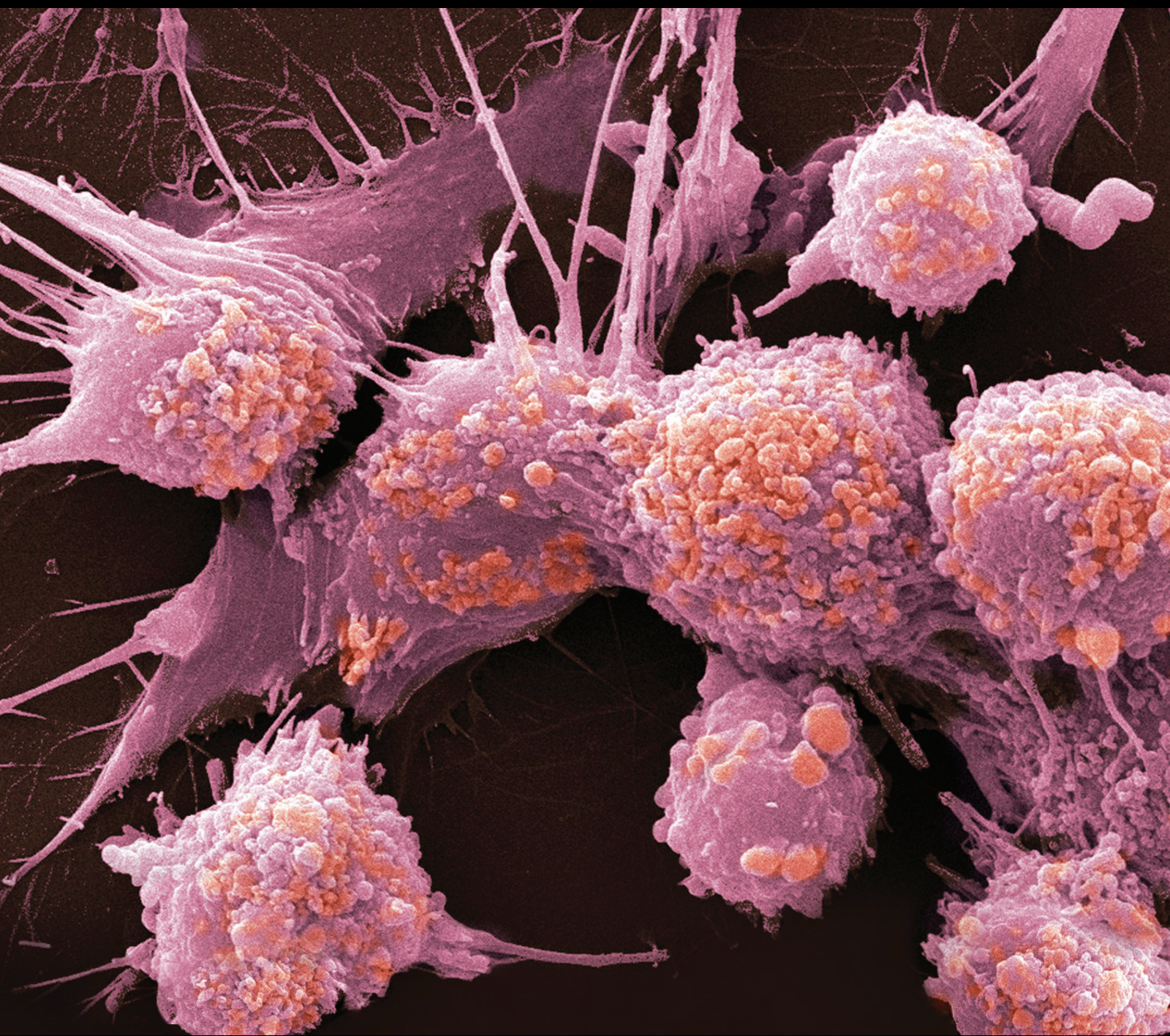
# Advances in Radiotherapy for Prostate Cancer Treatment

Guest Editors: Tarun Podder, Daniel Song, Timothy Showalter, and Luc Beaulieu



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# Editorial Board

# Contents

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*Editorial*

# Advances in Radiotherapy for Prostate Cancer Treatment

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Prostate cancer is one of the most common cancers in men, and there are a number of management options for localized disease, such as active surveillance, radical prostatectomy, chemotherapy, intensity-modulated radiotherapy, radiofrequency ablation, cryotherapy, stereotactic ablative radiotherapy, particle therapy, brachytherapy, and an emerging range of focal therapies. Among these options, multiple competing treatment modalities can be equally effective for any particular patient, with desirable clinical outcome. However, over the years, remarkable developments and improvements have been observed in regard to clinical practice. These changes are compounding effects originating from scientific findings, technological advancements, socioeconomic demands, patient's expectations, and improvements in clinical understanding. In this special issue, we have articles addressing recent advances in treatment, clinical outcome, and scientific findings related to radiation therapy (RT) for prostate cancer.

Depending on the stage of cancer, there can be single-modality or multimodality RT options. Multimodal image-guidance is very important for the latest prostate radiation therapy options in the era of precision medicine. For high-risk prostate cancer, long-term androgen deprivation therapy and dose escalated RT together comprise a standard of care combination approach. Evaluation of the latest evidence for management of high-risk prostate cancer, including consideration of emerging RT modalities such as moderately hypofractionated RT or stereotactic body radiation therapy (SBRT), is very useful. Along with the improvement of treatment techniques, this special issue includes emphasis on how improvement in imaging, especially multimodal MRI, plays an important role in prostate cancer diagnosis, staging and precise delineation of target volume, and treatment delivery. Precise target delineation is very critical for partial prostate treatment, which is also gaining popularity.

For early stage prostate cancer, low-dose-rate (LDR) brachytherapy is considered an effective treatment option. However, delivering LDR seeds precisely and retaining seeds in their planned locations can be challenging. For patients with biochemical recurrence due to underseeded areas after primary brachytherapy, salvage brachytherapy can be a successful procedure, with some increased side effects.

Finally, this issue includes emphasis on minimizing the side effects of prostate RT. Researchers have described the metabolic mechanisms by which increased activity levels and exercise can help to improve both outcomes for men treated for prostate cancer while lowering the side effects of treatment. It is important for clinicians to encourage and give patients support for physical activity during and after treatment for prostate cancer. A systematic review of late gastrointestinal toxicity has indicated that acute toxicity is significantly associated with late toxicity. It has been suggested that acute gastrointestinal toxicity could be considered as a predictive marker for increased risk of moderate to severe proctitis and to identify patients who may benefit from additional medical interventions.

Overall, the articles in this issue provide an overview of the tremendous recent improvements in technology and clinical understanding of prostate cancer and suggest future

directions for improving patient outcomes after prostate cancer treatment.

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*Review Article*

# Evolving Paradigm of Radiotherapy for High-Risk Prostate Cancer: Current Consensus and Continuing Controversies

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High-risk prostate cancer is an aggressive form of the disease with an increased risk of distant metastasis and subsequent mortality. Multiple randomized trials have established that the combination of radiation therapy and long-term androgen deprivation therapy improves overall survival compared to either treatment alone. Standard of care for men with high-risk prostate cancer in the modern setting is dose-escalated radiotherapy along with 2-3 years of androgen deprivation therapy (ADT). There are research efforts directed towards assessing the efficacy of shorter ADT duration. Current research has been focused on assessing hypofractionated and stereotactic body radiation therapy (SBRT) techniques. Ongoing randomized trials will help assess the utility of pelvic lymph node irradiation. Research is also focused on multimodality therapy with addition of a brachytherapy boost to external beam radiation to help improve outcomes in men with high-risk prostate cancer.

## 1. Introduction

Over 220,000 men are diagnosed with prostate cancer in the United States every year [1]. High-risk prostate cancer is an aggressive form of the disease with a higher risk of distant metastasis and mortality, representing a significant portion of the nearly 28,000 prostate cancer deaths a year [1]. Multiple definitions of high-risk prostate cancer exist with the National Cancer Care Network (NCCN) guidelines defining high-risk prostate cancer as cases with at least one of the following features: Gleason 8–10, clinical stage T3a or higher, or PSA > 20 ng/mL [2]. The use of radiation therapy in the definitive treatment of high-risk prostate cancer has been well studied in multiple prospective randomized trials. It is well understood that local disease control plays an important role in reducing the chance of distant metastasis and cancer-specific mortality [3, 4]. Here we review the current state of external beam radiation therapy (EBRT) for high-risk disease, including the use of androgen deprivation therapy (ADT), the role for hypofractionation and stereotactic body radiation therapy (SBRT), the evolving evidence for combined modality therapy, and controversies regarding pelvic nodal irradiation.

## 2. External Beam Radiation Therapy

An important clinical question in this high-risk population has been whether local therapy provides any benefit in patients that are at an increased risk of distant metastases. This has been addressed by two randomized trials that established the benefit of adding EBRT to androgen deprivation therapy (ADT) alone, outlined in Table 1. Widmark et al. [5] studied 875 patients with intermediate- or high-risk disease randomized to receive ADT + EBRT or ADT alone. The ADT regimen was 3 months of a GnRH agonist followed by continuous antiandrogen (flutamide), and the mean radiation dose was 70 Gy to the prostate and seminal vesicles (SV). The addition of radiation to ADT was shown to improve 10-year overall survival (70% versus 61%, $p = 0.004$), 10-year disease-specific survival (88% versus 76%, $p < 0.001$), and 10-year biochemical-free survival (74% versus 25%, $p < 0.001$), despite a radiation therapy dose that is less than what is currently utilized in the dose escalation era. These results are consistent with a randomized study from Warde et al. [6]. In the Intergroup T94-0110 trial, 1205 patients with high-risk prostate cancer were treated with lifelong ADT, through either bilateral orchiectomy or lifelong luteinizing

Table 1: Randomized trials examining the addition of radiation to ADT for high-risk patients.

| Trial | Study cohort | Median follow-up | Trial arms | Outcomes | Toxicity |
|---|---|---|---|---|---|
| Intergroup T94-0110 Warde et al. [6, 7, 10] | 1205 patients (1057 with T3-T4 disease) | 8 years | ADT versus ADT + RT (65–69 Gy) ADT: lifelong LHRH agonist or bilateral orchiectomy | 10-year OS (45% versus 55%, $p = 0.001$) | EBRT increased bowel, urinary, and sexual dysfunction at six months, but no difference at 3 years |
| SPCG-7 Widmark et al. [5] | 875 patients T1b-T2 G2-G3 or T3 (78%) and PSA < 70, N0 | 7.6 years | ADT versus ADT + RT (median 70 Gy) ADT: 3 months' GnRH agonist followed by continuous antiandrogen | 10-year OS (61% versus 70%, $p = 0.004$) 10-year DSS (76% versus 88%, $p < 0.001$) | RT arm with slightly increased rates of late urinary, GI, and sexual dysfunction at 4 years. Quality of life scores equal at 4 years |

hormone-releasing hormone (LHRH) agonist. Patients were then randomized to also receive EBRT or not; those treated with radiation received a dose of 65–69 Gy to the prostate and SV. Unlike the Widmark et al. trial, some patients were also treated to the pelvis with mean dose of 45 Gy. The recently published update of the trial [7] demonstrated that the addition of EBRT to ADT significantly improved 10-year overall survival (HR 0.70, 0.57–0.85, $p < 0.001$) and 10-year prostate cancer-specific survival (HR 0.46, 0.34–0.61, $p < 0.001$), again despite lower doses than those used with modern radiotherapy.

These trials provide strong evidence for the use of external beam radiation in these patients; even with lower radiation doses than those currently used, the addition of EBRT provided a 10% survival benefit. Randomized evidence has also demonstrated that conservative treatment with ADT alone provides no benefit compared to observation in this population. Studer et al. [8] examined the use of ADT alone in 985 patients with localized prostate cancer. Patients were randomized to treatment with upfront ADT (bilateral orchiectomy or LHRH agonist) or had ADT reserved until symptomatic disease progression. At median follow-up of 7.8 years, prostate cancer mortality was not significantly improved with upfront use of ADT (19% versus 20%). Thus, local treatment with curative intent is warranted, and the AUA and NCCN recommend the use of definitive radiation in this patient population [2, 9].

## 3. Role for ADT

Multiple randomized trials have demonstrated a benefit in overall survival with the addition of ADT to EBRT in high-risk patients, as shown in Table 2. RTOG 85-31 was among the first trials to establish this benefit [11]. Patients with locally advanced disease (T3 or N1) were treated to the whole pelvis (44–46 Gy) with a 20–25 Gy boost to the prostate. Patients in the RT + ADT arm were treated with an LHRH agonist, goserelin, starting at the end of radiation, while patients in the RT arm were treated with ADT only at the time of disease progression. At 10 years [12], treatment with adjuvant ADT improved overall survival (49% versus 39%, $p = 0.002$) and disease-specific mortality (84% versus 78%, $p = 0.005$). Subset analysis by Gleason score demonstrated that ADT did not provide a survival benefit in Gleason 2–6 patients (57 versus 51%, $p = 0.26$) but did for Gleason 7 (52% versus 42%, $p = 0.026$) and Gleason 8–10 (39% versus 26%, $p = 0.0046$). Disease-specific mortality was only reduced in patients with Gleason ≥8 disease (27% versus 40%, $p = 0.0039$).

RTOG 86-10 was a similar study examining the addition of 4 months of ADT, given prior to and during radiation in patients with bulky disease [13, 14]. Subset analyses demonstrated that, at 8 years, 4 months of ADT improved local and distant control as well as survival in Gleason 2–6 patients. However, in Gleason 7–10 patients, there was no demonstrated statistically significant benefit in any outcome, suggesting that patients with higher risk factors may need longer than 4 months of androgen deprivation to make a notable impact on the natural history of the disease.

EORTC 22863 examined the addition of 3 years of concurrent and adjuvant ADT in patients with prostate-confined disease with high-grade pathology as well as locally advanced patients treated with radiation [17]. At 10 years [18], overall survival (58% versus 40%, $p = 0.0004$) and disease-free survival (48% versus 23%, $p < 0.0001$) significantly improved with addition of ADT.

TROG 96-01 was a three-arm trial including patients with T2b-T4N0 disease treated with radiation and randomized to one of three arms, no ADT, 3 months' ADT, and 6 months' ADT. Randomization was stratified by PSA (greater and less than 20 ng/mL) and grade [16]. Of note, pelvic lymph nodes were not treated in this trial. Local failure, distant failure, and biochemical failure were significantly reduced with use of either 3 or 6 months of ADT compared to patients treated with radiation alone. At ten years, the addition of 6 months of ADT to EBRT alone also reduced distant failure (10.9% versus 20.6%, $p = 0.0006$) and improved overall (70.8% versus 57.5%, $p = 0.0005$) and disease-specific survival (88.6% versus 78%, $p = 0.0002$) [35].

The consensus of the randomized trial evidence suggests that ADT plays a vital role in disease control of high-risk prostate cancer patients. A subset analysis of RTOG 85-31 demonstrated that patients who were treated for longer than 5 years of ADT had the most benefit [36]. Indefinite treatment with androgen deprivation is not without implications on

Table 2: Randomized trials examining the addition of ADT to radiation for high-risk patients.

| Trial | Study cohort | Median follow-up | Trial arms | Outcomes |
|---|---|---|---|---|
| RTOG 85-31 [11, 12] | 945 patients T3 (82%) or N1 (18%) | 7.6 years | RT versus RT + ADT (44–46 Gy to whole pelvis; 20–25 Gy boost to prostate) ADT: goserelin at least 2 years, preferably until progression | 10-year OS (39% versus 49%, $p = 0.002$) 10-year DSS (78% versus 84%, $p = 0.005$) Overall survival benefit limited to patients with Gleason 7–10 |
| RTOG 86-10 [13–15] | 456 patients T2-T4, N0-1 with "bulky" disease (palpable ≥ 25 $cm^2$) | 11.9 years | RT versus RT + ADT (44–46 Gy to whole pelvis; 20–25 Gy boost to prostate) ADT: 4 months' goserelin + flutamide, starting 2 months prior to RT | 10-year OS (34% versus 43%, $p = 0.12$) 10-year DSS (23% versus 36%, $p = 0.01$) Subset analyses at 8 years showed that benefit was confined to Gleason 2–6 patients. No benefit to ADT in Gleason 7–10 |
| TROG 96-01 [16] | 802 patients T2b-T4N0 | 10.6 years | RT alone versus RT + 3 mo. ADT versus RT + 6 mo. (66 Gy, no pelvic node treatment) ADT: goserelin + flutamide given *neoadjuvantly* | At 10 years, addition of 6 months' ADT improved 10-year OS (70.8% versus 57.5%, $p = 0.0005$) 10-year DSS (48% versus 23%, $p < 0.0001$) |
| EORTC 22863 [17, 18] | 415 patients T1-2N0 grade 3 or T3-4N0-1 | 9.1 years | RT versus RT + 3 years' ADT (50 Gy to pelvis, 20 Gy boost) ADT: 1 month' cyproterone acetate, goserelin × 3 years starting with RT | 10-year OS (40% versus 58%, $p = 0.0004$) 10-year DSS (10% versus 30%, $p < 0.0001$) |

OS: overall survival, DSS: disease-specific survival.

quality of life; thus, it is important to find the optimal length of adjuvant ADT in the curative setting of high-risk patients. One study showed a survival benefit with three years of ADT, while another demonstrated a benefit with only six months of ADT, leaving open the question of duration of treatment needed.

Table 3 summarizes randomized trials that have attempted to help delineate optimal duration by comparing long-term (LTAD) and short-term androgen deprivation (STAD) after radiation. RTOG 92-02 was a large phase III trial in T2c-T4 patients comparing 4 versus 28 months of ADT along with radiation [20]. Use of LTAD significantly improved local and distant disease control, biochemical control, and disease-specific survival at ten years [21]. Only patients in the Gleason 8–10 subset had an overall survival advantage at ten years, 45% versus 32% ($p = 0.0061$). A subsequent cost-analysis of patients included in RTOG 92-02 demonstrated that use of LTAD was associated with increased quality-adjusted life years as well as decreased total costs, due to the salvage treatments associated with STAD [37].

EORTC 22961 showed that 36 months of ADT with EBRT significantly improved overall survival at 5 years (85% versus 81%) compared to 6 months of ADT [19]. As will be discussed, the recent DART 01/05 trial has demonstrated that use of 28 months of ADT is superior to 4 months of ADT in the dose-escalated EBRT era [22]. The body of evidence from these randomized trials shows that patients with high-risk disease have a survival benefit with LTAD. As such, currently the NCCN guidelines for high-risk prostate cancer include 2-3 years of androgen deprivation along with EBRT as a category 1 recommendation [2]. In practice, the optimal duration remains a moving target. In EORTC 22961, for example, 28% of patients in the LTAD arm did not complete the full 3 years of ADT due largely to quality of life factors [19].

A recent Canadian randomized trial [23] including 630 high-risk patients has suggested that ADT duration can potentially be reduced from 36 months to 18 months in this population with no significant difference in overall or disease-specific survival. However, the analysis was not powered for noninferiority; more patients are currently being accrued. The study also required treatment to the pelvic lymph nodes; it is unclear if such reduction in ADT duration would be possible in patients with untreated lymph nodes. The impact on quality of life in cutting the required ADT time by half also remains to be reported. While it has been established that high-risk patients need longer than 6 months of ADT, further work remains to be done in examining the safety and efficacy of reducing ADT duration to less than two years. Off protocol however, the goal should still be for these patients to finish at least a two-year course of androgen deprivation.

Androgen deprivation therapy can be associated with obesity, sexual dysfunction, insulin resistance, bone loss, gynecomastia, fatigue, and lipid abnormalities [38]. Side effects of nonsteroidal antiandrogens can also include diarrhea as well as significant hepatotoxicity. As discussed previously, RTOG 85-31, 86-10, and 92-02 established the survival benefit of addition of ADT to EBRT as well as the need for long-term ADT in high-risk patients (Tables 2 and 3).

Table 3: Randomized trials comparing LTAD and STAD with radiation in high-risk patients.

| Trial | Study cohort | Median follow-up | Trial arms | Outcomes |
|---|---|---|---|---|
| EORTC 22961 [19] | 970 patients with T2c-T4 or N1-2 | 6.4 years | RT + 6 months' ADT versus RT + 36 months' ADT (Prostate dose 70 Gy) ADT: 6 months' CAB (LHRH agonist + antiandrogen) ± 2.5 years' LHRH agonist | 5-year OS 81% versus 85% ($p = 0.02$) 5-year DSS 95% versus 97% ($p = 0.002$) QOL measures the same in each arm No difference in cardiac fatal event Increased rates of reported gynecomastia, incontinence, and sexual dysfunction with LTAD |
| RTOG 92-02 [20, 21] | 1514 patients with T2c-T4 | 11.3 years | RT + 4 months' ADT versus RT + 28 months' ADT (44–50 Gy to whole pelvis, boost to 65–70 Gy prostate) ADT: goserelin + flutamide 4 months total (prior to and during RT) ± 2 years' goserelin | 10-year OS 52% versus 54% ($p = 0.25$) 10-year DSS 84% versus 89% ($p = 0.0001$) Gleason 8–10 subset: 10-year OS 32% versus 45% ($p = 0.0061$) Increased grade 3 GI toxicity at 8 years with LTAD (2.9% versus 1.2%, $p = 0.04$) |
| DART 01/05 Spain [22] | 355 patients (47% int.-risk, 53% high-risk) | 5.3 years | RT + 4 months' ADT versus RT + 28 months' ADT (76–82 Gy to prostate) ADT: goserelin + antiandrogen for 4 months total (prior to and during RT) ± 2 years' goserelin | 5-year OS 86% versus 95% ($p = 0.009$) 5-year BRFS 81% versus 89% ($p = 0.019$) 5-year metastasis-free survival 83% versus 94% ($p = 0.009$) |
| PCS IV Trial Canada Nabid et al. [23] | 630 node-negative, high-risk patients | 6.5 years | RT + 18 months' ADT versus RT + 36 months' ADT (44 Gy to whole pelvis, 70 Gy to prostate) ADT: bicalutamide 1 month, goserelin q 3 months for 18 or 36 months | 10-year OS 59% versus 62% ($p = 0.28$) 10-year DSS 84.1% versus 83.7% ($p = 0.82$) |

LTAD: long-term ADT, STAD: short-term ADT, OS: overall survival, DSS: disease-specific survival, and BRFS: biochemical relapse-free survival.

At ten-year follow-up, analysis of outcomes in the roughly 3000 patients included in the three trials demonstrated that grade 3+ GI and GU late toxicity was not increased with the addition of ADT to radiation [39]. In fact, patients treated with long-term ADT had a significantly reduced rate of grade 3+ GU toxicity compared to patients treated with RT alone.

The role of ADT in potentiating cardiovascular disease has been an active area of study and remains an area of controversy. A pooled analysis of 1,372 patients who participated in 3 prospective randomized trials examining the addition of short-term ADT to radiation demonstrated that, in men 65 and older, use of 6 months of ADT led to shorter time to fatal heart attacks compared to those treated with radiation alone [40]. No such difference was observed in men younger than 65. More recently, Nguyen et al. published a large meta-analysis of 4141 patients from 8 randomized trials of patients with unfavorable-risk prostate cancer treated with and without ADT [41]. The rate of cardiovascular death was not significantly different in patients treated with ADT (11.0% versus 11.2%, $p = 0.41$). In addition, patients treated with LTAD had no increase in rates of cardiovascular mortality compared to patients treated with ADT for 6 months or less. In 4805 patients from 11 trials that reported survival, use of ADT significantly reduced rates of prostate cancer-specific mortality (13.5% versus 22.1%) as well as all-cause mortality (37.7% versus 44.4%) [41]. Patients with high-risk prostate cancer have a significant risk of mortality from prostate cancer and the magnitude of benefit provided by ADT far exceeds the additional risk of CV mortality that may potentially exist, though the Nguyen meta-analysis represents the largest patient group in which this has been studied and showed no increased risk. As such, the American Cancer Society, the American Urological Association, and the American Heart Association recommend use of ADT in these patients without any need for cardiovascular workup or intervention prior to initiation of treatment [42]. Some

Table 4: Randomized trials studying dose escalation in high-risk patients.

| Trial | Study cohort | Median follow-up | Trial arms | Outcomes |
|---|---|---|---|---|
| MDACC Kuban et al. [24] | 301 patients 20% low-risk 46% int.-risk 34% high-risk | 8.7 years | 70 Gy versus 78 Gy 4-field box or 3DRT techniques No ADT used | 8-year BRFS 55% versus 78% ($p = 0.004$) 8-year OS 78% versus 79% (NS) High-risk cohort: 8-year BRFS 26% versus 63% ($p = 0.004$) 1% versus 7% grade 3 late toxicity ($p = 0.02$) |
| Dutch [25, 26] | 664 patients T1b-4 18% low-risk 27% int.-risk 55% high-risk | 5.8 years | 68 Gy versus 78 Gy 3DRT technique ADT used | 7-year BRFS 45% versus 56% ($p = 0.04$) OS not significantly different Late grade 3+ GI (4% versus 5%) and GU toxicity (12% versus 13%) equivalent in both arms |
| UK MRCRT01 [27, 28] | 843 patients 19% low-risk 37% int.-risk 43% high-risk | 10 years | 64 Gy versus 74 Gy 3DRT technique ADT used | 10-year BRFS 43% versus 55% ($p = 0.0003$) OS not significantly different 6% versus 10% grade 3 late toxicity |

BRFS: biochemical relapse-free survival, NS: nonsignificant, and OS: overall survival.

evidence has suggested that patients with history of MI may be more adversely affected with use of ADT [43]. Prospective research is needed on the cardiovascular implications of ADT use in patients with preexisting coronary artery disease. Patients treated with long-term ADT should be counseled in reducing their cardiovascular risk factors.

## 4. Dose Escalation

Though EBRT has been shown to significantly improve survival outcomes in high-risk patients, the aforementioned randomized trials used doses from 65–70 Gy, not reflective of the modern dose escalation in practice. The advent of intensity modulated radiation therapy (IMRT) has allowed for increasing doses delivered to the prostate while avoiding increased normal tissue toxicity. Multiple trials have demonstrated benefit in biochemical control in patients with low-intermediate-risk prostate cancer treated with doses escalated to 74–79.2 Gy [24, 25, 27, 44, 45]. The largest of these is RTOG 01-26 [45], in which 1,499 patients with Gleason 6 or 7 disease were treated without ADT and randomized to either 70.2 Gy or 79.2 Gy in 1.8 Gy fractions. Patients treated to 79.2 Gy had significantly reduced rates of biochemical failure by the Phoenix definition [46], 26% versus 43% at 7 years.

Similarly, dose escalation in high-risk prostate cancer patients has become commonplace. Zelefsky et al. [47] retrospectively reviewed outcomes in 2,047 patients with clinically localized prostate cancer treated definitively with radiation with doses ranging from 66 to 86.4 Gy. In patients with high-risk features, multivariate analysis demonstrated significant reduction in biochemical failure and distant metastases with higher doses of radiation. Table 4 outlines the results of three large randomized trials that demonstrate the benefit of dose escalation in high-risk patients [24, 26, 27]. The MD Anderson trial did not include the addition of ADT; patients treated with dose escalation to 78 Gy had a roughly 20 percent benefit in biochemical-free survival at median follow-up of 8.7 years [24]. The Dutch [26] and UK [27] trials included more patients, a higher percentage of whom were categorized as high-risk. All three trials demonstrate that dose escalation improves biochemical control; however, there was no significant improvement in overall survival.

The UK and Dutch trials show that, even in the setting of ADT, there is still significant benefit in biochemical control with dose escalation. As discussed previously and outlined in Table 2, the addition of ADT to radiation has been shown to improve biochemical control and overall survival; however, these studies were done in an era of lower doses (65–70 Gy). The recently published DART 01/05 trial [22] randomized 355 patients with intermediate- or high-risk prostate cancer treated with high-dose radiation (76–82 Gy) to 4 months of neoadjuvant ADT alone or with the addition of 2 years of adjuvant ADT (total duration 28 months). Patients with high-risk disease had a significant benefit in biochemical control, distant disease control, and overall survival. Importantly, there was no noted significant increase in late grade ≥3 GI or GU toxicities. This is the first randomized trial to demonstrate a benefit to long-term ADT in the setting of high-dose radiation and it supports the continued use of ADT along with EBRT in the dose escalation era.

## 5. Impact of Pelvic Radiation

The majority of the discussed randomized EBRT + ADT trials (Tables 2 and 3) included patients treated with pelvic radiation, except for TROG 96-01. The rationale for pelvic irradiation is that a nontrivial proportion of clinically localized high-risk prostate cancer patients have micrometastatic nodal disease that is not otherwise apparent [34]. Elective pelvic radiation increases radiation exposure to the bowel and is associated with increased GI toxicities during and after radiation. Thus, patient selection for pelvic irradiation in this

Table 5: Pelvic nodal radiation in high-risk patients.

| Study | Study cohort | Median follow-up | Trial arms | Outcomes |
|---|---|---|---|---|
| RTOG 94-13 [29–31] | 1275 patients, 73% Gleason 7–10 | 12 years | PRT<br>NA/C ADT + pelvic RT<br>NA/C ADT + prostate RT<br>Adjuvant ADT + pelvic RT<br>Adjuvant ADT + prostate RT | Significant improvement in biochemical control, trend for improved progression-free survival with use of NA/C ADT + pelvic RT |
| GETUG-01 [32] | 444 patients, T1b-T3N0 (75% high-risk) | 3.5 years | PRT<br>Prostate RT versus pelvic RT prostate boost<br>46 Gy to the pelvis, 66–70 Gy to the prostate | No difference in PFS or OS with use of pelvic node radiation<br>No significant difference in toxicity or QOL measures |
| Yale<br>Aizer et al. [33] | 277 patients with ≥15% LN involvement per Roach formula [34] | 2.5 years | Retrospective review: Whole pelvic RT/prostate boost versus prostate RT alone<br>≥90% received ADT<br>Mean RT dose: 75.6 Gy | 4-year biochemical-free survival improved with pelvic RT (86% versus 70%, $p = 0.02$) in multivariate analysis<br>OS not reported<br>Increased acute GI toxicity with pelvic RT, no difference in late toxicity |

PFS: progression-free survival, OS: overall survival, PRT: prospective randomized trial, and NA/C: neoadjuvant/concurrent.

cohort has been somewhat controversial. In the DART trial, the decision of whether or not to include the pelvis in the radiation field was left up to the participating institutions [22].

Table 5 summarizes currently published studies looking at field size. RTOG 94-13 [29–31] included patients with an estimated ≥15% chance of lymph node involvement based on the Roach formula [34]. Patients were randomized to prostate-only or whole pelvic radiation; patients were also randomized to total 4 months of neoadjuvant and concurrent ADT or 4 months of adjuvant ADT. In patients treated with neoadjuvant/concurrent ADT, the use of whole pelvic radiation improved progression-free survival as well as biochemical control. However, in patients treated with adjuvant ADT, outcomes were equivalent irrespective of ADT timing. The authors presented their updated data with 12-year follow-up at ASTRO 2013 and conclude that there may be sequence-dependent biological interactions between the field size and ADT. However, as this was a 2 × 2 designed trial, there has been controversy on how these results should be interpreted. In order to address the remaining questions, RTOG 09-24 is currently accruing patients to further examine the impact of pelvic nodal radiation in a two-arm design. These patients will be treated by current standards, with high-dose radiation (45 Gy to the pelvis followed by boost to the prostate to 79.2 Gy) as well as long-term ADT (32 months).

GETUG-01 was a French randomized trial which did not show a benefit in overall survival or progression-free survival with whole pelvic radiation, though the radiation dose (mean total dose of 68 Gy) is low by modern standards [32] In contrast, Aizer et al. retrospectively demonstrated significant improvement in biochemical control with pelvic RT with use of higher doses (mean 75.6 Gy); however, longer follow-up is needed [33]. A recent National Cancer Data Base analysis [48] of more than 14,000 high-risk patients suggested there was no overall survival advantage with whole pelvic radiation compared to prostate-only EBRT, though there are inherent limitations in a retrospective analysis. Currently there is no consensus recommendation for pelvic radiation in this population, and it should be considered on a case-by-case basis until the results of RTOG 09-24 are available.

## 6. Node-Positive Disease

Patients with clinical or pathologic evidence of nodal disease represent a unique cohort of prostate cancer patients, technically classified as stage IV disease, though unlike those with distant metastases, a potential cure is possible. Thus, some have favored an aggressive multimodality therapy approach. A retrospective study published by Zagars et al. [49] demonstrated that, in patients with pathologically confirmed nodal disease (pN1) after a lymphadenectomy, those treated with prostate EBRT (mean dose of 68 Gy) + ADT had improved freedom from distant metastases and improved overall survival compared to those treated with initial ADT alone when controlling for other disease factors such as Gleason score, initial PSA, and T stage. A portion of patients (18%) included on RTOG 85-31 [11], which demonstrated a benefit to the addition of ADT to RT in high-risk patients, had pathologically node-positive disease. In subset analysis of these pN1 patients, the combination of ADT and RT improved OS and distant disease control compared to those treated with radiation alone [50]. Two large population analyses using SEER have also demonstrated improved overall survival and prostate cancer-specific survival in radiographic and pathologic node-positive patients treated with radiation therapy versus those treated with no local therapy, though these analyses are limited by lack of information regarding ADT [51, 52]. Current guidelines [2] recommend either the combination of long-term ADT and EBRT or long-term

ADT alone for node-positive patients, though the evidence suggests a rationale for aggressive combination therapy in these patients. However, there is a dearth of randomized evidence for this population and future studies should focus on the role for ADT with modern radiation doses as well as the role for pelvic nodal radiation in clinically node-positive patients.

There is also controversy regarding the management of pathologically node-positive patients after prostatectomy. Briganti et al. retrospectively compared outcomes in men treated with prostatectomy and lymph node dissection who were found to have positive lymph nodes and were subsequently treated with radiation therapy plus ADT or ADT alone. Ten-year overall survival (86% versus 70%) and prostate cancer-specific survival (74% versus 55%) were significantly improved with the combination of ADT + RT [53]. Recently, Abdollah et al. [54] published a large retrospective analysis of 1107 patients with pN1 disease who were treated with prostatectomy and lymph node dissection and adjuvantly with ADT ± RT. With a median follow-up of 7.1 years, those treated with RT had improved cancer-specific mortality. Further subset analyses identified two patient groups who benefited most from addition of radiation: (1) patients with two positive nodes or less who also had Gleason 7 disease, pT3 disease, or positive margins or (2) patients with 3-4 positive nodes. Conversely, a large population SEER analysis did not show any benefit in overall or cancer-specific survival to the addition of RT to patients with pN1 disease after surgery [55]. In clinical practice, adjuvant radiation is routinely offered to patients with pN1 disease, though randomized evidence is needed with further study warranted specifically in the subgroups identified in the Abdollah analysis.

## 7. Hypofractionation

Though conventionally fractionated EBRT is standard of care by NCCN guidelines in this population, 8 weeks of daily radiotherapy can be logistically challenging for patients, with increased travel costs and opportunity cost with regard to time [56, 57]. Furthermore, radiobiological studies have demonstrated a low alpha/beta ratio for prostate cancer, suggesting that increased fraction size may improve biochemical control without significantly increased toxicity to nearby tissues. Multiple randomized trials have demonstrated excellent biochemical control with acceptable toxicity profiles with hypofractionated courses in low-, intermediate-, and high-risk prostate cancer patients [58–63]. Arcangeli et al. [63] examined 168 patients, all with high-risk disease, randomized to conventional fractionation (80 Gy/40 fractions) or hypofractionation (62 Gy/30 fractions). All patients were treated with 9 months of ADT. No differences in toxicities were noted in the two arms [64]. At 5 years, freedom from biochemical failure (95% hypofractionated versus 83% conventional), local failure (100% versus 92%), and distant failure (98% versus 87%) was statistically equivalent in the two arms. However, in a subset analysis of high-risk patients with PSA < 20 ng/mL, hypofractionation improved all three outcomes.

More recently, the HYPRO trial group randomized 820 patients with intermediate- (27%) and high-risk (73%) prostate cancer to standard (78 Gy in 39 fractions, five fractions a week) or hypofractionated treatment (64.6 Gy in 19 fractions, three fractions a week). Early reporting of oncologic outcomes demonstrates equivalent outcomes in the standard and hypofractionated groups (5-year relapse-free survival 77% versus 80%, $p = 0.36$) [65]. However, 5-year reports of late toxicity data could not demonstrate that hypofractionation was noninferior to standard fractionation, with cumulative grade ≥3 genitourinary toxicity of 19% using hypofractionation (versus 12.9 % in the standard arm) [66]. Grade ≥2 GI acute toxicity was also reported to be worse in the hypofractionated arm (42% versus 31%) though acute GU toxicity was similar in both arms [58]. While the reported toxicity profiles with hypofractionation in this trial were worse than with standard treatment, some have argued that this may be due to lack of quality assurance with use of image guidance as well as lack of bladder dose constraints [67]. Another large scale European hypofractionation trial, the CHHiP study, included a portion of high-risk patients (12%) and randomized 2100 patients to either standard fractionation (74 Gy in 37 fractions) or one of two hypofractionated regimens: 60 Gy in 20 fractions or 57 Gy in 19 fractions [68]. While treatment efficacy has not yet been published, with median follow-up of 50 months, patient-reported outcomes of bowel toxicity are low and not different between standard and hypofractionated treatment groups. Longer follow-up is needed and, in clinical practice, careful patient selection and image guided radiation therapy with strong consideration for use of daily cone beam CT are warranted.

Though pelvic radiation is sometimes warranted in this patient population, only one published randomized trial, a Lithuanian study with 124 patients [69], included patients with hypofractionated regimens to the whole pelvis. 76 Gy in 38 fractions (arm 1) was compared to 63 Gy in 20 fractions (arm 2); the pelvic regimens included were 46 Gy in 23 fractions in arm 1 and 44 Gy in 20 fractions in arm 2. The hypofractionated arm had simultaneous pelvic and prostate treatment. Only acute toxicities have been reported thus far and incidence was found to be roughly equivalent in both arms, though patients undergoing hypofractionated treatment experienced acute toxicity earlier during treatment.

## 8. Role for Brachytherapy

Use of prostate brachytherapy allows for the ability to safely deliver higher biological equivalent dose to the prostate, which provides some theoretical advantages in high-risk prostate cancer patients. Multiple studies have demonstrated the efficacy of high-dose rate (HDR) brachytherapy as monotherapy or in conjunction with external beam radiation [70–73]. In a phase II trial of 200 high-risk and very high-risk patients, patients were treated with 54 Gy to the prostate and pelvic lymph nodes followed by 19 Gy to the prostate in four HDR treatments. Five-year results demonstrated 85.1% biochemical relapse-free survival without significant increase in toxicity. There is also randomized evidence suggesting a benefit to multimodality therapy with use of low dose rate

(LDR) brachytherapy. The results of a prospective randomized trial were recently presented by Morris et al. at ASCO in 2015 [74]. In this trial, 400 patients with intermediate- and high-risk disease were given an LHRH agonist for 8 months and then treated to the whole pelvis with 46 Gy in 23 fractions via EBRT; patients were then randomized to receive 32 Gy/16 fractions conformal EBRT boost or LDR-brachytherapy boost prescribed to minimum peripheral dose of 115%. The 9-year biochemical failure-free survival was 83% with use of LDR boost compared to 63% with external beam boost (HR 0.35, 95% 0.19–0.65; $p < 0.001$). These excellent results strongly support the consideration for dose escalation with multimodality therapy in high-risk patients. Patients with high volume disease and high Gleason score should be considered for this option of combined modality therapy.

## 9. Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) to the prostate represents an ultrahypofractionated regimen, providing definitive treatment, typically in 4–6 fractions. The initial phase 1 dose escalation studies were performed predominantly in low- and intermediate-risk patients [75], but prospective phase II studies have since been done that also included a small proportion of high-risk patients. A pooled multi-institutional analysis of 1100 patients (58% low-risk, 30% intermediate-risk, and 11% high-risk) treated with a median dose of 36.25 Gy in 4-5 fractions demonstrated 5-year biochemical recurrence-free survival of 95%, 84%, and 81% in low-, intermediate-, and high-risk patients [76]. Long-term quality of life measures in patients evaluated for 5 years showed an initial decline in urinary and bowel function within the first three months; however, these were found to return to baseline by six months [77]. Sexual decline was typically noted in the first nine months and then stabilized before declining by typical age-expected parameters.

There is limited data on the use of SBRT in high-risk patients alone. Given the inferior biochemical control after SBRT reported in patients with high-risk disease compared to those with low- and intermediate-risk disease, there have been attempts to dose-escalate. A recently published phase I/II trial examined the use of SBRT in high-risk patients with dose escalation to 40 Gy in 5 fractions along with 1 year of ADT [78]. Uniquely, this trial included treatment to pelvic nodes as well (25 Gy to the pelvic nodes and 40 Gy to the prostate in five total fractions). Four of the 15 patients treated had grade 3 or higher GI or GU toxicity at six months, and the trial was closed early. In the coming years there will be multiple published reports of experiences with use of SBRT in high-risk patients. As this modality becomes more established, it will be imperative to determine the appropriate use of ADT and role of pelvic lymph node irradiation with SBRT.

Boike et al. [75] also reported increased toxicities in their prospective dose escalation study for low- and intermediate-risk patients who were treated in cohorts of 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions. 7% of patients experienced grade ≥3 GI toxicity with 5 requiring a diverting colostomy (250). Based on these two studies, there has been concern about the safety of uniform prostate dose escalation and some have explored more heterogeneous techniques. Kotecha et al. recently reported outcomes in patients with intermediate- and high-risk prostate cancer treated with dose escalation utilizing a novel heterogeneous planning technique. Dosing was 36.25 Gy in 5 fractions with simultaneous integrated boost to 50 Gy in 5 fractions. 3 mm expansions around the urethra, rectum, and bladder were limited to 36.25 Gy with the rest of the gland treated to a mean dose of 50 Gy. With a median two years of follow-up, the 24 treated patients (13 high-risk) had 96% biochemical control (using the Phoenix definition) with no acute or late grade ≥3 GI or GU toxicities noted. Sixteen patients (67%) were treated with ADT for a median of six months. Testosterone levels were monitored regularly and at last follow-up, all patients were no longer castrate except for two undergoing long-term ADT (>24 months). Though longer follow-up is needed, the demonstrated excellent biochemical control in the setting of noncastrate levels of testosterone suggests that this heterogeneous dose escalation technique may represent a safe and efficacious model for treatment.

Another approach under study is SBRT utilizing dose escalation to visible prostate lesions seen on MRI, as opposed to previously published reports using homogenous dose escalation or the urethral sparing heterogeneous dose escalation technique published by Kotecha et al. [79]. This idea has been explored using conventional IMRT, with early reports demonstrating safety with boosting dose to visible MRI lesions to 80 Gy [80] or 95 Gy [81], though efficacy using this technique has yet to be demonstrated. Another recently reported approach utilized HDR brachytherapy boost to MRI lesions after hypofractionated external beam radiation therapy with good tolerance and excellent early toxicity profiles [82]. However, there is some concern regarding the efficacy of these techniques because it is unknown what the relationship is between a dominant lesion on imaging and the true biology of the disease. Some have argued that, because of the potentially multifocal nature of prostate cancer, it is important to maintain adequate whole organ dose in the setting of partial dose escalation. For example, some have performed partial brachytherapy to target the peripheral zone as delineated by MRI with the rationale that this area represents the most common site of prostate cancer [83]. However, this approach was shown to have inferior outcomes in men with favorable intermediate-risk cancer compared to traditional techniques. SBRT with a focal boost to MRI-visible lesions has been reported in low- and intermediate-risk patients; Aluwini et al. reported on 50 patients treated to 38 Gy in 4 fractions with a simultaneous boost to 44 Gy in 4 fractions for the MRI lesion. Biochemical control was excellent (100%) at two years with acceptably low toxicity [84]. Institutional studies using a similar focal dose escalation technique to MRI lesions in high-risk patients are currently accruing.

## 10. Conclusions

The combination of long-term ADT and external beam radiation in high-risk prostate cancer patients has been shown

in multiple randomized trials to maximize disease control and extend overall survival compared to single modality treatment. Current recommendations are for 2-3 years of ADT and dose-escalated RT to the prostate. Newly presented randomized data suggests that dose escalation with use of LDR-brachytherapy boost may be superior to dose escalation with EBRT alone. As we enter a new era of healthcare economics, it will be increasingly important to provide appropriate care while using fewer resources, and hypofractionation will almost certainly play a role. While results of long-term follow-up are needed, randomized trials have shown good efficacy with acceptable toxicity with significant reduction in treatment times. In the coming years, more randomized data utilizing hypofractionated regiments as well as SBRT will be available to help shape the guidelines. The decision of whether to target pelvic lymph nodes with radiation remains an unanswered question; results from RTOG 09-24 will help radiation oncologists counsel patients in regard to weighing the increased toxicities against the potential benefits.

## Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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*Research Article*

# Salvage Brachytherapy for Biochemically Recurrent Prostate Cancer following Primary Brachytherapy

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*Purpose*. In this study, we evaluated our experience with salvage brachytherapy after discovery of biochemical recurrence after a prior brachytherapy procedure. *Methods and Materials*. From 2001 through 2012 twenty-one patients treated by brachytherapy within University of Kentucky or from outside centers developed biochemical failure and had no evidence of metastases. Computed tomography (CT) scans were evaluated; patients who had an underseeded portion of their prostate were considered for reimplantation. *Results*. The majority of the patients in this study (61.9%) were low risk and median presalvage PSA was 3.49 (range 17.41–1.68). Mean follow-up was 61 months. At last follow-up after reseeding, 11/21 (52.4%) were free of biochemical recurrence. There was a trend towards decreased freedom from biochemical recurrence in low risk patients ($p = 0.12$). International Prostate Symptom Scores (IPSS) increased at 3-month follow-up visits but decreased and were equivalent to baseline scores at 18 months. *Conclusions*. Salvage brachytherapy after primary brachytherapy is possible; however, in our experience the side-effect profile after the second brachytherapy procedure was higher than after the first brachytherapy procedure. In this cohort of patients we demonstrate that approximately 50% oncologic control, low risk patients appear to have better outcomes than others.

## 1. Introduction

The use of interstitial brachytherapy with permanent seed implantation is a well-established means of treating localized prostate cancer [1, 2]. Permanent interstitial brachytherapy for prostate cancer patients involves the insertion of radioactive seeds (containing $^{125}$I, $^{103}$Pd, or $^{131}$Cs), encased in titanium shells, into the prostate gland. Benefits of this treatment modality include a single procedure rather than weeks of daily external beam radiation therapy (EBRT) and equivalent oncologic control for low and intermediate risk disease [1]. Other studies have shown superior quality of life regarding sexual function and urinary bother scores for prostate seed implant compared to prostatectomy [3].

Unfortunately, up to as high as 10% to 15% of men may experience prostate-specific antigen (PSA) failure in five to ten years after interstitial brachytherapy for clinically localized prostate cancer [2, 4]. Some of these men will harbor a component of micrometastatic disease at the time of PSA failure, but a significant number will have a true local-only recurrence and potentially can be cured with a salvage local therapy. Currently, there is no consensus regarding the optimal management of patients who are believed to have a local-only recurrence after prostate radiotherapy. Palliative management options include androgen deprivation therapy or expectant management. A number of salvage therapies with curative intent have also been assessed including cryotherapy, EBRT, high-intensity focused ultrasound (HIFU), brachytherapy, and radical prostatectomy [5, 6].

Data on salvage brachytherapy after primary brachytherapy is extremely limited. Much of the data in the current literature comes from patients that were included in cohorts

of patients treated with primary radiation therapy with the majority of patients undergoing EBRT. To our knowledge, there are only 2 studies that evaluate salvage brachytherapy for patients who were initially treated with brachytherapy, one in 1990 [7] in the pre-PSA era and one in 2003 [8]. In this single center review of 21 patients, we describe our experience with salvage brachytherapy for prostate cancer patients with biochemical recurrence after primary brachytherapy focusing on oncologic and functional outcomes.

## 2. Methods and Materials

From July 2001 until February 2012, we reviewed the records of all patients who underwent salvage reimplantation at our center. During this time frame 21 patients underwent a repeat brachytherapy procedure. Of the 21 patients in this analysis, 3 had a biopsy before the repeat brachytherapy procedure and the remainder did not. Of these 21 patients, 14 had their initial brachytherapy procedure performed at the University of Kentucky (UK). One of the patients initially treated at UK was found to have poor coverage at the one-month postimplant CT evaluation and subsequently had a planned reimplantation. The other 13 patients initially treated at UK had adequate postimplant dosimetry; years later they developed a rising PSA. The remaining 7 men in this cohort had their initial brachytherapy procedure at other institutions. One of these 7 patients underwent open brachytherapy procedure in 1984 and many years later developed a rising PSA. Thus, of the patients in this cohort 20 of 21 patients had an acceptable brachytherapy procedure and were later identified as having a biochemical failure defined by either the ASTRO criteria or Phoenix criteria [9]. D'Amico criteria were used to stratify risk category [10]. All patients who met the criteria for biochemical failure had a bone scan and a computed tomography (CT) scan of the abdomen and pelvis to rule out evidence of metastasis. The pelvic CT scan was also evaluated by radiation oncology and urology faculty to assess brachytherapy seed placement within the prostate. If both radiation oncology and urology faculty clinically agreed that a 3-dimensional volume of the prostate was underseeded from the initial brachytherapy procedure and the scans revealed no evidence of metastases, those patients were considered for a brachytherapy salvage procedure. If the prostate appeared to be well seeded with no gaps or evidence of metastasis the patient was excluded from a second brachytherapy procedure. There were no other exclusion criteria, with no restrictions on presalvage PSA or International Prostate Symptom Score (IPSS) survey results.

A preplanning TRUS volume study was performed, and target volumes were outlined by a radiation oncologist with urology collaboration. The target volume to receive radioactive seeds only included the underseeded portion of the prostate with a small margin, of 2 mm. In addition, care was taken to keep the urethral doses low; our goal was to keep the urethral dose to no more than that of the prescribed dose. BrachyVision software was utilized for brachytherapy planning. Sample planning scans are shown in Figure 1(a). All patients were treated using $^{125}$I seeds, and the prescribed dose ranged from 108 Gy to 144 Gy (Table 1). When the dosimetric plan was completed, stranded seeds were purchased from a vendor (IsoAid) and the patient returned for implant in approximately 2 weeks.

Epidural anesthesia was administered and patients were placed in the dorsal lithotomy position. A urethral catheter was inserted and instilled with ultrasonic contrast (surgical lubricant with air bubbles) to visualize the urethra. A TRUS probe was placed into the rectum, and the ultrasound images were matched to the preplanned images acquired in the same manner. When the real-time images of the prostate matched the preplan images, the needles carrying the radioactive seeds were inserted and the seeds were placed. Representative postoperative CT images showing seed distribution after reimplantation with and without reimplant isodose distributions are shown in Figure 1(b).

Androgen deprivation therapy (ADT) was concurrently administered at the discretion of the treating physician. Three of 21 (14.3%) patients received one 3-month injection of Lupron along with their salvage brachytherapy. Two of these patients ultimately had biochemical failure after their reseeding.

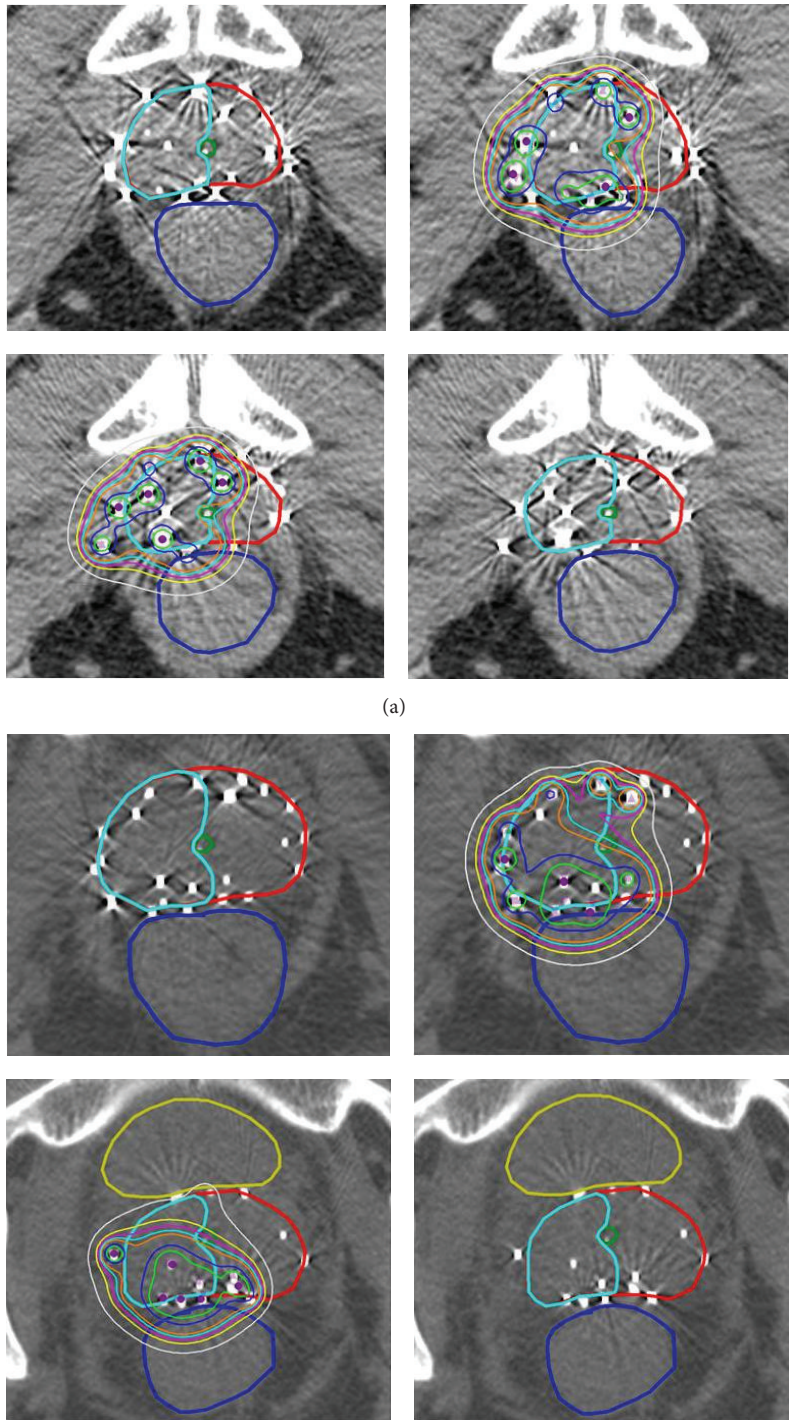
Patients were followed up in a multidisciplinary urologic oncology clinic by both urology and radiation oncology faculty. PSA values were obtained and patients were questioned regarding potential treatment related toxicity. Lower urinary tract symptoms were evaluated and categorized by their IPSS, which were self-reported by the patients immediately prior to each appointment. Patients were also questioned about gastrointestinal complaints and other concerns and scored according to the RTOG acute and late toxicity criteria.

Summary statistics such as median and range values were calculated for patient characteristics and disease outcomes. Kaplan-Meier curves and Wilcoxon tests were used to evaluate the association between time to biomedical failure and patient categorical characteristics. Paired two-sample $t$-tests were used to determine the statistical significance of differences in a continuous variable between two different measurement times. Fisher's exact tests were used to determine the statistical significance of differences in binary outcomes between two patient groups. Significance was considered using a two-sided $p$ value $<0.05$. Statistics were carried out using Microsoft Excel, SAS version 9.2, and R version 3.0.1.

## 3. Results

Radiation dosing utilized for the salvage therapy in this study is summarized in Table 1. At initial diagnosis of patients in this study, 3 of 21 (14.3%) patients received EBRT with their initial brachytherapy. One of 21 (4.7%) patients underwent open brachytherapy seed placement as his initial brachytherapy. Risk categories were determined based on initial PSA, Gleason score, and initial clinical stage. Thirteen of 21 (61.3%) patients were low risk, and 6 of 21 (28.6%) patients were intermediate risk; 7of 21 (33.3%) patients had initial brachytherapy at other institutions and had incomplete information to adequately calculate their risk category.

Mean presalvage PSA was 3.49 (median 3.6, range 17.41–1.68). PSA dynamics for individual patients during the study



(a)

(b)

Figure 1: (a) Sample brachytherapy planning scans using BrachyVision software. (b) CT images showing seed distribution after reimplantation with and without reimplant isodose distributions.

are shown in Table 2. Mean follow-up was 61 months. Median nadir was 0.7 ng/mL (range 2.97–0.01 ng/mL) and median time to nadir was 15 months. All men undergoing a salvage brachytherapy procedure demonstrated an initial decline in their serum PSA. Median time to biochemical failure (according to the Phoenix criteria) of the men failing the second implant was 25 months (range 11–71 months).

*3.1. Toxicity.* A few patients experienced adverse outcomes following salvage brachytherapy during our study period.

Table 1: Radiation dosing.

| Patient # | Age at initial treatment (yr) | Prostate cancer risk strata[@] | ADT with BRT #1 | ADT with BRT #2 | Initial dose | Time b/w Rx (mo) | Salvage dose | Volume treated (cc) |
|---|---|---|---|---|---|---|---|---|
| 1[≠] | 57 | Low | No | No | 115 Gy | 38 | 144 Gy | 21.55 |
| 2 | 61 | Low | No | No | 144 Gy | 32 | 144 Gy | 13.23 |
| 3 | 65 | Low | No | Yes | 144 Gy | 26 | 144 Gy | 7.56 |
| 4 | 63 | Intermediate | No | No | 144 Gy | 34 | 144 Gy | 9.98 |
| 5 | 59 | Low | No | No | 144 Gy | 26 | 108 Gy | 21.58 |
| 6[≠] | 50 | Low | No | Yes | 115 Gy | 67 | 108 Gy | 26.66 |
| 7 | 48 | x | No | No | x | 287 | 108 Gy | 21.31 |
| 8 | 60 | Low | No | No | 144 Gy | 123 | 108 Gy | 6.84 |
| 9 | 55 | Low | Yes | No | 144 Gy | 120 | 108 Gy | 7.76 |
| 10 | 57 | Low | No | No | 144 Gy | 19 | 120 Gy | 23.78 |
| 11 | 48 | Low | Yes | No | 144 Gy | 25 | 125 Gy | 16.03 |
| 12 | 66 | Low | No | No | 144 Gy | 46 | 108 Gy | 18.16 |
| 13 | 44 | Low | No | No | 144 Gy | 31 | 144 Gy | 12.05 |
| 14 | 50 | Intermediate | No | No | 144 Gy | 87 | 144 Gy | 15.51 |
| 15[*] | 66 | Intermediate | Yes | No | 108 Gy | 42 | 108 Gy | 8.1 |
| 16 | 71 | Intermediate | No | No | 144 Gy | 45 | 108 Gy | 29.36 |
| 17[*] | 63 | Intermediate | No | Yes | 108 Gy | 48 | 108 Gy | 9.74 |
| 18[**] | 42 | x | Yes | No | x | 50 | 120 Gy | 12.94 |
| 19[*] | 58 | Intermediate | Yes | No | 108 Gy | 105 | 108 Gy | 8.67 |
| 20 | 59 | Low | Yes | No | 144 Gy | 48 | 144 Gy | 27.31 |
| 21 | 72 | Low | Yes | No | 140 Gy | 21 | 140 Gy | 19.93 |

[*] Patients who underwent initial external beam radiation therapy.
[**] Patients who underwent initial open brachytherapy.
[≠] Patients who had palladium-103 seeds for initial brachytherapy.
x = data point not known.
ADT = androgen deprivation therapy; BRT = brachytherapy.
@ = D'amico risk strata [10].

Two patients experienced Clavien grade I urinary incontinence; one patient experienced each of the following: Clavien grade IIIb bladder neck contracture, rectourethral fistula, and leiomyosarcoma.

Figure 2 depicts urinary tract toxicity obtained from IPSS questionnaires. As expected, IPSS scores increased from a median of 7 to a median of 23 at 3 months following therapy ($p < 0.0001$). Median IPSS dropped to 11 at 9 months ($p = 0.0005$). IPSS continued to decrease at 18 months with a median of 5, which was not significantly different from baseline ($p = 0.294$).

Two of 21 (9.6%) patients developed de novo urinary incontinence, and 1 of 21 (4.8%) developed a rectourethral fistula. One of 21 (4.8%) patients developed bladder outlet obstruction secondary to fibrosis, requiring endoscopic correction (transurethral incision of bladder neck). One patient developed a leiomyosarcoma that ultimately required cystoprostatectomy but had biochemical control of prostate cancer.

Table 3 summarizes changes in sexual function during the study. Eleven of 21 (52.3%) patients had sufficient data to compare pre- and posttherapy sexual function. Six of 11 (54.5%) patients had stable sexual function, and 5 of 11 (45.5%) had decreased sexual function.

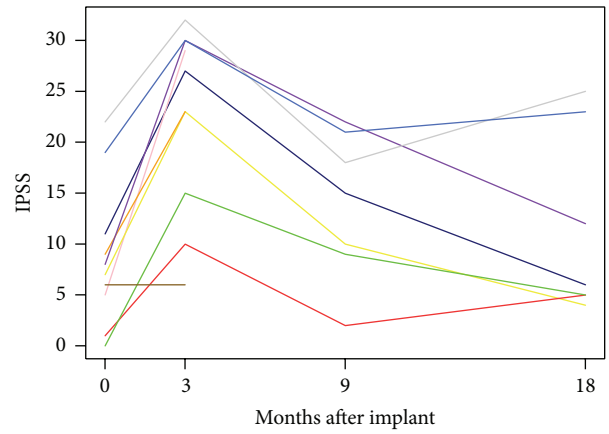



Figure 2: IPSS scores throughout follow-up after salvage brachytherapy.

*3.2. Time to Failure.* The mean decrease in PSA was 4.5 ng/dL (median 3.4, range 0.3–15.0) after salvage brachytherapy. At the time of analysis, 11 of 21 (52.4%) patients had not experienced biochemical recurrence with a mean follow-up of 61 months. Figure 3 shows a Kaplan-Meier curve for time

Table 2: PSA dynamics.

| Patient # | Age at initial treatment (yrs) | Time between 1st and 2nd Brachytherapy (mo) | Pre-salvage PSA (ng/mL) | Presalvage PSA (ng/dL) | Follow-up (mo) | Time to nadir (mo) |
|---|---|---|---|---|---|---|
| 1 | 57 | 38 | 6.3 | 3.6 | 149 | 21 |
| 2 | 61 | 32 | 5.3 | 3.6 | 132 | 31 |
| 3 | 65 | 26 | 4.5 | 4.4 | 86 | 73 |
| 4 | 63 | 34 | 10 | 2.5 | 111 | 6 |
| 5 | 59 | 26 | 4.9 | 2.7 | 119 | 10 |
| 6 | 50 | 67 | 8 | 14.9 | 83 | 10 |
| 7 | 48 | 287 | x | 8.6 | 34 | 22 |
| 8 | 60 | 123 | 7.2 | 17.41 | 10 | 9 |
| 9 | 55 | 120 | 6.3 | 1.53 | 67 | 7 |
| 10 | 57 | 19 | 5.3 | 3.49 | 49 | 48 |
| 11 | 48 | 25 | 6.93 | 2.77 | 41 | 41 |
| 12 | 66 | 4 | 4.7 | 1.86 | 15 | 4 |
| 13 | 44 | 31 | 8.7 | 2.41 | 41 | 29 |
| 14 | 50 | 87 | 7.4 | 7.3 | 39 | 33 |
| 15 | 66 | 42 | 19.1 | 1.68 | 52 | 9 |
| 16 | 71 | 45 | 6.4 | 3.11 | 40 | 5 |
| 17 | 63 | 48 | 8.2 | 13.8 | 49 | 3 |
| 18 | 42 | 50 | 1 | 0.98 | 40 | 41 |
| 19 | 58 | 105 | x | 11.58 | 52 | 17 |
| 20 | 59 | 48 | 5.7 | 4.24 | 25 | 7 |
| 21 | 72 | 21 | 5.8 | 3.1 | 21 | 15 |
| Mean | **57.8** | **62.9** | **6.9** | **5.5** | **61.4** | **20.9** |
| Median | **59.0** | **45.0** | **6.3** | **3.5** | **49.0** | **15.0** |
| SD | **8.4** | **60.2** | **3.5** | **4.9** | **37.9** | **18.3** |
| *n* | **21** | **21** | **19** | **21** | **21** | **21** |

x = data point not known.

to biochemical recurrence based on initial risk category. For the men that failed a second brachytherapy procedure, the median time to failure was 25 months, with a range of 11 to 71 months. There was a trend towards increased time to biochemical failure in the low risk group compared to the intermediate risk group (47 months versus 27 months, $p = 0.12$).

## 4. Discussion

Prostate cancer patients who experience biochemical failure after initial radiotherapy have a number of options for subsequent treatment: observation, androgen deprivation therapy, salvage radical prostatectomy, salvage cryotherapy, high-intensity focused ultrasound (HIFU), and additional radiotherapy. Salvage therapy is extremely important to control locally recurrent disease and prevent metastases, as lack of further treatment after biochemical recurrence is correlated with the development of clinical disease within 5 years in up to 75% of patients [11].

Biochemical disease-free survival rates of 55–61% at 5-year follow-up have been reported with salvage radical prostatectomy. These were relatively small series with 42, 100, and 138 patients [12–14]. Surgical intervention is even able to achieve a 51% disease-free survival rate at 5-year follow-up in patients with a Gleason score of 8 or higher [15, 16]. However, there are a number of drawbacks to this technique as well. It can be a technically challenging procedure due to residual irradiated tissue damage with increased risk of a number of major complications. Up to 40% of patients are afflicted with urinary incontinence and 25% suffer from bladder neck stricture following this intervention [17]. The risk of rectal injury is 2–9% and urinary fistula is <4% [18].

On the other hand, salvage cryotherapy after initial radiation is a minimally invasive option with improved efficacy, especially following the development of modern techniques to combat issues such as incomplete freezing of tissue. One study reported biochemical disease-free survival, defined as PSA <0.5 ng/mL, at 73% for low risk patients, 45% for intermediate risk patients, and 11% for high risk patients after a median 33.5-months follow-up and actuarial projection of 60 months [19]. Salvage cryotherapy may be a less challenging procedure to perform than salvage radical prostatectomy, giving it minimal variation in outcome across

Table 3: Erectile function.

| Patient # | Age (yrs) | Baseline ED | 18 mo f/u |
|---|---|---|---|
| 1 | 57 | 1 | 2 |
| 2 | 61 | 1 | 2 |
| 3 | 65 | 1 | 3 |
| 4 | 63 | 1 | 2 |
| 5 | 59 | 2 | x |
| 6 | 50 | 3 | x |
| 7 | 48 | 1 | 1 |
| 8 | 60 | 1 | 2 |
| 9 | 55 | 3 | x |
| 10 | 57 | x | x |
| 11 | 48 | x | x |
| 12 | 66 | 2 | 2 |
| 13 | 44 | 2 | 2 |
| 14 | 50 | 3 | 3 |
| 15 | 66 | x | 2 |
| 16 | 71 | 2 | x |
| 17 | 63 | 3 | x |
| 18 | 42 | 3 | 3 |
| 19 | 58 | 2 | 2 |
| 20 | 59 | 3 | x |
| 21 | 72 | 1 | x |

1 = no difficulty with erection.
2 = erectile function, but not significant enough for penetration.
3 = impotent.
x represents missing data.

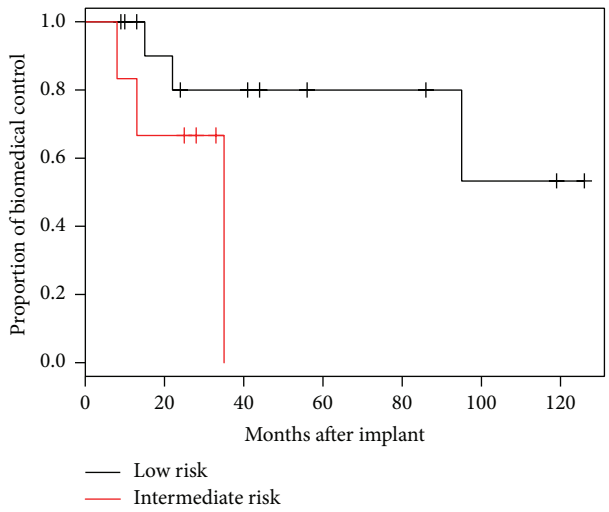



Figure 3: Effect of initial risk category on risk of biochemical recurrence.

health providers [20]. In addition, the reported rates of complication are low enough to make it an attractive option for older patients, with urinary incontinence affecting less than 10% of patients [20, 21]. Cryosurgical ablation of the whole prostate gland has also been strongly associated with impotence. Focal cryoablation techniques may limit this adverse effect by relying on targeted image-guided biopsy to guide therapy towards undertreated areas or areas of recurrence, decreasing morbidity [22].

Salvage HIFU has also been studied as a treatment for locally recurrent prostate cancer following external beam radiation therapy (EBRT) only. In a study of 167 European patients, the biochemical disease-free survival was 53%, 42%, and 25% for low, intermediate, and high risk patients, respectively [23]. While the rate of metastatic disease development in this cohort of patients was comparable to that seen in patients treated with other salvage therapies, the complication rate was remarkably low, especially with regard to urinary incontinence and bladder outlet obstruction. Another European study showed that the rate of bladder outlet obstruction decreased from 30% to 15% while the rate of surgical intervention for urinary incontinence decreased from 15% to 5% [24]. Salvage HIFU, however, is not recommended for patients who had initial brachytherapy due to the reflective capacity of the implants, which can redirect excess energy onto surrounding structure such as the rectum and urethra [25].

In recent years, single center brachytherapy studies have shown up to 75% biochemical disease-free survival at 4 years with permanent brachytherapy [17, 26]. In low risk patients who underwent EBRT alone, one recent study showed a biochemical disease control percentage of 85.6% after 5 years [27]. High dose rate (HDR) brachytherapy is now being used as a more customizable form of dosage for patients [28, 29]. However, these doses could cause further toxicity to irradiated damaged tissue and were found in two studies to cause grade 2 urethral strictures in 71% of patients [28, 30]. One prospective study that used MRI-guided seed placement rather than TRUS guidance found that this method was able to keep the incidence of gastrointestinal and genitourinary toxicity requiring surgical treatment at 15% in 4 years [17]. They also found that toxicity was decreased in men who had longer than 4.5-year interval between radiation therapies.

Data on salvage brachytherapy following primary brachytherapy, however, is limited. Studies usually mix patients that were treated with primary brachytherapy with those who initially underwent EBRT. One study from 1990 reported outcomes of salvage brachytherapy seed implantation in 13 patients after initial brachytherapy treatment [31]. Recurrence in this study was detected by digital rectal examination and confirmed with prostate biopsy. A study by Grimm et al. [32] showed that of 31 patients who were reimplanted with seeds for salvage brachytherapy after initial brachytherapy, 87% had biochemical disease control at 31 months using the ASTRO criteria. Interestingly, all but one of these patients underwent 3 months of ADT at the time of salvage brachytherapy. Twenty of 31 (64.5%) of these patients had local recurrence within the prostate, and 11of 31 (35.5%) had disease within the seminal vesicles. Eleven of 31 (35.5%) patients were treated with salvage therapy within 24 months of their primary therapy, and 20 of 31 (64.5%) were treated more than 24 months after their initial therapy. In light of these results, treatment of local recurrence of prostate cancer after initial brachytherapy is an area of evolving interest.

In our series, we show 52.4% freedom from biochemical recurrence with a mean follow-up of 61 months. These data

are not as efficacious as those in the Koutrouvelis series, perhaps due to the longer follow-up in our series. It is also possible that 3 months of ADT with salvage brachytherapy led to their superior results, though, in our small subset of patients who received ADT with their salvage therapy, two-thirds of patients had biochemical recurrence during our study. Alternatively, this finding in our study could be due to a selection bias by the treating physician based on the individual patients' risk factors.

When it comes to selecting any salvage therapy modality, accurately characterizing the presence, location, and extent of cancer recurrence in an individual is paramount. Improved cancer targeting and staging techniques significantly improve the risk-benefit ratio for patients with low and intermediate risk disease by allowing physicians to remove malignancy while preserving as much normal tissue and anatomy as possible [33]. In one study, however, the widely used 12-core TRUS biopsy technique was only able to predict unilateral prostate cancer in less than 30% of cases, making it less effective at choosing patients for focal therapy [34]. Instead, using a transperineal template-guided mapping biopsy (TTMB) technique provides better access to the apical and anterior portions of the prostate where up to one-third of significant cancer is located [35, 36]. A recent study used TTMB with multiparametric MRI to assess their combined ability to detect clinically significant cancer, defined as Gleason 6 with tumor length over 3 mm and any Gleason 7 and above [37]. The result of the combined testing was a positive predictive value of 83% and negative predictive value of 91%, which reliably demonstrates the ability to rule out clinically significant prostate cancer [37]. In light of a rising PSA, the negative predictive value of these additional criteria would be helpful in focusing salvage therapy towards patients with clinically significant disease [38].

Alternatively, metabolic imaging offers a less invasive method of detection of both localized and systemic tumor burden. The available literature varies with regard to the optimal PSA value at which to initiate $^{18}$F-Choline PET/CT imaging, but there appears to be a strong correlation between increasing PSA values and the positive predictive ability of this tool [39]. In one study of 250 prostate cancer patients with biochemical recurrence, $^{18}$F-Choline PET/CT showed 77% sensitivity for cancer detection at a PSA level greater than 0.3 ng/mL and had a particularly high sensitivity in patients treated with ADT as compared to those who did not receive ADT [40].

Our study has several key limitations that warrant discussion. It is a retrospective, nonrandomized study with inherent selection and treatment biases. Patients were treated with salvage therapy based on biochemical recurrence alone, analogous to the delivery of salvage external radiation therapy for a recurrence following a radical prostatectomy. Therefore, the majority of patients did not undergo TTMB or repeat TRUS biopsy prior to salvage therapy, leaving the possibility that their pathology was different from that of their original prostate biopsy and skewing their presalvage risk stratification. Follow-up was not standardized, leading to incomplete data on erectile function, lower urinary tract symptoms, and GI toxicity. Finally, while all patients underwent primary brachytherapy prior to their salvage brachytherapy, the cohort remains somewhat heterogeneous. Three of 21 (14.3%) patients underwent EBRT with their primary brachytherapy. Seven of 21 (33.3%) patients had ADT with primary therapy and 3 of 21 (14.3%) had ADT with their salvage brachytherapy. One of 21 (4.7%) patients had open brachytherapy seed placement as initial treatment.

Salvage brachytherapy is an intriguing treatment option for patients with biochemically recurrent prostate cancer who underwent primary brachytherapy. In our study, this modality appears to provide adequate prostate cancer control in select men with underseeded areas on cross-sectional imaging. There is a trend towards decreased efficacy of salvage brachytherapy in patients who were intermediate risk at initial presentation. Side effects of treatment are higher than expected with a single brachytherapy implantation; out of 21 patients 3 individuals developed grade 3 toxicities. The majority of lower urinary tract symptoms resolve within 9 months of treatment and minimal gastrointestinal side effects. Further studies are warranted to compare this treatment modality to other salvage therapies in patients who underwent primary brachytherapy. Further studies would perhaps be made more meaningful by utilizing more advanced methods to evaluate for location of the recurrence within or beyond the prostate. Technologies have emerged which may be beneficial in better selecting patients for salvage brachytherapy. For example, methods such as transperineal mapping, multiparametric MRI, and/or $^{18}$F-Choline PET/CT scans may make partial prostate implants more successful by better localization of the recurrent disease. However, we are unaware of any of these new technologies being used to select patients for salvage prostate brachytherapy. Metabolic imaging using PET/CT likely will increase the detection of metastatic prostate cancer [41] thereby better selecting a population that could benefit from the added brachytherapy procedure.

## Abbreviations

CT: Computed tomography scan
PSA: Prostate-specific antigen
TRUS: Transrectal ultrasound
IPSS: International Prostate Symptom Score
EBRT: External beam radiation therapy
HIFU: High-intensity focused ultrasound
ADT: Androgen deprivation therapy
MRI: Magnetic resonance imaging
HDR: High dose rate
GI: Gastrointestinal
GU: Genitourinary
TTMB: Transperineal template-guided mapping biopsy.

## Additional Points

In this project, the authors describe the eleven years of experiences at a single institution of salvage therapy in prostate cancer patients with biochemical failure and no evidence

of metastatic disease after interstitial brachytherapy. Images from the CT scans were evaluated by radiation oncology and urology faculty. Patients with underseeded areas on the CT images were considered for reimplantation with I-125 interstitial brachytherapy; 21 patients were reimplanted. Our results indicated that the salvage brachytherapy to underseeded areas after primary brachytherapy in patients with biochemical recurrence can be a successful procedure.

## Competing Interests

The authors declare that they have no competing interests.

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*Review Article*

# Prostate Radiotherapy in the Era of Advanced Imaging and Precision Medicine

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Tremendous technological advancements in prostate radiotherapy have decreased treatment toxicity and improved clinical outcomes for men with prostate cancer. While these advances have allowed for significant treatment volume reduction and whole-organ dose escalation, further improvement in prostate radiotherapy has been limited by classic techniques for diagnosis and risk stratification. Developments in prostate imaging, image-guided targeted biopsy, next-generation gene expression profiling, and targeted molecular therapies now provide information to stratify patients and select treatments based on tumor biology. Image-guided targeted biopsy improves detection of clinically significant cases of prostate cancer and provides important information about the biological behavior of intraprostatic lesions which can further guide treatment decisions. We review the evolution of prostate magnetic resonance imaging (MRI) and MRI-ultrasound fusion-guided prostate biopsy. Recent advancements in radiation therapy including dose escalation, moderate and extreme hypofractionation, partial prostate radiation therapy, and finally dose escalation by simultaneous integrated boost are discussed. We also review next-generation sequencing and discuss developments in targeted molecular therapies. Last, we review ongoing clinical trials and future treatment paradigms that integrate targeted biopsy, molecular profiling and therapy, and prostate radiotherapy.

## 1. Introduction

Prostate cancer is the most common solid organ malignancy in American men with an estimated 220,800 newly diagnosed cases and projected 27,540 deaths for the year 2015 [1]. Prostate cancer screening was originally performed via the digital rectal exam (DRE). While still routinely performed and an important factor in risk stratification, the DRE is a limited screening tool as it bears subjectivity and primarily detects larger palpable lesions in the posterior prostate through the rectal vault. In fact, studies examining the utility of DRE in prostate cancer screening fail to demonstrate a reduction in cancer specific mortality in any age group [2]. In the 1980s, prostate specific antigen (PSA) and the transrectal ultrasound (TRUS) revolutionized the screening process for prostate cancer. Using PSA as a screening tool, the incidence of prostate cancer more than doubled from the 1970s to the 1990s. Ever-changing absolute PSA thresholds, age adjusted PSA thresholds, and PSA dynamic parameters have been used to trigger TRUS-guided biopsy.

The current method of using DRE, PSA, and TRUS biopsy to determine treatment has come under scrutiny. While the incidence of prostate cancer has risen with this screening algorithm, cases of clinically significant disease still go unrecognized and there is concern for overtreatment of more indolent, clinically insignificant cancers as current methods are not able to effectively detect patients who would render a survival benefit from definitive treatment [3, 4]. Furthermore, this screening process carries significant risk of infectious complications with antibiotic resistant organisms as well as downstream costs of treatment and treatment-related side effects and complications [5]. These problems

have prompted search for alternative, more effective methods of screening for clinically significant prostate cancer.

## 2. Advances in Prostate Cancer Detection and Biopsy

*2.1. Evolution of Multiparametric MRI in Prostate Cancer Detection.* In the 1990s, clinicians began using magnetic resonance imaging (MRI) as a tool for staging men diagnosed with prostate cancer. The primary utilization of MRI at that time was identification of extracapsular extension and seminal vesicle invasion because early techniques poorly visualized intraprostatic lesions [5, 6]. The addition of an endorectal coil improved the signal-to-noise ratio of prostate MRI allowing for higher resolution T2-weighted (T2W) imaging and enhanced delineation of the prostatic capsule. Improved technology made MRI increasingly useful in identifying and characterizing lesions within the prostate as well as detecting local disease recurrence following primary definitive treatment [7, 8]. An early apparent advantage of MRI was preferential detection of high-risk features in large or more aggressive tumors compared to low grade tumors.

On T2W MRI, hypointense intraprostatic lesions correlate well with cancerous foci found in radical prostatectomy specimens. Similarly, these tumor foci also tend to preferentially enhance dynamic contrast enhanced (DCE) MRI series. The development of magnetic resonance spectroscopic imaging (MRSI), a functional study that detects relative levels of choline and citrate within tumors, adds to the specificity of MRI for intraprostatic lesions [8]. Diffusion-weighted imaging (DWI) is also useful in detecting prostate cancer. Quantitative evaluation of DWI with calculated apparent diffusion coefficient (ADC) values correlates with Gleason grade, making it applicable in risk stratification [9]. Combining MRI modalities, including T2W, DCE, and DWI, improves visualization and accurate detection of intraprostatic lesions. Furthermore, MRI improves the ability to detect central and anterior prostate cancers that are not routinely sampled on standard TRUS biopsies [10, 11].

The inclusion of multiple MRI parameters is known as multiparametric MRI (mpMRI). Overlapping modalities in the mpMRI approach corrects for deficiencies inherent in any individual sequence. The use of 2 or more parameters improves the accuracy of detection and localization of prostate cancer [12–15]. Combining the functional characteristics of different modalities also differentiates between low and intermediate/high-grade disease [16–18]. Increased utilization of mpMRI to detect and diagnose prostate cancer could lead to a decrease in biopsy and treatment utilization of patients with clinically insignificant disease.

While mpMRI provides valuable anatomic information that often correlates with high-risk histopathology, tissue diagnosis is still essential and remains the gold standard for diagnosing prostate cancer. Recent technological advances have allowed for the integration of mpMRI with ultrasound guided biopsies and this is currently being evaluated as a potential alternative or supplement to the standard TRUS biopsy. Three approaches have emerged that use mpMRI for guiding prostate biopsies including direct "in-bore" MRI biopsies, cognitive fusion, and MRI-TRUS fusion-guided biopsy [19].

*2.2. MRI "In-Bore" Guided Biopsy.* Initial studies using mpMRI to guide biopsy performed the biopsy under direct visualization in the MRI gantry. The patient first gets a diagnostic mpMRI and returns for biopsy if suspicious lesions are identified. Upon return, biopsies of the lesions are obtained under direct visualization using serial MRI scans to confirm biopsy needle placement. Advantages of this method are that only visualized lesions are biopsied, which decreases the total number of biopsies the patient receives, and this allows for precise documentation of biopsy needle locations [20–22]. The disadvantages of this technique are cost and patient tolerance. The closed magnetic environment requires the use of nonmagnetic needles and other supplies which are expensive and limit accessibility should a patient need immediate intervention. There have been a limited number of studies recording the utility of direct in-bore biopsies. One notable study performed by Hambrock et al. compared mpMRI with a 10-core TRUS and found that in-bore MRI-guided biopsies performed significantly better than TRUS-guided biopsies in predicting final pathology after radical prostatectomy (88 versus 55%, $p = 0.001$) [23].

*2.3. Cognitive Fusion Biopsy.* Cognitive fusion biopsy is the simplest method of combining mpMRI and prostate biopsy. The urologist reviews previously acquired mpMRI images and then biopsies the general location of suspicious MRI lesions using the standard TRUS biopsy technique. The advantage of cognitive fusion biopsy is that it requires no additional equipment or cost, making it most easily adaptable to current practice models. The main disadvantage is strong operator dependency in correlating static MRI findings with dynamic real-time ultrasound findings. Cognitive fusion biopsy also lacks the ability to archive the exact location of the biopsy which could be important for focal therapy or surveillance purposes. Despite these potential shortcomings, the use of cognitive fusion biopsies increases prostate cancer detection and more accurately depicts overall disease burden in high-grade disease [24, 25]. Specifically, one study demonstrated prostate cancer detection rates up to 10% higher (15% for high-grade disease) with cognitive fusion biopsy compared to systematic biopsies in a similar population of patients [26].

*2.4. MRI-TRUS Fusion Biopsy.* The newest and most promising form of MRI-targeted prostate biopsy is the fusion of mpMRI with real-time TRUS imaging with postimage processing and software technology. In MRI-TRUS fusion biopsy, a diagnostic mpMRI is used to localize the tumor and a specialized software program fuses these images to a real-time TRUS image seen in the biopsy suite. An important practical advantage of MRI-TRUS fusion biopsy is that the MRI and the TRUS do not have to be physically or temporally linked. MRI data is transferred to one of several models of fusion software enabled 3D-TRUS units that can be located in a standard ultrasound suite. After upload, images of the

prostate are remodeled using identification of landmarks (e.g., points, curves, and surfaces) that are present on both the MRI and TRUS platform. Since the prostate on MRI (with or without an endorectal coil) often differs in shape and contour from the same image on TRUS, the superimposed image must be transformed before successful fusion can occur. This is done through either an elastic or rigid transformation or a combination of both fusion algorithms. These images are shown as either a side-by-side display of the MRI and TRUS images or a single fused image allowing for targeted biopsy of the predelineated regions of interest from the diagnostic mpMRI on the real-time TRUS after fusion. The fusion enabled 3D-TRUS contains a tracking method that fixes the prostate in a 3D coordinate system so that movements of the US probe are mirrored on the fused MRI display. While this method appears to be less operator dependent, there is still need for operator input to assess and adjust altered gland contours or misregistration artifacts.

The data supporting the use of MRI-TRUS fusion biopsy is promising. Puech et al. compared the effectiveness of standard 12-core biopsy and MRI-TRUS fusion biopsy and found that fusion biopsy detected 10% more prostate cancer overall and 15% more clinically significant prostate cancer [26]. In the diagnostically challenging patient population of men with negative standard biopsies and elevated PSA, fusion biopsy detects 40% more clinically significant cancers but just 15% of clinically insignificant cancers compared to repeat standard biopsy [27]. Siddiqui et al. compared standard sextant TRUS biopsy, fusion biopsy, and combined biopsies. Out of 1003 patients, MRI-TB diagnosed 461 cases of prostate cancer and standard biopsy diagnosed 469. Among these, fusion biopsy diagnosed 30% more high-risk cancers and 17% fewer low-risk cancers compared to standard biopsy. In the 170 patients who went on to receive prostatectomies, fusion biopsy was more accurate (73%) than standard (59%) or the 2 combined (69%) in diagnosing intermediate- to high-risk disease [28]. These results have been replicated in several studies and suggest that MRI-TRUS fusion biopsy is superior to standard TRUS biopsy in detecting clinically significant disease and excluding insignificant disease, and it will play a prominent role in the future of the prostate cancer diagnosis and surveillance [29–32].

## 3. Prostate Radiotherapy Advances

Radiation therapy has been a mainstay in the treatment of prostate cancer since the 1960s with the development of high-energy teletherapy units and linear accelerators. Shortly thereafter, interstitial prostate brachytherapy became a primary treatment modality for organ-confined prostate cancer. Major advances in diagnostic imaging since that time have dramatically improved the ability to accurately target the prostate with smaller and smaller treatment volumes. This, in turn, led to better toxicity profiles, safe dose escalation, and improved disease control [33–39]. More recently, on-board imaging devices used to image the prostate during treatment have led to further increase in dose delivered per treatment and an associated decrease in total treatment duration. Trends toward earlier diagnosis during the PSA screening era have led to detection of more focal and smaller volume disease within the prostate. In an effort to deintensify treatment and avoid adverse effects in these patients, focal ablative techniques have been used to target only intraprostatic lesions as opposed to traditional treatment of the whole gland. Furthermore, in the era of precision medicine, advances in our understanding of cancer biology have led to genomic tests that describe the biological behavior of tumors and their risks for adverse outcomes. These tests allow the clinician to personalize prostate cancer therapy when combined with existing techniques.

*3.1. Radiation Dose Escalation.* The evolution of external beam radiation techniques and advanced imaging techniques has allowed for increasingly focal radiation therapy with margins around the prostate as small as 5 mm when using standard fractionation schemes [33]. Significant reduction in margins around the prostate, and thus volume of irradiated normal tissue, has been made possible by the use of daily on-board (cone-beam computed tomography) imaging prior to each treatment delivery [34]. Historically, the prostate was treated with four static radiation fields targeting a generous pelvic volume based on anatomic landmarks. With advancements in imaging, more focal three-dimensional treatment plans were developed to target the prostate and seminal vesicles only. Further advances in radiation delivery techniques such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) led to greater sparing of adjacent normal tissue to reduce toxicity. Lastly, on-board imaging has allowed daily localization of the prostate and/or fiducial markers to further narrow target volume margins. Improved accuracy and organ avoidance thus provided the opportunity to investigate dose escalation as a means of improved disease control. Retrospective series at that time demonstrated both an apparent dose response relationship for prostate cancer with improved local control and no significant toxicity increase when dose was increased using conformal techniques. Five large randomized trials (Table 1) have demonstrated that increased dose to the prostate of 74–80 Gray (Gy) in standard 1.8–2 Gy fractions results in improved biochemical recurrence-free survival and disease specific survival [35–39]. A large population study has demonstrated improved overall survival with dose escalation in men with high- and intermediate-risk prostate cancer suggesting that, in large enough populations, improved biochemical control can translate into a survival benefit [40].

*3.2. Proton Therapy.* A second strategy toward dose escalation involves heavy ion-based irradiation such as proton therapy. Proton therapy differs from conventional photon-based radiation therapy in that protons are charged particles that deposit a higher proportion of energy toward the end of their path of travel in a tissue and little to no energy beyond. Therefore, a very steep dose gradient can be created to minimize dose spill into adjacent tissue as compared to photon therapy. Unfortunately, population studies and experiences from large proton centers do not show superiority in disease control or toxicity for proton therapy [41–43].

Table 1: Randomized controlled trials evaluating the efficacy of radiation dose escalation for prostate cancer.

| Trial | *N*, inclusion criteria | Dose comparison (Gray) | Outcome |
|---|---|---|---|
| MD Anderson [35] | 301<br>cT1-3 N0 M0 | 70 versus 78 | 78% versus 59% Freedom from biochemical or clinical failure |
| PROG 95-09 [37] | 393<br>cT1b-2b, PSA ≤ 15 | 70.2 versus 79.2 | 32% versus 17% 10-year biochemical failure |
| MRC RT01 [39] | 843<br>cT1b-3a N0 M0, PSA < 50 | 64 versus 74 | 43% versus 55% 10-year biochemical recurrence-free survival |
| Dutch [36] | 664<br>cT1b-4 | 68 versus 78 | 54% versus 64% Freedom from failure |
| GETUG 06 [38] | 306<br>cT1b-3a N0 M0, PSA < 50 | 70 versus 80 | 39% versus 28% Biochemical failure |

PSA: prostate specific antigen.

Table 2: Randomized controlled trials evaluating the efficacy and toxicity of hypofractionated radiation regimens.

| | Trial | *N*, inclusion criteria | Dose (dose per fraction) | Outcome |
|---|---|---|---|---|
| Early hypofractionation trials | Lukka et al. [44] | 936<br>GS 6–10 | 52.5 Gy (2.625 Gy)<br>66 Gy (2 Gy) | 40% versus 43% 5-year freedom from biochemical failure |
| | Yeoh et al. [45] | 217 | 55 Gy (2.75 Gy)<br>64 Gy (2 Gy) | 53% versus 34% 7-year freedom from biochemical failure |
| Modern superiority trials | Hoffman et al. [47] | 204<br>99% low-intermediate risk | 72 Gy (2.4 Gy)<br>75.6 Gy (1.8 Gy) | 96% versus 92% 5-year freedom from biochemical failure |
| | Pollack et al. [49] | 303<br>GS 6+ | 70.2 Gy (2.7 Gy)<br>78 Gy (2.17 Gy) | 23% versus 21% 5-year biochemical or clinical disease failure |
| | Arcangeli et al. [48] | 168<br>GS 7+ | 62 Gy (3.1 Gy)<br>80 Gy (2 Gy) | 85% versus 79% 5-year freedom from biochemical failure |
| Modern noninferiority trials | Dearnaley et al. [46] | 457 | 57 Gy (3 Gy)<br>60 Gy (3 Gy)<br>74 Gy (2 Gy) | Similar GU and GI toxicity ≥ grade 2 (<5%) |
| | Incrocci [52] | 820<br>Intermediate-high risk | 64.6 Gy (3.4 Gy)<br>78 Gy (2 Gy) | Worse GI toxicity ≥ grade 2, similar GU toxicity |
| | RTOG 0415 [51] | 1101<br>Low risk | 70 Gy (2.5 Gy)<br>73.8 Gy (1.8 Gy) | Noninferior biochemical recurrence and overall survival, similar toxicity |
| | PROFIT [53] | Intermediate risk | 60 Gy (3 Gy)<br>78 Gy (2 Gy) | Pending |

GS: Gleason score. Gy: Gray.

*3.3. Hypofractionation.* One of the disadvantages of dose-escalated fractionated radiation to the prostate is the prolonged duration of treatment using standard fractionation schemes of 1.8 to 2 Gy per fraction to total doses of 74 to 80 Gy. In addition, there is a biological rationale for delivering higher radiation dose over a shorter period of time. Thus, multiple phase III trials have been conducted to demonstrate the safety, feasibility, and efficacy of hypofractionated, or shorter than standard, regimens [44–53]. The biological rationale for hypofractionated radiation therapy is to take advantage of the hypothetical differences in radiation sensitivity between malignant and normal prostate, decrease time and cost of treatment, and further escalate dose with the intention of improved local control.

Cell survival after radiation therapy is modeled by an exponential function that accounts for both direct, called alpha, and indirect, called beta, mechanisms of DNA damage. The ratio, or alpha/beta ratio, of these types of damage can give a general sense of the ability of the tissue to repair that damage. This repair ability is inversely proportional to the alpha/beta ratio. Generally, normal tissues have an alpha/beta ratio around 3 and tumors around 10. Historically, most radiation treatment schedules have been designed to capitalize on these differences in damage repair between tumor and normal tissue by delivering small doses of radiation over a prolonged period of time. This is the case for standard fractionation prostate radiation. More recent data, however, suggests that prostate cancer may actually have a lower alpha/beta ratio than previously suspected. This would mean that there is less benefit to lower dose, fractionated regimens.

Using this rationale, recent studies have investigated shorter courses of radiation therapy with higher doses per treatment (Table 2). Two early, phase three hypofractionation trials were designed prior to the dose escalation era

Table 3: Randomized controlled trials evaluating the efficacy and toxicity of extreme hypofractionated radiation regimens.

| Trial | Inclusion criteria | Dose (dose per fraction) |
|---|---|---|
| HYPO-RT-PC [54] | Intermediate risk | 78 Gy (2 Gy) versus 42.7 Gy (6.1 Gy) |
| PACE [55] | Low-intermediate risk | (1) Radical prostatectomy versus 36.25 Gy (7.25 Gy)<br>(2) 78 Gy (2 Gy) versus 36.25 Gy (7.25 Gy) |
| Proton cooperative group [56] | Low-intermediate risk | 79.2 Gy (1.8 Gy) versus 38 Gy (7.6 Gy) |

and demonstrated similar outcomes to non-dose-escalated standard fractionation therapy [44, 45]. Three later studies were designed to test the superiority of hypofractionated radiation for biochemical control compared to dose-escalated standard fractionation [47–49]. Outcomes in these trials were similar, including toxicity. Three more modern noninferiority trials have compared toxicity outcomes between standard and moderate hypofractionation regimens [46, 50–52]. RTOG 0415 recently reported the noninferiority of a 70 Gy at 2.5 Gy per fraction regimen and similar toxicity to standard fractionation [51]. In the other trials, toxicity has been similar with the exception of the HYPRO trial which shows worse early GI toxicity with hypofractionation [52]. The initial results of a fourth noninferiority trial (PROFIT) are pending at this time [53].

Extremely hypofractionated radiation regimens consisting of 5 treatments or less have also been investigated (Table 3). Three randomized trials are currently investigating the efficacy and toxicity of extreme hypofractionated regimens in comparison to standard fractionation (Table 3) [54–56]. In these trials, treatment consists of 5 to 7 fractions of 6.1 to 7.6 Gy per fraction. RTOG 0938 is a randomized phase II trial investigating two extreme hypofractionation regimens in patients with favorable risk prostate cancer [57]. Treatment is delivered over 2 to 2.5 weeks with either 36.25 Gy in 5 nonconsecutive fractions or 51.6 Gy in 12 daily fractions. Importantly, the short- and long-term toxicity profiles of these extreme hypofractionated regimens will need to be determined.

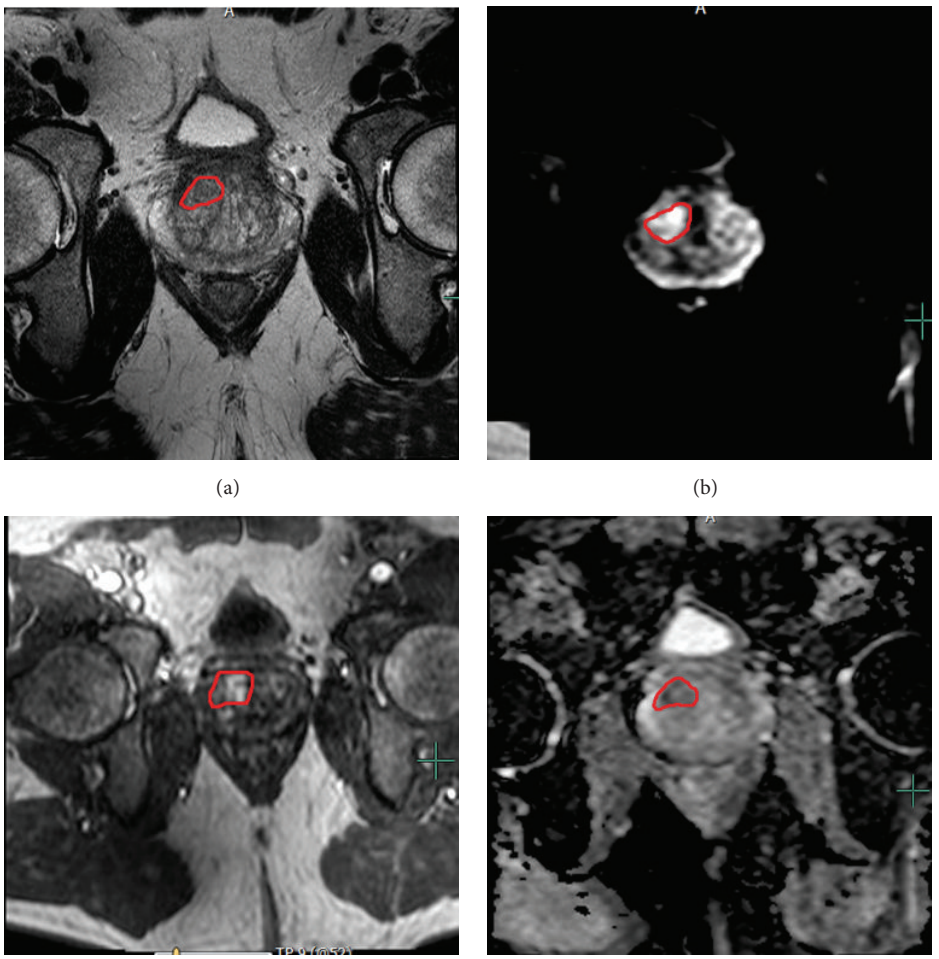
*3.4. Focal Targeting of Intraprostatic Lesions.* External beam radiation dose escalation and hypofractionation trials increased dose homogeneously to the entire prostate. Despite this, the most common location of recurrence is within the prostate [58]. 80% of prostate cancers, particularly higher grade cancers, have multiple foci of disease in the prostate gland as demonstrated in radical prostatectomy specimens.

More recent evidence supports the idea that dominant intraprostatic lesions, as opposed to multifocal disease, drive the natural course of disease. Furthermore, these dominant lesions are the site of most recurrences [59–61]. Unfortunately, it remains challenging to identify and target volumes within the prostate at the highest risk of harboring clinically relevant disease. In other disease sites, differential doses of radiation are delivered to different volumes depending on their perceived risk of tumor involvement. Prostate cancer has been classically diagnosed by needle biopsy sampling of the entire gland. TRUS is inaccurate in localizing focal disease. Transperineal template-guided prostate mapping biopsy (TTMP) has previously been the gold standard for localizing disease within the prostate, but this procedure is very invasive. Focal therapies, therefore, have primarily relied upon imaging, particularly MRI, to identify and target treatment to dominant lesions. Yet, there still remains the uncertainty between the appearance of a dominant lesion and its true biology with imaging alone. Now, with MRI-US fusion-guided biopsy, the imaging can be used to identify cancer presence and define grade in a targeted fashion with 3D mapping of the areas of interest as well as precise documentation of sites biopsied. Due to the concern regarding overtreatment of early stage disease and with technological improvements allowing more focal radiation delivery, many have sought to develop more focal therapies to avoid normal tissue toxicity related to definitive treatment.

Radiation techniques to deliver focal therapy to prostate lesions involve both external beam radiation and prostate brachytherapy. External beam techniques include IMRT, VMAT, and helical tomotherapy. Multiple dosimetric studies demonstrate the feasibility of escalating dose to an intraprostatic lesion up to 100 Gy with little to no potential for excess toxicity compared to standard whole-gland treatment. A single phase II trial has demonstrated feasibility of escalating dose to an intraprostatic lesion to 80 Gy with toxicity comparable to standard homogeneous dosing [62].

Unfortunately, sacrificing whole-organ dose for focal boost results in inferior biochemical control using both external beam and brachytherapy techniques, especially with intermediate and high-risk disease [63]. In the setting of whole-organ treatment, though, preliminary data from the ASCENDE-RT trial demonstrate improved RFS in men with intermediate- and high-risk disease who had brachytherapy boost over conventional external beam boost [64]. These data suggest that there is still a role for further dose escalation for high-risk prostate cancer. Similar benefit to HDR brachytherapy dose escalation after external beam radiation has also been demonstrated in randomized trials [65, 66].

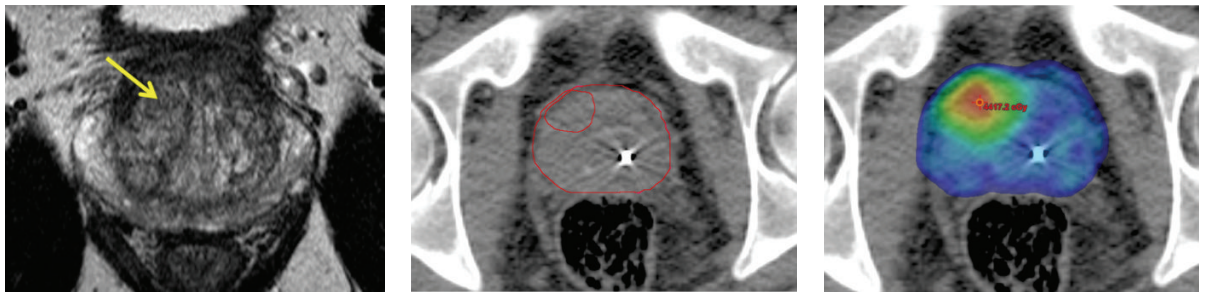
The approach used in current prostate radiotherapy trials investigating hypofractionation and extreme hypofractionation utilizes a technique called simultaneous integrated boost (SIB) to deliver higher dose to dominant intraprostatic lesions while still delivering an adequate lower dose to the whole prostate. Figure 2 shows the dose distribution within the prostate of an extreme hypofractionation SIB plan. However, this technique continues to rely on radiographic assessment



(a) (b)

(c) (d)

Figure 1: Multiparametric MRI evaluation and MRI-TRUS fusion biopsy in patient with multifocal intraprostatic lesions. The index lesions based upon MRI were identified in the right mid anterior central gland as an area of (a) T2 hypointensity, (b) increased signal on high *b*-value DW-MRI, (c) early enhancement on DCE-MRI, and (d) diffusion restriction on ADC map of DW-MRI. The right mid anterior central gland lesion demonstrated Gleason 3 + 4 disease on fusion biopsy. A second right base posterior peripheral zone lesion demonstrated Gleason 3 + 3 disease.



(a) (b) (c)

Figure 2: Axial views of the patient in Figure 1 with Gleason 3 + 4 disease found in right mid anterior central gland using MRI-TRUS fusion biopsy. The T2 hypointense lesion is shown in (a) with clinical target volumes drawn around the prostate and nodule on axial CT in (b). A 36 Gy dose colorwash to the whole prostate and simultaneous integrated boost of 40 Gy to the T2 hypointense lesion using an extreme hypofractionation radiation treatment plan are shown in (c). Note the fiducial markers used for daily image-guided localization.

of risk of intraprostatic lesions and correlation with sextant biopsy to guide focal therapy.

*3.5. Tumor Biology Directed Treatment Intensification.* We now know that delivering higher radiation doses benefits men with the most high-risk disease. We also know that only targeting individual lesions within the prostate in these men leads to worse outcomes. Doses as high as 85 Gy have been delivered to the entire prostate with external beam radiation therapy [67]. The preliminary results of the ASCENDE-RT trial suggest that further dose escalation in high-risk disease has further potential benefit. However, increasing whole-prostate dose comes at the cost of increased toxicity. Therefore, the rational progression of these ideas leads to a treatment paradigm where the entire prostate is treated to an adequate dose with focal dose escalation to high-risk lesions within the prostate. This approach, in theory, could optimize dose escalation and normal organ toxicity. We may also find that this approach allows dose to be decreased to the whole-prostate and further escalated to intraprostatic lesions.

A newer approach to more accurately and appropriately intensify therapy is to combine information obtained by MR-TRUS fusion biopsy with SIB radiation therapy. Fusion biopsy identifies more clinically relevant, high-risk disease, which benefits most from treatment intensification. It also provides direct correlation between imaging and histopathologic findings. Furthermore, other intraprostatic lesions can be biologically risk-stratified to guide treatment planning. A phase II protocol at the University of Alabama at Birmingham (NCT01856855) is investigating the efficacy and toxicity of such an approach [68]. This protocol uses MR-TRUS fusion biopsy to guide selection of high-risk intraprostatic targets for escalated therapy. mpMRI is then used in the treatment planning process to identify the prostate and high-risk targets. The entire prostate is prescribed a total dose of 36.25 Gy in 5 fractions and high-risk volumes are prescribed a total dose of 40 Gy in 5 fractions using the SIB technique. Gold fiducial markers and daily cone-beam CT scans are used to accurately deliver the prescribed dose to the appropriate volume.

*3.6. Genomic Predictors of Prostate Cancer Outcomes and Targeted Therapy.* A big challenge in choosing adequate therapy and determining outcomes from clinical trials in prostate cancer is the significant disease heterogeneity within risk groups. Genomic and molecular analyses of prostate cancer specimens will hopefully help us better characterize disease risk and personalize treatment. Multiple genomic panels have been developed and validated in predicting outcomes based on tissue from radical prostatectomy or biopsy specimens. Prolaris (Myriad Genetics, Salt Lake City, UT, USA) is a 46-gene expression panel for biopsy and TURP specimens that predicts prostate cancer death. It has been validated in radical prostatectomy specimens to predict biochemical recurrence and distant metastases [69, 70]. Decipher (GenomeDX Biosciences, Vancouver, BC, Canada) is a 22-gene panel that predicts survival after radical prostatectomy [71]. Lastly, Oncotype DX Genomic Prostate Score (Genomic Health Inc., Redwood City, CA, USA) is a 17-gene panel that predicts recurrence, prostate cancer death, and high-risk pathology based on biopsy specimens. Genomic panels, applied to MR-TRUS biopsy samples, could potentially provide important information about the underlying biology of individual prostate lesions that could then be targeted with focally intensified therapy.

## 4. Summary

Despite significant advances in prostate cancer therapy over the last few decades, many men, particularly those with high-risk disease, will have PSA recurrence, develop symptomatic local or distant disease, or die from their prostate cancer. Prostate cancer is a heterogeneous disease and can even manifest heterogeneously within the prostate of a single patient. Prostate cancer therapy is moving rapidly toward personalization, and this approach could significantly improve outcomes for men with high-risk biology. Future clinical trials and standard therapy will biologically risk-stratify patients in order to optimize treatment outcome. Personalized prostate cancer therapy, therefore, will depend on our ability to accurately identify, biopsy, analyze, and treat areas of high-risk disease within the prostate for men with organ-confined disease. The incorporation of MR-TRUS biopsy, molecular testing of biopsy specimens, and focal treatment intensification will make personalized therapy a reality.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Review Article*

# Fortifying the Treatment of Prostate Cancer with Physical Activity

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Over the past decade, significant data have shown that obese men experience a survival detriment after treatment for prostate cancer. While methods to combat obesity are of utmost importance for the prostate cancer patient, newer data reveal the overall metabolic improvements that accompany increased activity levels and intense exercise beyond weight loss. Along these lines, a plethora of data have shown improvement in prostate cancer-specific outcomes after treatment accompanied with these activity levels. This review discusses the metabolic mechanisms in which increased activity levels and exercise can help improve both outcomes for men treated for prostate cancer while lowering the side effects of treatment.

## 1. Introduction: Prostate Cancer, Obesity, and Metabolic Health

In 1985, the Radiation Therapy Oncology Group (RTOG) set out to examine the benefit of hormonal therapy in the treatment of prostate cancer. RTOG 85-31 randomized 945 men with locally advanced prostate cancer to radiation therapy (RT) and immediate (concurrent) versus delayed androgen deprivation therapy (ADT) [1]. The study revealed a benefit with the addition of immediate ADT, which is now the standard of care for men undergoing definitive RT for high-risk prostate cancer. Several other studies have revealed similar survival benefits with the addition of ADT to RT [2, 3]. Interestingly, subset analysis of long-term results from yet another positive ADT study revealed that those patients without a history of comorbid illness, such as myocardial infarction or diabetes, may not derive similar benefits [4].

Both RT and ADT work by interfering with tumor cell replication. RT primarily inflicts tumor cell injury through both direct and indirect DNA damage via the generation of free radicals. The mechanisms with which ADT treats prostate cancer remain more elusive, and it is thought to work primarily by reducing the transcription of genes involved in cell-cycle regulation and proliferation [5]. Circulating androgens like testosterone and dihydrotestosterone (DHT) bind to the androgen receptor on prostate gland and prostate cancer cells, leading to gene transcription. ADT is achieved via medical or surgical castration to reduce levels of circulating androgens. In combination, it is felt that ADT can sensitize cells to enhance damage from RT.

While RTOG 85-31 revealed a benefit to the addition of immediate ADT, further analysis of the dataset revealed that those patients with a body mass index (BMI) of 30 or more had a significant detriment in prostate cancer-specific survival [6]. This was one of the first major randomized trials to illustrate the importance of a healthy metabolic state for men with prostate cancer during and after treatment. Other epidemiologic data have confirmed this relationship [7] and revealed an increase in prostate cancer metastases in obese men [8]. In a meta-analysis published in 2011, it was estimated

that for every 5 kg/m$^2$ increment in BMI there was a 21% higher risk of biochemical recurrence and a 20% higher risk of prostate cancer-specific mortality [9].

Although BMI cannot provide an exact quantification of muscle, bone, and adipose tissue, it has been shown to be useful as a crude measure of excess adiposity. As such, BMI is correlated with several other physiologic factors characteristic of metabolic dysregulation and metabolic syndrome [10]. Metabolic syndrome, also known as insulin insensitivity syndrome, is defined as central obesity in addition to two of the following risk factors: elevated glucose, insulin resistance, elevated triglycerides, reduced high-density lipoproteins (HDL), and hypertension [11]. This metabolic state has been shown to potentially provide cancer cells with an enhanced ability to withstand damage from RT [12], while obesity leads to a state of alteration of testosterone, estrogen, insulin, insulin-like growth factor-1 (IGF-1), and leptin, all hormones linked to prostate cancer, which could potentially interfere with hormonal therapy [13]. Along these lines, several reasons for the correlation of poorer outcomes for men with prostate cancer who also have a surplus of adipose tissue exist and will be discussed below.

*Inflammation and Adipose Tissue as an Endocrine Organ.* Obese patients experienced poorer outcomes in RTOG 85-31. Similar findings have revealed worse outcomes in obese men treated with prostatectomy for their prostate cancer [14, 15]. In these studies, obese men were found to have higher grade tumors, higher biochemical failure rates, and an increased risk of positive margins after surgery. Additional data reveal that adipose tissue acts as an endocrine organ to secrete inflammatory hormones called adipokines and is associated with insulin resistance [16]. Insulin resistance leads to elevating levels of circulating insulin, serum glucose, and inflammation, all factors which can fuel cancer progression, along with weight gain and poorer responses to cancer treatment [17].

Newer studies have implicated central obesity and waist circumference, as opposed to BMI, as the culprit that leads to obesity-related health risk due to the physiologic mechanisms by which adipose tissue acts as an endocrine organ, leading to global metabolic dysfunction [18]. As men tend to accumulate adipose tissue centrally, this is a concern in the prostate cancer patient (refer to Figure 1).

Several inflammatory effects result from excess adipose tissue via the secretion of adipokines. These include dysregulation of cellular growth, angiogenesis stimulation, and extracellular matrix remodeling favoring tumor progression and recurrence [19]. Fat cells secrete the inflammatory mediators tumor necrosis factor-alpha (TNF-$\alpha$) and interleukin 6 (IL-6), which promote cancer induction [20]. Both have been associated with shorter survival, worse disease, and metastases in men with prostate cancer [21]. The third common inflammatory factor released by adipose tissue is C-reactive protein (CRP) [22]. CRP is associated with both obesity and central adiposity and predicts for poor outcomes in men with metastatic prostate cancer, independent of their serum PSA [23]. Similar results have been seen with breast cancer survivors, as discussed previously [17].

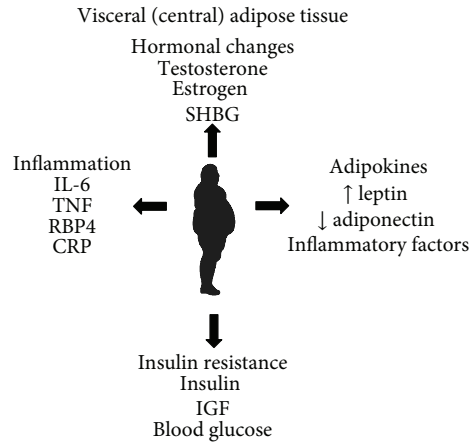


Figure 1: Central obesity leads to the secretion of multiple inflammatory mediators that can worsen prostate cancer-specific outcomes.

Finally, an increased inflammatory cytokine profile has been linked to cancer related fatigue (CRF) [24], a state characterized by overall weakness and increased need for sleep and rest. Greenberg et al. showed that symptoms of CRF increased during the course of RT in prostate cancer patients independent of depressive symptoms but connected to changes in serum IL-1 levels [25]. This provides a plausible mechanism for adiposity augmenting treatment-induced fatigue and increasing the risk for prolonged and more severe posttreatment CRF [26].

*Hormonal Production of Adipose Tissue and Insulin Dysregulation.* Excess adipose tissue works though many indirect mechanisms to cause insulin insensitivity and chronically elevated levels of serum glucose, which can lead to cancer progression and resistance to cancer treatments. One direct mechanism is through the release of a hormone known as resistin (resistance to insulin), which impairs glucose tolerance and the action of insulin to lower blood glucose levels [27]. Adipose tissue accumulation also leads to elevated levels of plasma free fatty acids, which inhibit the normal physiologic uptake of peripheral glucose via insulin stimulation. This potentially occurs via the inhibition of glucose transport, via a decrease in muscle glycogen synthase activity, or via the stimulation of insulin secretion, ultimately leading to insulin insensitivity and hepatic glucose overproduction [28].

Dietary-induced hyperinsulinemia via excessive consumption of carbohydrate food sources has been shown to increase levels of IGF-1 and activate the insulin pathway and AKT, increasing prostate cancer growth in mouse studies [29]. Other studies reveal that glucose in itself can bind and activate the insulin receptor and pathway [30], fueling cancer growth and proliferation, while aiding in the repair of tumor damage from RT [12]. Accordingly, the uptake of the glucose analog tracer $^{18}$F-fluorodeoxyglucose in preoperative positron emission tomography scans has been shown to predict for prostate cancer stage and 5-year progression free survival after radical prostatectomy [31].

Activation of the insulin pathway can lead to cancer progression and resistance to current treatment modalities, including RT [32, 33]. IGF-I upregulates the insulin pathway, stimulating the growth and progression of prostate cancer cells [34]. DHT appears to work synergistically with IGF-1 to enhance prostate cancer progression. Conversely, insulin-like growth factor binding proteins (IGFBPs) can bind and inactivate IGF-1 to offset its potentially negative effects on cancer outcomes [35]. IGFBP-3 has specifically been shown to induce apoptosis in prostate cancer cells [36]. Accordingly, Rundqvist et al. have shown that serum taken from male subjects after intense exercise inhibited growth of prostate cancer cell lines in SCID mice through an increase in IGFBP [37]. Obese individuals have lower levels of IGFBP-1 and IGFBP-2, with saturation of IGFBP-3, and subsequently higher levels of IGF-1 [38].

Sex hormone-binding globulin (SHBG) works similar to ADT by endogenously binding to circulating DHT and testosterone to reduce their bioavailability to bind to prostate cells. However, serum insulin inhibits SHBG production within the liver. In this regard, insulin and BMI are inversely related to SHBG [39].

Minimizing excess adipose tissue and the reduction of blood glucose and insulin levels may be a potent method of reducing prostate cancer risk and improving outcomes.

## 2. Activity Levels and Exercise: Metabolic Modification to Improve Prostate Cancer Outcomes

A prudent method to increase patient outcomes would thus incorporate techniques to mitigate levels of circulating glucose and insulin, reduce excess adipose tissue, limit inflammation, and optimally balance hormonal levels. Exercise is generally felt to improve global metabolic status. As discussed below, a plethora of data have linked activity levels with positive prostate cancer-specific outcomes. The exact activities that lead to the largest benefit remain unknown, and data generally and nearly unanimously reveal that increased overall activity levels provide overall and prostate-specific health benefits.

In a study following over 2,000 men with prostate cancer, it was found that men who were more active lived significantly longer [40]. Furthermore, men who walked 90 or more minutes per week at a brisk pace experienced half the risk of dying versus those who did not walk or did so at a slow pace. Three or more hours per week of vigorous activity was associated with a 61% decreased risk of dying from prostate cancer. Finally, men who exercised vigorously before and after their diagnosis had the lowest risk of dying from prostate cancer.

Other data have paralleled the importance of more vigorous activity. In a dataset of 1,455 men diagnosed with clinically localized prostate cancer, those who walked at a pace of over 3 miles per hour had a 57% lower rate of progression than those who walked at a slower pace for under three hours per week. This benefit was also independent of duration [41]. The authors went as far to suggest that "Brisk walking after diagnosis may inhibit or delay prostate cancer progression among men diagnosed with clinically localized prostate cancer."

Recent studies have begun to parse the benefits of specific activities. In a cohort of 4,623 men diagnosed with localized prostate cancer, a 37% reduction in overall mortality rates was seen in those men who engaged in five or more metabolic equivalent tasks (MET) [42]. Men who walked or bicycled for 20 or more minutes per day experienced a 30% reduction in overall mortality and those who exercised for an hour or more per week had a 26% reduction. Interestingly, men who performed an hour or more of household work per day also experienced a 29% reduction in overall mortality. While briskness holds importance, there appears to be a variety of activities that can provide significant benefit. These activities have as significant an effect on prostate cancer-specific mortality (PCSM) as well; men who walk or ride a bike for 20 or more minutes per day experience a 39% reduction in PCSM and men that exercise for an hour or more per week have a 32% reduction in PCSM.

## 3. Physiological Benefits of Physical Activity

While data is mixed, exercise has generally been considered to result in weight loss and, specifically, lower amounts of adipose tissue [43, 44]. Indeed, a reduction in adipose tissue serves to eliminate several heads of the metabolic hydra seen with central obesity. However, the major benefits of exercise may consist of the metabolic alterations that accompany increased activity levels and specifically brisk and intense activities.

A single bout of high-intensity exercise results in the breakdown of glucose and muscle glycogen, significantly lowering serum glucose levels and enhancing insulin sensitivity [45]. Such effects may have little impact on acute weight loss but would result in metabolic alterations favoring a more inhospitable environment for tumor cells, especially during treatment with RT. Furthermore, even a single bout of low-intensity exercise leads to metabolic alterations, including the enhancement of insulin sensitivity and breakdown of fatty acids that persist for the following day [46].

The intensity level of exercise may lead to different benefits. With regard to intense exercise, described as "briskness" in the studies mentioned above, serum glucose uptake and glycogen oxidation are increased [47], thus improving glucose and insulin-based metabolic dysfunction. Lower intensity exercise may lead to more beneficial effects with regard to the reduction of adipose tissue; data reveal maximal peripheral lipolysis and fatty acid release from low-intensity exercise. The body appears to shift to triglyceride lipolysis when intensity is increased, which would further affect one of the hallmarks of metabolic syndrome. Thus, it appears that there are significant benefits from both intense activities like weight lifting and sprinting along with less intense activities like walking, riding a bicycle, or even performing household chores, as described by Bonn et al. [42].

## 4. Muscle Mass and Mitochondrial Biogenesis

Just as adipose tissue works as endocrine organ, muscle tissue appears to work in a nearly opposite manner to release

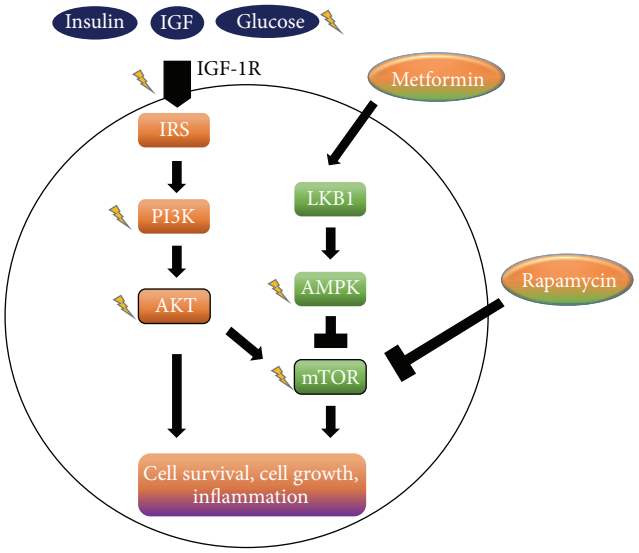


Figure 2: Metabolic manipulation of the AMPK overlaps with activation via exercise. Lightning bolts indicate pathways that affect radiosensitivity. AMPK, AMP-activated protein kinase; IGF-1, insulin growth factor-1; IRS, insulin receptor substrate; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase. Image is used with permission from Champ et al., 2013 [33].

factors that counter inflammation. When muscle contraction occurs during activity and exercise, adenosine triphosphate (ATP) is consumed for energy derivation. As the intracellular ATP/AMP ratio is reduced, there is cellular activation of the liver kinase B1- (LKB1-) adenosine monophosphate-activated protein kinase (AMPK) pathway. AMPK inhibits the mammalian target of rapamycin (mTOR) protein, which has been implicated in prostate cancer cell progression [48] and is a current target of prostate cancer treatment [49]. Elevation of the insulin pathway, on the other hand, reverses the antitumor effects of inhibition of the mTOR pathway [49] (Figure 2).

Studies assessing human muscle after exercise reveal increased levels of AMPK expression with intense exercise [50], and powerful muscle contraction results in the potent stimulation of AMPK [51]. Interestingly, in those individuals who exercise frequently, AMPK protein levels remain elevated in skeletal muscle afterwards during periods of inactivity [52]. Perhaps most importantly for the prostate cancer patient with diabetes or some degree of insulin insensitivity, muscle contraction-stimulated release of AMPK and the mitigation of serum glucose levels via cellular influx are independent of insulin sensitivity [53]. Furthermore, muscle contractions and activation of AMPK result in translocation of the GLUT-4 receptor in myocytes, leading to glucose influx and the lowering of serum glucose levels [54], which would have a favorable impact on metabolic syndrome, serum insulin levels, inflammation, and even obesity.

In contrast to the ample data in skeletal muscle, data regarding exercise modulation of AMPK levels or phosphorylation in prostate tumors remain elusive. One study using a murine breast cancer model found no differences in AMPK protein expression between tumors from wheel-running and sedentary animals, but contrary to other tumor models these tumors also did not differ in growth rates [55]. More data exist regarding an effect of exercise on AMPK via modulating adiponectin levels which correlate negatively with obesity and increase moderately during various exercise regimes [56]. AMPK activation by adiponectin has been shown to inhibit prostate and colon cancer cell viability [57] but paradoxically also enhanced prostate cancer cell migration and metastatic potential [58]. Adding to this controversy, Rider et al. recently found that high expression of the adiponectin receptor 2 in prostate tumors was associated with increased proliferation and worse survival but was not associated with BMI or PSA levels [59]. The role of exercise-induced AMPK activation in prostate cancer therefore remains somewhat speculative, while the metabolic benefits of global upregulation of AMPK remain clearer.

Faubert et al. have shown that stimulation of AMPK suppresses tumor growth, the uptake of glucose, and aerobic glycolysis of tumor cells, known as the Warburg effect [60]. Their data also revealed that the activation of AMPK serves to downregulate HIF-1$\alpha$, which can potently increase the radiosensitivity of tumor cells [61]. Metformin has similarly been shown to increase AMPK and enhance radiosensitivity of tumor cells [62] and is now being assessed in clinical trials [63]. Other data reveal that the activity of AMPK directly increases RT efficacy and regulates tumor survival after irradiation [64, 65]. Hence, its effect on prostate cancer cells certainly may be similar.

While activation of the AMPK pathway may have direct antitumor effects, the global metabolic changes may indirectly affect cancer treatment and outcomes. AMPK activation results in the oxidation of lipids and an increase in the ratio of NAD+/NADH, enhancing metabolism via the upregulation of the NAD+-dependent deacetylase silent mating type information regulation 2 homologue 1 (SIRT1) [36]. This pathway affects cellular metabolism via epigenetic alterations on gene transcription and protein modification. Further along, this leads to mitochondrial biogenesis [37]. Preclinical data have revealed that mitochondrial biogenesis and upregulation alone may have antitumor properties [66, 67].

During the generation of ATP, AMPK promotes the breakdown of glucose, glycogen, and fatty acids while inhibiting anabolic processes such as the synthesis of cholesterol, triglycerides, or fatty acids [68] (refer to Figure 3). As tumor metabolism is largely dependent on glycolysis and multiple studies have revealed poorer outcomes with elevated levels of glucose [17], exercise and AMPK activation may be one method to combat the glycolytic phenotype of most cancers.

The data correlating briskness and resistance training with increased benefits may be due to the recruitment of muscle activation during intense activity or heavy lifting. Quite opposite of adipose tissue, the stimulation of muscle releases myokines that appear to lower systemic inflammation [69]. Studies assessing human muscle after exercise reveal increased levels of AMPK expression with intense exercise [50], and powerful muscle contraction results in

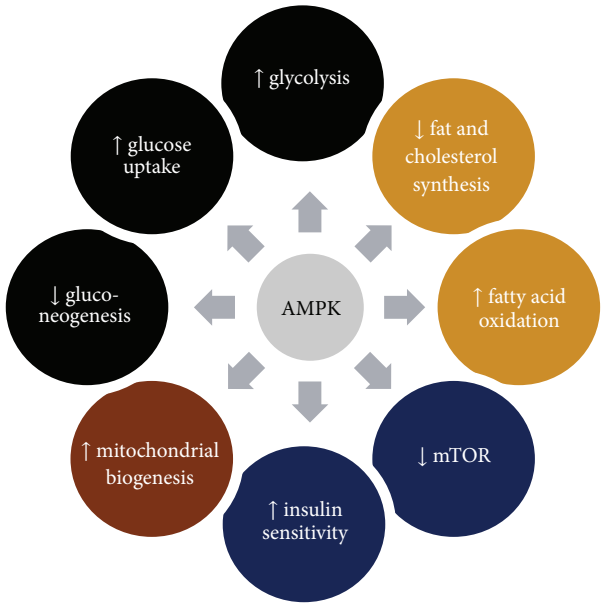


Figure 3: AMPK activation leads to multiple metabolic alterations.

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Intense activity may have a more potent effect on lowering increased insulin sensitivity, thus decreasing systemic levels of insulin and serum glucose. General exercise lowers systemic inflammation [70], and the stimulation of one of the best-studied inflammation-modulating myokines is IL-6. While adipose tissue-derived IL-6 and IL-6 produced by macrophages have proinflammatory effects, muscle-derived IL-6 appears to have anti-inflammatory properties [69]. Up to 100-fold transcription of the muscular IL-6 gene occurs after 30 minutes of exercise and has been confirmed with muscle biopsies [71]. This myokine counteracts the proinflammatory action of TNF-alpha [72], which is associated with significantly worse outcomes in men treated for prostate cancer [21]. Furthermore, it has been postulated that muscle-derived IL-6 helps against CRF by decreasing levels of IL-1 and TNF-alpha and elevating levels of cortisol, which in itself has anti-inflammatory effects [73]. Thereby a chronic exercise routine of longer low-to-moderate exercise intermixed with short intense bouts that stimulate muscular contraction may be preferred over infrequent prolonged and/or strenuous sessions; the former may improve the tumoricidal action of macrophages while promoting an overall anti-inflammatory state, while the latter may augment inflammatory and fatigue signaling to the central nervous system [74]. In particular, data indicate that patients at risk for CRF during treatment should refrain from protracted high-intensity competitions such as ultraendurance races as these have been shown to result in a prolonged inflammatory state with compromised immune function and increased fatigue [75].

Much like AMPK, muscle-derived IL-6 works as a sensor of energy "status," ultimately leading to glucose uptake, lowering of serum glucose levels, and lipid oxidation, all changes that improve global metabolic function and may synergize with cancer treatment with chemotherapy and RT. Muscle-based IL-6 also appears to directly activate AMPK in rat studies [76]. Finally, IL-6 stimulates the breakdown and oxidation of fat, further improving the global metabolic state [77].

Lastly, exercise stimulates the expression of brain-derived neurotrophic factor in muscle and brain, with the latter contributing to an increase in its serum concentration [78]. This mechanism has also been implicated in the beneficial effects of exercise on chronic fatigue [79].

## 5. Decrease in Radiation Treatment-Related Side Effects

While exercise provides an abundance of metabolic benefits potentially improving cancer-specific outcomes, it also appears to improve quality of life and side effects related to treatment with RT. Men with prostate cancer receiving three months of ADT were randomized to an intervention group that engaged in a resistance exercise program three times per week for a period of 12 weeks versus a control group [80]. Those men that engaged in resistance training experienced a significant reduction in fatigue and higher quality of life versus those in the control group. These men also experienced elevated levels of upper and lower body muscular fitness. These benefits were found to be independent of bodyweight and BMI, as they were similar between the groups after the study.

Other randomized data reveal similar findings in sedentary men on ADT for prostate cancer with exercise leading to decreased fatigue [81]. This study also revealed a durable response seen in exercise behaviors. Similar trials reveal that a supervised exercise training program yields additional benefits over material given to patients, with significant improvements in physical functioning, muscle strength, muscle mass [82], mental health, and sexual function [83].

The same group later randomized men receiving RT with and without ADT to usual care during RT versus aerobic exercise and resistance training [84]. Training regimens were carried out over a 24-week period and the primary endpoint assessment was fatigue, the most common side effect of RT. They found that resistance training improved aerobic fitness, quality of life, strength, and triglycerides when compared with usual care. Aerobic exercise improved both fitness and fatigue. Resistance training resulted in longer-term benefits, which may be consistent with the additional metabolic benefits derived from more intense activity.

Monga et al. randomized men to exercise group or a control group while undergoing RT for prostate cancer [85]. The men in the exercise group experienced improvements in cardiovascular fitness, flexibility, muscle strength, and overall quality of life and less fatigue.

## 6. Metabolic Management of Metabolic Dysregulation from ADT

While conclusive data support the usage of ADT in conjunction with RT for high-risk prostate cancer, toxicity from this treatment remains a concern for the treating physician. As discussed above, ADT works to reduce prostate cancer cell gene transcription through the reduction of circulating androgens capable of binding to the androgen receptor signaling proliferation [5]. Androgen deprivation is most commonly achieved with gonadotropin-releasing hormone (GnRH) agonists. Data have shown poorer results for men receiving ADT with a history of moderate-to-severe comorbidities [86]. Interestingly, ADT causes similar comorbidities and side effects from metabolic and physiologic alterations, including increased adipose tissue, cardiovascular disease, QT interval prolongation, insulin insensitivity, and diabetes [87]. As these changes could hinder both prostate-specific and overall health outcomes, methods to offset these side effects are of importance.

For instance, increased insulin resistance results in both elevated serum glucose and insulin, both of which can stimulate the IGF and other proliferative pathways, leading to increased cancer growth and resiliency from damage induced by RT [12]. Elevated insulin also correlates with increased risks of prostate cancer diagnosis [88] and recurrence after treatment [89]. Frequent exercise leads to persistently elevated levels of AMPK protein in skeletal muscle [52]. As the stimulation of AMPK increases insulin sensitivity [53] and decreases circulating glucose levels [54], these activities may serve to offset potential side effects of ADT while also enhancing the treatment effects of ADT.

The hormonal milieu induced by ADT may hinder the loss of fat mass seen during exercise, as corresponding results of exercise interventions reveal mixed results with regard to a reduction in body fat [90]. In a recent study by Nilsen et al. there were also no changes in fat mass between the control group and men performing high-intensity strength training over 16 weeks with 3 sessions per week performed in an undulating periodization style [91]. However, apart from changes in body composition, several beneficial effects of exercise have been reported on patients undergoing ADT [90].

For example, the Trans-Tasman Radiation Oncology Group randomized men receiving RT and ADT to six months of supervised exercise followed by an additional home-based exercise program or printed educational material [82]. Those men on the supervised exercise regimen experienced significant improvement in cardiorespiratory fitness performance, lower body physical function, self-reported physical functioning, appendicular skeletal muscle, and objective measures of muscle strength. Perhaps most importantly, these benefits persisted at one year in those on a home-based program.

In a similar study, 100 sedentary men with locally advanced or metastatic prostate cancer on long-term ADT were randomized to a three-month intervention of aerobic exercise and resistance training [81]. Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaires at 3 and 6 months after the intervention revealed significant improvements in quality of life scores on FACT-P at 3 months and FACT-F at 3 and 6 months. Exercise levels were maintained in these men at the conclusion of the study.

Other data in men receiving ADT randomized to resistance training reveal significant reduction of fatigue, improved upper and lower body muscular fitness, and improved quality of life [80]. Again, the benefits in this study were seen even without improvement in body weight, body mass index, waist circumference, or subcutaneous skinfolds.

Men receiving ADT are interested in adding exercise regimens to their treatment. According to a survey, 79% of men are willing to participate in an aerobic exercise program during treatment and 81% are willing to engage in muscle-strengthening programs [92]. Men also preferred to exercise at home; flexible, spontaneous, and self-paced regimens were preferred. Due to the multiple physiologic, metabolic, and physical benefits of exercise, benefits that directly offset the potential toxicity of ADT, along with randomized evidence of benefit of both aerobic exercise and resistance training, exercise in conjunction with ADT and RT should be part of the standard of care in those men capable of safely engaging in these activities. Indeed many are now recommending that exercise interventions should be offered to all patients receiving ADT and should continue afterwards [93].

## 7. Moving Forward: Patient-Oriented Exercise

Many patients do not wish to exercise intensely or at a gym [94] and, unfortunately, only 19% of men receiving treatment for prostate cancer with ADT meet guidelines for weekly physical activity [92]. Although it seems that supervised activities provide more benefit than those that are unsupervised [95], tangible activities that are more likely to be adhered to by men with prostate cancer may also provide benefits. For example, according to data in the Harvard Health Publications, many activities provide a similar amount of calories burned which do not involve a gym or are not even considered as exercise by most people [96]. As listed in Table 1, many typical household activities burn a similar amount of calories as dedicated activities or exercise, and this can be emphasized to patients in an effort to increase overall activity levels.

Along these lines, discussions can ensue with patients to favor simple and tangible changes in activity levels to significantly increase overall daily activity levels. For instance, with a simple switch from three hours of television viewing per night (33 calories) to reducing television time to an hour and replacing those remaining hours with cooking, reading, and gardening in the morning (361 calories), patients can substantially increase their activity levels.

Additionally, advances in technology are allowing physicians to better track and quantify exercise habits for further

Table 1

| | Calories expended* |
|---|---|
| *Gym activities* | |
| Weight lifting (general) | 133 |
| Water aerobics | 178 |
| Stretching, Hatha yoga | 178 |
| Calisthenics (moderate) | 200 |
| Riders (i.e., HealthRider) | 222 |
| Aerobics (low impact) | 244 |
| Stair-stepper machine (general) | 266 |
| Teaching aerobics | 266 |
| Weight lifting (vigorous) | 266 |
| Aerobics, step (low impact) | 311 |
| Aerobics (high impact) | 311 |
| Bicycling, stationery (moderate) | 311 |
| Rowing, stationery (moderate) | 311 |
| Calisthenics (vigorous) | 355 |
| Circuit training (general) | 355 |
| Rowing, stationery (vigorous) | 377 |
| Elliptical trainer (general) | 400 |
| Ski machine (general) | 422 |
| Aerobics, step (high impact) | 444 |
| Bicycling, stationery (vigorous) | 466 |
| *Outdoor activities* | |
| Planting seedlings and shrubs | 178 |
| Raking lawn | 178 |
| Sacking grass or leaves | 178 |
| Gardening (general) | 200 |
| Mowing lawn (push, power) | 200 |
| Operate snow blower (walking) | 200 |
| Plant trees | 200 |
| Gardening (weeding) | 205 |
| Carrying and stacking wood | 222 |
| Digging and spading dirt | 222 |
| Laying sod/crushed rock | 222 |
| Mowing lawn (push, hand) | 244 |
| Chopping and splitting wood | 266 |
| Shoveling snow (by hand) | 266 |
| *Home and daily life activities* | |
| Sleeping | 28 |
| Watching TV | 33 |
| Reading (sitting) | 50 |
| Standing in line | 56 |
| Cooking | 111 |
| Child care (bathing, feeding, etc.) | 155 |
| Food shopping (with cart) | 155 |
| Moving (unpacking) | 155 |
| Playing w/kids (moderate effort) | 178 |
| Heavy cleaning (wash car and windows) | 200 |
| Child games (hopscotch, jacks, etc.) | 222 |
| Playing w/kids (vigorous effort) | 222 |
| Moving (household furniture) | 266 |
| Moving (carrying boxes) | 311 |
| *Home repair* | |
| Autorepair | 133 |
| Wiring and plumbing | 133 |
| Carpentry (refinish furniture) | 200 |
| Lay or remove carpet/tile | 200 |
| Paint, paper, remodel (inside) | 200 |
| Cleaning rain gutters | 222 |
| Hanging storm windows | 222 |
| Paint house (outside) | 222 |
| Carpentry (outside) | 266 |
| Roofing | 266 |

Table 1: Continued.

*In 30 minutes for a 185 lb man. Table created with data from Harvard Health Publications.

discussions on methods to increase or improve activity levels. Current studies are underway at the University of Pittsburgh assessing activity levels during RT and mechanisms to increase these levels. As patient-centered technology and device designs increase, the opportunities to quantify patient activity and exercise levels are arming the physician with data that was unattainable even a few years ago. All aspects of activities, from intense exercise to low-intensity walking, appear to provide benefit [47]. High-intensity activity entails a strong myokine-mediated anti-inflammatory response and directly alters the metabolic environment via reductions in glucose, insulin, and the insulin pathway; if performed on a regular basis, this fosters an inhospitable setting for tumor growth and reduces the ability of cancer cells to overcome treatment-related damage [12]. Less intense activities improve antitumoral immune function [74] and help reduce adipose tissue via lipolysis, which can result in a global reduction of inflammation and secreted hormones that can fuel the growth of prostate cancer cells.

Such findings are encouraging for the treating physician and patient alike. Evidence that a variety of activities can improve a patient's overall and prostate-specific outcome provides options and flexibility to guide patients and increase the odds of success in following an exercise regimen. This may be a major challenge for patients in the midst of treatment when new physical and emotional difficulties serve as obstacles to adopting or continuing with exercise and healthy habits.

## 8. Conclusions

Based on the data presented above, a prudent exercise and activity goal for the prostate cancer patient to increase his chance of cure would be a multifaceted approach to reduce overall and central adipose tissue deposition and to mitigate circulating levels of inflammation, insulin, and detrimental sex hormones. Further studies to assess the most efficacious techniques are needed. Activity levels, ranging from walking

to more intense activities and exercise regimens, provide unique benefits. Randomized data continue to accumulate regarding the positive effect that exercise has on treatment outcomes for men with prostate cancer and the implementation of exercise during and after treatment for prostate cancer should be part of the standard of care.

The radiation oncologist is provided with a unique opportunity to reiterate healthy lifestyle approaches and modifications due to the extensive time spent with patients on a weekly basis during treatment. Prostate cancer is one of the more prolonged treatment regimens, and the oncologist is given multiple opportunities to suggest and help implement these exercise and lifestyle changes. Our challenge as clinicians is to create opportunities to guide, encourage, and support patients as they adopt healthy lifestyle behaviors for physical activity. As demonstrated by this review, these approaches are increasingly evidence based and mechanistically understood.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Review Article*

# Systematic Review of the Relationship between Acute and Late Gastrointestinal Toxicity after Radiotherapy for Prostate Cancer

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A small but meaningful percentage of men who are treated with external beam radiation therapy for prostate cancer will develop late gastrointestinal toxicity. While numerous strategies to prevent gastrointestinal injury have been studied, clinical trials concentrating on late toxicity have been difficult to carry out. Identification of subjects at high risk for late gastrointestinal injury could allow toxicity prevention trials to be performed using reasonable sample sizes. Acute radiation therapy toxicity has been shown to predict late toxicity in several organ systems. Late toxicities may occur as a consequential effect of acute injury. In this systematic review of published reports, we found that late gastrointestinal toxicity following prostate radiotherapy seems to be statistically and potentially causally related to acute gastrointestinal morbidity as a consequential effect. We submit that acute gastrointestinal toxicity may be used to identify at-risk patients who may benefit from additional attention for medical interventions and close follow-up to prevent late toxicity. Acute gastrointestinal toxicity could also be explored as a surrogate endpoint for late effects in prospective trials.

## 1. Introduction

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in men in developed countries. Definitive external beam radiotherapy (RT) is a treatment option for the majority of patients who present with localized disease. Additionally, RT may be offered after radical prostatectomy for patients whose pathology demonstrates adverse pathologic features or as salvage therapy for recurrent disease after surgery.

Regardless of the treatment technique used, RT for prostate cancer exposes a portion of the lower gastrointestinal (GI) tract to ionizing radiation and consequently carries a risk of GI toxicity. GI toxicity is categorized as occurring within two possible phases: acute (typically within 3 months of treatment) and late (more than 3 months after treatment) [1, 2]. Symptoms can range from a mild increase in bowel movement frequency to more severe complications such as rectal bleeding, pain, or fistula. The acute phase of RT injury is characterized by inflammation in response to therapy, while the late phase is characterized by fibrosis and sclerosis within the GI tract [3]. While mild to moderate acute GI toxicity is more common than late toxicity, the potential permanent impact of late GI toxicity is thought to bear more clinical significance.

In an analysis of 35 studies including nearly 12,000 patients, rates of moderate (generally grade $\geq 2$) and severe (grade $\geq 3$) late GI toxicity following definitive external beam RT for prostate cancer were 15% and 2%, respectively [4]. Dose-escalated RT, which has been shown to improve disease control rates [5] and is now standard of care, increases the risk of late GI toxicity [4–7]. Reported rates of late GI toxicity appear to be decreased when dose-escalated RT is delivered using advanced treatment techniques such as intensity-modulated radiotherapy (IMRT) [4]. Other measures to limit GI toxicity, such as the administration of radioprotective medications [8] or the use of spacers to separate the prostate and rectum [9], are being explored. Randomized clinical trials,

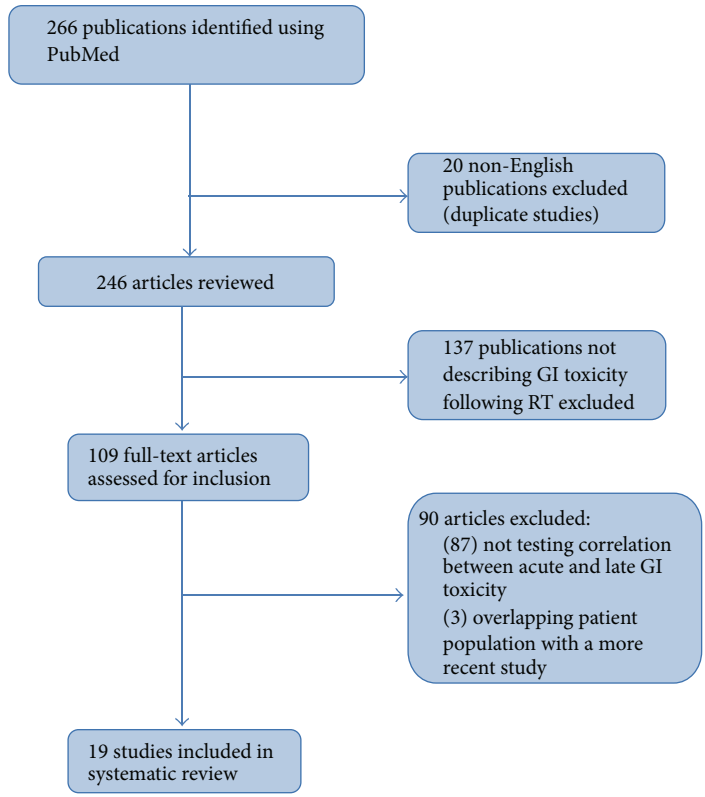


Figure 1: Selection strategy for systematic review of the published literature evaluating the relationship between acute and late gastrointestinal toxicity following prostate radiation therapy.

with large numbers of patients and lengthy follow-up, will be required to establish the efficacy of these toxicity prevention strategies.

There may be a consequential relationship between temporary acute GI toxicity and permanent late GI toxicity in prostate cancer patients treated with RT [10]. In this paper, we perform a systematic review to characterize the relationship between acute and late GI complications from prostate RT. We detail mechanisms by which acute toxicity may lead to consequential late effects. Finally, we explore the possibility of exploiting this connection for the identification of patients at risk of late GI toxicity and for the development of novel clinical trials for toxicity prevention.

## 2. Methods

*2.1. Study Selection.* We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) on May 1, 2013, for the terms "radiation therapy", "late", "early", and "side effects", with no limits placed on publication date. Duplicates and non-English language articles were excluded, and abstracts of all remaining manuscripts were read. Articles focusing on acute and late toxicity from external beam RT for prostate cancer were selected and examined in detail. Studies that examined the potential relationship between acute and late GI sequelae prostate RT were included in the final analysis. When two reports seemed to describe overlapping patient populations, the most recent publication was utilized for this analysis.

*2.2. Data Extraction and Clinical Endpoints.* Data abstraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11]. For each study, the following information was extracted: name of the first author, year of publication, name of the clinical trial (if applicable), sample size, and RT protocol. The primary measure of interest for this analysis was the association between late GI toxicity and acute GI toxicity. Hazard ratios, risk ratios, correlation coefficients, and other statistical measures describing the relationship between acute and late GI toxicity were extracted. Our preliminary analysis indicated that available data were not appropriate for meta-analysis, so we proceeded to perform a PRISMA-style systematic review.

## 3. Results

*3.1. Study Selection.* Search results are summarized in Figure 1. Our initial search yielded 266 results. Removal of duplicates and non-English language manuscripts reduced this number to 246. 109 papers met initial eligibility criteria and were read at full length to determine if statistical tests for a link between acute and late GI toxicity were reported. Most of the papers were eliminated for merely reporting rates of acute and/or late GI toxicity in the study population. Others were excluded because they combined GI and genitourinary effects in their analyses. Three papers described patient populations that were likely included in subsequent reports

from the same institutions. In total, 19 manuscripts met all eligibility requirements and were included in this report.

Ten manuscripts reported results from prospective trials [12–21] (Table 1), and nine were retrospective reviews of institutional experiences or databases [22–30] (Table 2). The trials that examined acute and late side effects involved a variety of techniques including conventional prostate RT [19], 3D conformal RT (3DCRT) [14, 15, 17, 24, 25, 30], high dose intensity modulated RT (IMRT) [27], hypofractionated IMRT [20, 23], combination brachytherapy + IMRT [29], and a mixed population treated with IMRT and 3DCRT [28]. Comparisons were also made in the manuscripts between different techniques including 3DCRT versus conventional RT [18]; 3DCRT dose escalation versus standard dose RT [12, 21]; 3DCRT versus hypofractionated 3DCRT [13]; a varied experience of 3DCRT and conventional RT ± ADT [22]; high dose IMRT versus high dose 3DCRT [26]; and high dose IMRT ± whole pelvis RT [16] (Table 1). The primary objective of most papers was to examine clinical factors leading to the development of acute GI and late GI toxicity [12–14, 16–18, 22, 28, 30], while some specifically focused on the relationship between acute and late side effects [14, 19, 21, 30]. The goal of other manuscripts was to simply report acute and late effects of a particular treatment [15, 20, 21, 23–27, 29]. Some of these studies tested medications to decrease toxicity, including rectal prostaglandin administration [15] and rectal sucralfate [19].

*3.2. Evidence of Association between Acute and Late GI Toxicity.* The manuscripts specifically looking for associations between acute and late effects demonstrated mild to strong correlations in various aspects of GI toxicity. Pinkawa et al. reported that acute bowel bothersome scores were associated with poor long-term bowel bothersome scores on univariate analysis, although with a HR of only 1.05; this relationship was not statistically significant in a multivariate analysis that accounted for RT dose and volume parameters [14]. Moderate to strong associations were found between multiple aspects of acute and late GI toxicity by Heemsbergen et al., where multivariable analysis suggested minimal contribution of RT dose and volume effects [21]. Acute proctitis was strongly (HR 2.9) associated with long-term diarrhea, defined as ≥6 stools a day. Acute mucosal discharge was predictive of later use of incontinence pads (HR 2.1). Interestingly, the authors note that more objective factors of GI toxicity such as bleeding not included in RTOG had a stronger correlation. This suggests that a different scoring scheme may better demonstrate consequential GI toxicity relationships [21]. Perhaps the strongest evidence of this relationship came from O'Brien et al., who found that grade ≥2 acute rectal pain was associated with grade ≥2 late rectal toxicity with a HR of 3.4 [19]. However this manuscript did not examine dosimetric parameters, so observations were not adjusted for potential RT dose-volume interactions.

The strongest findings attesting to the relationship of acute and late GI toxicity came from manuscripts not primarily interested in determining this effect. Zelefsky et al., while specifically looking at late toxicity response to 3DCRT dose escalation in 1571 participants, found that acute grade ≥2 GI toxicity was a strong predictor of late grade ≥2 GI toxicity (HR 6.95, $p < 0.001$). There was little contribution from dosimetric factors on multivariate analysis [28]. A similarly strong relationship was found between acute grade ≥2 proctitis and late grade ≥1 GI toxicity (OR 6.05, $p = 0.03$) in a trial looking at the effect of misoprostol suppository on late rectal toxicity following 3DCRT [15]. Further, multivariate examination of late GI toxicity in over 100 patients subjected to high dose 3DCRT demonstrated that grade ≥2 acute fecal incontinence was associated with chronic/late grade ≥2 fecal incontinence (OR 4.43, $p = 0.004$) and a stronger relationship for acute grade 3 fecal incontinence (OR 6.9, $p = 0.001$) [17]. Of the remaining papers, most of the correlations were mild to moderate or were not significant once placed in multivariate analysis with dosimetric considerations (Tables 1 and 2).

*3.3. Mechanism for Associations.* With some exceptions [13, 18, 19, 21, 30], most of the manuscripts that demonstrated an association between acute and late toxicities did not delve into the mechanism behind their findings. Koper et al. briefly discussed that their findings were most likely the result of consequential effects [18], namely, that acute toxicity leads to inflammation, leading to leakage of intestinal contents and eventual fibrosis manifesting as late toxicity. Alternatively, Arcangeli et al. concluded that the association between acute and late toxicity was evidence for a consequential mechanism but instead was a result of shared dosimetric risk factors. Interestingly, the association between acute and late effects observed in their conventionally fractionated RT arm was not observed in their hypofractionated RT arm [13].

Complementing their thorough data analysis, Heemsbergen et al. provided a more comprehensive explanation of the observed relationship between acute and late toxicity [21]. The authors put forth two possible mechanisms: the first a simple dose-volume relationship, and the second a continuum of consequential damage as has been observed in animal models [31]. In the former mechanism, severity of acute and late GI toxicity may correlate due to independent dose-volume effects on the RT at each time frame. Having the benefit of a large patient population, adequate follow-up, and uniform characterization of acute and late toxicity, the authors found on multivariate analysis that acute toxicity remained independently associated with late effects after adjusting for dosimetric variables and concluded that the relationship was most likely a combination of consequential effects and some dose volume effects. Of note, the group indicated that the acute RTOG score was not the most correlative factor; rather, tracking of individual GI symptoms was more revealing of the consequential pattern [21].

Heemsbergen indicated that other studies looking at acute-late correlation suffered from a lack of dose-volume considerations in their analysis [21]. This included the work of O'Brien et al. whose authors concede to not including dosimetric data but attest to dose-volume effects not contributing to acute toxicity in another study of a similar population and technique [19]. Koper et al. [18] offer alternative explanations to the observed correlation including inherent properties in individuals, such as yet described genetics or comorbidities that lead to greater tissue sensitivity to radiation both acutely

Table 1: Summary of prospective manuscripts studying relationship of acute and late GI toxicity after prostate RT.

| Study name [citation] | Study design | Toxicity analysis time points | | Toxicity grading system | | Follow-up duration | Acute & late toxicity correlation |
|---|---|---|---|---|---|---|---|
| | | Acute end | Late start | Acute | Chronic | | |
| Medical Research Council RT01 trial, Barnett et al. 2011 [12] | (i) Arm 1: 74 Gy/37 F ($n = 394$) 3DCRT<br>(ii) Arm 2: 64 Gy/32 F ($n = 394$) 3DCRT | 6 W PTC | 2 Y PTC | Acute RTOG | Late RTOG, LENT/SOMA, UCLA-PCI, RMH | Median not reported (2–5 Y) | Yes |
| Arcangeli et al. 2011 [13] | (i) Arm 1: 80 Gy in 40 F ($n = 85$) 3DCRT<br>(ii) Arm 2: 62 Gy in 20 F ($n = 83$) 3DCRT | 1 M PTC | 6 M PTC | Modified acute RTOG | Modified LENT/SOMA | (i) Arm 1 median 32 M (8–66 M)<br>(ii) Arm 2 median 35 M (7–64 M) | Yes |
| Pinkawa et al. 2010 [14] | 70.2 or 72 Gy in 1.8–2.0 Gy/F ($n = 298$), 3DCRT | 6 M PTC | 12 M PTC | Expanded Prostate Cancer Index Composite (EPIC) | Expanded Prostate Cancer Index Composite (EPIC) | Median 16 M (12–20 M) | Yes |
| Kertesz et al. 2009 [15] | (i) 60–72 Gy, 1.8–2 Gy/F, ($n = 100$), 3DCRT<br>(ii) Unreported number on ADT | TRT | Assume 90 D PTC | CTC v2 | RTOG, LENT/SOMA | Median 50 M (9–59 M) | Yes |
| Guckenberger et al. 2010 [16] | (i) 76.23 Gy/33 F ($n = 74$) IMRT<br>(ii) 73.91 Gy/32 F ($n = 26$) post prostatectomy IMRT | 6 W PTC | 6 M PTC | CTCAE v3.0 | CTCAE v3.0 | Median 26 M | Yes |
| AIROPROS 0102, Fellin et al. 2009 [17] | 70 Gy, 1.8–2 Gy/F ($n = 718$), 3DCRT | 1 M PTC | 6 M PTC | Custom fecal incontinence and bleeding questionnaire | Custom fecal incontinence and bleeding questionnaire | Median 36 M | Yes |
| Koper et al. 2004 [18] | (i) 66 Gy in 2 Gy/F ($n = 123$) 3DCRT<br>(ii) 66 Gy in 2 Gy/F ($n = 125$) Conventional<br>(iii) 15% got adjuvant ADT | Assume 90 D PTC | 1 Y PTC | Acute RTOG, modified Tait, and Fransson questionnaire | Late RTOG, modified Tait, and Fransson questionnaire | Median not reported, 93% followed to 2 Y | Yes |
| Heemsbergen et al. 2006 [21] | (i) 68 Gy in 2 Gy/F ($n = 275$) 3DCRT<br>(ii) 78 Gy in 2 Gy/F ($n = 278$) 3DCRT | 28 to 120 D PTC | 120 D PTC | Acute RTOG, maximum score of acute mucous discharge | Late RTOG | Median 44 M | Yes |

Table 1: Continued.

| Study name [citation] | Study design | Toxicity analysis time points | | Toxicity grading system | | Follow -up duration | Acute & late toxicity correlation |
|---|---|---|---|---|---|---|---|
| | | Acute end | Late start | Acute | Chronic | | |
| Trans-tasman radiation oncology group, O'Brien et al. 2002 [19] | 52.5 Gy in 20 F ($n$ = 23) or 63–65 Gy in 2 Gy/F fractions ($n$ = 63), conventional | Assume 90 D PTC | Assume 90 D PTC | Assume RTOG/EORTC | RTOG/EORTC | Median 63 M | Yes |
| Goineau et al. 2013 [20] | (i) 76 Gy in 38 F ($n$ = 38), IMRT (ii) $n$ = 21 ADT (6 M to 3 Y) | 2 M PTC | 6 M PTC | CTCAE V3, QLQ-C30, and QLQ-PR25 | CTCAE V3, QLQ-C30, and QLQ-PR25 | 54 M | No |

PTC = posttreatment completion, univariate (UV), multivariate (MV), androgen deprivation therapy (ADT), and TRT = throughout radiotherapy.
Acute RTOG = Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer acute morbidity rating scale.
Late RTOG = Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer late morbidity rating scale.
LENT = Late Effects Normal Tissue Task Force scale.
SOMA = Subjective, Objective, Management, and Analytic (SOMA) scales.
UCLA-PCI = University of California Loss Angeles Prostate Cancer Index.
RMH scale = Royal Marsden Hospital scale.
EPIC = Expanded Prostate Cancer Index Composite.
CTC v2 = Common Toxicity Criteria v2.0.
CTCAE V3 = Common Terminology Criteria for Adverse Events v3.0.
QLQ-C30 = EORTC QLQ-C30 quality of life questionnaire.
QLQ-PR25 = EORTC QLQ-PR25 quality of life questionnaire.
WHO = World Health Organization criteria.

Table 2: Summary of retrospective manuscripts studying relationship of acute and late GI toxicity after prostate RT.

| Study name [citation] | Study design | Toxicity analysis time points | | Toxicity grading system | | Follow-up duration | Acute/late GI toxicity association |
|---|---|---|---|---|---|---|---|
| | | Acute end | Late start | Acute | Chronic | | |
| Zilli et al. 2011 [23] | (i) IMRT 56 Gy in 4 Gy/F ($n = 82$)<br>(ii) Neoadjuvant ± concurrent ADT ($n = 12$) | 6 W PTC | 6 M PTC | Acute RTOG | Late RTOG | Median 48 M (9–67 M) | No |
| Fiorica et al. 2010 [24] | (i) 78 Gy in 2 Gy/F, 3DCRT ($n = 26$)<br>(ii) 78 Gy in 2 Gy/F + 6 M AST, 3DCRT ($n = 81$) | TRT | 3 M PTC | WHO | SOMA | Median 35 M (9–88 M) | No |
| Ballar et al. 2009 [25] | 74 Gy in 2 Gy/F, 3DCRT ($n = 104$) | 6 M PTC | 6 M PTC | Acute RTOG | Late RTOG | Median 30 M (20–50 M) | No |
| Shu et al. 2001 [26] | 72.0 to 79.2 Gy, 3DCRT ($n = 26$) or IMRT ($n = 18$) | 6 M PTC | 6 M PTC | Acute RTOG | Late RTOG | Median 23.1 M (10–84.7 M) | No |
| Cahlon et al. 2008 [27] | (i) 86.4 Gy/48 F IMRT ($n = 478$)<br>(ii) Some had adjuvant 3–6 M ADT | 90 D PTC | 90 D PTC | CTCAE V3 | CTCAE V3 | Media 53 M | Yes |
| Zelefsky et al. 2008 [28] | (i) 66–81 Gy, 1.8 Gy/F, 3DCRT or IMRT ($n = 1571$)<br>(ii) Neoadjuvant ADT 3 M ($n = 678$) | Assume 90 D PTC | Assume 90 D PTC | Assume CTCAE V3 | CTCAE V3 | Median 8 Y (5–18 Y) | Yes |
| Jereczek-Fossa et al. 2010 [30] | (i) Definitive RT 76 Gy in 2 Gy/F, 3DCRT ($n = 542$)<br>(ii) Postprostatectomy RT 70 Gy in 2 Gy/F, 3DCRT ($n = 431$) | 3 M PTC | 3 M PTC | Acute RTOG | Late RTOG | Median 25.2 M (1–129 M) | Yes |
| Liu et al. 2004 [22] | (i) Prospective database ($n = 1192$)<br>(ii) 52.5–72 Gy in 20–36 F, conventional or 3DCRT<br>(iii) Neoadjuvant ($n = 459$), median duration (5.1 M), concurrent ($n = 285$), adjuvant ($n = 222$), and median duration (11 M) | Assume 90 D PTC | Assume 90 D PTC | Assume Acute RTOG | Modified RTOG/SOMA | Median 49 M (24–105 M) | Yes |
| Zelefsky et al. 2008 [29] | $I^{25}$ implantation (110 Gy) followed in 2 M by 50.4 Gy of IMRT in 1.8 Gy/F ($n = 127$) | 90 D PTC | 90 D PTC | CTCAE | CTCAE | Median 30 M | No |

PTC = posttreatment completion, univariate (UV), multivariate (MV), androgen deprivation therapy (ADT), and TRT = throughout radiotherapy.
Acute RTOG = Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer acute morbidity rating scale.
Late RTOG = Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer late morbidity rating scale.
LENT = Late Effects Normal Tissue Task Force scale.
SOMA = Subjective, Objective, Management, and Analytic (SOMA) scales.
UCLA-PCI = University of California Loss Angeles Prostate Cancer Index.
RMH scale = Royal Marsden Hospital scale.
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CTC v2 = Common Toxicity Criteria v2.0.
CTCAE V3 = Common Terminology Criteria for Adverse Events v3.0.
QLQ-C30 = EORTC QLQ-C30 quality of life questionnaire.
QLQ-PR25 = EORTC QLQ-PR25 quality of life questionnaire.
WHO = World Health Organization criteria.

and chronically. A different explanation offered by Heemsbergen et al. is that some patients are more likely to communicate their symptoms and thus will verbalize both acute and late side effects alike [21]. However, the authors felt this theory was unlikely, as more objective findings such as acute and late rectal bleeding demonstrated strong associations [21]. The article by Jereczek-Fossa et al. was the most recent manuscript to thoroughly expand upon a proposed mechanism behind their demonstrated acute-late GI toxicity association [30]. The group believed, given the lack of prostate dose influence on late toxicity in a cohort of nearly 100 patients, that the association stemmed from consequential effects initiated by damage to the GI mucosa in the acute phase, citing works looking at consequential rectal toxicity in cervical cancer. Additionally, the authors asserted that age factored into the development of consequential damage when applied to multivariable analysis, in particular affecting acute toxicity as a result of comorbidities or an indirect effect of treatment decision-making [30].

Although not identified in the literature review, we are aware of the work by Campostrini et al. that showed more robust evidence of pathological consequential toxicity in humans [32]. Their group followed the progress of 130 patients from immediately after prostate RT and throughout the late period endoscopically (median follow-up of 84 months). It was noted that acute damage affected both the rectum and the anal canal macroscopically, with the most notable finding of hemorrhoid congestion, which was a major contributor to acute rectal bleeding. Interestingly, two patients had acute proctoscopic findings that were not manifested clinically. The finding of clinical and/or proctoscopic acute proctitis was strongly predictive of late toxicity (HR 5.6. 95% CI 2.1–15.2, $p = 0.001$) on multivariate analysis that incorporated dosimetric parameters [32].

*3.4. Difficulties in Reporting the Correlation between Acute and Late Toxicities.* Some of the authors of the manuscripts that did not observe a correlation between acute and late toxicities commented on the lack of findings, when viewed from the perspective of contradictory findings. Ballar et al. attributed the observed lack of correlation to a lower than normal acute toxicity found in their particular study compared to others [25]. Similarly, Zelefesky and colleagues manuscript did not identify a relationship between acute and late toxicities after combination brachytherapy and external beam RT, and they stated that this was likely due to fewer acute and late side effects than found in most similar studies [29]. Likewise, some manuscripts that did observe a relationship between acute and late toxicities also indicated potential study shortcomings that would underestimate the true consequential effect, such as short follow-up and newer RT techniques including IMRT that may cause less severe toxicity in both the acute and late setting [30]. Jereczek-Fossa et al. also noted that retrospective studies may suffer from underreported acute and late GI toxicity rates, complicated by the complexity of reporting late term side effects in prostate RT [30]. It has also been suggested that physician-based toxicity scoring, rather than patient-directed assessments, may introduce significant reporting bias [23].

## 4. Discussion

*4.1. Acute Toxicity Is Predictive of Late Toxicity.* The heterogeneity of the available data precludes quantitative synthesis in a formal meta-analysis, but we believe that the findings from this review shed significant light on the relationship between acute and late GI complications from prostate RT. Thirteen of the 19 studies that met inclusion criteria demonstrated an association between acute and late complications. Reports where no such associations were found tended to have a significantly smaller sample size than "positive" studies. Restricting our analysis to series with at least 200 subjects, for example, would leave nine remaining studies, all of which report a statistically significant link between acute and late complications. We therefore conclude that the overwhelming majority of the published evidence supports the presence of an association between acute and late GI toxicity following RT for prostate cancer.

Campostrini et al. provided strong evidence of pathologically confirmed acute toxicity as a significant predictor of late GI toxicity, even when dosimetric parameters as well as RT technique are taken into account. These findings are further bolstered by animal studies showing a stepwise pathologic progression from acute to late effects [33, 34]. Therefore, the trends found in this systematic review of clinical studies, combined with observations from animal models, support a second important conclusion: acute toxicity may serve as an appropriate surrogate for late GI toxicity as a way to identify patients at high risk of developing permanent late GI toxicity, potentially for clinical trials of novel therapies intended to prevent development of consequential late GI toxicity, and as a surrogate endpoint for clinical trials.

*4.2. Significance of Consequential Effect for Research.* Since clinically significant late GI toxicity occurs in a minority of patients, clinical trials of medical interventions designed to prevent GI toxicity after prostate RT may require an excessively large sample size, if the trial designs are such that any prostate RT patient is eligible. However, establishing a consequential relationship between acute and late GI toxicity presents the opportunity to develop more efficient trial designs by focusing on a high-risk population. If acute GI toxicity is used as an eligibility criterion, which would restrict the study population to those at highest risk of late GI toxicity, a candidate medical intervention could be studied in clinical trial with a higher likelihood of identifying an effective strategy to reduce late GI toxicity. For example, if the study population has a 40% risk of late GI toxicity after IMRT (based on including only patients with significant acute toxicity), then a randomized, controlled trial of intervention versus placebo with a sample size of just 100 subjects would have 71% power to detect a 50% reduction in late toxicity events (personal communication, Nolan Wages, Ph.D.). If the baseline toxicity risk was 10% and all other parameters were unchanged, the study would only have a power of 25%. Notably, this hypothetical example is potentially realistic, based on the available evidence identified in this report: assuming a 15% average risk of grade 2 or higher late GI toxicity [4] and a three- to sixfold increase in rates of late

GI toxicity among patients with grade 2 or higher acute GI toxicity [19, 21, 28], the risk of late toxicity among those patients with acute toxicity would be at least 40% and likely much higher.

The consequential nature of GI toxicity could be therefore exploited in research trials looking at interventions to avoid late toxicity in a number of ways:

(1) In future studies, acute toxicity may be used as a surrogate endpoint for late toxicity. This could decrease the duration and sample size required for prospective trials.

(2) Patients who demonstrate acute toxicity can be selected for long-term studies of late toxicity.

(3) Previously treated cohorts for which acute toxicity data are recorded can be assessed selectively for late toxicity, sampling only those patients who demonstrated acute GI toxicity.

*4.3. Future Potential Studies: Pharmacological.* With the above study framework, there are a number of pharmacological and nonpharmacological interventions than can be explored, some of which have already demonstrated the ability to prevent GI toxicity in pelvic radiation. This topic has been detailed in several recent reviews [35–37]. In regard to pharmacological interventions, the Cochrane review by Ali and Habib best summarizes the available options including such interventions as aminosalicylic acid (ASA) derivatives, sucralfate, arginine, vitamin E, probiotics, misoprostol, short chain fatty acid enemas, corticosteroids, cholestyramine, vitamin A, estrogen/progesterone, and octreotide [38]. Highlights from that review included manuscripts demonstrating the prevention of acute GI toxicity with oral sulphasalazine in prostate RT [39], as well as a decrease in acute and late GI toxicity when oral sucralfate is applied during and after RT for prostate and bladder cancer [40]. However, the previously cited work [19] and an earlier manuscript [41] by O'Brien et al. counter these findings when sucralfate is applied as a suppository during prostate RT in studies of similar size. Lastly, Ali and Habib referenced a small study showing that misoprostol suppositories applied before prostate external beam RT had protective properties [38]. Again, works encountered in this systematic review with larger numbers of participants did not find any benefit of misoprostol suppositories in the acute and late term [15].

There are other promising potential pharmacological compounds for preventing GI toxicity during pelvic RT. In regard to ASA derivatives, patients randomized to oral balsalazide during prostate RT achieved a CTC v2.0 prostate index of 35.3 versus 74.1 in placebo at two weeks after therapy ($p = 0.04$) [42]. However, a trial arm examining the rectal application of the ASA derivative mesalazine was prematurely terminated because of increased acute toxicity during prostrate 3DCRT in comparison to sucralfate enema control (HR 2.5, 95% CI 1.1–5.7, and $p = 0.03$) [43]. In the same study, no difference was found between sucralfate enema and hydrocortisone enema in preventing acute rectal toxicity [43]. Intrarectal application of the steroid beclomethasone in a more recent placebo controlled study did demonstrate an improved irritable bowel disease quality of life index, less rectal bleeding, and superior Vienna Rectoscopy Score up to 12 months following prostate RT [44]. Hyaluronic acid suppositories have also demonstrated the ability to decrease and delay acute radiation proctitis, according to RTOG scoring, when compared to historical prostate RT controls [45].

The free radical scavenger amifostine, when administered regularly during RT, has shown great potential in preventing acute rectal toxicity. In a randomized trial of 36 patients undergoing a mix of pelvic RT, intrarectal amifostine resulted in a significant decrease in RTOG score ($p < 0.001$), a decrease in LENT-SOMA score ($p = 0.002$), and improved proctoscopic tissue examination compared to controls [46]. More recent work has shown that increasing the dose of amifostine results in greater reduction of GI toxicity as determined by the EPIC bowel bothersome score during treatment and at 12 months after external prostate RT [47]. Lastly, the feasibility of rectal injections of Botox as a preventative measure against acute rectal toxicity has recently been studied based on Botox's effect on muscle spasticity, with future efficacy trials planned [48]. In total, there are a great deal more pharmaceutical compounds that have shown success in treating acute GI toxicity than treating late GI toxicity or preventing acute or late GI toxicity. Reassessment of some of these compounds as outlined above may be able to tease out greater usefulness in the above and other compounds.

*4.4. Future Studies: Nonpharmacological.* In regard to nonpharmacological strategies to prevent GI toxicity from pelvic RT, rectal balloons have been studied for a number of years and are used routinely in some practices, particularly in proton beam RT. However, there appears to be only one small work to show decreased late GI toxicity, compared to treatment without a rectal balloon, as determined by proctoscopic assessment at two-year follow-up [49]. Rectal balloons have shown good patient compliance and tolerance [50]. The use of injectable spacers is an alternative approach that creates space between the prostate target volume and the rectum. For example, prospective evaluation with a polyethylene glycol hydrogel spacer in small study of 10 patients demonstrated very low acute GI toxicity. [51]. Collagen injections have also been used to increase prostate-rectal distance, resulting in a 50% decrease in the RT dose to the rectum [52]. Recently, a hybrid idea that in simulation appears to function well is the biodegradable interstitial balloon [53]. In comparison to some of the pharmacologically based preventative measures, studies of spacer interventions are for the most part lacking assessment on late term effects and would greatly benefit from study designs where acute toxicity was applied as a surrogate for late toxicity or used for patient selection in long-term trials.

## 5. Conclusions

Published data strongly support the presence of an association between acute and late GI toxicity following RT for prostate cancer. We suggest that acute GI toxicity may be used by physicians to identify patients who may benefit from

personalized counseling and supportive care to address a high risk of permanent late GI toxicity. Furthermore, trials of strategies to prevent late morbidity might be enhanced by the preferential enrollment of subjects who develop acute toxicity in order to evaluate potential preventive strategies in a cohort of patients at high risk of late toxicity.

## Conflict of Interests

The authors have no conflict of interests to report.

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