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Radical Prostatectomy versus Intensity Modulated Radiation Therapy in the Management of Localized Prostate Cancer

Ayal Aaron Aizer
Yale University

Radical Prostatectomy versus Intensity Modulated Radiation Therapy in the Management of Localized Prostate Cancer

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by
Ayal A. Aizer
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Abstract

Purpose: To determine whether radical prostatectomy (RP) or intensity modulated radiation therapy (IMRT) to ≥72 Gy, plus hormonal therapy if indicated, results in improved biochemical disease free survival (BDFS) in localized prostate adenocarcinoma.

Methods and Materials: Between 1997-2005, a consecutive sample of 556 patients who underwent RP (n=204) or IMRT (n=352) at two referral centers was analyzed. Patients were stratified into prognostic groups based on clinical stage, Gleason score, and pretreatment prostate specific antigen (PSA) level as outlined by schemes designed by Memorial Sloan Kettering (MSK) and the National Comprehensive Cancer Network (NCCN). The outcome used in this study was BDFS. Median follow up in the RP and IMRT cohorts was 46 months and 40 months, respectively.

Results: IMRT patients had more advanced and aggressive disease at baseline ($p<.001$). No difference was found in five-year BDFS rates between RP and IMRT in the favorable prognosis (92.8% vs. 85.3%, $p=.20$) or the MSK intermediate prognosis (86.7% vs. 82.2%, $p=.46$) subsets. A difference favoring IMRT was seen in the NCCN intermediate prognosis (70.7% vs. 83.3%, $p=.03$), MSK poor prognosis (38.4% vs. 62.2%, $p<.001$), and NCCN poor prognosis (37.0% vs. 56.8%, $p=.005$) subsets. Within the entire cohort, after adjustment for

confounding variables, Gleason score (p<.001) and clinical stage (p<.001) predicted BDFS, but treatment modality (p=.06) did not. Within the MSK poor prognosis subset, treatment modality (p=.006) was predictive of BDFS, favoring IMRT.

Conclusion: Biochemical disease free survival is similar between RP and IMRT for patients with a good prognosis. Patients with a poor prognosis, and some with an intermediate prognosis, may benefit from IMRT to ≥72 Gy plus hormonal therapy.

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Table of Contents

Introduction

Prostate cancer is second only to nonmelanoma skin cancer as the most common form of cancer in American men and it is estimated that 218,890 American men were diagnosed with prostate cancer in 2007.[1] Prostate cancer represents the second leading cause of cancer-related death in American men, accounting for an estimated 27,050 deaths in 2007.[1] Over the past two decades, prostate cancer has become more commonly diagnosed at earlier stages of disease, likely due to the increased availability of prostate specific antigen (PSA) assays.[2] Currently, over 80% of newly diagnosed prostate cancer patients have clinically localized disease,[3] and as a result the number of men receiving local treatment with curative intent has increased.[4]

Treatment of patients diagnosed with localized prostate cancer (T1-T3N0M0)[5] centers around one of four options: observation, radical prostatectomy (RP), external beam radiation therapy, or brachytherapy. Observation alone has been shown in a prospective, randomized, controlled study to yield inferior outcomes when compared to surgery.[6, 7] This study randomized 695 men with stage T1-T2 prostate cancer (i.e., cancer confined to the prostate) to either RP or observation. With a median follow up of 8.2 years, RP yielded a statistically significant improvement in overall survival and disease-specific survival when compared to observation alone.[6, 7] As a result, observation is generally only appropriate for older patients with significant comorbidities and limited life expectancy, as these patients may not be candidates for more aggressive treatment, such as surgery or radiation. However, the debate regarding

observation versus treatment in patients with very early, localized, non-aggressive (i.e., low Gleason score and PSA levels) cancer continues.[8, 9]

Only patients with early, low-grade cancers are candidates for brachytherapy alone, as several series have reported poorer outcomes in patients with a clinical stage greater than T2a (i.e., the tumor can be palpated in less than half of one of the prostate gland's two lobes), a Gleason score of greater than 6, or a pretreatment PSA of greater than 10 ng/mL.[10, 11] In a retrospective study, which examined 1872 men treated with either RP, brachytherapy, or external beam radiation therapy, brachytherapy was found to yield statistically worse rates of biochemical control in patients with a clinical stage of T2b or greater, a Gleason score of greater than 6, or a pretreatment PSA of greater than 10 ng/mL when compared to the other two treatment modalities.[11] Other retrospective studies[12] and systematic reviews[13] have found similar results.

Unlike brachytherapy or observation, RP and external beam radiation therapy (with or without hormonal therapy) are appropriate options for almost all patients with localized prostate cancer, regardless of clinical stage, Gleason score, or pretreatment PSA.[10, 14] To date, only one prospective trial has been performed comparing RP and external beam radiation therapy in American men.[15] The trial was published in 1982 and included 97 patients, all with T1-T2 disease (i.e., disease confined to the prostate). Forty one patients were randomized to RP and 56 patients were randomized to external beam radiation therapy. This trial found that RP yielded higher progression-free survival than

external beam radiation therapy at five years post-therapy (p=.04). However, this study is now outdated and was limited by numerous methodological flaws.[16-18] Some physicians who enrolled patients in the trial did not use the specified randomization scheme, raising concern for physician selection bias. The study permitted cross-over between treatment arms and the analysis was not done on an intent-to-treat basis; rather, the analysis was based on the actual treatment given, which generally is not standard practice when designing randomized trials. Pathologic stage C patients (i.e., those with the poorest prognosis) were excluded from the surgical arm but allowed in the radiation arm and a worse than previously reported outcome was seen among external beam radiation therapy patients. Additionally, the authors did not provide data as to the pretreatment characteristics of each cohort (e.g. Gleason score, acid phosphatase level, age, race etc…), and no multivariable analysis was performed. A multivariable analysis would be necessary to account for the impact of clear differences in the respective cohorts, such as the pathologic stage of patients included in the study. As a result of these limitations, it is difficult to form any meaningful conclusions regarding RP versus external beam radiation therapy in the treatment of localized prostate cancer based on this single trial.[16-18]

A number of retrospective reviews have attempted to compare RP and external beam radiation therapy.[11, 19-25] Of the contemporary reviews (i.e., those published in the past twelve years, in which all patients received PSA follow up), all used biochemical disease free survival (BDFS) as the primary outcome measure. Nearly all studies stratified patients based on the proven prognostic

factors of pretreatment PSA, Gleason score, and clinical stage. Patients treated with surgery almost always underwent a radical retropubic prostatectomy, often times with a lymph node dissection, while patients treated with external beam radiation therapy frequently were treated via a conformal technique. Radiation doses ranged from a median of 66 Gy to a median of 70.2 Gy, with the exception of the review by Keyser et al.[19] in which the median dose of radiation was 74 Gy (range 70 Gy to 83 Gy).

Most prior retrospective reviews found no difference in outcome between RP and external beam radiation therapy in all prognostic groups,[11, 19-21, 24] with the following exceptions. A review by D'Amico et al. found improved BDFS in patients who underwent a radical prostatectomy, as opposed to external beam radiation therapy, if they had a favorable prognosis (defined as patients with a pretreatment PSA of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage of T2a or less) or an intermediate prognosis (defined as patients with a pretreatment PSA of greater than 10 ng/mL but less than 20 ng/mL, a Gleason score of 7, or a clinical stage of T2b), provided that these patients carried a low tumor volume (defined as <34% of positive biopsies). However, in patients with an intermediate prognosis, the difference in outcome was no longer significant at 10 years post therapy.

In a retrospective review by Kupelian et al., initial analysis revealed no difference in BDFS in any prognostic group. However, on subgroup analysis of patients with a poor prognosis (defined as a pretreatment PSA of greater than 10 ng/mL, a Gleason score of 7 or greater, or a clinical stage of T2b or greater),

patients who received external beam radiation therapy to a dose of at least 72 Gy had significantly better BDFS when compared to patients who underwent RP ($p=.004$), while patients treated with external beam radiation therapy to a dose less than 72 Gy had significantly poorer BDFS than patients who underwent RP ($p<.001$).[22] A subsequent retrospective study by Kupelian et al. also found that external beam radiation therapy to a dose of less than 72 Gy yielded inferior biochemical disease free survival when compared to RP. This result was seen in the whole cohort and among each prognostic group.[23]

Collectively, these retrospective studies seem to indicate that RP and external beam radiation therapy generally yield similar outcomes in patients with prostate cancer, but also that the dose of radiation used to treat patients may impact the results of the trial.

Since the last study comparing RP and external beam radiation therapy was carried out, novel strategies in the management of localized prostate cancer have been adopted by the oncology community. The standard of care for external beam radiation therapy now centers on a relatively new approach, intensity modulated radiation therapy (IMRT).[26-29] IMRT, which became widely available 5-10 years ago, offers the ability to modulate individual beams of radiation so that the intensity of photons within a particular beam can be varied. This facilitates the ability to deliver high doses of radiation to the tumor, while administering relatively low doses of radiation to surrounding tissues, such as the bowel and bladder in cases of prostate cancer.[30] High doses of radiation (those exceeding 72 Gy) have been decidedly shown to improve outcomes in patients

with prostate cancer[31-33] (as suggested by the retrospective studies comparing RP and external beam radiation therapy), and IMRT is the preferred radiotherapy technique because its lower side effect profile, compared to other forms of external beam radiation therapy, allows higher doses of radiation to safely be used in the treatment of prostate cancer.[23, 34-36] With non-IMRT based approaches, it may not be feasible to safely deliver high doses of radiation to the prostate without exceeding the tolerance of the surrounding bowel and bladder, thereby resulting in serious acute and late radiation toxicity.[37, 38] To date, no study has compared IMRT to RP in the treatment of prostate cancer. In addition, no previous review has only included patients treated to 72 Gy or higher, now considered the standard of care.[39]

Since the publication of the last retrospective review comparing RP to external beam radiation therapy, hormonal therapy has become a mainstay adjunctive treatment for patients with an intermediate or poor prognosis when given in conjunction with radiation.[40-44] In Radiation Therapy Oncology Group Trial 8610, patients were randomized to external beam radiation with or without four months of goserelin (a gonadotropin releasing hormone agonist) plus flutamide (an androgen receptor antagonist) in the neoadjuvant/concurrent setting. At a median follow up of 12.5 years, the cohort randomized to hormonal therapy displayed decreased disease-specific mortality, distant metastases, and biochemical failures.[45] Another prospective trial randomized locally advanced prostate cancer patients to either external beam radiation alone or radiation plus three years of concurrent/adjuvant goserelin plus one month of cyproterone (an

androgen receptor antagonist). At a median follow up of 66 months, hormonal therapy significantly improved disease free survival and overall survival.[46, 47] Other prospective studies have found similar results.[48] As a result, hormonal therapy is generally indicated in patients treated with external beam radiation therapy who have an intermediate or poor prognosis (i.e., patients with a pretreatment PSA of greater than 10 ng/mL, a Gleason score of greater than 6, or a clinical stage of greater than T2a); hormonal therapy is not indicated in patients who undergo surgery because no benefit has been seen in surgical patients who undergo adjuvant hormonal therapy.[40, 48, 49]

In all previous reviews, patients receiving hormonal therapy were excluded from the analysis[19-21, 24, 25] or only a small percentage of patients in the review received hormonal therapy. Specifically, in a review published by Kupelian et al., 17% of RP patients and 23% of external beam radiation therapy patients received hormonal therapy. In another review by Kupelian et al. 17% of RP patients and 5-39% of external beam radiation therapy patients (depending on prognostic group) received hormonal therapy.[22, 23] In all other retrospective studies cited in this thesis, no patients were treated with hormonal therapy.

Another limitation of prior retrospective studies comparing RP and external beam radiation therapy pertains to the varying definitions of "post-treatment biochemical failure" used in each review. Although all definitions of post-treatment biochemical failure are based on PSA levels,[50] each definition carries a different sensitivity and specificity for true clinical failure.[51-53] Therefore, it is difficult to interpret the results of previous retrospective studies. For example, of

the aforementioned retrospective reviews comparing RP to external beam radiation therapy, four definitions of post-RP biochemical failure were used including “two PSA levels of greater than 0.2 ng/mL”,[22-24] “two detectable PSA levels”,[20] “a single PSA of at least 0.2 ng/mL”,[19, 21] and “three consecutive PSA rises”.[11, 25] Post external beam radiation therapy definitions have varied as well and have included “three consecutive rises in PSA level”,[11, 21-25] “two consecutive rises in PSA level”,[20] and “PSA nadir plus one ng/mL”.[19] To combat this problem, in 2006 the American Society for Therapeutic Radiology and Oncology (ASTRO) published guidelines recommending that the definition of post-external beam radiation therapy biochemical failure be established as absolute PSA nadir + 2 ng/mL.[54] No retrospective study has used this definition of post external beam radiation therapy biochemical failure. Another benefit of the updated definition of post-external beam radiation therapy biochemical failure is that it can be applied if a patient receives external beam radiation therapy and hormonal therapy, which is not the case with previous definitions because data used to derive these definitions was obtained from patients who were not treated with hormonal therapy.[54] For patients treated with RP, the American Urological Association (AUA) guidelines, published in 2007, define post-treatment failure as a single PSA of 0.2 ng/mL, with a second confirmatory PSA exceeding 0.2 ng/mL.[55] No review has used this definition of post-RP failure, although many have used similar definitions.

The primary goal of this study was to retrospectively compare radical prostatectomy to dose-adequate intensity modulated radiation therapy plus

hormonal therapy, if indicated, in patients with localized prostate cancer, using modern definitions of biochemical disease free survival as the outcome measure.

Hypothesis and Specific Aims

The primary goal of this study was to retrospectively compare radical prostatectomy to dose-adequate intensity modulated radiation therapy plus hormonal therapy, if indicated, in patients with localized prostate cancer, using modern definitions of biochemical disease free survival as the outcome measure.

Methods and Materials

Study Design and Patient Populations

We conducted a retrospective observational cohort study of a consecutive sample of 708 patients treated for localized prostate adenocarcinoma between 1997-2005; 495 patients received radiation therapy and 213 underwent surgery. Patients receiving post-operative radiation were excluded from the study. Patients treated with radiation therapy received treatment at either Yale New Haven Hospital (New Haven, CT, 373 patients) or Lawrence & Memorial Hospital (New London, CT, 122 patients). All 213 patients treated surgically underwent a radical retropubic prostatectomy at Yale New Haven Hospital. Patients were excluded from the IMRT group if they lacked three post-treatment PSA levels (n=97), were treated to doses under 72 Gy (n=45), or lacked adequate pretreatment staging (n=1), leaving 352 patients in the IMRT group. Patients were excluded if they lacked three post-treatment PSA values because of the inability to apply the “nadir + 2” definition of failure in such cases. Patients were excluded from the RP cohort if they lacked an accessible follow up PSA (n=7) or underwent a salvage prostatectomy after failed radiation therapy (n=2), leaving 204 patients in the RP cohort.

Staging

Before receiving therapy, all patients underwent a clinical history and physical including digital rectal examination, PSA level, and ultrasound guided transrectal prostate biopsy with Gleason score histological grading. Other staging modalities such as computed tomography of the pelvis, magnetic resonance imaging of the prostate or pelvis, positron emission tomography, or bone scanning were performed at the discretion of the attending physician. No patient was found to have metastatic disease after staging evaluation. Staging was performed in accordance with the 1992 AJCC staging system.[5] A summary of the AJCC clinical staging of prostate cancer, as presented by the National Cancer Institute, is presented below:

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Clinically unapparent tumor not palpable nor visible by imaging

- T1a: Tumor incidental histological finding in 5% or less of tissue resected
- T1b: Tumor incidental histological finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2: Tumor confined within prostate

- T2a: Tumor involves 50% or less of one lobe
- T2b: Tumor involves more than 50% of one lobe but not both lobes
- T2c: Tumor involves both lobes

T3: Tumor extends through the prostate capsule

- T3a: Extracapsular extension (unilateral or bilateral)

T3b: Tumor invades seminal vesicle(s)

T4: Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Prognostic Groups

Patients were stratified into prognostic groups based on the prognostic parameters of clinical stage, Gleason score, and PSA level. Each of these prognostic factors independently predicts outcome in patients with prostate cancer.[56-60] Two prognostic group schemes were chosen; these appear to be the schemes most commonly used by clinicians in practice.[3, 19, 20, 23, 61]

In the Memorial Sloan Kettering (MSK) scheme,[62, 63] the favorable prognosis group consisted of patients with a clinical stage ≤T2a, a Gleason score ≤6, and a pretreatment PSA ≤10 ng/mL. Patients in the intermediate and poor prognosis groups presented with one and two or more unfavorable prognostic parameters (clinical stage >T2a, Gleason score >6, or PSA>10), respectively.

The data were also analyzed using the National Comprehensive Cancer Network (NCCN) scheme,[64] in which the favorable prognosis group also consisted of patients with a clinical stage ≤T2a, a Gleason score ≤6, and a pretreatment PSA ≤10. The intermediate prognosis group contained patients with a clinical stage of T2b-T2c, a Gleason score of 7, or a pretreatment PSA between 10-20 ng/mL. The poor prognosis group consisted of patients with a clinical stage of ≥T3a, a Gleason score ≥8, or a pretreatment PSA of >20 ng/mL.

Treatment

Patients who opted for surgery underwent radical retropubic prostatectomy with bilateral lymph node dissection. Nearly all of the surgeries were performed by the same surgeon, an experienced urologic oncologist practicing at Yale New Haven Hospital, a tertiary care medical center.

The vast majority (96.3%) of patients opting for radiation received exactly 75.6 Gy in 1.8 Gy fractions (others treated to 72.0 - 77.4 Gy). Radiation was delivered with an isocentric, five-field technique, using 18 MV or 10 MV photons. IMRT was utilized, at least in part, to treat all patients undergoing radiation; 112 patients (31.8%) received 3D conformal radiation therapy (3DCRT) and IMRT, 203 patients (57.7%) received IMRT alone, and 37 patients (10.5%) received four-field whole pelvic radiation with an IMRT guided boost to the prostate.

Patients treated with 3DCRT and IMRT were treated to 66.6 Gy with 3DCRT using a planning target volume (PTV) defined as a 1.5 cm margin around the tumor volume (TV) in three dimensions, followed by a 9.0 Gy IMRT based cone down using a margin of 1.0 cm around the tumor volume, except for the rectal-prostate interface, where a 0.6 cm margin was used. Patients treated with IMRT alone were treated to 66.6 Gy with IMRT using a PTV defined as a 1.2 cm margin around the tumor volume in three dimensions, followed by a 9.0 Gy IMRT based cone down using a margin of 1.0 cm around the tumor volume, except for the rectal-prostate interface, where a 0.6 cm margin was used.

Whole pelvic radiation patients received 45.0 Gy to the whole pelvis with a 30.6 Gy IMRT based cone down as described above. To deliver whole pelvic radiation, a four-field technique utilizing bony landmarks was employed. A four-field technique was chosen, as opposed to an IMRT-based plan, because of data suggesting that IMRT does not improve lymph node coverage in advanced prostate cancer.[65] Whole pelvic radiation was designed to cover the obturator, internal iliac, external iliac, pre-sacral, and peri-rectal nodes, as these are the most common lymph node groups involved in prostate cancer.[65] The superior, lateral, and inferior borders of the whole pelvic field were at L5/S1, 2.0 cm lateral to the pelvic brim, and 0.5 cm inferior to the obturator foramen, respectively.[66] The inferior border employed in our study has been shown to adequately cover the apex of the prostate.[67] The decision to administer whole pelvic radiation was made at the discretion of the attending physician. Commonly, patients with at least a 15% likelihood of lymph node involvement, as predicted by the Roach formula,[68] were considered for whole pelvic radiation therapy. The Roach formula accounts for Gleason score and pretreatment PSA in ascertaining the likelihood of lymph node involvement and is presented here:

% likelihood of lymph node involvement = 2/3*(PSA) + 10*(Gleason score-6)

Within the IMRT group, 30 patients in the MSK favorable prognosis group (37.5%), 138 patients in the intermediate prognosis group (89.0%), and 114 patients in the poor prognosis group patients (97.4%) received hormonal therapy,

consisting of a gonadotropin releasing hormone agonist in 56.5% of patients, an androgen receptor antagonist in 3.6% of patients, and combined modality therapy in 39.9% of patients. Patients in the intermediate and poor prognosis groups generally received 6 months and 12-24 months of hormonal therapy, respectively. After treatment, patients were followed up routinely with PSA testing and digital rectal exams. Follow-up visits typically occurred one month after completion of treatment, every 3-6 months for the following two years, and every 6-12 months thereafter. The median follow up was 46 months in the RP cohort and 40 months in the IMRT cohort.

Verification of Data

We employed methods recommended in the literature to ensure the validity and reliability of data collected.[69] Upon completion of data collection, a second reviewer blindly reabstracted a random sample of 30 charts, representing 5.4% of the 556 charts reviewed. The overall mean percentage agreement between the two reviewers was 100% across all variables. To measure interrater agreement for nominal variables, a kappa statistic was calculated and found to be 1.0.

Statistical Methods

Baseline patient characteristics were compared using the chi-square test for categorical variables and the unpaired t-test for continuous variables. If a categorical variable contained less than five patients, Fisher's exact test was used instead.

Biochemical failure was defined in IMRT patients as absolute PSA nadir + 2 ng/mL. The date of failure was defined as the date at which the post-treatment PSA exceeded the nadir + 2 ng/mL. Post-RP biochemical failure was defined as a single PSA of at least 0.2 ng/mL, with a second confirmatory PSA of greater than 0.2 ng/mL. The date of failure was defined as the date at which the PSA reached 0.2 ng/mL. Data was censored at the date of last PSA level. The data were not analyzed with alternative definitions of biochemical failure or with an alternative prognostic group scheme.

Biochemical disease free survival was calculated using the Kaplan-Meier method, graphically displayed, and compared with the log-rank test. Biochemical disease free survival rates at individual post-treatment times were compared by calculating the quotient of the difference in survival (between RP and IMRT cohorts at a given time point) squared and the weighted variance of the survival functions, and subsequently comparing this quotient to the chi-square distribution using one degree of freedom.[70]

With the use of proportional hazards analysis, hazard ratios and 95% confidence intervals were generated for the unadjusted association between baseline characteristics and biochemical failure. To examine the impact of confounding factors, a Cox proportional hazards multivariate analysis was

performed using the following variables: age, race, prior transurethral resection of the prostate (TURP), clinical stage, Gleason score, pretreatment PSA, treatment modality (RP vs. IMRT), type of radiation therapy employed, hospital of treatment, and hormonal therapy. To remain in the model, variables were required to have a p value of <.20.

All reported p values are two-sided. Statistical analysis was performed using SAS version 9.1. This study was approved by the Institutional Review Board of Yale School of Medicine. The study was carried out in a manner consistent with the Helsinki Declaration of 1975, as revised in the year 2000. Written consent was not obtained from participants (i.e., a waiver was granted) because this was a retrospective review of existing patient data.

Contributions to Thesis Project

Ayal A. Aizer was at least partially responsible for the conception and design of the study, data collection and analysis, and drafting of the manuscript. The study was primarily designed by Ayal A. Aizer, Dr. John Concato, and Dr. Richard Peschel, the senior investigator of the study. The majority of data collection was performed by Anne M. McKeon MS, although Ayal A. Aizer retrieved a portion of the data used in this study. Data analysis was performed by Ayal A. Aizer, although statistical and software-related assistance was provided by Dr. James B. Yu. The manuscript was prepared by Ayal A. Aizer, although Dr. John Concato, Dr. Joanne Weidhaas, Dr. Lynn Wilson, and Dr. Richard Peschel

reviewed and edited the manuscript. Dr. John W. Colberg and Dr. Roy H. Decker provided valuable advice regarding the conception and design of the study and provided support and guidance throughout the research project.

Results

Patient Characteristics

Pretreatment and treatment-related patient characteristics are summarized by treatment modality in Table 1.

Table 1. Pretreatment and Treatment-Related Patient Characteristics

Pretreatment Parameter		**RP patients**		**IMRT patients**		**All patients**		**P**
		N	**%**	**N**	**%**	**N**	**%**	
Age								<.001
	≤65	179	88	100	28	279	50	
	>65	25	12	252	72	277	50	
Race								0.27*
	White	174	85	284	81	458	82	
	African American	29	14	62	18	91	16	
	Asian	0	0	4	2	4	1	
	Hispanic	1	0.5	2	1	3	1	
Prior TURP								<.001
	Yes	2	1	23	7	25	4	
	No	202	99	329	93	531	96	
Clinical Stage								0.01†
	T1-T2a	152	75	294	84	446	80	

	T2b-T2c	51	25	31	9	82	15	
	T3a	1	0.5	26	7	27	5	
	T3b	0	0	1	0.3	1	0.2	
Gleason Score (total)								<.001
	≤6	144	71	126	36	270	49	
	7	49	24	145	41	194	35	
	≥8	11	5	81	23	92	17	
Pretreatment PSA								<.001
	≤4	29	14	28	8	57	10	
	>4 to ≤10	138	68	191	54	329	51	
	>10 to ≤20	29	14	89	25	118	29	
	>20	8	4	44	13	52	9	
MSK Prognosis Group								<.001
	Favorable	103	50	80	23	183	33	
	Intermediate	59	29	155	44	214	38	
	Poor	42	21	117	33	159	29	
NCCN Prognosis Group								<.001
	Favorable	103	50	80	23	183	33	
	Intermediate	84	41	150	43	234	42	
	Poor	17	8	122	35	139	25	
Method of Radiation								n/a

	3DCRT+IMRT	n/a		112	32	n/a		
	IMRT alone	n/a		201	57	n/a		
	Whole Pelvic IMRT	n/a		39	11	n/a		
Treatment Site								<.001
	Lawrence & Memorial Hospital	0	0	71	20	71	13	
	Yale New Haven Hospital	204	100	281	80	485	87	
Hormonal Therapy								<.001
	Yes	6	3	282	80	288	52	
	No	198	97	70	20	268	48	

*p value represents Chi-Square between White patients and African American patients

†p value represents Chi-Square for clinical stage ≤ T2a vs. >T2a

Abbreviations: RP = Radical Prostatectomy; IMRT = Intensity Modulated Radiation Therapy; 3DCRT = 3 Dimensional Conformal Radiation Therapy; PSA = Prostate Specific Antigen; MSK = Memorial Sloan Kettering; NCCN = National Comprehensive Cancer Network; TURP = Transurethral Resection of the Prostate

Patients in the IMRT group were older, and had higher Gleason scores and pretreatment PSA levels, than patients in the RP group (p<.001 in all cases). Although more RP patients had a clinical stage ≥T2b (p=.01), more IMRT patients had T3 disease (p<.001). Patients in the IMRT cohort had more advanced disease, as judged by both the MSK and NCCN prognostication schemes (p<.001). There was no significant difference in race between RP and IMRT cohorts.

Treatment Outcome

Three-year and five-year biochemical disease free survival rates for the combined and individual prognostic groups are displayed in Table 2.

Table 2. Biochemical Disease Free Survival Rates in RP and IMRT Patients

Cohort		3 yr BDFS	95% CI	p	5 yr BDFS	95% CI	p
Whole cohort				0.004			0.37
	RP	83.5	76.9-88.3		78.4	70.5-84.3	
	IMRT	91.7	87.7-94.5		74.8	66.2-81.5	
MSK favorable				0.45			0.20
	RP	95.1	87.4-98.1		92.8	83.0-97.1	
	IMRT	97.3	89.7-99.3		85.3	68.6-93.5	
MSK inter				0.13			0.46
	RP	86.7	72.4-93.9		86.7	72.4-93.9	
	IMRT	94.0	88.2-97.0		82.2	69.3-90.1	

MSK poor				<.001			<.001
	RP	53.8	36.8-68.0		38.4	21.8-54.8	
	IMRT	85.8	76.8-91.6		62.2	47.0-74.3	
NCCN favorable*				0.45			0.20
	RP	95.1	87.4-98.1		92.8	83.0-97.1	
	IMRT	97.3	89.7-99.3		85.3	68.6-93.5	
NCCN inter				0.002			0.03
	RP	77.5	65.7-85.6		70.7	57.2-80.6	
	IMRT	91.7	85.0-95.5		83.3	72.0-90.4	
NCCN poor				<.001			0.005
	RP	49.3	23.0-71.2		37.0	11.6-63.1	
	IMRT	88.0	79.3-93.3		56.8	39.4-71.0	

*The favorable prognosis group in the MSK and NCCN prognostication schemes consists of the same patients.

Abbreviations: RP = Radical Prostatectomy; IMRT = Intensity Modulated Radiation Therapy; MSK = Memorial Sloan Kettering; NCCN = National Comprehensive Cancer Network; CI = Confidence Interval

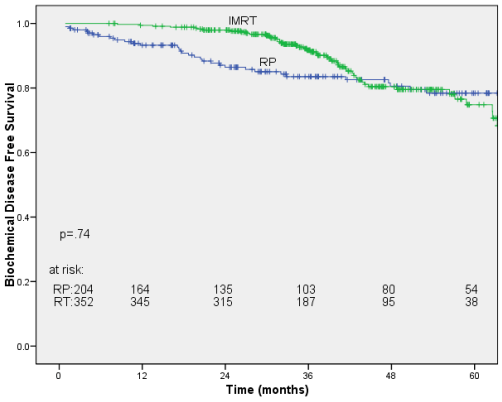
No significant difference in biochemical disease free survival was observed between RP and IMRT at any time point within the MSK/NCCN favorable and the MSK intermediate prognosis subsets. Differences in biochemical disease free survival favoring the IMRT group were seen in the MSK poor prognosis subset at three (p<.001) and five (p<.001) years post-treatment, the NCCN poor prognosis subset at three (p<.001) and five (p=.005) years post-

treatment, and the NCCN intermediate prognosis subset at three (p=.002) and five (p=.03) years post-treatment.

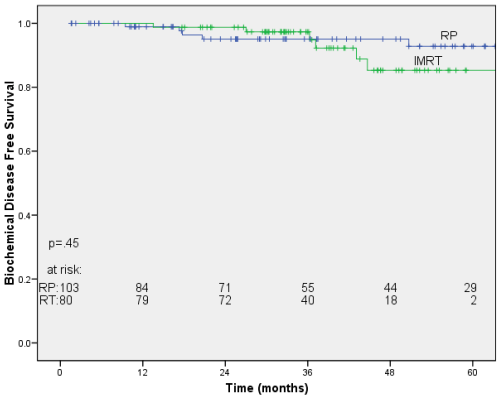
Kaplan-Meier curves comparing biochemical disease free survival in RP and IMRT patients are displayed in Figure 1:

Figure 1: Biochemical Disease Free Survival Rates for Whole Cohort and Individual Prognostic Groups

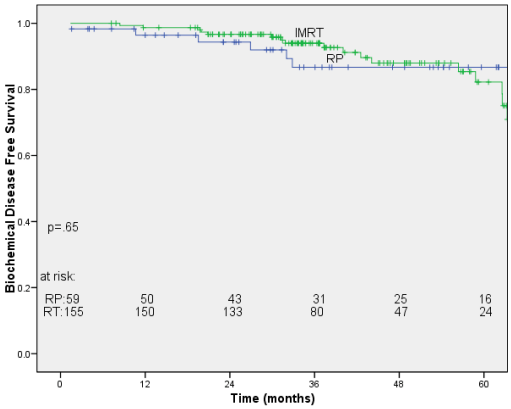
Whole Cohort (Figure 1a)



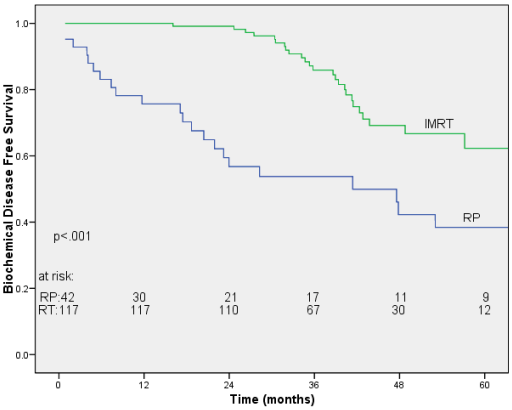
MSK/NCCN Favorable Prognostic Group (1b)



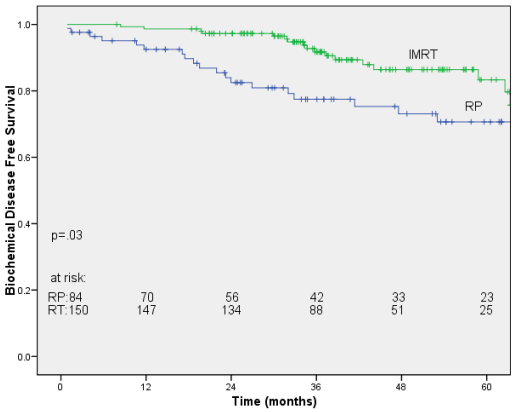
MSK Intermediate Prognostic Group (1c)



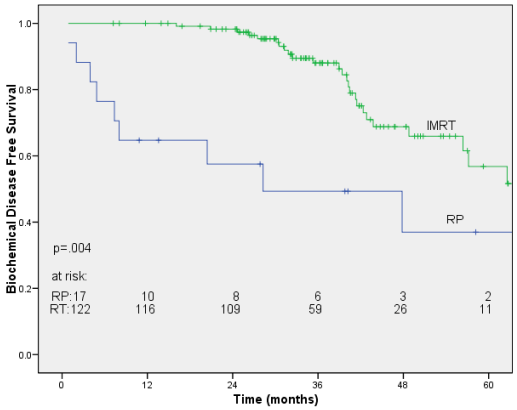
MSK Poor Prognostic Group (1d)



NCCN Intermediate Prognostic Group (1e)



NCCN Poor Prognostic Group (1f)



Legend: Biochemical disease free survival in RP and IMRT patients in the whole cohort (a), MSK/NCCN favorable prognosis group (b), MSK intermediate prognosis group (c), MSK poor prognosis group (d), NCCN intermediate prognosis group (e), and NCCN poor prognosis group (f).

No significant difference in survival curves was seen in the overall study population, MSK/NCCN favorable prognosis subset, or MSK intermediate prognosis subset. Patients in the MSK poor prognosis subset (p<.001), NCCN intermediate prognosis subset (p=.03), and NCCN poor prognosis subset (p=.004) displayed higher biochemical disease free survival when treated with IMRT.

An unadjusted analysis and Cox proportional hazards multivariable (adjusted) analysis of the entire study population are shown in Table 3.

Table 3. Unadjusted and Adjusted Analysis of Patient Characteristics and Biochemical Failure for Entire Cohort

Clinical Parameter†	Unadjusted p value	Unadjusted Hazard Ratio	95% CI	Adjusted p value	Adjusted Hazard Ratio	95% CI
Age	0.68	1.00	0.97-1.02			
Race*	0.51	1.19	0.70-2.03			
Prior TURP	0.40	1.83	0.44-7.52			
Clinical Stage	<.001	3.60	2.34-5.53	<.001	2.42	1.52-3.85
Gleason Score (total)	<.001	2.19	1.66-2.90	<.001	2.02	1.47-2.79
Pretreatment PSA	0.009	1.42	1.09-1.83	0.19	1.20	0.92-1.56
Treatment Modality	0.74	0.93	0.59-1.45	0.06	0.62	0.38-1.03
Method of Radiation††	0.08	0.55	0.28-1.06			
Treatment Site†††	0.43	1.42	0.60-3.35			
Hormonal Therapy	0.02	1.64	1.07-2.52			

*only Whites and African Americans were compared in this analysis

† Coding of clinical parameters: Age (continuous, per year), Race (reference = white),

Prior TURP (reference = no TURP), Clinical Stage (T1-T2a versus T2b-T2c versus T3a-T3b, reference = T1-T2a), Gleason Score (<7 versus 7 versus >7, reference = <7), Pretreatment PSA (continuous, per ng/mL increment), Treatment Modality (reference = RP), Method of Radiation (reference = 3DCRT + IMRT), Treatment Site (reference = Lawrence & Memorial Hospital), Hormonal Therapy (reference = no hormonal therapy)

††only 3DCRT+IMRT and IMRT alone were compared in this analysis

†††only includes patients treated with radiation

Abbreviations: IMRT = Intensity Modulated Radiation Therapy; 3DCRT = 3 Dimensional Conformal Radiation Therapy; PSA = Prostate Specific Antigen; TURP = Transurethral Resection of the Prostate; CI = Confidence Interval

In unadjusted analysis, clinical stage (Hazard Ratio 3.60, 95% CI 2.34-5.53, p<.001), Gleason score (Hazard Ratio 2.19, 95% CI 1.66-2.90, p<.001), and pretreatment PSA (Hazard Ratio 1.42, 95% CI 1.09-1.83, p= .009) predicted BDFS, but treatment modality did not (p=.74). After adjustment, clinical stage (Hazard Ratio 2.42, 95% CI 1.52-3.85, p<.001) and Gleason score (Hazard Ratio 2.02, 95% CI 1.46-2.79, p<.001) were predictive of BDFS, but the impact of treatment modality (Hazard Ratio 0.62, 95% CI 0.38-1.03, p=.06, favoring IMRT) and pretreatment PSA (Hazard Ratio 1.20, 95% CI 0.92-1.56, p=.19) did not achieve statistical significance. Additionally, race (p=.22) and age (p=.58) did not affect biochemical disease free survival on multivariable analysis.

An unadjusted and adjusted analysis were performed on the MSK poor prognosis group as well (Table 4).

Table 4. Unadjusted and Adjusted Analysis of Patient Characteristics and Biochemical Failure for MSK Poor Prognosis Subset

Clinical Parameter†	Unadjusted p value	Unadjusted Hazard Ratio	95% CI	Adjusted p value	Adjusted Hazard Ratio	95% CI
Age	0.003	0.43	0.24-0.76	0.08	0.96	0.92-1.00
Race*	0.81	1.08	0.56-2.08			
Prior TURP	0.79	1.21	0.29-5.15			
Clinical Stage	0.02	2.02	1.11-3.68			
Gleason Score (total)	0.04	1.69	1.03-2.80	0.001	2.20	1.36-3.57
Pretreatment PSA	0.41	0.87	0.62-1.22			
Treatment Modality	<.001	0.36	0.20-0.63	0.006	0.39	0.20-0.77
Method of Radiation††	0.12	0.45	0.16-1.22			
Treatment Site†††	0.28	3.02	0.41-22.40			
Hormonal Therapy	0.08	0.60	0.34-1.06			

*only Whites and African Americans were compared in this analysis

† Coding of clinical parameters: Age (continuous, per year), Race (reference = white), Prior

TURP (reference = no TURP), Clinical Stage (T1-T2a versus T2b-T2c versus T3a-T3b, reference = T1-T2a), Gleason Score (<7 versus 7 versus >7, reference = <7), Pretreatment PSA (continuous, per ng/mL increment), Treatment Modality (reference = RP), Method of Radiation (reference = 3DCRT + IMRT), Treatment Site (reference = Lawrence & Memorial Hospital), Hormonal Therapy (reference = no hormonal therapy)

††only 3DCRT+IMRT and IMRT alone were compared in this analysis

†††only includes patients treated with radiation

Abbreviations: IMRT = Intensity Modulated Radiation Therapy; 3DCRT = 3 Dimensional Conformal Radiation Therapy; PSA = Prostate Specific Antigen; TURP = Transurethral Resection of the Prostate; CI = Confidence Interval

In unadjusted analysis, age (Hazard Ratio 0.43, 95% CI 0.24-0.76, p=.003), clinical stage (Hazard Ratio 2.02, 95% CI 1.11-3.68, p=.02), Gleason score (Hazard Ratio 1.69, 95% CI 1.03-2.80, p=.04), and treatment modality (Hazard Ratio 0.36, 95% CI 0.20-0.63, p<.001) were significant predictors of biochemical disease free survival. In multivariable analysis, only Gleason score (Hazard Ratio 2.20, 95% CI 1.36-3.57, p=.001) and treatment modality (Hazard Ratio 0.39, 95% CI 0.20-0.77, p= .006) predicted biochemical failure. The p value for age (p=.08) did not reach statistical significance.

Discussion

We conducted a retrospective cohort study to investigate whether RP or IMRT, plus hormonal therapy if indicated, is associated with improved biochemical disease free survival compared to the alternative modality. Our results suggest that there is no difference in outcome for patients with a favorable prognosis, but patients with a poor prognosis and some patients with an intermediate prognosis (those in the NCCN intermediate prognosis group) may have improved outcomes when treated with IMRT and hormonal therapy.

Patients in the IMRT cohort had more advanced and aggressive disease than their RP counterparts, as indicated by the significantly higher Gleason scores, pretreatment PSA values, and amount of extracapsular (T3) disease at presentation. This explains the change in unadjusted (p=.74) versus adjusted (p=.06) p values associating treatment modality to outcome (Table 3) and should be considered in the interpretation of our results.

Interestingly, the rates of BDFS seen in the RP cohort are similar to rates seen in other studies[20, 25] and are marginally better than those predicted by the Kattan nomogram for post-RP patients;[71] in the MSK favorable, intermediate, and poor prognostic groups, the Kattan nomogram-predicted versus our observed five-year biochemical disease free survival rates (respectively) are 90.8% versus 95.1%, 81.8% versus 86.7%, and 43.8% versus 53.8%.

Our rates of BDFS for patients treated with IMRT are similar to those reported in other series,[20, 25, 61] including the Kattan nomogram-predicted rates

for post external beam radiation patients,[72] with the exception of patients in the poor prognostic group subsets of the IMRT cohort. These patients may have better outcomes than those in some previously reported series. This finding may be attributable to our study including patients treated to at least 72 Gy, which other studies suggest yields better outcomes than doses less than 72 Gy. Kupelian et al. found that, on unplanned subgroup analysis, patients with an unfavorable prognosis (clinical stage ≥T2b, Gleason Score ≥7, or pretreatment PSA >10) have significantly higher biochemical disease free survival rates when treated with external beam radiation therapy to ≥72 Gy as opposed to RP, but a significantly worse biochemical disease free survival when treated with external beam radiation therapy to <72 Gy compared to RP.[22] Additional support for treating patients to doses ≥72 Gy comes from a randomized trial comparing external beam radiation therapy of 78 Gy to external beam radiation therapy of 70 Gy, which showed improved five-year biochemical disease free survival in the 78 Gy arm (78% vs. 68%, p=.03). This result was even more striking when patients with a pretreatment PSA of >10 ng/mL were examined (72% vs. 43%, p=.01), suggesting that patients with an unfavorable prognosis derive the most benefit from dose escalation.[39] Another prospective trial randomized patients to external beam radiation therapy to a dose of either 68 Gy or 78 Gy. Patients in the 78 Gy arm showed significantly higher disease free survival rates than patients in the 68 Gy arm.[32] A similar result was seen by Zelefsky et al., who noted improved BDFS in patients treated to 81.0 Gy, as compared to those treated to 64.8 Gy.[33] Dose escalation could explain why our study found an

improvement in BDFS in the poor prognosis subsets of the IMRT cohort, relative to the RP cohort, as no other previous study utilized radiation doses as high as those used in our study.

The higher biochemical disease free survival seen in IMRT patients with a poor prognosis could also be attributable to the hormonal therapy given in conjunction with radiation, as hormonal therapy is theorized to eliminate residual local disease in patients treated with external beam radiation therapy. Hormonal therapy has been shown in prospective trials to improve overall survival and disease-specific survival in poor prognosis patients, and some intermediate prognosis patients, treated with external beam radiation therapy, as illustrated by RTOG 8610 and a prospective study published by Bolla et al (discussed in the introduction).[40, 41, 45, 47] We unfortunately do not have the capability to determine whether the improvement in BDFS seen in patients who received IMRT is the result of increased dose, the presence of hormonal therapy, the combination of both, or other reasons.

The novel definitions of biochemical disease free survival used in this paper do not alter the significance of the result. Our definition of post-RP failure is more stringent than most others used in past retrospective studies,[11, 19-25, 51] and the definition of post-IMRT failure used in this study has a higher sensitivity for failure than that used in other retrospective studies, with the exception of the review published by Keyser et al.[19, 51] Therefore, it is extremely unlikely that the novel definitions of failure utilized in this study could account for the improved

outcome seen in IMRT patients with an intermediate or poor prognosis relative to their RP counterparts.

Strengths of our study include a blind reabstraction to ensure reliability of data collection and the utilization of recommended definitions of biochemical failure. Additionally, the data was analyzed with the ASTRO and AUA recommended definitions of failure using standard prognostic group schemes.

Limitations of our study include the restrictions of a retrospective analysis. Although we tried to account for all possible confounding factors, it is possible that we did not account for a patient characteristic that contributes to outcome. Despite the fact that we have a reasonable sample size, analysis of individual subgroups of patients, although preplanned, was conducted on a smaller group of patients. As a result, certain known adverse prognostic factors did not achieve statistical significance when assessing their impact on biochemical disease free survival.

In addition, had the median follow up of our study been longer, we may have been able to use a more robust outcome measure in place of BDFS, such as overall survival, disease-specific survival, or metastasis free survival. Also, we can not conclusively say that five-year BDFS rates in each cohort would correlate with ten-year BDFS rates, the latter of which would also represent a more meaningful outcome measure.

The variable definitions of failure that we utilized for RP and IMRT patients represent an unavoidable limitation of the study. Although we used definitions of failure recommended by the American Urological Association and

the American Society for Therapeutic Radiology and Oncology in their respective consensus statements,[54, 55] we recognize that the implications of these definitions of failure are in fact different. We feel that there is no single definition of biochemical failure that is appropriate for patients receiving a radical prostatectomy and patients receiving external beam radiation therapy, because after successful radical prostatectomy, no prostate tissue remains in the body and therefore the PSA should be undetectable (or nearly undetectable, as indicated by the 0.2 ng/mL threshold set by the American Urological Association).[55] After external beam radiation therapy, however, viable prostate tissue may remain, and therefore such a definition of failure would be inappropriate. After vigorous deliberation, the American Society for Therapeutic Radiology and Oncology decided that the appropriate definition of failure in such cases should be “PSA nadir + 2 ng/mL”.[54] In addition, the American Urological Association recognizes that patients treated by external beam radiation therapy will be evaluated with a different definition of failure: “The Panel recommends the use of the American Society for Therapeutic Radiology and Oncology criteria for patients treated with radiation therapy”.[55] In addition, six of the eight retrospective studies cited in this manuscript comparing radical prostatectomy to external beam radiation therapy have used varying definitions of biochemical failure. Although a single definition of failure would have been optimal, variable post-treatment prostate physiology precluded us from using such a definition in our study.

Another limitation of our study pertains to the fact that 37% of patients in the favorable prognosis group of the IMRT cohort received hormonal therapy, as hormonal therapy is generally not indicated for this group of patients. Because we chose biochemical disease free survival as the endpoint of the study, and because hormonal therapy significantly reduces PSA levels, the results of our trial could be biased in favor of the IMRT cohort, particularly the value obtained by the log-rank test comparing Kaplan Meier curves.

Additionally, it is possible that the improved outcome seen in the IMRT subset of the NCCN intermediate prognosis group and both the MSK and NCCN poor prognosis groups (relative to the RP subset) is secondary to the transient PSA-lowering effect of hormone therapy. As already discussed, this could certainly affect the p value obtained from the log-rank test comparing survival curves. However, five-year BDFS rates were significantly higher in IMRT patients when compared to RP patients, and any testosterone-lowering effects caused by hormonal therapy will have long dissipated by five years post-therapy (or 3-4 years after the conclusion of hormonal therapy). Therefore, the significant difference in five-year BDFS rates between the RP and IMRT cohorts likely reflects the established long-term benefit of hormonal therapy on intermediate and poor prognosis group patients treated with external beam radiation therapy, rather than a statistical artifact.

Zelefsky et al. have reported improved biochemical disease free survival and distant metastases free survival rates with dose escalation beyond 75.6 Gy in patients with an intermediate and poor prognosis,[73] indicating that further dose

escalation may be of benefit to such patients. We are now using image-guided IMRT to dose escalate above 80 Gy, particularly in patients with an intermediate or poor prognosis.

In conclusion, biochemical disease free survival rates in patients with prostate adenocarcinoma appear to be related to intrinsic tumor characteristics such as clinical stage, Gleason score, and pretreatment PSA. In addition, for patients with a poor prognosis, and some patients with an intermediate prognosis, IMRT to a dose greater than 72 Gy administered with hormonal therapy may yield improved BDFS when compared to radical prostatectomy.

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