Prophylactic Breast Irradiation for Prevention of Bicalutamide-induced Painful Gynecomastia in Patients with Low- and Intermediate-risk Prostate Cancer

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ABSTRACT **Background:** Bicalutamide monotherapy (BMT) is an option for androgen deprivation therapy (ADT) in patients with low- and intermediate-risk prostate cancer (LIR-PC). Painful gynecomastia (PG) is a common side effect of BMT. Few therapeutic options are available for preventing BMT-induced PG.

Objectives: To assess the efficacy and side effects of single fraction (SF) prophylactic breast irradiation (PBI) to prevent painful gynecomastia (PG) in patients LIR-PC treated with BMT.

Methods: We reviewed the results of bilateral PBI in a prospective cohort of LIR-PC patients who received 150 mg bicalutamide daily as a first-line treatment for at least 12 months. A single fraction of 8 Gy was administered to both breasts by a stationary field of 10 × 10 cm, using 10–15 MeV electron beam. PBI was commenced on the same day as BMT, but prior to the first dose of bicalutamide. A radiotherapy treatment plan was designed to cover breast tissue by the 90% isodose line. Subsequent monthly physical examinations were scheduled for all patients during the first year of BMT to evaluate any PG symptoms.

Results: Seventy-six patients received BMT and PBI, 80% (61/76) showed no signs of PG; 20% (15/76) experienced mild gynecomastia. The main adverse effect of PBI was grade 1 radiation dermatitis.

Conclusions: PBI using a SF of 8 Gy is an effective, safe, and low-cost strategy for the prevention of BMT-induced PG in LIR-PC patients.

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KEY WORDS: bicalutamide, breast, prophylactic irradiation, prostate cancer

Prostate cancer (PC) is the second most common non-skin malignant neoplasm among men worldwide, outnumbered only by lung cancer. It is the second leading cause of cancer-related death in males [1-3]. Nearly 90% of PC patients are diagnosed while having either localized or regional stage disease where the 5-year survival rate may be as high as 99% with the correct treatment [1,2]. In addition, over 90% of such patients survive for a minimum of 15 years [3]. However, for men diagnosed with PC that has metastasized to other regions of the body, the 5-year survival rate may drop to well below 30% [1-3].

Treatment options are available for the primary management of low- and intermediate-risk PC (LIR-PC) patients, including active surveillance (AS), radical prostatectomy (RP), and definitive external beam radiotherapy (EBRT) [4]. No difference in terms of 10-year overall survival between AS, RP, and EBRT was reported in a randomized control study, but higher rates of disease progression and metastases were seen in the AS group [5]. Although a significant proportion of patients on AS will eventually need to undergo either RP or EBRT, it is unlikely that this delay would have any effect on treatment outcomes [6]. There is wide consensus that RP and EBRT may result in similar survival rates in LIR-PC patients [4,5]; however, higher rates of urinary incontinence and erectile disfunction were noted after RP compared to EBRT [7]. However, the disadvantages of EBRT include longer treatment course duration, temporary bladder and/or bowel side effects during treatment, as well as a low but definite risk of protracted rectal symptoms due to radiation proctitis [8,9].

RP may not be a viable option in the management of elderly and/or frail LIR-PC patients with co-morbidities due to the high risks associated with general anesthesia and the increased probability of late side effects [10]. These men may also be reluctant to give consent for EBRT, given the inconvenience of the long treatment duration and the fear of radiation-related morbidities [9]. Observation is a reasonable management option for such patients because existing co-morbidities have a high likelihood of causing death even before PC [10].

In patients who do not agree to observation, androgen deprivation therapy (ADT) is another treatment option [10]. In community practice, ADT is often proposed as a primary therapy for LIR-PC patients who qualify but are unwilling to consent to definitive treatment and still are feeling uncomfortable with observation [11]. ADT is usually performed using luteinizing hormone-releasing hormone (LHRH) agonists that are injected subcutaneously or intramuscularly every 1 to 6 months depending on formulation type [10]. LHRH-agonist therapy is associated with significant morbidity, which may be exacerbated in elderly men. Co-morbidities include, but are not limited to cardiovascular events, diabetes, bone mineral density loss, and

sexual dysfunction such as impotence [4,10,12]. Utilizing an androgen receptor antagonist without the LHRH-agonist side effects may be an alternative in primary ADT in such patients.

Bicalutamide is a non-steroidal competitive androgen receptor agonist that inhibits androgen-regulated prostate cancer cell growth, leading to apoptosis [13]. It is administered orally as a once-daily dose of 150 mg and is approved as a monotherapy for treatment of non-metastatic prostate cancer as an alternative to LHRH-agonist-induced medical castration. Results have shown reduced morbidity with respect to sexual dysfunction and loss of bone mineral density [13-15]. Painful gynecomastia (PG) is the most frequent debilitating side effect of BMT due to its hypergonadotropic action. Other side effects are less common and include fatigue, back pain, skin rash, constipation, hot flushes, and arthralgia [13]. Exacerbation of cardiovascular and diabetic morbidity was not reported. BMT may serve as a replacement for LHRH-agonists in the initial treatment of selected patients with LIR-PC [14,16,17].

PG has been reported to develop within the first 6 months of treatment with BMT in nearly 75% of PC patients [14,15]. Radiotherapy is one of the few modalities that can be used to prevent PG development in such settings. Several radiotherapy delivery methods are used to administer prophylactic breast irradiation (PBI), with dose range variation from 10 to 15 Gy, given in one, two, or four fractions [18-22].

We conducted a prospective study to evaluate the potential role of a low-dose single fraction (SF) PBI in prevention of PG in LIR-PC patients treated with BMT. Given the possible side effects of irradiation, we set the SF dose to 8 Gy to achieve maximal efficacy with minimal adverse effects.

PATIENTS AND METHODS

This prospective study was conducted at the Legacy Heritage Cancer Center for the Negev, in affiliation with Soroka University Medical Center and Ben Gurion University of the Negev. The study protocol and informed consent form was approved by the institutional review board of the Soroka University Medical Center (Beer Sheva, Israel). We assessed the efficacy and side effects of SF PBI in the prevention PG in LIR-PC patients treated with BMT.

The study was designed to include LIR-PC patients unfit to undergo radical prostatectomy due to co-morbidities and/or patients reluctant to give consent to definitive EBRT or observation but who wanted to preserve sexual function. Once cancer staging was completed, BMT was started at an oral daily dose of 150 mg for at least 12 months with no predetermined drug cessation. SF PBI to both breasts was started on the same day as BMT, just prior to the first drug dose.

Radiotherapy treatment plans were calculated using Eclipse 3.1 software by Varian (Palo Alto, CA, USA). A single square field of 10 × 10 cm at SSD 100 cm was applied using a 10–15 MeV electron-beam. Field center was set at the nipple. A SF of 8 Gy was prescribed with the objective of covering the entire breast tissue by 90% isodose. Electron beam irradiation was selected as this method is capable of significantly diminishing the volume of irradiated surrounding tissue, thus minimizing exposure of underlying critical structures such as the lungs and heart. Radiotherapy was delivered with a DHX-2000 linear accelerator by Varian (Palo Alto, CA, USA).

All patients were examined on daily basis for 2 weeks following PBI to assess any acute adverse effects. Regular follow-up visits were set at 1-month intervals for the first 12 months after completion of PBI, with the aim of evaluating symptoms of PG.

RESULTS

Seventy-six patients with LIR-PC qualified and participated in the study. Patient characteristics are presented in Table 1. The median patient age was 73.9 years (range 65–83). The Gleason score was 6 or less in approximately 2/3 of patients with a score of 7 in the remaining patients. The average prostate-specific antigen level at the time of diagnosis was 11.5 ng/ml (range 5.65–19.7 ng/ml).

Table 1. Patient characteristics, n=76

Parameter	Value (absolute / percent)
Age (years)	
≤ 70	23 / 30
71–80	48 / 63
> 80	5 / 7
Median	73.9
Range	65–83
Gleason score	
≤ 6	50 / 66
7	26 / 34
Prostate-specific antigen (ng/ml)	
< 10	52 / 68
10–20	24 / 32
Mean	11.5
Range	5.65–19.7
Risk group	
Low	49 / 64
Intermediate	27 / 36
Co-morbidities	59 / 78
Cardiovascular disease	39 / 51
Diabetes mellitus	24 / 32
Pulmonary disease	12 / 16
Other	8 / 11
> 1 co-morbidity	22 / 29
Karnofski performance status	
60	26 / 34
70	32 / 42
80	14 / 18
90	5 / 6

Sixty-four percent and 34% were assigned to the low- and intermediate-risk groups, respectively. In all, 87% of patients were not fit for radical prostatectomy due to co-morbidities, and the remaining 23% refused to undergo surgery. All patients were reluctant to consent to EBRT. ADT with LHRH-agonist was proposed to all patients but was rejected due to fear of impotence. All patients received BMT as a first-line treatment regimen and PBI.

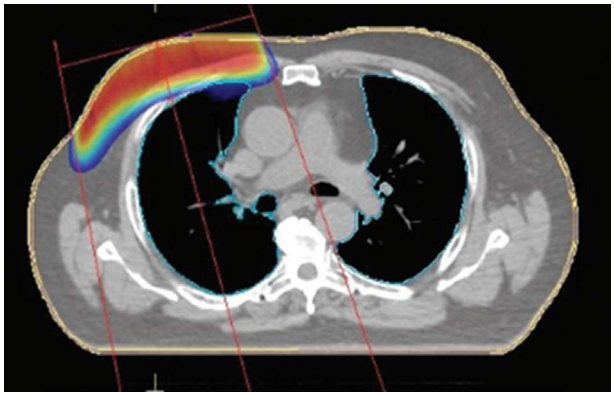
Examples of radiotherapy treatment plans for PBI of the right and left breast are presented in Figure 1 and Figure 2, respectively. The entire breast tissue was covered by a 90% isodose line in all plans. Mean lung and heart doses were kept well below the limit of tolerance [Table 2].

Grade 1 radiation dermatitis appeared in all patients at a median time of 4 days (average 1–6 days) post-PBI. This condition was treated with topical steroids and was completely resolved at a median time of 5 days (range 2–8) days. Other acute adverse effects included transient grade 1 swelling within the radiation field occurring in 32 (41%) patients, temporary grade 1 pain at the radiation site in 26 (33%) patients, and transient grade 1 fatigue in 12 (15%) patients. No grade 2–4 acute toxicity events were noted.

All patients underwent a monthly examination for the first 12

Figure 1. Radiation therapy treatment plan for prophylactic irradiation of the right breast by single anterior electron beam: 90% isodose line shown in orange

[A] Axial view



[B] Sagittal view

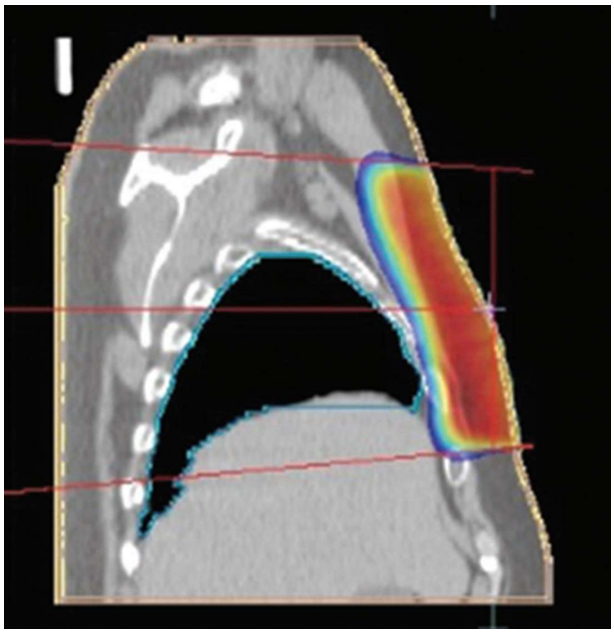
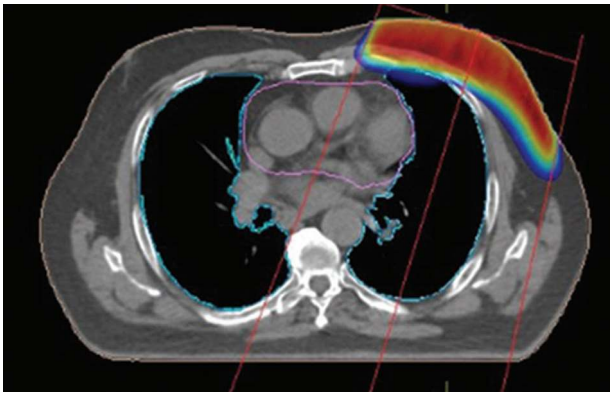


Figure 2. Radiation therapy treatment plan for prophylactic irradiation of left breast by single anterior electron beam; 90% isodose line shown in orange

[A] Axial view



[B] Sagittal view

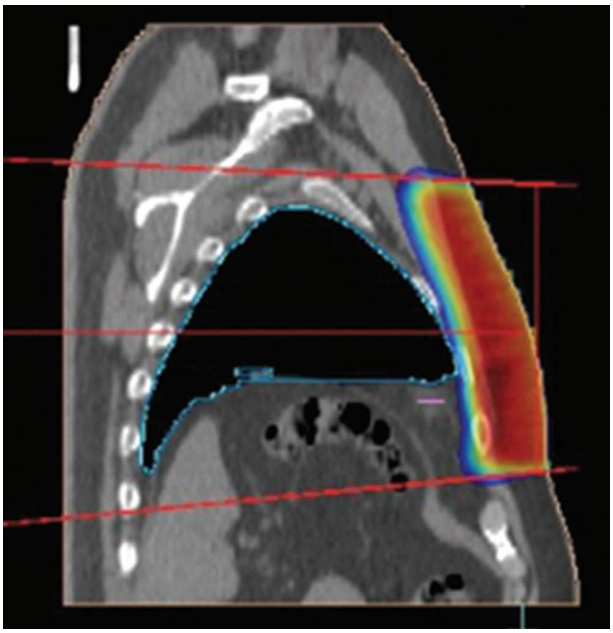


Table 2. Radiation dose to critical structures

Dose parameter	Organ treated	
	Right breast	Left breast
Mean lung dose, Gy		
Median	0.21	0.23
Range	0.16–0.42	0.14–0.46
Mean heart dose, Gy		
Median	0.11	0.26
Range	0.04–0.23	0.12–0.39

months after receiving BMT to evaluate symptoms of gynecomastia and delayed side effects of PBI. Subsequently, the follow-up time interval was increased to 3 months. At a median follow-up of 3.7 years (range 12–60 months), 61 (80%) patients had experienced no signs of gynecomastia. Grade 1 gynecomastia accompanied by transitory grade 1 pain not requiring analgesics was reported in 25 (20%) patients. No delayed side effects of PBI were noted.

DISCUSSION

In this prospective study, we evaluated the efficacy and toxicity of low dose SF PBI in preventing PG in 76 LIR-PC patients treated with BMT as a first-line therapy. At a median follow-up of 3.7 years, only 20% of patients had experienced grade 1 PG. Grade 1 radiation dermatitis, successfully treated with topical steroids, was the main adverse effect of PBI. No delayed side effects of PBI were noted.

PG, accompanied by breast swelling and disfigurement is a frequent disabling side effect of antiandrogen therapy for PC. These symptoms can significantly affect a patient's quality of life. However, PG can be effectively prevented by either drug therapy or PBI [18,23].

Tamoxifen appeared to be an effective drug for prevention of PG in PC patients on BMT with reported PG rates of 12-28% [23]. However, to achieve this efficacy, tamoxifen had to be administered daily for at least 1 year, where common side effects of tamoxifen, such as dizziness and hot flashes, may last for the entire treatment duration. In addition, an increased risk of thromboembolic events should not be overlooked when considering tamoxifen in elderly and frail PC patients with co-morbidities, in particular cardiovascular disease. Anastrozole was ineffective in preventing PG in PC patients receiving BMT [23].

In contrast to tamoxifen, PBI is a short duration treatment. PBI protocols for the treatment of gynecomastia are well described in literature [18-22], where typically a higher radiation dose of 10–15 Gy is delivered in 2–4 fractions [18-20,22]. SF PBI of 10–15 Gy has also previously been a successful treatment option [21]. PBI side effects are modest and limited to a few days or weeks following completion of the radiotherapy course. No late adverse effects were reported in the studies reviewed [18-22]. In our study, we further decreased the SF PBI dose to 8 Gy to potentially reduce the risk of cardiotoxicity. The mean heart doses varied from 0.04 Gy to 0.39 Gy [Table 2], which was well below generally accepted limits of tolerance in breast radiotherapy [24].

The risk of secondary radiation-induced cancer (RIC) is a concern for any type of radiotherapy. Because RIC usually develops in low dose areas at the radiotherapy-field edge, reducing the volume of irradiated tissue is important [25]. This dosage can be achieved by using a single electron-beam, which is characterized by a sharp dose fall-off outside the designated treatment volume. Unfortunately, the follow-up time in our study was substantially shorter than the latent period required for the advancement of solid RIC. This limitation made it impossible to generate a clear statement on the side effects of RIC in electron-beam PBI compared to other radiotherapy delivery methods. Nonetheless, there were no reports of RIC events in other relevant studies [18-22].

The cost of radiotherapy set by the Israeli Ministry of Health is calculated based on the number of radiotherapy-field multiplied by the number of fractions. This situation results in SF PBI being 2–4 times cheaper than PBI delivered in 2–4 fractions.

A single investigative group was a limitation of our study, making a direct comparison with other methods of PBI impossible; however, the PG prevention rate was similar to available reports [18-22]. A short follow-up time was another limitation of this study, as it prevented a definitive conclusion on the risk of RIC after low dose SF PBI.

This method of PBI has been adopted as the standard of care in our department due to its high efficacy, negligible morbidity, and relatively low cost. PBI is the preferred treatment in contrast to drug prophylaxis of gynecomastia due to its swift therapeutic effect and low side effect profile, especially when considering patients of an advanced age with potential co-morbidities.

CONCLUSION

SF PBI using 8 Gy delivered by electron-beam is an effective, safe, and cost-efficient strategy for the prevention of BMT-induced PG in LIR-PC patients.

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There is a fountain of youth: it is your mind, your talents, the creativity you bring to your life and the lives of the people you love. When you learn to tap this source, you will have truly defeated age.

Sophia Loren (b. 1934), Italian actor and singer

Capsule

An epithelial cell-derived metabolite tunes immunoglobulin A secretion by gut-resident plasma cells

Recent data have described metabolic and microbial inputs controlling T cell and innate lymphoid cell activation in the gut; however, whether IgA-secreting lamina propria plasma cells are tuned by local stimuli is completely unknown. Although antibody secretion is thought to be imprinted during B cell differentiation and therefore largely unaffected by environmental changes, a rapid modulation of IgA levels in response to intestinal fluctuations might be beneficial to the host. **Ceglia** and associates showed that dietary cholesterol absorption and commensal recognition by duodenal intestinal epithelial cells lead to the production of oxysterols, evolutionarily conserved lipids with immunomodulatory functions. Using conditional cholesterol 25-hydroxylase deleter mouse line the authors demonstrated that 7α,25-dihydroxycholesterol from epithelial cells is critical to restrain IgA secretion against commensal- and pathogen-derived antigens in the gut. Intestinal plasma cells sense oxysterols via the chemoattractant receptor GPR183 and couple their tissue positioning with IgA secretion. These findings revealed a new mechanism linking dietary cholesterol and humoral immune responses centered around plasma cell localization for efficient mucosal protection.

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