treatment | Nontreatment |                | Gynecomastia                                                                                            | Mastalgia                                            |                        |
| Widmark <i>et al.</i> , 2003 <sup>16</sup>                                                    | 253         | 174       | 79           | Every 3 months | Physical examination calipers                                                                           | Questionnaire                                        | 0.55<br>(0.33 to 0.78) |
| Boccardo <i>et al.</i> , 2005 <sup>10</sup>                                                   | 114         | 76        | 38           | Every 3 months | Calipers and ultrasonography:<br>Grade 1: <2 cm<br>Grade 2: 2–4 cm<br>Grade 3: 4–6 cm<br>Grade 4: >6 cm | Questionnaire                                        | 0.54<br>(0.32 to 0.89) |
| Perdonà <i>et al.</i> , 2005 <sup>12</sup> ,<br>Di Lorenzo <i>et al.</i> , 2005 <sup>19</sup> | 151         | 100       | 51           | Every 1 month  | Calipers:<br>Grade 1: <2 cm<br>Grade 2: 2–4 cm<br>Grade 3: 4–6 cm<br>Grade 4: >6 cm                     | Questionnaire:<br>None<br>Mild<br>Moderate<br>Severe | 0.26<br>(0.15 to 0.44) |
| Saltzein <i>et al.</i> , 2005 <sup>13</sup>                                                   | 107         | 53        | 54           | Every 3 months | Physical examination calipers                                                                           | Questionnaire                                        | 0.37<br>(0.19 to 0.71) |
| Van Poppel <i>et al.</i> , 2005 <sup>18</sup>                                                 | 51          | 41        | 10           | Every 3 months | Physical examination and questionnaire                                                                  | Questionnaire                                        | 0.47<br>(0.24 to 0.93) |
| Fradet <i>et al.</i> , 2007 <sup>11</sup>                                                     | 182         | 140       | 142          | Every 3 months | Questionnaire                                                                                           | Questionnaire                                        | 0.16<br>(0.10 to 0.27) |
| Tyrrell <i>et al.</i> , 2007 <sup>15</sup>                                                    | 106         | 53        | 53           | Every 3 months | Calipers:<br>Grade 1: <2 cm<br>Grade 2: 2–5 cm<br>Grade 3: >5 cm                                        | Questionnaire:<br>Mild<br>Moderate<br>Severe         | 0.83<br>(0.49 to 1.4)  |
| Bedognetti <i>et al.</i> , 2010 <sup>17</sup>                                                 | 80          | 41        | 39           | Every 3 months | Ultrasonography                                                                                         | Questionnaire                                        | 0.60<br>(0.32 to 1.13) |
| Ozen <i>et al.</i> , 2010 <sup>14</sup>                                                       | 125         | 53        | 72           | Every 3 months | Physical examination                                                                                    | Questionnaire                                        | 0.37<br>(0.19 to 0.71) |

OR = odds ratio; CI = confidence interval.

20 mg and low-dose radiotherapy are associated with a low incidence of gynecomastia in pCa patients receiving bicalutamide. Further pooled adjusted estimates from the prospective studies showed that daily tamoxifen 20 mg is the most beneficial of all available modalities and a better option in pCa patients receiving bicalutamide, with significant breast reduction and fewer adverse events. However, the prolonged administration (at least 24–48 weeks), optimal duration (discontinuation of the drug ends the prophylactic effect), cost issues, and possible biochemical and clinical progression of pCa with daily tamoxifen make this drug unsuitable for some patients.

Saltzein *et al.*<sup>13</sup> evaluated the relationship between tamoxifen use and increase in serum prostate-specific antigen. They found an increase in serum testosterone in a tamoxifen–anastrozole group (likely

because of blockade of the negative feedback of estradiol on the hypothalamic–pituitary axis), but the elevated serum testosterone levels were not found to affect prostate-specific antigen and treatment outcome. In contrast, Fradet *et al.*<sup>11</sup> found no difference in median serum testosterone for groups receiving tamoxifen 20 mg daily and receiving placebo. Our meta-analysis found that the patients on tamoxifen experienced 5.8%–16.7% ischemic cardiovascular and thromboembolic events. Those side effects should be discussed with patients before tamoxifen is initiated.

For patients who are not candidates for tamoxifen 20 mg daily, prophylactic radiotherapy is an appropriate option. The advantage of prophylactic radiotherapy is its short treatment time (1 or 2 days) and manageable adverse events. However, radiotherapy-related

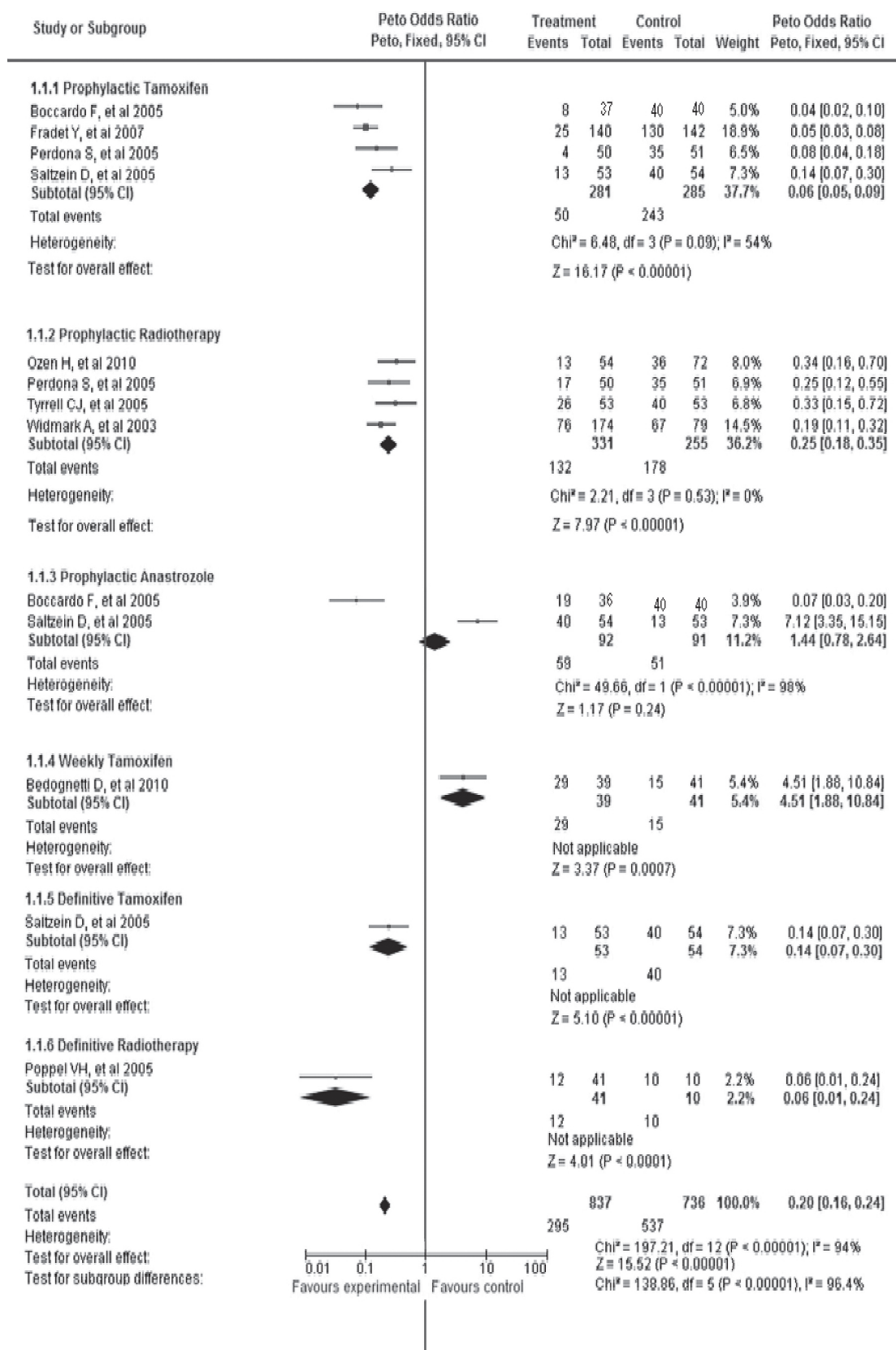


FIGURE 2 Forest plot showing the effects of various prophylactic and definitive treatment modalities on bicalutamide-induced gynecomastia and breast tenderness.

cardiotoxicity is of great concern, especially in *pca* patients less than 60 years of age. The included studies did not address the incidence and causes of cardiotoxicity, but the explanation could be the short follow-up in the study cohorts. Tyrrell *et al.*<sup>15</sup> described a 5.8% incidence of cardiotoxicity in patients who received prophylactic radiotherapy (Table III), but failed to describe the cause. Nieder and various colleagues<sup>20,21</sup> studied exposure of the heart during computed tomography–based prophylactic radiotherapy in 17 *pca*

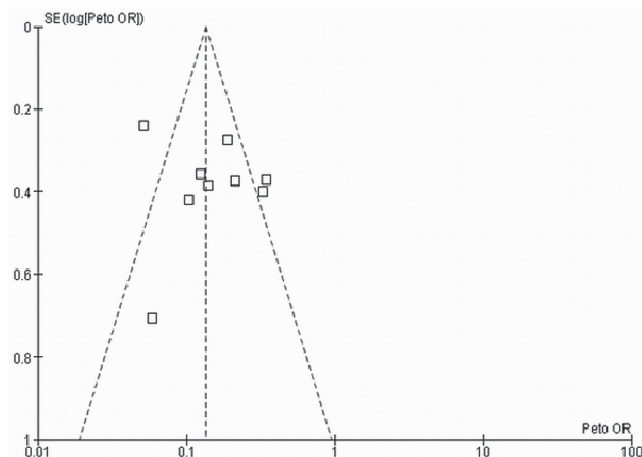


FIGURE 3 Funnel plot showing study asymmetry, with statistical significance by Egger test ( $p < 0.00001$ ).

patients (65 and 75 years of age; 50% each) and found that skin-to-heart distance decreased with the age group (3.1 cm in the group 65 years of age, 2.6 cm in the group 75 years of age). The authors concluded that skin-to-heart distance is the most important prognostic factor for radiotherapy-related cardiotoxicity. They also advocated using computed tomography–based prophylactic radiotherapy rather than clinical radiotherapy, as is most common.

In our meta-analysis, aromatase inhibitors and tamoxifen 20 mg weekly failed to significantly reduce breast events in patients receiving bicalutamide. Neither option should be considered for first-line prophylaxis in gynecomastia. The reasons for the disappointing efficacy of these prophylactic measures are questionable; further clinical trials are warranted. The large heterogeneity in the included studies can be criticized; however, the explanation could be the low power of studies included in the present meta-analysis. Moreover, the pooled adjusted estimate from treatment studies showed that definitive radiotherapy significantly reduced gynecomastia [OR: 0.06 (95% CI: 0.01 to 0.24)] compared with definitive tamoxifen 20 mg daily [OR: 0.14 (95% CI: 0.07 to 0.30)].

One limitation of our meta-analysis is that it did not include studies of surgical therapy for bicalutamide-induced gynecomastia. The reason is that prospective randomized controlled surgical trials are

TABLE III Toxicity profile (all grades) for the treatment group in the included studies

| Treatment group | Reference                                                                                     | Site [% (n)] |                 |         |                   |         |            |             |                      |          |
|-----------------|-----------------------------------------------------------------------------------------------|--------------|-----------------|---------|-------------------|---------|------------|-------------|----------------------|----------|
|                 |                                                                                               | Skin         | Cardio-vascular | Lung    | Gastro-intestinal | Hepatic | Neurologic | Hot flushes | Erectile dysfunction | Asthenia |
| Radiotherapy    |                                                                                               |              |                 |         |                   |         |            |             |                      |          |
|                 | Widmark <i>et al.</i> , 2003 <sup>16</sup>                                                    | 5 (5)        | —               | —       | —                 | —       | —          | —           | —                    | —        |
|                 | Perdonà <i>et al.</i> , 2005 <sup>12</sup> ,<br>Di Lorenzo <i>et al.</i> , 2005 <sup>19</sup> | 3 (2)        | —               | —       | 6 (5)             | —       | 1.2 (1)    | 2.3 (2)     | —                    | 6 (5)    |
|                 | Van Poppel <i>et al.</i> , 2005 <sup>18</sup>                                                 | 7.3 (3)      | —               | —       | —                 | —       | —          | —           | —                    | —        |
|                 | Tyrrell <i>et al.</i> , 2007 <sup>15</sup>                                                    | 5.8 (3)      | 5.8 (3)         | 1.9 (1) | —                 | —       | —          | —           | —                    | —        |
|                 | Ozen <i>et al.</i> , 2010 <sup>14</sup>                                                       | —            | —               | —       | —                 | —       | —          | —           | —                    | —        |
| Tamoxifen 20 mg |                                                                                               |              |                 |         |                   |         |            |             |                      |          |
|                 | Boccardo <i>et al.</i> , 2005 <sup>10</sup>                                                   | 0            | 8.1 (3)         | 0       | —                 | —       | 2.7 (1)    | 2.7 (1)     | —                    | 8.1 (3)  |
|                 | Perdonà <i>et al.</i> , 2005 <sup>12</sup> ,<br>Di Lorenzo <i>et al.</i> , 2005 <sup>19</sup> | —            | —               | —       | 9.8 (9)           | —       | 2.2 (2)    | 4.1 (3)     | —                    | 2.2 (2)  |
|                 | Saltzein <i>et al.</i> , 2005 <sup>13</sup>                                                   | —            | —               | —       | 13.2 (14)         | 0.9 (1) | 8.8 (5)    | 14.7 (7)    | —                    | 8.8 (5)  |
|                 | Fradet <i>et al.</i> , 2007 <sup>11</sup>                                                     | —            | —               | —       | 14.3 (5)          | —       | 14.3 (5)   | 8.6 (3)     | 2.9 (1)              | 8.6 (3)  |
|                 | Bedognetti <i>et al.</i> , 2010 <sup>17</sup>                                                 | 2.2 (1)      | 15.6 (7)        | 2.2 (1) | 4.4 (2)           | 2.2 (1) | —          | 15.6 (7)    | —                    | 13.3 (6) |
| Anastrozole     |                                                                                               |              |                 |         |                   |         |            |             |                      |          |
|                 | Boccardo <i>et al.</i> , 2005 <sup>10</sup>                                                   | 5.5 (2)      | 16.7 (6)        | 2.8 (1) | —                 | —       | 16.7 (6)   | 2.8 (1)     | —                    | 2.8 (1)  |
|                 | Saltzein <i>et al.</i> , 2005 <sup>13</sup>                                                   | —            | —               | 8.3 (4) | 5.6 (3)           | —       | 2.8 (2)    | 8.3 (4)     | —                    | 11.1 (5) |

TABLE IV Radiotherapy techniques used for prophylactic radiotherapy in the included cohorts

| Reference                                                                                     | Dose (Gy)                      | Energy (MeV) | Treated volume                                                                                            |
|-----------------------------------------------------------------------------------------------|--------------------------------|--------------|-----------------------------------------------------------------------------------------------------------|
| Widmark <i>et al.</i> , 2003 <sup>16</sup>                                                    | 12–15 Gy in a single fraction  | 6–9          | 5-cm Diameter around nipple designed to deliver a minimum dose of 90% between the skin and the chest wall |
| Perdonà <i>et al.</i> , 2005 <sup>12</sup> ,<br>Di Lorenzo <i>et al.</i> , 2005 <sup>19</sup> | 12 Gy in a single fraction     | 6–12         | 5-cm Diameter around nipple designed to deliver a minimum dose of 90% between the skin and the chest wall |
| Van Poppel <i>et al.</i> , 2005 <sup>18</sup>                                                 | 6 Gy × 2 fractions over 2 days | 6–9          | 5-cm Diameter around nipple designed to deliver a minimum dose of 90% between the skin and the chest wall |
| Tyrrell <i>et al.</i> , 2007 <sup>15</sup>                                                    | 10 Gy in a single fraction     | 6–12         | 5-cm Diameter around nipple designed to deliver a minimum dose of 90% between the skin and the chest wall |
| Ozen <i>et al.</i> , 2010 <sup>14</sup>                                                       | 12 Gy in a single fraction     | 6–12         | 5-cm Diameter around nipple designed to deliver a minimum dose of 90% between the skin and the chest wall |

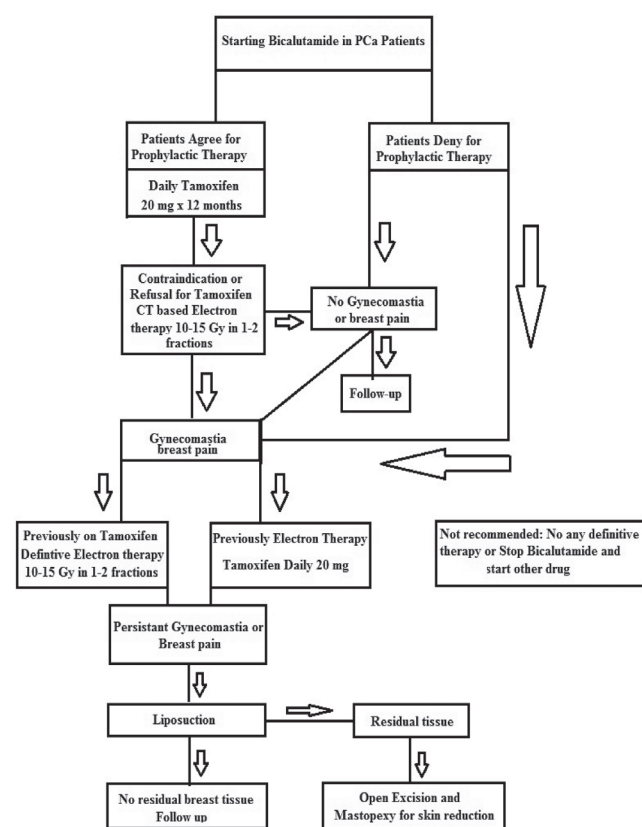


FIGURE 4 Proposed algorithm to prevent and treat bicalutamide-induced breast events, based on the results of the meta-analysis.

lacking. To date, only one case report and one case series have been published concerning the surgical management of bicalutamide-induced gynecomastia<sup>22,23</sup>. In both surgical studies, histopathologic examination of the excised glands from patients who received bicalutamide for pCa showed a decrease in ductal proliferation and a progressive increase in fibrosclerotic tissue. Keeping the present meta-analytic results in mind, surgical therapy could be offered if definitive radiotherapy and definitive tamoxifen fail to reduce breast tenderness and gynecomastia.

In the literature, a broad range of surgical techniques have been used in cases gynecomastia, and surgeons often find it difficult to choose the technique that will achieve the best results for a given patient. In their systematic review, Fruhstorfer and Malata recommended ultrasonography-based liposuction as the first-line option. Open excision should be performed only if a residual lump or firmness is present. After liposuction and open excision, any excess skin settles to some degree, depending on skin quality. Mastopexy is indicated only if noticeable skin excess remains, as occurs when the breasts are very large or the skin is of poor quality<sup>24</sup>.

## 5. CONCLUSIONS

Our meta-analysis found that tamoxifen 20 mg daily for 48 weeks is efficient prophylaxis for bicalutamide-induced gynecomastia and that definitive radiotherapy is the preferred first-line treatment option

for established bicalutamide-induced gynecomastia. Both modalities were found to be well tolerated. However, prophylactic radiotherapy should be reserved for patients who are not candidates for tamoxifen. Anastrozole and weekly tamoxifen should never be considered for bicalutamide-induced adverse breast events. Surgery is the treatment of choice only after the foregoing noninvasive modalities fail.

When starting bicalutamide for pca, the merits and drawbacks of prophylactic or definitive therapy (at the time that adverse breast events occur, to avoid unnecessary treatment) should be discussed with patients using the algorithm we propose based on the results of the present meta-analysis (Figure IV).

## 6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest, and no funding or grants were received for this study.

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