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National And Institutional Outcomes In Prostate Cancer Radiotherapy

Ann Raldow

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Ann Caroline Raldow

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Abstract

Purposes: This thesis represents the composition of three different research topics within prostate cancer radiation therapy. *Part I* examines the delivery of curative therapy (CTx) in older men with localized prostate cancer across strata of potential clinical benefit and examines treatment trends over time. *Part II* is an institutional retrospective review of patients treated to 75.6 Gy to the prostate using intensity modulated radiation therapy (IMRT) without the explicit contouring of the seminal vesicles. *Part III* is a literature review of adjuvant (ART) and salvage (SRT) radiation therapy to examine the optimal timing of radiation therapy after radical prostatectomy.

Methods:

In *Part I,* we used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to identify 64,192 men ages 67-85 with localized prostate cancer diagnosed from 1996 through 2005. We assessed CTx use, defined as either prostatectomy or radiation, across strata of potential likelihood of clinical benefit. *In Part II,* patients treated from January 2000 through January 2007 at our institution for clinically localized prostate cancer using IMRT were identified and consecutive patients were selected if they had more than 3 years of follow up and received at least 75.6 Gy. Clinical information was gathered, toxicity was recorded, and biochemical disease-free survival was calculated. *In Part III,* pub-med was searched using keywords prostate cancer and: radiation therapy; adjuvant radiation therapy; salvage radiation therapy; post-operative radiation therapy

Results:

Part I. Among patients with the lowest likelihood of clinical benefit (low risk cancer and LE <5 years), those diagnosed in 2004-2005 were more than twice as likely to receive CTx as those diagnosed in 1996-1997 (35.3% vs. 16.0%, respectively). *Part II.* Two hundred twenty three (223) eligible patients received primary IMRT for prostate cancer and the median follow up was 4.4 years. 5-year BDFS for poor, intermediate, and favorable prognostic group patients was 59.0% [95% Confidence Interval (95% CI) 41.8-72.7%], 83.4% [95% CI 72.4-90.4%], and 92.1% [95% CI 77.4-97.4%], respectively. Acute and late genitourinary and gastrointestinal Grade-3 toxicities were rare and there were no Grade-4 toxicities. *Part III.* Although there are multiple randomized trials suggesting that early intervention with ART can improve biochemical disease-free, metastasis-free and overall survival in patients at high risk of recurrence, a similar level of evidence does not exist for the use of SRT.

Conclusions:

Part I. Curative therapy for prostate cancer may be increasingly utilized among patients with the lowest likelihood of clinical benefit. *Part II.* Dose escalation using IMRT to treat the prostate without explicit contouring of the seminal vesicles is safe and effective. *Part III.* We anticipate the results from randomized clinical trials to answer further questions regarding the comparison of ART to SRT following biochemical relapse.

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Introduction

This thesis represents the composition of three different research topics within prostate cancer radiation therapy, and will therefore be presented in three parts. The treatment of prostate cancer with radiotherapy is changing rapidly, as new technology and new clinical evidence have been associated with increased numbers of patients being treated with curative therapy. Given the increasing number of patients diagnosed with prostate cancer and concerns regarding healthcare costs, the impact of life expectancy and cancer risk on the delivery of curative treatment is becoming ever more important. Emerging radiation technologies such as intensity modulated radiation therapy (IMRT) have impacted how we treat patients with the assumption that side effects are minimized and cancer cure is maximized. Additionally, as new evidence is emerging regarding the treatment of prostate cancer after surgery, the literature needs to be aggregated for the benefit of clinicians. *Part I* of this thesis therefore relates to national outcomes in prostate cancer curative therapy. Specifically, we examined the temporal trends in the treatment of older men with localized prostate cancer, and studied the effects of life expectancy and cancer risk on the receipt of curative therapy. *Part II* of this thesis concerns the Yale institutional outcomes of patients treated with intensity modulated radiation therapy (IMRT) for prostate cancer without explicit contouring of the seminal vesicles. *Part III* of this thesis represents a literature review of adjuvant and salvage radiotherapy after prostatectomy. Please refer to the statement of purpose, specific hypothesis and specific aims of the thesis on pages 11-12 for further details.

Part I

In 2010, there will be approximately 217,730 incident cases of and 32,050 deaths from prostate cancer in the U.S., making it the second most common cause of cancer-related death in American men[1]. As a result of widespread prostate specific antigen (PSA) testing, the majority of patients are diagnosed with asymptomatic, clinically localized prostate cancer. However, there are limited data available from randomized trials to help inform treatment management of patients with localized disease, complicating the decision process and creating significant variation in treatment use [2].

Both non-cancer and cancer-related clinical factors can affect the potential benefits of prostate cancer treatment. Estimates of life expectancy (LE) have emerged as important factors in treatment decision-making, because prostate cancer is an indolent disease and may take many years before affecting patient health. Hence, treatment of patients with shorter LE may therefore contribute to additional costs, side effects, complications, and mortality without a commensurate improvement in quality of life or survival [3-5]. In addition to LE, the benefits of curative therapy in patients with clinically localized prostate cancer vary substantially according to cancer characteristics. Conventional wisdom suggests that the more aggressive the cancer, the more significant the benefit of treatment for prevention of disease progression and recurrence [6-7].

The National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology provides treatment recommendations based on both life expectancy (LE) and tumor characteristics [8]. The NCCN recommends active surveillance rather than curative therapy for patients with low-risk prostate cancer who have LE < 10 years. For patients with intermediate-risk prostate cancer and LE ≥ 10 years, radical prostatectomy or radiation therapy should be recommended. In addition, the guidelines state that for patients opting for expectant management,

surveillance may be completed less frequently for men with LE < 10 years as compared to those with ≥10 years.

Prior analyses have suggested that cancer characteristics as well as age, comorbidity and sociodemographic characteristics are key factors in treatment selection [2, 9]. However, these studies are limited in that they do not explicitly assess patients according to both tumor aggressiveness and underlying health risk, precluding their ability to explain fully how therapies are utilized in practice. Moreover, treatment options for prostate cancer patients have expanded considerably in recent years. While these newer modalities, such as IMRT, may be associated with better clinical outcomes and decreased side effects, many older patients with less aggressive cancers may not benefit from treatment. These newer treatments are significantly more expensive than existing alternatives and little is known about how these resources are allocated.

Part II

As previously mentioned, many of the newer radiation treatment modalities such as intensity modulated radiation therapy (IMRT) may be associated with better clinical outcomes and decreased side effects. The escalation of radiation dose above 72 Gy for prostate cancer has been strongly correlated with improved biochemical disease free survival [10-17] and clinical outcomes [18-19]. Multiple retrospective and prospective trials have also clarified the risks associated with dose escalation [13-15, 17, 20-22] , and it appears that even doses up to 81-86.4 Gy are associated with acceptable toxicity [13, 21, 23]. In addition, the utilization of IMRT for prostate cancer has been shown to allow dose escalation without a significant increase in toxicity [13, 17, 20, 24-25] potentially above and beyond what is possible with 3D conformal radiotherapy alone [13].

Nevertheless, prostate IMRT is not standardized, and prescription of prostate dose with IMRT varies from institution to institution, with some dose prescriptions based on isocentric dose, maximum point dose within the tumor, or a planning target volume (PTV). Therefore, for Part II of this thesis, we completed a retrospective institutional study to review clinical outcomes from patients with prostate cancer treated by a single radiotherapy department using a uniform radiation technique with dose escalation using IMRT.

The Yale Department of Therapeutic Radiology technique incorporates high doses of radiation to the prostate, but unlike some other departments, we do not explicitly irradiate the seminal vesicles, except for the proximal portion that is incidentally included in the PTV expansion around the prostate. The incorporation of these structures into the treatment volume is controversial, and there are several reasons why we exclude them, even in the case of patients at high risk for seminal vesicle invasion [26-29]. 1) Although patient age, Gleason score, clinical stage, the amount of cancer in biopsy cores from the base of the prostate and pre-treatment PSA are features that successfully predict the presence of seminal vesicle involvement, we are not

aware of any known factors that correlate with the extent of invasion to include in the clinical target volume (CTV) [30-35]. 2) The seminal vesicles are situated superior and posterior to the prostate. The tails of the seminal vesicles run posterior–laterally, with their distal ends frequently sitting adjacent to the anterior rectal wall. Incorporating the seminal vesicles into the CTV significantly increases the dose to the rectum [28, 36-37]. Therefore, we theorized that the risk for acute and late toxicity is much reduced by not including the seminal vesicles in the treatment plan. 3) The majority of research has found that the pattern of invasion from the prostate to the seminal vesicles is continuous and usually limited to the proximal half of the structures [38]. Without explicitly incorporating the seminal vesicles into the CTV, the base of the seminal vesicles is often included in the radiation treatment plan anyway, as the irradiated volume is the outlined prostate plus a volumetric expansion that takes into account microscopic extension, movement of the prostate, and daily set up error. To our knowledge, our study represents the only single-institutional report of IMRT for prostate cancer that has not explicitly included any portion of the seminal vesicles into the CTV.

Part III

While radical prostatectomy provides excellent control for clinically localized prostate cancer, approximately one-third of patients undergoing surgery will have positive surgical margins and another 9% will have seminal vesicle invasion [39-42].Around one-third of patients will also have extracapsular extension [42].These adverse pathological risk factors, in addition to the Gleason score and initial PSA level, are independent predictors of biochemical recurrence of cancer. Indeed, 40%-50% of high-risk patients have a biochemical recurrence after surgery, and many of those patients eventually develop metastases [43-48]. Currently, the majority of post-surgical patients without high-risk features are observed for signs of disease progression without active treatment. However, recently updated randomized trials have shown a very significant benefit to immediate "adjuvant" radiation therapy (ART) for prostate cancer at high risk of recurrence, such as pT3 disease [49-51].Controversy surrounds the optimal timing of postoperative radiotherapy, as well as what to do when prostate cancer recurs months or years after initial prostatectomy, and whether the risks and morbidity of radiation therapy in the "salvage" setting outweigh the intended benefits. In Part III of this thesis, we review the evidence for ART from three randomized clinical trials [49-51] as well as the retrospective evidence for the use of SRT. In addition, we discuss the technical aspects of treatment, including dose escalation and treatment target volume, as well as the cost-effectiveness of ART and SRT based upon current available literature. Although radiation therapy in the post-prostatectomy setting has generally been well tolerated, we also examine the complication data associated with treatment.

Statement of purpose, specific hypothesis, and specific aims

Part I

Given the increasing number of treatment candidates and concerns about rising Medicare costs, efficient allocation of prostate cancer treatment resources will become ever more important [52]. We therefore developed a framework for stratifying patients according to the complementary domains of cancer risk and LE. We applied this framework to a retrospective study of Medicare beneficiaries diagnosed with prostate cancer in 1996 through 2005. Specifically, we assessed: 1) Patient and tumor characteristics associated with receipt of curative therapy; 2) Patterns of curative therapy use across strata of potential clinical benefit, as defined by tumor aggressiveness and LE; and 3) Temporal trends in the use of curative therapy across strata of potential clinical benefit. We hypothesized that on a national scale, our results would suggest increasing utilization of curative therapy over time, especially among patients with the lowest likelihood of clinical benefit.

Part II

In patients with prostate cancer, multiple retrospective and randomized trials have demonstrated that higher dose irradiation of the prostate is safe, with low morbidity, and has been strongly correlated with improved clinical outcome. This study presents a single institution retrospective review of patients treated to 75.6 Gy to the prostate using intensity modulated radiation therapy (IMRT) without the explicit contouring of the seminal vesicles (SV). We hypothesized that the risk for acute and late toxicity would be reduced by not including the seminal vesicles in the treatment plan. We also hypothesized that the risk for biochemical disease free survival would be similar to other studies in the literature.

Part III

Several issues surround the use of adjuvant and salvage radiotherapy for post-prostatectomy patients, and the literature needs to be aggregated for the benefit of clinicians. We therefore performed a literature review of adjuvant and salvage radiation after prostatectomy.

Methods

Part I

- Ann Raldow, Cary Gross, James Yu, Carolyn Presley, Richa Sarma, Danil Makarov, and Laura Cramer were involved in study design. Cary Gross is the principal investigator of Part I of this thesis. Statistical analysis was completed by Laura Cramer. Ann Raldow took the lead role with writing of the manuscript, with extensive suggestions and help from other team members mentioned above.

Study Design Overview

In this retrospective study, we determined the use of curative therapy (CTx) across cancer-risk and LE strata. In addition, we studied the temporal trends of CTx delivery across these strata from 1996-2005. CTx was defined as prostatectomy or any form of radiation therapy. We divided the study sample into low- and moderate-risk categories and defined low-risk patients with LE < 5 years as those least likely to benefit from treatment and moderate-risk patients with LE ≥ 10 years as those most likely to benefit (Figure 1). This study was approved by the Yale Human Investigation Committee.

Data Sources

We used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database [53]. The SEER program of the National Cancer Institute (NCI) is comprised of 17 high-quality cancer registries throughout the U.S. The coverage rate of SEER registries was approximately 14% and 26% of the U.S. population during 1991-1999 and 2000-2006, respectively, and the patients included are representative of the U.S. population with respect to poverty and education [53-55]. For every patient in the database, SEER provides patient

demographics and tumor characteristics. Community-level demographics and information on Medicare enrollment are linked from U.S. Census data and Medicare [53].

Inclusion Criteria

We studied patients diagnosed with stage T1 and T2 prostate cancer during the years 1996 through 2005. We excluded patients with missing grade, missing stage and those with prior malignancy or a second primary tumor diagnosed within a year of their prostate cancer diagnosis. To ensure completeness of the data, we excluded patients who did not have full Medicare Parts A and B coverage or those enrolled in a health maintenance organization within a window 2 years prior to diagnosis through 9 months after diagnosis. Because Medicare benefits begin at age 65, it was necessary to limit the sample to patients at least 67-years-old at diagnosis in order to allow for this assessment period. Patients were also excluded if they were over the age of 85 years at diagnosis, died within one month of diagnosis or if the reporting source of the cancer was a death certificate or autopsy report. Finally, patients must have had at least one Medicare claim billed within the 2- year window prior to diagnosis through 9 months after. The resulting study sample contained 64,192 patients (Figure 2).

Defining prostate cancer risk

We divided the sample into low- and moderate-risk categories using the NCCN guidelines, excluding PSA values, which were not recorded in SEER-Medicare prior to 2004. Low-risk disease was defined as SEER grade 1 or 2 and stage T1 or T2a disease and moderate-risk as SEER grade 3 or 4 or T2b-T2c disease.

Construction of Variables

The independent variables included in our analysis were age, race, comorbidity, marital status, year of diagnosis and LE. We categorized age into 4 groups: 67–69, 70–74, 75–79 and 80-85; race into white, black, or other; and marital status into married, not married, or unknown. In order to identify comorbid conditions, we searched inpatient, outpatient, and physician claims billed between 3 and 24 months prior to Prostate cancer diagnosis. We only used International Classification of Diseases, 9^{th} revision (ICD-9) codes that appeared on at least one inpatient claim or two or more outpatient/physician claims. Using the comorbidity categories outlined by Elixhauser et al. [56], a Cox proportional hazards model was constructed to identify conditions were significantly associated with survival for a noncancer sample who met the same age and administrative eligibility criteria as our cancer patients (Appendix 1). The number of conditions a patient had was then summed to create a comorbidity score, and patients were categorized into 3 groups: 0, 1-2, and ≥3 comorbid conditions. A standard life table approach was used to estimate LE. A 5% non-cancer sample of age, sex and registry matched Medicare beneficiaries was used to determine annual mortality rates for each age and comorbidity stratum. We assumed that as patients moved up to the next age group (i.e., from 67-69 to 70-74), 20% of the surviving patients advanced to the next comorbidity category. This assumption was founded on clinical judgment and our investigational results.

Treatment

Prostate cancer treatment was assessed by searching the claims for specific diagnosis, procedure and revenue center codes (Appendix 2). We defined CTx as receipt of any form of radiation (including external beam radiation therapy and brachytherapy) or prostatectomy during the 9 months following diagnosis. Patients were considered to be under watchful waiting if there

were no claims billed with the listed codes or if they received primary androgen deprivation therapy (PADT).

Statistical Analysis

Chi-square tests were used to ascertain bivariate associations between the independent variables and receipt of CTx. Multivariable logistic regression was used to model the likelihood of receipt of therapy controlling for the independent variables and SEER registry. Different models were used for each cancer-risk category. For the analysis of temporal trends, we excluded the 4 SEER registries that were added in 2000 to reduce bias due to treatment variation across registries. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Part II

- Ann Raldow, Anne McKeon, Nicole Anderson, and Ayal Aizer helped with data accrual. Nicole Anderson updated toxicity as well as PSA data on Lawrence and Memorial Hospital patients. Ann Raldow rewrote the introduction, did background research, updated the toxicity data on the Yale New Haven Hospital patients, and updated the tables. James Yu analyzed the data and rewrote and edited the methods, results, and discussion sections. Richard Peschel and Roy Decker were responsible for reviewing and approving the project. James Yu is the principal investigator on Part II of this thesis.

Data Collection and Baseline Patient Characteristics

After approval from the Yale Human Investigational Committee, clinical information from all patients undergoing prostate IMRT administered by the Yale Department of Therapeutic Radiology at the Yale New Haven Hospital - Hunter Radiation Therapy Center (New Haven, CT) and Lawrence and Memorial Hospital Department of Radiation Oncology (New London, CT) from January 2000 through January 2007 was retrospectively collected and compiled using the TrialDB Clinical Study Data Management System [57]. Patients were categorized into poor, intermediate, and favorable prognostic groups using the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology [8].

Clinical information including diagnostic and prognostic information, pre and post radiation urinary function, patient and physician reported toxicity information, radiation dose, schedule, and technique, adjuvant therapy and supportive therapy, sexual health, and all recorded PSA values were abstracted. Any reported toxicity, regardless of whether it was due to a preexisting condition, was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 guidelines [58]. Urethral and testicular pain were recorded as genitourinary toxicities.

All consecutive patients treated from 1/1/2000 until 1/31/2007 with localized prostate cancer, who had received at least 75.6 Gy of radiation, who had not received prior radical prostatectomy, who were able to be staged clinically, and who had at least 3 years of follow up PSA values were selected for analysis. Two hundred and twenty three (223) patients were identified, and the characteristics of these patients are listed in Table 3. Median follow up was 4.4 years (range 3.0 – 7.9 years). Median age at diagnosis was 69 years. Median PSA at diagnosis was 9.0 ng/mL (range 2.7 – 178 ng/mL, SD 17.0). 63.2% of patients had a clinical stage of T1c. 32.7% of patients had poor prognostic group disease, 47.5% of patients had intermediate disease, and 19.7% of patients had favorable prognostic group disease. 97.8% of patients received 75.6 Gy, and 5 patients (2.2%) received 75.9 – 77.8 Gy.

Pelvic radiotherapy was given to 15 (6.7%) patients with a higher risk of nodal involvement based on the clinical judgment of the treating physician. Pre-sacral, internal and external iliac, and obturator nodes were included in the treatment volume for these patients. Adjuvant hormonal therapy was also given based on the clinical judgment of the treating physician. Patients with intermediate and high-risk group disease usually received short (6 months) and long-term (1-3 year) hormonal therapy. In addition, patients with significant obstructive urinary symptoms prior to radiotherapy sometimes received 3 months of androgen deprivation therapy for cytoreduction and mitigation of acute obstructive urinary toxicity during radiotherapy. Almost all patients with poor prognostic group disease received adjuvant hormone therapy (97.3%) compared to less than a third of all patients with favorable group disease (29.6%).

Statistical Analysis, Definition of Biochemical Disease Free Survival

Biochemical disease free survival (BDFS) was calculated using the RTOG-ASTRO Phoenix Consensus definition of the date of biochemical failure [59] (the date when the absolute PSA reaches a level equal to or greater than 2 ng/ml above the post-radiotherapy nadir). There was no backdating allowed. Kaplan-Meier curves for BDFS were constructed for each prognostic group and compared with the log-rank test. Univariable and multivariable biochemical disease free survival analyses were performed using Cox proportional hazards analysis. Logistic regressions were performed to estimate the likelihood odds ratios of receiving adjuvant hormonal therapy or pelvic radiation, based on prognostic group. Statistical analysis was performed using Stata/SE 9.2 (College Station, TX).

IMRT Technique

A standard dose escalated prostate IMRT protocol was institutionally developed based on available literature and our own institutional analysis of daily setup error and quality analysis parameters. All patients underwent 3D CT simulation and treatment planning. The treating physician contoured the prostate in its entirety. The seminal vesicles were not explicitly contoured.

Patients were treated in the supine position and were asked to evacuate their bowels prior to CT simulation and prior to each therapy session. From January 2000 to June 2003, patients were initially treated with 3D conformal radiation followed by an IMRT boost. These patients received 66.6 Gy in 37 fractions of 1.8 Gy using a 3D conformal technique, followed by a 9 Gy boost (in 5 fractions of 1.8 Gy) using IMRT. The 3D conformal radiation was delivered to the physician-contoured prostate plus a symmetric 1.5 cm margin. The IMRT boost was delivered to the prostate plus a 1.0 cm symmetric margin in all directions, except for a 0.6 cm posterior margin at the interface of the prostate and rectum.

From June 2003 until January 2007, patients undergoing prostate radiation (without pelvic radiation) were treated with IMRT through the entire treatment course. The planning treatment volume (PTV) was defined as the physician contoured prostate plus a symmetric 1.2 cm margin to encompass microscopic extension and prostate motion. This PTV was treated to 66.6 Gy in 37 daily fractions as the "primary plan", with dose prescribed to the entire PTV. The seminal vesicles were not explicitly contoured. As the patients approached the completion of the initial 66.6 Gy, they received a second CT treatment simulation, and a prostate "cone down" plan was developed based on this resimulation. The patient then underwent 5 additional fractions of 1.8 Gy to a PTV defined as the contoured prostate plus a 1.0 cm margin in three dimensions, save for a margin of 0.6 cm at the posterior border with the rectum. There were no scheduled treatment breaks. Therefore, total dose to the prostate was 75.6 Gy in 42 fractions of 1.8 Gy.

An isocentric five-field technique with 18 MV photons was typically used, using institutionally standardized normal tissue constraints. D_{max} was constrained to 115% of prescribed dose. Rectal constraint for patients receiving 75.6 Gy was $D_{25} \leq 70$ Gy, with the 50% isodose line not covering the entire rectum, and the 90% isodose line covering half of the rectum width on a slice-by-slice inspection of the entire rectum. Deviations from the standard criteria were allowable when unavoidable and approved by the attending physician. All plans (including both "primary" and "cone down" plans) were presented at institutional chart rounds for clinical and dosimetric review.

Quality Assurance

A medical physicist verified all treatment plans with phantom dose measurements prior to initiation of therapy. Maximum tolerable deviation from planned dose was +/- 3%.

Part III

- Ann Raldow was responsible for literature research and review. She was also the principal author of the manuscript. James Yu, Sung Kim, and Daniel Hamstra edited and added to and made significant changes to the manuscript. James Yu is the senior author.

Pub-med was searched using keywords Prostate cancer and: Radiation therapy; Adjuvant radiation therapy; Salvage radiation therapy; Post-operative radiation therapy

Results

Part I

The study sample was composed of 64,192 patients. Approximately 61.6% and 38.4% of the sample was characterized as low- and moderate-risk, respectively. Nearly 85% of the patients in the study sample were white, 9.3% were black, and the median age was 73 years. Overall, 57.8% of the patients had no comorbid conditions, 33.3% had 1-2 conditions and 8.9% had ≥3 conditions. Diabetes, cardiac arrhythmia and chronic pulmonary disease were the 3 most prevalent comorbidities.

Curative treatment was delivered to 64.4% of patients with low-risk and 70.0% of patients with moderate-risk prostate cancer (Table 1). Among the low-risk patients, 24.1% with LE <5, 50.7% with LE 5 to <10, 74.2% with LE 10 to <15 and 80.7% with LE ≥15 years received CTx (Figure 3). Among the moderate-risk patients, CTx was administered to 31.6% with LE <5, 60.0% with LE 5 to <10, 79.5% with LE 10 to <15 and 84.5% with LE ≥15 years. Thus, treatment rates increased with increasing LE. More moderate- than low-risk patients underwent CTx across all LE groups. Among those with the lowest (low-risk cancer and LE <5 years) and highest (moderate-risk cancer and LE ≥ 10 years) likelihood of clinical benefit, 24.1% and 80.4% received CTx, respectively (Table 1).

Age and number of comorbidities were significant determinants of receiving CTx (Tables 1 and 2). Older patients were less likely to be treated (adjusted odds ratio [OR] 0.77; 95% CI 0.73,0.81 for ages 70-74; 0.38; 95% CI 0.36,0.40 for ages 75-79; and 0.11; 95% CI 0.11, 0.12 for ages 80-85 (Table 2). CTx was more likely to be delivered to patients with fewer comorbidities (adjusted OR 0.94; 95% CI 0.90, 0.97 for patients with 1-2 comorbidities and 0.57; 95% CI 0.53, 0.60 for patients with ≥3 comorbidities) (Table 2).

Race and marital status were also significantly associated with receipt of CTx (Tables 1 and 2). Compared to white patients, black patients (adjusted OR 0.64; 95% CI 0.60, 0.68) and patients of other races (0.64 for other race; 95% CI 0.60, 0.69) were less likely to undergo treatment (Table 2). Married men were more likely to undergo CTx as compared to unmarried men (adjusted OR 0.67; 95% CI 0.64, 0.70) (Table 2).

Temporal Trends

The rate of CTx administration increased with time, such that 57.7% and 65.3% of low-risk and 66.9% and 71.4% of moderate-risk patients received treatment in 1996 and 2005, respectively (Table 1). The percentage of low- and moderate-risk patients receiving CTx over time differed by LE category (Figure 4). Patients with the lowest life expectancies (LE <5 years and LE 5-<10 years) experienced the most substantial increase in CTx rates during the study period. For instance, the percentage of patients with LE <5 years receiving CTx in 1996-1997 was 16.0% and 21.2% for patients in the low- and moderate-risk categories, respectively. Among those same groups during 2004-2005, the percentage receiving treatment was 35.3% and 34.2%. The percentage of those with lowest likelihood of clinical benefit who received treatment more than doubled during the study period. The proportion of patients with the highest likelihood of clinical benefit who received CTx increased slightly with time, from 78.8% in 1996-1997 to 81.6% in 2004-2005.

Part II

Five year BDFS by favorable, intermediate, and poor prognostic groups were 92.1% [95% Confidence Interval (95% CI) 77.4-97.4%], 83.4% [95% CI 72.4-90.4%], and 59.0% [95% CI 41.8-72.7%] respectively. By the log-rank test, the Kaplan-Meier curves for poor, intermediate, and favorable prognostic groups were significantly different (p=0.0012) (Figure 5).

Patients in the poor and intermediate prognostic groups were more likely to receive adjuvant hormone therapy (Table 4). There were no patients with favorable risk group disease who received pelvic radiation. Poor prognostic group patients were more likely to have received pelvic radiation in comparison to intermediate risk group patients (p<0.001).

As expected, in unadjusted univariable Cox proportional hazards analysis (Table 5), higher Gleason score (p = <0.0001), and poor prognostic group (p=0.0020) were statistically significant predictors of BDFS. When prognostic group, race, adjuvant hormone therapy, and use of pelvic radiation were included in a multivariable model, only prognostic group (poor vs. favorable) achieved statistical significance.

Prostate IMRT with dose escalation was very well tolerated. Acute toxicity from IMRT was defined as reported toxicity during or within 60 days of the end of radiation therapy (Table 6). Acute grade-3 genitourinary toxicity was 7.6%. Acute grade-3 gastrointestinal toxicity was rare, occurring in 2.7% of patients. There were no acute grade-4 gastrointestinal or genitourinary events.

Late toxicity from IMRT was also low (Table 6). Late genitourinary grade-3 toxicity occurred in 0.45% of patients, and late gastrointestinal grade-3 toxicity occurred in 1.35% of patients. No patients experienced grade-4 gastrointestinal or genitourinary toxicity.

Part III

Definition of Salvage Radiotherapy (SRT), and the Distinction Between SRT and Adjuvant RT (ART)

Generally, "salvage" radiotherapy (SRT) is defined as radiation treatment given for suspected recurrent malignant disease after a period of observation after prostatectomy. In contrast, "adjuvant" radiotherapy (ART) refers to treatment directly after prostatectomy in patients potentially without residual disease and with an undetectable PSA. There are several important distinctions between SRT and ART: 1) There is a higher likelihood of local residual disease without distant metastatic disease for patients in whom ART is indicated immediately post-prostatectomy versus a patient for whom SRT is being considered; 2) The burden of disease may be higher for SRT vs. ART; and 3) Multiple prospective randomized trials have shown a benefit to ART, whereas similar evidence is lacking for SRT [49-51] (although a randomized trial comparing SRT and ART is underway [60].

ART is given for patients at high risk of localized recurrence, generally defined as: evidence for prostate cancer outside the capsule (extracapsular extension), positive surgical margins, or seminal vesicle invasion. In contrast, SRT patients can have recurrence years after RP, and it is often unclear whether the detected PSA represents recurrence locally within the prostate bed, seminal vesicle remnants, pelvis, or at a distant site. This is obviously important for RT planning, as delivering RT to the prostate bed is useless if no disease remains locally.

In general, the burden of disease may be different for ART patients versus SRT patients. Though ART patients can have gross residual disease remaining after radical prostatectomy, they also often have an undetectable PSA indicative of, at most, microscopic residual disease. In contrast, all patients who undergo SRT for a biochemical recurrence have either a large enough burden of disease to cause a detectable PSA, a palpable nodule on digital rectal exam, or gross

disease detected on CT or MRI. Therefore, some authors suggest that in general, SRT patients have roughly ten times the disease burden of ART patients [61].

Evidence for ART

Evidence from three randomized ART trials suggests that early treatment can extend biochemical progression-free, prostate cancer-specific and overall survival (Table 9). The European Organization for Research and Treatment of Cancer (EORTC) 22911 was a multi-institutional prospective-controlled trial that randomized 1005 post-prostatectomy patients with pathological T3 disease or positive surgical margins to a "wait-and-see" arm (n = 503) or an ART arm (n = 502) [49]. In the ART arm, radiation was initiated a median of 90 days after surgery when patients had recovered with no significant voiding problems. Conventional irradiation with a target total dose of 60 Gy was delivered over 6 weeks. More specifically, a dose of 50 Gy was delivered in 25 fractions over 5 weeks to a target volume that encompassed the surgical limits extending from the seminal vesicles to the apex, and a 10-Gy boost was subsequently delivered in five fractions over a week to a smaller volume targeting the prostatic bed. Simulation was performed with an urethrogram and rectal enema and a four-field isocentric box technique was employed for most of the patients. For the first planning volume, patients were treated with >9 × 9 cm equivalent square fields, and the majority of patients were treated with a <9 × 9 cm equivalent square field for the smaller volume. Noteworthy findings in favor of ART included increased biochemical progression-free survival at 5-years (74.0% vs. 52.6%; $P < 0.0001$) with a 50% reduction in the risk of biochemical recurrence (Hazard ratio: 0.48 [95% CI: 0.37–0.62]. In addition, this translated into better clinical progression-free survival (with any clinical failure at 5-years of 8.8% in the ART group as compared to 19.0% in the observation group, $p = 0.0009$), the majority of which was due to a decreased rate of cumulative loco-regional failure (with 5-year rates of 5.4% vs. 15.4%, $p = 0.0005$). Overall at 5-years this study suggests a number needed to treat of 2 to prevent biochemical failure and 10 to prevent clinical failure with longer follow-up

necessary to address survival end-points. However, given that almost half of the men who relapsed in the observation group were eventually given post-operative radiation this may decrease the ability to detect differences in metastasis and prostate cancer-specific death. While the EORTC had initially concluded that all pathologic categories (extracapsular extension, seminal vesicle invasion, positive margins) benefited from ART, after central pathology review, they have recently concluded that only patients with positive margins significantly benefit from ART [62]. Limitations of the study included incomplete central pathological review, the modest dose of conventional radiation, variations in post-operative PSA nadirs (some men had detectable PSA post-surgery), as well as different indications for and types of salvage treatment used in the observation arm.

The Southwest Oncology Group (SWOG) 8794 is a US multi-institutional, prospective clinical trial that has also provided evidence in favor of using ART in patients with pathologically advanced prostate cancer. The study randomized 425 men with stage pT3N0M0 disease or positive surgical margins, to observation (n = 211) or ART arms (n = 214) [50]. This study did involve a central pathology review, though they note that a significant proportion of patients did not have this performed. Interestingly, when local and central pathology results were compared, they were very concordant (95%), unlike in the EORTC study. In the ART arm, radiation was initiated within 122 days. The radiation dose ranged from 60–64 Gy and was given in 30–32 fractions, with treatment portals including the prostatic fossa and paraprostatic tissues. Median follow-up was considerable at 12.7 and 12.5 years for the radiation and observation arms, respectively. In this study the use of ART was associated with a significant reduction in the risk for PSA recurrence for patients treated with ART, similar to the EORTC study with a 50% reduction in the risk of PSA recurrence in the ART group (Hazard ratio: 0.43 [95% CI: 0.31–0.58], $p < 0.001$). However, with longer follow-up in the SWOG study this improvement in biochemical control also translated into clinically meaningful end-points including decreased

clinical recurrence (local or metastatic) or death by 38% ($p = 0.001$). More importantly the use of ART was also associated with a 10% improvement in metastasis-free survival at 10 years (71% vs. 61%, $p = 0.016$) and an 8% improvement in overall survival (74% vs. 66%, $p = 0.023$). The magnitude of benefit was similar for those with or without detectable PSA post-operatively as well as for those with or without seminal vesicle invasion. Though men benefit from radiation regardless of whether their post-operative PSA is detectable or not, those with an undetectable PSA fared better-among the radiation patients; men with an undetectable PSA had a longer metastasis-free survival than those with a detectable PSA ($p = 0.03$). And unlike the EORTC study, all pathologic subgroups significantly benefited in terms of metastases free survival. Like the EORTC study this results in a number needed to treat for improvement in biochemical control of approximately 2 with the added knowledge of metastasis and survival benefits observed in 1 in 10 and 1 in 12 men, respectively. These findings are even more compelling when considering that roughly one-third of patients in the observation group received delayed SRT and that their use of androgen suppression therapy was almost double that of the adjuvant treatment group.

The third randomized study was the ARO96-02/AUO AP 09/95 trial, which investigated the role of adjuvant treatment after radical prostatectomy in men with pT3-4N0 disease. Unlike the EORTC and SWOG studies, however, in order to be eligible for randomization men had to have an undetectable (<0.1 ng/ml) post-operative PSA [51]. The trial initially enrolled 388 patients. One hundred and ninety-four were assigned to each of the wait-and-see and ART treatment arms. Of these, 81 patients were excluded because they received hormonal treatment (3) or did not achieve an undetectable PSA (78). Of the remaining 307 patients, 34 patients on the RT arm did not receive RT and five patients on the wait-and-see arm received RT. Ultimately, 114 patients underwent ART and 154 men were in the "wait-and-see" arm. In contrast to the two other randomized ART trials, all patients in the ARO96-02/AUO AP 09/95 study had three-dimensional treatment planning. ART was delivered with a three- or four-field technique and was initiated between 6 and 12 weeks after prostatectomy, lasting a median of 44 days. A target dose

of 60 Gy was given in 30 fractions to a volume that encompassed the surgical limits from the seminal vesicles to the apex, with an additional 1-cm margin to include residual microscopic disease. The follow-up was 5 years. The study, like the EORTC and SWOG studies revealed that biochemical progression-free survival in the treatment group was significantly better than in the observation group (72% vs. 54%; HR = 0.53, $p = 0.0015$) in an intention to treat analysis, suggesting that patients with an undetectable PSA after surgery still obtain benefit from ART. Univariate analysis in the ARO96-02/AUO AP 09/95 study showed a treatment benefit in patients with positive surgical margins, pre-surgical PSA level > 10 ng/mL, or extracapsular extension without seminal vesicle invasion. There was no subgroup broken down by Gleason score that did not benefit from ART compared to observation. In multivariate analysis of progression-free survival, ART (versus observation), pre-operative PSA level of >10, and pT3a/b (vs. pT3c) were all independent predictors of biochemical outcome.

While all three are commendable studies, the published SWOG data is by far the most mature, with a median follow-up of over 12 years. As Pound et al. demonstrated, median time from biochemical recurrence (defined as PSA of at least 0.2 ng/mL) to clinically evident bone metastasis is about 8 years, with time to biochemical progression ($P < .001$), Gleason score ($P < .001$), and PSA doubling time ($P < .001$) being factors in determining the probability and time to progression to metastatic disease [63]. With a follow-up of only 5 years, it is not surprising that the EORTC and ARO 96-02 trials do not yet demonstrate a metastases or overall survival advantage although both did demonstrate an approximately 50% reduction in the risk of biochemical progression. Intriguingly, the hazard ratio for reduction of biochemical failure was nearly identical across all three studies (0.48, 0.43, and 0.53 for the EORTC, SWOG, and ARO96 studies, respectively), so it may be just a matter of time before this translates to a clinical benefit. An explanation for the discrepancy in benefit across studies for positive vs. negative margins is not easily forthcoming. It could have to do with the quality and prevalence of central pathology review or the variances in patient population or radiation technique.

Arguments and evidence in favor of SRT

As discussed, recent evidence from these three randomized trials suggests that early intervention with ART can lengthen biochemical disease-free, metastasis-free and overall survival in patients with pathologically advanced prostate cancer [49-51]. However, a disadvantage of routine ART is treating those who would never develop biochemical recurrence after RP, and unnecessarily exposing an increased number of patients to the side effects of RT. In addition, there is some evidence that the use of ART may be associated with an increased risk of toxicity as compared to SRT. A retrospective multi-institutional analysis of 959 men treated with either adjuvant (19%) or salvage (81%) RT found a low rate of toxicity with a 5-year rate of late grade 2 or higher genitourinary (GU) toxicity of 12% and a late grade 2 or higher gastrointestinal (GI) toxicity of 4%. More serious toxicity was rare, with grade 3 GU toxicities in only 1% of all patients and grade 3 GI toxicities in 0.2% of all patients. Given the small number of events, there were no predictors that correlated with late GI toxicity, and there was no difference in GI toxicity between ART and SRT.

However, on multivariate analysis adjuvant RT as compared to both salvage RT (16% vs 11%) and the use of hormonal therapy (19% vs 11%) predicted for increased risks of grade 2 or greater urinary toxicities [64].Therefore, the use of SRT might protect a significant portion of men who do not ever require radiotherapy, and in addition, even for those treated with RT may provide a modest reduction in GU toxicity. However, the cost of a strategy of using SRT in lieu of ART is that a certain portion of patients may have a lower chance of successful eradication of their disease with SRT. Whether an equivalent survival benefit can be attained with vigilant surveillance and early initiation of SRT upon PSA relapse is an unanswered question, and SRT cannot at present be considered to be equivalent to ART.

Given this uncertainty, two groups of investigators have attempted to define prognostic factors that predict the likelihood of obtaining a benefit from SRT. Trock et al. retrospectively analyzed 635 men, who either received no salvage treatment (n=397), SRT alone (n=160), or SRT combined with hormonal therapy (n=78) [65].The authors found that 70% of all deaths during follow-up were from prostate cancer with 10-year rates of prostate cancer–specific survival of 86% in those treated with salvage RT as compared to 62% without RT. This represented a 3-fold increase in prostate cancer–specific survival compared to those who received no salvage treatment (hazard ratio [HR], 0.32; P < .001). The addition of hormonal therapy to SRT did not improve prostate cancer–specific survival. Also noteworthy was that when SRT was restricted to the population of patients with pT3 disease who would have been candidates for ART, the use of salvage RT also provided an OS benefit with 10-year OS of 98% vs 89%.

Interestingly, the prostate cancer–specific survival benefit of SRT was only seen in men with a PSA doubling time of < 6 months, independent of pathologic stage or Gleason score. This runs counter to the more commonly held principle that a short doubling time is indicative of distant disease and, therefore, a lack of benefit to SRT [66]. Moreover, patients who received SRT more than 2 years from the time of biochemical recurrence did not experience significant increases in prostate cancer–specific survival.

Further evidence for the use of SRT in prostate cancer comes from a retrospective study by Stephenson et al, in which they developed a model using a cohort of 1,540 patients [67]. The authors described several prognostic features that should be considered when predicting improved biochemical control after SRT: These included PSA level < 2.0 ng/mL at time of SRT, Gleason score of 7 or less, PSA doubling time > 10 months, positive surgical margins, androgen-deprivation therapy before or during SRT, and the absence of lymph node metastasis. It was again demonstrated that SRT may significantly alter the natural course of the disease, as 60% to 70% of patients with disease recurrence develop metastasis within 6 years if they do not receive salvage

therapy [63]. In addition, SRT is recommended to patients with more favorable prognostic features, as they are thought to be at lower risk for widely disseminated disease [68].

However, the Stephenson study, like the one by Trock et al., suggests that patients with unfavorable prognostic features may also benefit from SRT if treatment is initiated early after biochemical recurrence. Indeed the Trock study would suggest that patients with the shortest doubling time are at the greatest risk for prostate cancer–specific death. Although these patients may be less likely to have PSA control, given their greater risk of death from prostate cancer if they do achieve disease control, this translates into a cause specific survival benefit. In contrast, those with a longer PSA doubling time may be more likely to achieve PSA control with SRT, but given the lower clinical risk this does not appear to change the risk of prostate cancer–specific death.

Discussion

Part I

We found that the use of curative therapy for men with prostate cancer who were in the lowest likelihood of clinical benefit more than doubled. The NCCN Practice Guidelines in Oncology provide treatment recommendations based on non-cancer "health status" in addition to cancer-specific prognostic factors [69]**.** However, our results suggest that patients may not receive CTx in accordance with these strata, and that treatments are diffusing into practice in a pattern that does not correspond to the likelihood of clinical benefit.

Treatment trends indicate that the rates of treatment in both the low- and moderate-risk categories have increased significantly with time. Compared to baseline rates in 1996-1997, the treatment of patients with the lowest and highest likelihood of clinical benefit both increased. While the treatment of those with the lowest likelihood of clinical benefit more than doubled over the study period, there was a relatively modest increase in the rates for patients with the highest likelihood of clinical benefit. A recent study by Cooperberg et al. suggested that overtreatment of low-risk patients decreased from 1990 through 2007, but that undertreatment of high-risk disease was becoming more worrisome in recent years [2]. However, PADT was included as a therapeutic option in the prior analysis, so the discrepancy in results may be due to the documented decrease in PADT utilization after reimbursement changes made by the Medicare Modernization Act of 2003[70-71].

Our findings highlight two important and potentially problematic patterns of treatment: possible lack of treatment of patients with the highest likelihood of clinical benefit and overly aggressive treatment of patients with the lowest likelihood of clinical benefit. The implication of overtreatment and undertreatment is that clinicians are choosing to treat clinically localized Prostate cancer patients based on factors external to

their LE and cancer-risk. We hypothesize that as side effects from CTx lessen through advances in therapeutic knowledge and new technology, the threshold for acceptable baseline health and cancer-risk for candidates of CTx is becoming reduced.

While failing to treat a potentially fatal cancer can reflect poor-quality care**,** aggressive management of disease that is unlikely to progress may also be inappropriate since it puts patients at risk for considerable morbidity and adds to cost without bestowing medical benefits [3-5]. Acknowledging that superfluous care is suboptimal, and considering the collective financial and health burdens that stem from Prostate cancer and its treatment, the reallocation of CTx from patients in whom it is unnecessary or even harmful to those in whom it is necessary would create more equitable cancer care and likely improve outcomes for men with Prostate cancer.

At the same time, we recognize that overtreatment and undertreatment will never be eradicated as long as patients maintain autonomy over their own treatment decisions, as CTx is highly sensitive to patient preferences [72]. The prediction of LE and cancer progression in its current state is an imperfect science [73]. When side effects are low, some patients may prefer to be treated aggressively, as the psychological and physical burden of metastatic cancer can be devastating. Other patients may chose to forgo treatment, as Prostate cancer is generally considered to be a more indolent cancer with treatment options including active surveillance. The optimal rates of over- and under-treatment are difficult to define, but treatment decisions should correspond to the likelihood of potential clinical benefit as defined by tumor aggressiveness and LE.

Consistent with other studies, we found that age was a key factor in treatment selection [73-77]. In a New Mexico Tumor Registry study of patients diagnosed with local stage Prostate cancer between 1969 and 1982, 14% as compared to only 4% of patients did not receive definitive treatment for age groups ≥85 and 55-64 years, respectively [73]. Several age-dependent

factors may explain our results. Older men may elect not to undergo CTx because of lack of adequate social or emotional support, misinterpretation of presented information, or a feeling of resignation due to increasing age [78-81]. At the same time, clinicians may be more hesitant to recommend aggressive therapy to older men due to increased concern about side effects and mortality. However, age alone should not be the basis for withholding care, especially in otherwise healthy men with higher-risk clinically localized disease and longer LE.

We also found that married and white patients were more likely to receive CTx as compared to unmarried and black patients, respectively. The association between marital status and cancer treatment is well documented and reflects the influence of spousal support on health maintenance [82]. Our findings with respect to race support a recent study using SEER-Medicare data from 1992-2002, which found that racial disparities in Prostate cancer patients receiving definitive treatment were present and did not improve over time [83]. The Council on Ethical and Judicial Affairs of the American Medical Association has stressed the necessity of practice guidelines that minimize racial disparities in treatment decisions [84].

Patients with low-risk Prostate cancer and short LE should be considered for active surveillance and educated regarding its benefits, while the majority of men with moderate-risk disease and long LE, regardless of age, race, or marital status, should be counseled regarding the efficacy of therapy with either radiation or surgery.

There are several limitations to our study. Medicare claims may not capture all cancer-mitigating procedures and comorbid illnesses. Our study population was limited to men aged 67–85 years, so our findings may not be generalizable to younger men with Prostate cancer. Also, Medicare beneficiaries and privately-insured patients may not be representative of all older men diagnosed with Prostate cancer in regards to risk profile and treatment options. In addition, grading and staging can be subject to intra- and inter-observer variation, affecting the risk

assignment of patients. Lastly, the Elixhauser Comorbidity Index classifies only 31 possible comorbidities, of which 25 were included in the analysis. The use of total number of comorbidities to predict survival may not be optimal because certain comorbidities may have more significant impact on LE than others. Controlling for other potential unmeasured confounders such as patient education and income, as well as physician awareness and training, could potentially increase the validity of our findings.

Strengths of our study include the large number of patients and the relatively comprehensive nature of Medicare billing claims. Additionally, our sample was drawn from a large national cohort of patients who were treated by all physician types, including primary care physicians, urologists, medical oncologists and radiation oncologists. The findings of our study are relevant from a health policy standpoint as our results reflect national treatment trends over time and represent the use of public funds, which the government is obliged to spend in the most effective manner possible. Given the policy to reduce national healthcare expenditures and the questions surrounding the appropriate treatment of older men with clinically localized Prostate cancer, this analysis can be used to inform the future allocation of treatment resources.

Conclusion

The receipt of CTx for Prostate cancer is highly correlated with LE. Additionally, being older, of non-white race, unmarried or having comorbid illness is associated with a lower likelihood of receiving CTx for Prostate cancer. Compared to baseline rates in 1996-1997, the treatment of both patients with both the lowest and highest likelihood of clinical benefit has increased. The geographic allocation of healthcare resources and the impact of new surgical and radiation technologies on overtreatment and undertreatment are areas in urgent need of study.

Part II

While increased doses of prostate external beam radiation therapy above 72 Gy have previously been shown to improve BDFS, this report represents the only single-institutional study that has not explicitly incorporated the seminal vesicles into the IMRT treatment plan [10-14, 16, 85]. Biochemical disease free survival for our cohort of patients is presented in the context of the most recent prostate dose escalation trials in Table 6. Both our institutional technique and that of other institutions show excellent BDFS and toxicity outcomes.

Intermediate prognostic group patients had worse 5-year biochemical disease free survival in comparison to favorable prognostic group patients though this was not a statistically significant difference due to an underpowered cohort. During the period of study, our institutional practice was to treat patients in the intermediate prognostic group with 6 months of adjuvant hormonal therapy, which has been shown to improve overall survival over standard radiotherapy alone with doses less than 72 Gy [86]. As follow up of these patients continues, it will be interesting to see whether this non-statistically significant trend to a difference in biochemical disease free survival persists and whether it will lead to metastatic disease free survival and overall survival differences. Biochemical disease free survival has been shown to be a useful surrogate for clinical disease free survival and overall survival [59] given the long natural course of most prostate cancers. Based on a higher proportion of metastatic disease among patients receiving lower doses of radiotherapy as to those with higher doses, Kuban et al. reported possible future improvement in survival in patients treated to doses as high as 78Gy [15].

In multivariable analysis, poor prognostic group status (compared to favorable) was the only significant predictor of biochemical disease free survival. At our institution, however, almost all patients with high risk disease are treated with adjuvant long term hormonal therapy (1-3 years), in conjunction with IMRT dose escalation. The addition of long term hormonal therapy

has been definitively shown to significantly improve clinical disease free survival and overall survival over 70 Gy alone [87].

The improvement in biochemical disease free survival has been made possible without significant additional toxicity due to improvements in radiotherapy technique allowing the sparing of local normal tissue, either by 3D conformal technique [13, 15-16, 85, 88-89], proton therapy [14], or more recently, IMRT [13, 21]. Other authors have reported a low rate of acute and late gastrointestinal and genitourinary toxicity, and our results are consistent with these reports, [17, 20] listed in Table 5. In another series, average time to late grade-3+ toxicity after therapy was 23.1 – 23.2 months [22], and it is therefore unlikely that significant additional toxicities will develop in our cohort.

Our reported acute grade-3 genitourinary toxicity was slightly higher than some reported rates, partly as a result of our broader definition of morbidity. Any genitourinary toxicity, regardless of whether the clinician thought it was due to radiotherapy or was due to a preexisting condition was reported. In addition, toxicity that was coded in other CTCAE-3 categories such as pain or infection were counted as genitourinary toxicity if it was due to or pertaining to the genitourinary system, even though the CTCAE-3 codes pain as a separate category. Nonetheless, our rates of genitourinary toxicity were still very low and consistent with the reported literature. Whether acute grade-3 renal / genitourinary toxicity correlates to pretreatment American Urological Association (AUA) symptom score and other preexisting conditions remains the subject of further analysis.

Gastrointestinal toxicity was low, with grade-3 acute toxicity of 2.7% and a late grade-3 gastrointestinal toxicity of 1.35%. As noted previously, there were no grade-4 GI or GU toxicities. This excellent profile was likely due to the careful attention to rectal dose tolerances and consistent and careful quality analysis performed on each patient plan performed by our

physics staff. We also did not explicitly contour the seminal vesicles, which allowed for a shorter segment of rectum to be irradiated during the course of prostate radiotherapy. Although we theorized that the risk for acute and late toxicity should be much reduced by not including the seminal vesicles in the treatment plan, similarly excellent toxicity has been obtained while irradiating a larger portion of seminal vesicles to the same radiation dose (Table 5). Other investigators have noted that it is still possible to irradiate the entire seminal vesicles using IMRT and remain under acceptable dose constraints and normal tissue complication probability [90]. A randomized controlled trial comparing our institutional radiation technique to that of other institutions is unlikely at this time.

As new technology allows the precise location of the prostate with each radiotherapy treatment, further prostate dose escalation to 79.2Gy with image guided intensity modulated radiation therapy (IG-IMRT) is now offered to all patients at our institution. Doses up to 81-86.4 Gy treated with IMRT have been shown to offer low acute toxicity [14, 21, 23].Whether we can improve on outcomes with the addition of hormonal therapy to dose escalation for the intermediate and poor prognostic groups remains to be seen. The integration of image guidance to IMRT has allowed further dose escalation with the relative sparing of normal tissue. This further dose escalation will hopefully open yet another door to improved patient outcomes and cure rates.

Conclusion

Prostate dose escalation using IMRT is safe and effective. Durable biochemical disease free survival remains the subject of further study, but current trends are promising. Moderate acute genitourinary morbidity is uncommon, and moderate late genitourinary morbidity is rare. Severe grade-4 gastrointestinal or genitourinary morbidity has not occurred in our cohort of 223 patients. Patients with a poor prognosis will require more aggressive treatment with doses higher

than 75.6 Gy to the prostate, in combination with hormonal therapy. The optimal combination of pelvic radiotherapy, further dose escalation, and hormonal therapy for prostate cancer remains the subject of further investigation. Whether biochemical disease free survival rates will translate into metastasis free and overall survival remains the subject of further longitudinal study.

Part III

Current Treatment—Defining the Surgical Bed

Although some authors have reported on the use of low-dose rate [91] or high-dose rate [92] brachytherapy for the treatment of prostate cancer that has recurred after RP, by far the most commonly used treatment modality is external beam radiotherapy (EBRT). Therefore, our discussion will concern EBRT only. External beam salvage radiotherapy typically involves 3D conformal or Intensity Modulated Radiation Therapy (IMRT) to the prostate bed alone, with radiation fields designed to treat areas at the highest risk for local recurrence. Radiation therapy treatment volumes are in principle identical to those used for ART; therefore, lessons from ART randomized trials and ART consensus statements apply.

The randomized trials mentioned earlier were conducted in the era before the widespread adoption of 3D conformal or IMRT techniques, and therefore involved 9 × 9 cm or 10 × 10 cm fields centered around the prostatic fossa [49-51]. However, 3D conformal and IMRT techniques allow for the targeting of the prostatic fossa, urethrovesical anastamosis, and surrounding tissues at risk, with relative sparing of the rectum, bladder, and penile bulb. Multiple consensus guidelines have been created for the definition of the clinical target volume (CTV), most significantly from the EORTC, RTOG, and RADICALS groups [93-95].

All three consensus groups generally advocate for the treatment of the vesicourethral anastamosis (VUA) and surrounding periurethral tissue. However, they advocate therapy to different amounts of additional tissue such as the bladder and seminal vesicle beds. The RTOG and RADICALS groups recommend defining the VUA using the most inferior visualized urine in the bladder on sagittal reconstruction, while the EORTC defines the VUA as 15 mm cranial to the penile bulb. At the level of the pubic symphysis, anteriorly and posteriorly, all three consensus groups essentially cover the region from the pubic symphysis to the rectum, and laterally the medial border of the obdurator internus and levator ani muscles. The lateral borders were

generally the pelvic fascia superior to the pubic symphysis. At the bladder wall, the EORTC has perhaps the most limited CTV definition, and in contrast to the RTOG and RADICALS groups, does not advocate for the inclusion of 1.5 cm of posterior bladder and bladder wall. In the rectovesical /seminal vesicle bed space, the EORTC and RTOG advocate for the coverage of the seminal vesicle beds if there is pathologic involvement of the seminal vesicles in the surgical specimen, but to otherwise largely spare the seminal vesicle beds (though they do say to cover where the base of the seminal vesicles used to reside). Any retained seminal vesicle remnants should be included if the seminal vesicles were involved pathologically. The superior border in the rectovesicular space is at or 5 mm above the level of the cut end of the vas deferens or at the level of the most superior surgical clips. Inferiorly, the RADICALS group recommends placing the border at 8-12 mm below the vesicourethral anastamosis, but not to include the penile bulb. There was some concern in the RTOG group that apical tumors could extend into the genitourinal (GU) diaphragm and inferior urethral sphincter, and this was the reason it was recommended that the inferior aspect of the CTV extend to a level just above the penile bulb [94].

Separately, Miralbell et al. recommend a cylindrical CTV centered 0.5 cm posterior and 3 mm inferior to the VUA, measuring 4 cm in height and 3 cm in diameter [96]. This volume considerably spared the rectum, and may represent a way in which to limit radiation-associated toxicities and improve the quality of life of prostate cancer patients. This CTV recommendation was based on an MRI series of 60 men, and is consistent with another MRI study showing recurrences largely around the VUA [97] However, this very VUA-centric volume stands in contrast to another MRI study which showed more local recurrences in the rectovesicular space outside of the proposed CTV [98]. Further studies regarding the optimal volume of treatment are necessary, and it is hoped that information from the RADICALS trial will shed more light.

Minimizing daily set-up error and ensuring reproducible localization of the prostate bed is a current area of study. Calypso beacon localization has been suggested as a useful tool for

localization of the prostate bed as has daily portal imaging with implanted gold fiducial markers [99] or daily cone-beam imaging or kilovoltage imaging [100]. These techniques attempt to minimize daily setup error and take into account any variation in the location of the VUA depending on day-to-day differences in rectal volume and bladder distension. A general consensus on the differential benefit of these techniques has not been found, though most authors agree that daily localization is important for reducing treatment margins and thus further reducing radiation to normal tissue.

Dose

The proper radiation dose that delivers a balance of optimal disease control while limiting side effects is not clear; however, it is thought that the use of increased RT doses may provide higher chances of cure. Until recently, there were only three retrospective studies with small sample sizes that showed that doses above 64.8 Gy are beneficial [101-103]. While doses of 78 Gy are used for RT in the definitive setting, doses for ART or SRT are generally lower because it is assumed that the tumor burden is microscopic [12, 14, 89] and the presence of bladder and rectum within the prostate resection fossa increases the normal tissues radiated. As noted previously, randomized ART trials delivered radiation in the range of 60-64 Gy to relatively large fields [49-51]. The RADICALS trial is testing a dose of 66 Gy in 33 fractions, or 52.5 Gy in 20 fractions [60]. King et al. recommend at least 70 Gy based on a retrospective study showing a significant dose response between 60 and 70 Gy of radiation to the prostate bed [104]. Specifically, King et al. analyzed 122 patients with pathologically negative lymph nodes with a median follow-up > 5 years. Thirty-eight patients received a median dose of 60 Gy to the prostate bed and 84 patients received a median dose of 70 Gy. Sixty-eight patients received four months of androgen suppression therapy and 72 patients received whole-pelvic RT. The authors observed a significant dose response from 60 to 70 Gy (25% vs 58% biochemical disease-free survival at 5 years, respectively; $P < .0001$). On multivariate analysis the two clinical factors that predicted

improved biochemical-free survival were a pre-RT PSA level of 1 ng/mL (HR 0.28, P <.0001), and no seminal vesicle involvement (HR 0.44, P = .009). Thus, this study suggests that higher doses may help increase the likelihood of optimal disease-free survival. The dose of 70 Gy correlated with an increased dose of 6 Gy required for SRT vs ART, which King et al. argued in a separate manuscript was due to the additional disease burden carried by SRT patients vs ART patients [61]. In the absence of evidence that this additional dose causes worse late toxicities in patients undergoing SRT, a radiation dose in the region of 70 Gy is reasonable [64]. Currently, the American Society for Therapeutic Radiology and Oncology (ASTRO) advises the use of the highest dose of radiation that can be delivered with acceptable morbidity (at least 64 Gy at conventional fractionation) for SRT [105].

Hypofractionated radiotherapy (daily radiation doses of greater than 2 Gy) has been considered for SRT in a retrospective analysis of 50 patients [106]. Hypofractionated therapy is potentially desirable due to its shorter overall treatment length and theoretically higher biologically equivalent dose. Though toxicity and 2-year biochemical control rate appeared equivalent to published data for standard fractionation, additional follow-up and greater numbers of patients are needed before widespread adoption of this technique.

Hormone Therapy

The use of hormone therapy in combination with post-operative RT is an area of controversy that will hopefully be clarified by three randomized trials: 1) The RTOG 96-01 trial, 2) The RTOG 05-34 SSPORT trial, and 3) The RADICALS trial. The RTOG 96-01 trial is a prospective randomized trial comparing postoperative RT with and without 2 years of bicalutamide 150 mg/day which has completed and should be presented in 2010 [107]. The RTOG 0534 is an ongoing phase III trial of short-term androgen deprivation with pelvic lymph node or prostate bed–only radiotherapy (SPPORT) in prostate cancer patients with a rising PSA after RP. This 3-

arm randomized trial is assessing prostate bed RT vs prostate bed RT with short-term androgen ablation vs pelvic and prostate RT along with short-term androgen ablation [107]. As noted previously, the RADICALS trial is a prospective trial with two randomizations.

The first randomization will investigate immediate ART versus delayed SRT at the time of biochemical recurrence. Patients receiving RT will then be further randomized to RT alone, RT + 6 months of hormones, or RT + 2 years of hormones [60]. Although hormone therapy has been shown to improve overall survival in combination with EBRT for men with prostate cancer of intermediate- or high-risk disease, the value of hormone therapy has not yet been proven for men undergoing either ART or SRT [86-87, 108].

Side Effects and Toxicities Associated With Radiotherapy After Prostatectomy

Radiation treatment is the only potentially curative treatment available for most patients with biochemical failure after RP. However, some would argue that quality of life (QOL) is as important as survival. Despite the evidence in support of using RT in this setting, the decision to use it must take into account the side effects associated with treatment. There have been multiple reports of acute and late toxicities after post-operative radiation therapy in prostate cancer. Overall, RT appears to be well-tolerated in patients undergoing ART and SRT, and lessons drawn from patients undergoing ART are therefore also broadly applicable to SRT.

In the SWOG 8794 study, no patients had to interrupt their RT secondary to side effects, although grade 2 or greater complications were more common in the ART group than in the observation arm (23.8% vs 11.9%, respectively; P = .002) [50]. Urethral strictures (17.8% vs 9.5%; P = .11), and rectal complications (3.3% vs 0%; P = .02) were the most frequent toxicities. In a companion health-related QOL study, 217 of 425 SWOG 8794 patients completed a questionnaire at baseline, 6 weeks, 6 months, and annually for 5 years [109]. The 6-week assessment was included to record side-effects at their peak at the end or RT. Not surprisingly,

patients being treated with RT had a greater likelihood of a decline in bowel QOL at the end of RT as compared to the observation arm, but after 2 years, there was no significant difference between the two groups in bowel QOL. With respect to genitourinary QOL, patients in the ART arm experienced significantly more urinary urgency than those in the observation arm. However, there was no statistically significant difference in erectile dysfunction (ED), but given that the SWOG trial was performed prior to adoption of nerve sparing RP, > 90% of patients in both the ART and observation arms had severe ED, limiting the ability to comment on the effect of RT on erectile function in this patient population. Most noteworthy was that although global health-related QOL was worse in the ART group initially, it became similar by year 2, and at 5 years, patients in the ART group reported an overall better QOL compared to those in the observation arm. This is not surprising when taking into account the increased risk for metastasis and death as well as the burden of salvage and hormonal therapies among the patients in the "wait-and-see" arm.

In EORTC trial 22911, radiation treatment was interrupted as a result of toxic effects in 3.1% of patients, consisting of diarrhea, urinary frequency, proctitis, cystitis and anal pain [49]. Grade 2 or 3 late effects were significantly more numerous in the ART arm (P = .0005), but grade 3 toxicities were uncommon, with a 5-year rate of 2.6% in the observation arm and 4.2% in the ART arm (P = .0726). No grade 4 or higher late toxic effects were reported. In comparison to the EORTC 22911 and SWOG 8794 trials, the patients in the ARO 96-02/AUO AP 09/95 study had a significantly lower rate of severe (grade 3 and higher) toxicities at only 0.3% [51]. This relatively low rate of complications is likely due to the use of three-dimensional treatment planning, which is known to reduce acute and late toxicities for RT for prostate cancer.

In addition to the toxicity data from these randomized ART trials, there have been several assessments of complications following SRT. In a phase II prospective study by Pearse et al., 75 patients with biochemical relapse or local recurrence after RP were evaluated for acute and late

complications after SRT and 2 years of ADT [110]. Twelve percent of patients had gastrointestinal (GI) dysfunction and 40% had genitourinal (GU) dysfunction prior to receiving RT. Median follow-up was 45.1 months. No patients interrupted treatment secondary to side effects. Overall, 94% of patients experienced acute complications, but grade 3 toxicities were rare and the cumulative incidences for severe GI and GU toxicities were 1.6% and 2.8% at 36 months, respectively. There were no late grade 4 complications.

Patients with preexisting GU dysfunction and acute GU toxicity were more likely to have persisting late GU toxicity. In addition, the more severe the acute GU toxicity, the more likely it was to persist. Peterson et al. reported on late toxicities (those occurring more than 90 days after completion of radiation treatment) in 308 postprostatecomy patients who had undergone salvage therapy [111]. In the study, radiation dose ranged from 54.0 to 72.4 Gy with a median dose of 64.8 Gy and was given in 1.8-2.0 Gy fractions. Median follow-up from the end of treatment was 60 months. Thirteen percent of patients reported late complications, but only an estimated 0.7% (95% CI, 0.0–1.6%) of patients would experience severe (grade 3 or higher) toxicities by 5 years. Among those reported in the study were grade 3 cystitis and grade 4 rectal complications. These results are consistent with those of other reports, including data from the three recently randomized trials on ART.

Finally, as mentioned previously, Feng et al. reported on 959 patients who received ART or SRT, with a median dose of 64 Gy [64]. At 5 years, grade 3 urinary complications were observed in 1% of patients and grade 3 bowel complications were only seen in 0.3%, indicating excellent tolerance to ART and SRT. Similar toxicity was seen in a series from UCSD [100] and Germany [112] which showed resolution of acute urinary symptoms without grade 3 toxicity. Long-term toxicity was rare, and health related QOL changes were minor in comparison to baseline scores. Together, these studies support a low incidence of severe toxicities in patients receiving RT after RP.

The Effect of Post-operative Radiation Treatment on Sexual Functioning

Of particular concern for many men is the issue of erectile dysfunction after prostate cancer treatment. Indeed, there have been many studies showing that men feel discouraged and emasculated by this sexual dysfunction [113-116]. It can take erectile functioning 18 months to 2 years to recover after prostatectomy, and radiation may further damage vascular structures in the penis [4, 117]. It is unknown whether receiving RT before healing completely from surgery exacerbates the problem. In addition to avoiding overtreatment of patients, SRT has the benefit over ART of allowing patients more healing time. Of course, this advantage must be weighed against decreasing chances of efficacy if RT is postponed for too long [118].

Research on the post-surgical effects of RT on erectile functioning is in the beginning stages and results are ambiguous. In the companion SWOG health-related quality-of-life study described previously, there was no statistical difference in erectile dysfunction between the ART and observation arms [109]. However, more than 90% of patients in both groups experienced sexual side effects, and the ART group's erectile functioning was consistently lower. Although not statistically significant, these results may suggest that RT exacerbates erectile dysfunction in post-operative patients. In a study by Hu et al, men who received SRT after surgery had worse sexual functioning than men who had surgery alone [119].

However, this study had several limitations in that it was not randomized, and patients who received radiation treatment had higher risk features and a lower use of nerve-sparing radical prostatectomy, as compared to the surgery-only group. Therefore, the lower erectile functioning of the SRT group could actually be related to confounding factors. Formenti et al. reported on a prospective study in which 94 (37%) of 255 patients received 45-54 Gy of ART after prostatectomy [120]. Three years after surgery, there was no difference between the ART and

observation groups with respect to sexual functioning. However, the strength of these results is limited because higher radiation doses are delivered in current clinical practice.

Cost-Effectiveness of Post-Operative Radiotherapy After Radical Prostatectomy

In the past decade, considerable advances in planning and delivery of radiotherapy took place in the form of IMRT, resulting in the delivery of higher doses and improved toxicity profiles. Despite the tremendous gains these technologies may represent in terms of quality of life and tumor control, they are also associated with significant healthcare costs. Given the American government's major policy priority to curtail the growth of healthcare costs, it is appropriate to evaluate the cost-effectiveness of post-operative radiotherapy with this treatment modality.

Although a formal assessment on the cost-effectiveness of post-operative radiotherapy has not been performed to date, it is worthwhile presenting the available information on costs and quality of life that is relevant to treatment. Surprisingly, the most significant costs of advanced disease are the indirect costs, such as income lost from missing work, loss of productivity due to hospitalization, pain or disfigurement, as well as shortening of life years. Taking all cancers into account, the annual costs in the United States of lost productivity due to sickness and lost productivity due to early death are estimated to be $18.8 billion and $116.1 billion, respectively [121].In addition to these losses are the direct medical costs associated with metastatic disease, which is also accompanied by tremendous pain and a worse quality of life. In a study by Schulman et al., anonymous patient-level data on health care utilization and cost was obtained on 396,200 cancer patients from the Thomson Medstat MarketScan research databases, and patients with metastatic bone disease were matched to patient controls without metastatic bone disease. A 2-part linear regression model was subsequently used to estimate the incremental cost of metastases, and they found that the cost of treating a prostate cancer patient with metastatic bone disease ($56,281) is nearly three times that of treating a man with confined disease ($19,781) [122].

In a different study by Zubek et al., the cost and utility of various prostate cancer treatments and disease states were described [123]. In the analysis, costs were based on the year 2006, and "utility" was a measure of patient preferences on a scale of 0–1, with death having a utility of 0 and perfect health having a utility of 1. Utility values were measured with the EQ-5 EuroQol quality of life instrument [124] or obtained from the literature. IMRT after prostatectomy was estimated to cost $27,080 and be associated with a utility of 0.909, whereas end-of-life-care was associated with values of $30,000 and 0.6. The cost and utility for androgen suppression therapy, which is more commonly used in patients who are not treated with ART, were $9000 and 0.74, respectively. Considering the substantial costs and decreased quality of life associated with metastatic disease, it is very likely that the most cost-effective approach to treatment of patients with high-risk prostate cancer is the one that offers the best chances for progression-free survival.

As previously mentioned, results from the SWOG trial indicate that when treating patients with ART, only 10 and 12 men need to be treated to prevent one metastasis and one death, respectively. These outcomes are especially convincing since the use of androgen suppression therapy in the observation group was almost twice that of the adjuvant treatment arm and about one-third of patients in the observation group eventually underwent delayed SRT. The acceptable NNT value depends on the type of medical scenario, although a NNT of $\leqslant$20 is generally used to justify the majority of treatments [125-128]. To put the value of ART into perspective, Bill-Axelson et al. found a NNT of 19 at 12 years when comparing radical prostatectomy to watchful waiting in patients with localized prostate cancer [129]. If it is recommended that this group of patients undergoes surgery and that other patient populations receive chemotherapy with an even higher NNT, it should also follow that patients with high-risk pathological features ought to receive ART for an even greater (1:12) chance of improving survival.

In addition, there are several studies indicating that salvage radiotherapy does not significantly decrease health-related QOL [64, 100, 112].Therefore, with a conservative estimate of a 4 year 40%–50% progression-free survival for selected patients who undergo salvage radiotherapy compared to a 0–20% progression free probability, it is also easy to see that salvage radiotherapy would be acceptable under the generally accepted $50,000/QALYcost-effectiveness standard. To our knowledge, a formal study of the cost-effectiveness of salvage radiotherapy compared to hormone therapy or best supportive care has not been performed.

Risk-Prediction Tools Can Improve Cost-Effectiveness of Salvage Radiotherapy Post-Prostatectomy In order to minimize costs and prevent overtreatment with SRT, it becomes necessary to identify which patients would benefit from radiation post-prostatectomy. Approximately two-thirds of men who do not receive treatment for PSA recurrence after radical prostatectomy will develop metastatic disease within 10 years [63]. As local disease could be successfully treated with SRT, one important question is whether biochemical failure represents regional or disseminated disease. Currently, there is no imaging technique that is able to reliably detect sites of local recurrence in patients with low PSA levels. However, endorectal coil magnetic resonance imaging has recently emerged as a promising new technology to assess post-surgical patients who may have local failure. There are two major studies that have evaluated this technology's accuracy in recognizing local tumor relapse sites. In Silverman et al., sagittal and axial fat-saturated T2-weighted fast spin-echo images and axial T1-weighted unenhanced and gadolinium-enhanced eMR images were obtained in a prospective study of 41 post-prostatectomy patients [97]. They achieved a sensitivity and specificity of 100%, with biopsy-proven disease as the standard. In a retrospective study by Sella et al., T1- and T2-weighted sequences (without gadolinium administration) from 48 patients were reviewed, and a sensitivity of 95% and specificity of 100% was achieved [98]. Taken together, these studies suggest that endorectal coil MRI may be a useful risk-prediction tool when evaluating post-surgical patients for local

recurrence of malignancy. Although promising in initial studies, endorectal coil MRI has not been prospectively validated for pre-SRT risk stratification, or routinely adopted at this time.

A number of studies have looked at clinical features that may predict a favorable clinical outcome with SRT. The reports from single-institutional studies with respect to prognostic features have been Inconsistent. However, in a retrospective multicenter review by Stephenson et al. of 501 patients, the features associated with progression after SRT were a Gleason score of 8 to 10, a pre-radiotherapy PSA level greater than 2.0 ng/mL, negative surgical margins, PSA doubling time (PSADT) of 10 months or less, and seminal vesicle invasion [130]. Favorable patients were defined as those without any of these poor prognostic factors, and 70% of favorable patients remained progression-free 4 years after SRT.

However, Stephenson et al. also revealed that certain patients with adverse features such as high-grade disease or rapid PSADT may still benefit from SRT. For instance, when treatment was given with PSA still < 2.0, if a patient had a rapid PSADT (<10 months), positive surgical margins, and Gleason scores between 4–7, 4-year progression-free survival (PFP) was 64%. For patients with Gleason 8-10 disease, but with a PSA < 2.0, positive surgical margins, and PSADT > 10 mos, 4-year PFP was 81%. These results suggest that if a patient elected to not receive ART in the immediate post-operative setting, then the benefit of SRT is likely greater even in the setting of higher risk features if SRT is administered upon first sign of biochemical recurrence.

Nomograms have been designed to predict the outcome of SRT based on several patient characteristics. In a separate study by Stephenson et al., they developed such a model using multivariable Cox regression analysis and a multi-institutional cohort of 1,540 patients [67]. The nomogram had a concordance index of 0.69. They found several features that should be taken into account when predicting the 6-year-progression-free probability after SRT in post-prostatectomy patients. These included PSA level < 2.0 ng/mL, Gleason score of 7 or less, PSA

doubling time greater than 10 months, positive surgical margins, androgen-deprivation therapy before or during SRT, and the absence of lymph node metastasis. This nomogram has been externally validated by Moriera et al. [131]. The validation study involved 102 patients from the Shared Equal Access Regional Cancer Hospital (SEARCH) database who were treated with SRT for PSA failure after surgery. Even though the cohort was composed of lower-risk patients as compared to the original series, the overall concordance index of the Stephenson nomogram was reasonable, at 0.65. These authors also found that though the nomogram successfully predicted failure at the extremes of risk, it was less accurate in the intermediate groups. Negative surgical margins and high preradiotherapy PSA level were the only nomogram variables that were significantly linked to disease progression [131]. Although the Stephenson nomogram is the best available prediction tool currently available to predict who will obtain long-term benefit from SRT, there is still significant room for improvement in this risk-prediction model.

Conclusion

New evidence indicates that immediate treatment with ART, rather than watchful waiting, is more appropriate for the patient with pathologically advanced disease because it can improve cancer-specific and overall survival. While post-operative radiation may cause side effects, evidence suggests that the overall long-term quality of life is improved in patients who are treated immediately after surgery rather than monitored for disease recurrence with the possibility of later treatment. In addition, numerous consensus guidelines exist to aid the physician in planning treatment fields. Although prostate cancer treatment decisions should take into account patient preferences, cost of treatment, and treatment-related side effects, we suggest that patients with long life-expectancies and positive surgical margins or pathological T3 disease, as well as an undetectable PSA, should see a radiation oncologist to discuss the possibility of entering a clinical trial such as RADICALS that addresses the best possible timing of post-operative RT. If a clinical trial is not available, it is the opinion of the authors that patients with the above

mentioned high-risk pathologic features should undergo immediate adjuvant radiation therapy. This recommendation is made with the acknowledgement that there is no level-1 evidence favoring ART over delayed SRT in a patient who has been followed carefully and SRT initiated at low levels of PSA.

Randomized controlled trials are necessary to fully determine the utility of dose escalation. We anticipate the results from the RADICALS trial to answer further questions regarding the comparison of immediate ART to early SRT following biochemical relapse, and the role of hormone therapy.

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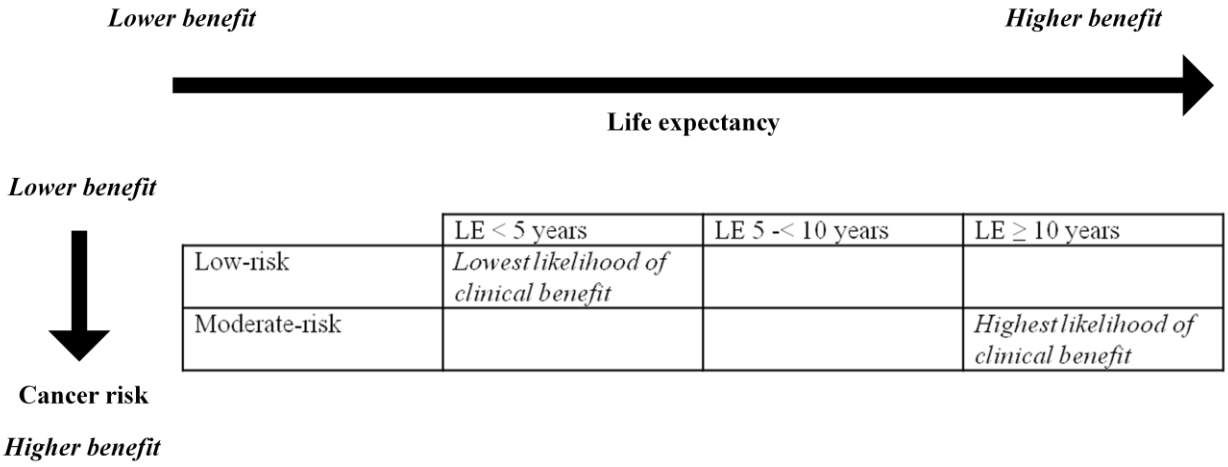
Part I

Figure 1. Schematic of patient likelihood of clinical benefit stratification framework



	LE < 5 years	LE 5 -< 10 years	LE ≥ 10 years
Low-risk	*Lowest likelihood of clinical benefit*		
Moderate-risk			*Highest likelihood of clinical benefit*

Figure 2. Inclusion Criteria

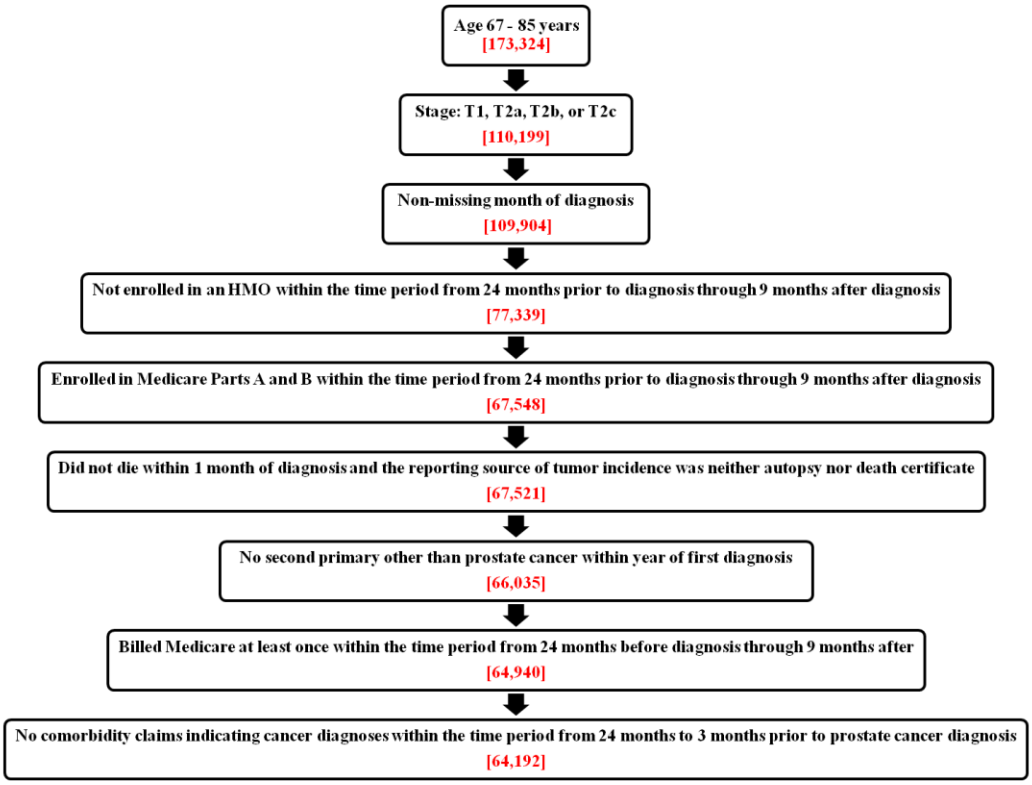


Table 1. Bivariate analysis of factors associated with receipt of curative therapy for low- and moderate-risk prostate cancer patients

		Low risk			Moderate risk		
		N	%treated	p-value	N	%treated	p-value
Age	67-69	8768	79.1		5019	83.9	
	70-74	14716	74.1		8370	79.9	
	75-79	10918	57.1		7040	67.1	
	80-85	5120	27.1	<.0001	4241	39.2	<.0001
Race	White	33954	66.0		20466	72.0	
	Black	3365	58.6		2568	59.8	
	Other	2203	50.1	<.0001	1636	61.8	<.0001
Marital status	Married	28808	68.1		17568	74.8	
	Not married	7763	57.4		5148	61.5	
	Unknown	2951	47.6	<.0001	1954	49.9	<.0001
Comorbidity	0	22939	68.1		14141	72.5	
	1-2	13203	62.3		8173	69.9	
	≥3	3380	48.2	<.0001	2356	55.6	<.0001
Life expectancy (years)	< 5	922	24.1		737	31.6	
	5-<10	15492	50.7		10747	60.0	
	10-<15	19269	74.2		10955	79.5	
	≥15	3839	80.7	<.0001	2231	84.5	<.0001
	≥10	*23108*	*75.3*		*13186*	*80.4*	
Year of diagnosis (all registries)	1996	2639	57.7		1252	66.9	
	1997	2835	61.8		1290	67.5	
	1998	2736	61.9		1154	70.7	

	1999	2729	64.7		1124	69.1	
	2000	5097	67.2		2210	68.1	
	2001	5325	66.4		2299	70.1	
	2002	5346	66.1		2301	69.7	
	2003	4096	63.2		2630	70.4	
	2004	4491	64.4		5209	70.9	
	2005	4228	65.3	<.0001	5201	71.4	0.0112
Overall		39522	64.4		24670	70.0	

Figure 3. Percent of prostate cancer patients receiving curative treatment, stratified by risk category and life expectancy

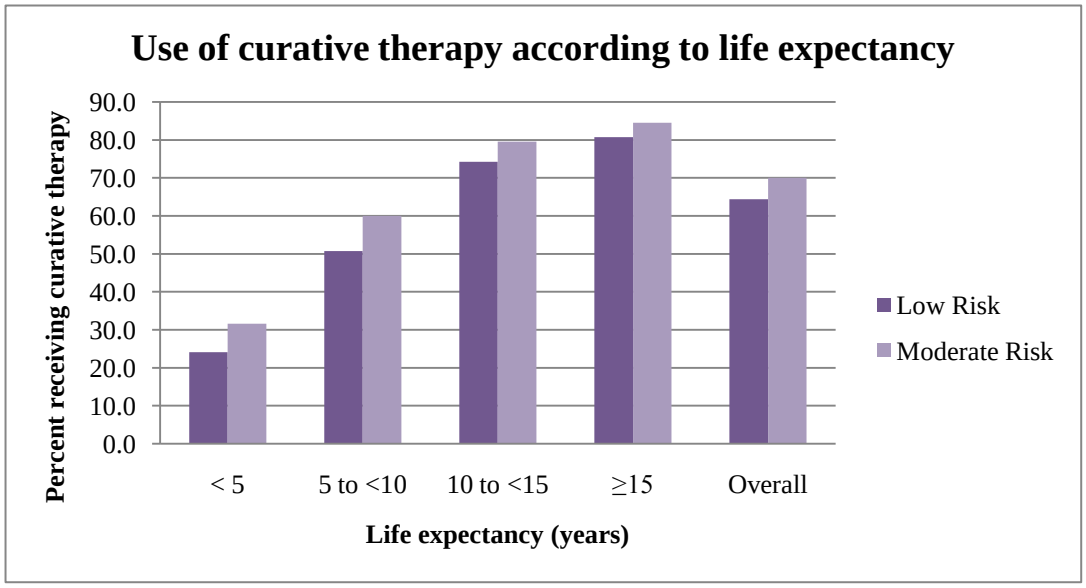


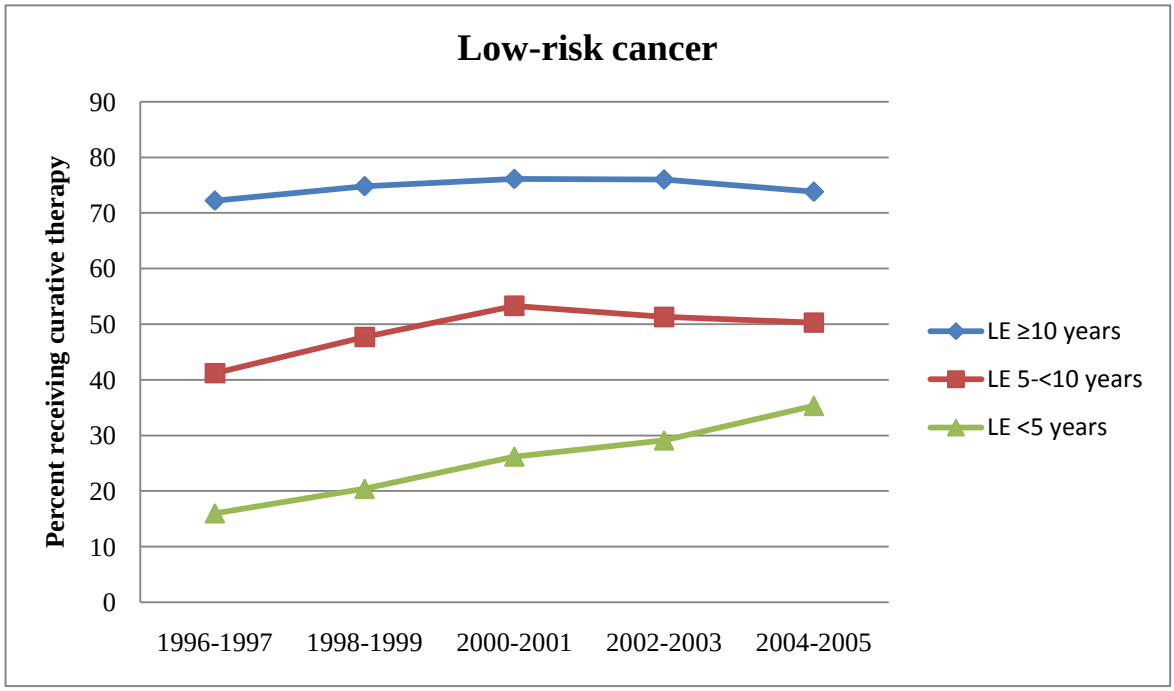
Table 2. Odds ratios of low- and moderate-risk prostate cancer patients receiving curative therapy by patient characteristics and risk group, unadjusted and adjusted for age, race, marital status, comorbidity, risk category, and year of diagnosis

		LOW RISK TUMOR CHARACTERISTICS		MODERATE RISK TUMOR CHARACTERISTICS		FULL SAMPLE	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	67-69	1.00	1.00	1.00	1.00	1.00	1.00
	70-74	0.76 (0.71, 0.81)	0.77 (0.72, 0.82)	0.76 (0.70, 0.84)	0.77 (0.70, 0.85)	0.76 (0.72, 0.80)	0.77 (0.73, 0.81)
	75-79	0.35 (0.33, 0.38)	0.37 (0.34, 0.39)	0.39 (0.36, 0.43)	0.40 (0.37, 0.44)	0.37 (0.35, 0.39)	0.38 (0.36, 0.40)
	80-85	0.10 (0.09, 0.11)	0.10 (0.10, 0.11)	0.12 (0.11, 0.14)	0.13 (0.11, 0.14)	0.12 (0.11, 0.12)	0.11 (0.11, 0.12)
Race	White	1.00	1.00	1.00	1.00	1.00	1.00
	Black	0.74 (0.68, 0.79)	0.71 (0.66, 0.77)	0.58 (0.53, 0.63)	0.55 (0.50, 0.60)	0.67 (0.64, 0.71)	0.64 (0.60, 0.68)
	Other	0.52 (0.48, 0.57)	0.58 (0.53, 0.64)	0.63 (0.57, 0.70)	0.73 (0.65, 0.82)	0.57 (0.53, 0.61)	0.64 (0.60, 0.69)
Marital status	Married	1.00	1.00	1.00	1.00	1.00	1.00

	Not married	0.63 (0.60, 0.67)	0.71 (0.67, 0.75)	0.54 (0.50, 0.58)	0.61 (0.56, 0.65)	0.60 (0.58, 0.63)	0.67 (0.64, 0.70)
	Unknown	0.43 (0.40, 0.46)	0.47 (0.43, 0.51)	0.34 (0.31, 0.37)	0.37 (0.33, 0.41)	0.39 (0.37, 0.42)	0.42 (0.40, 0.45)
Comorbidity	0	1.00	1.00	1.00	1.00	1.00	1.00
	1-2	0.78 (0.74, 0.81)	0.90 (0.85, 0.94)	0.88 (0.83, 0.93)	1.01 (0.95, 1.08)	0.81 (0.78, 0.84)	0.94 (0.90, 0.97)
	≥3	0.44 (0.41, 0.47)	0.55 (0.51, 0.60)	0.47 (0.43, 0.52)	0.60 (0.54, 0.66)	0.46 (0.43, 0.48)	0.57 (0.53, 0.60)
Risk group	Low					1.00	1.00
	Moderate					1.29 (1.25, 1.34)	1.52 (1.46, 1.58)

Figure 4. Percent of low- and moderate-risk prostate cancer patients receiving curative therapy over time, stratified by life expectancy.

A



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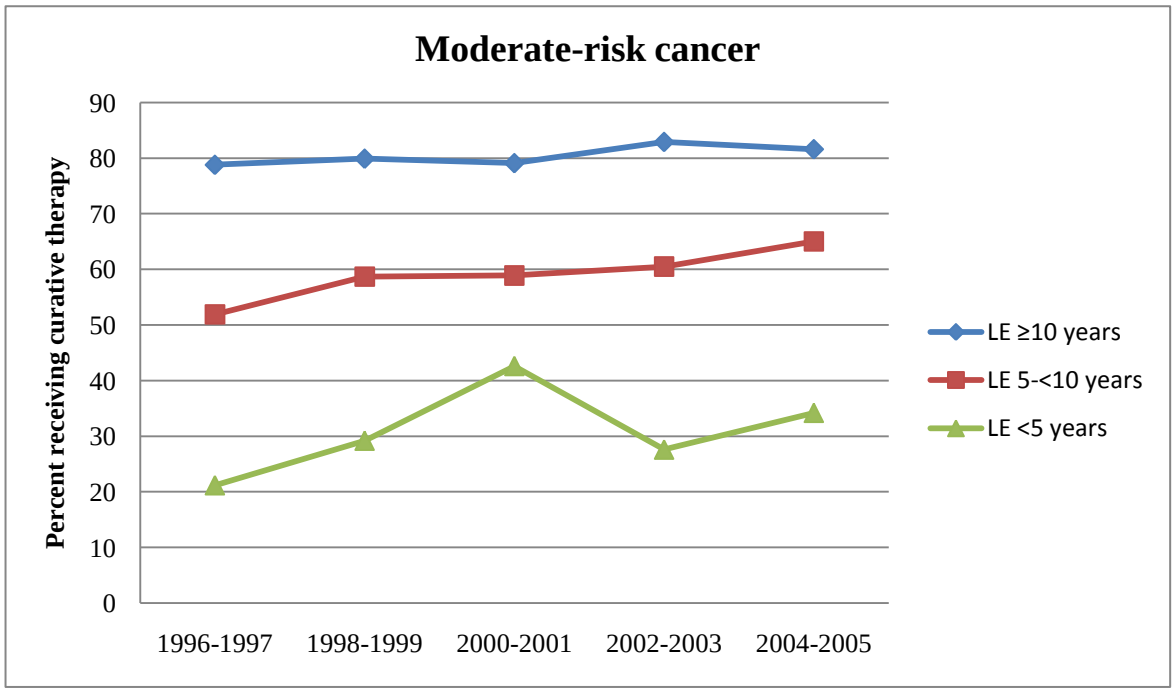

Note: Data reflective of the registries participating in SEER throughout 1996-2005, only.

Appendix 1. Elixhauser conditions included in sample analysis

Condition
Congestive Heart Failure
Cardiac Arrhythmia
Valvular Disease
Pulmonary Circulation Disorders
Peripheral Vascular Disorders
Paralysis
Other Neurological Disorders
Chronic Pulmonary Disease
Diabetes Uncomplicated
Diabetes Complicated
Renal Failure
Liver Disease
AIDS/HIV
Lymphoma
Rheumatoid Arthritis/collagen
Coagulopathy
Weight Loss
Fluid and Electrolyte Disorders
Deficiency Anemia
Alcohol Abuse
Drug Abuse
Psychoses
Depression

Appendix 2. Prostate cancer treatment billing codes.

Treatment		Code
Any form of radiation (including brachytherapy)	ICD-9 Procedure	92.2x
	ICD-9 Diagnosis	V58.0, V66.1, V67.1
	HCPCS	77261 – 77799; 55859, 55860, 55862, 55865, 76965, C1715-C1720, C2633-C2642, Q3001
	Revenue center	0330-0339
Any prostate surgery	ICD-9 Procedure	60.3, 60.4, 60.5, 60.62, 60.69
	HCPCS	55810, 55812, 55815, 55840, 55842, 55845, 55866, 55801, 55821, 55831

Note: The HCPCS codes C2643, C2698, C2699, and ICD-9 Procedure code 60.6 were also investigated but not found within our sample.

Part II

Table 3. Patient characteristics (n=223)

Category	Number of patients	Percent
Race		
White	180	80.7%
Black	40	17.9%
Hispanic	1	0.45%
Asian / Other / Unknown	2	0.9%
Gleason score		
6	73	32.7%
7	103	46.2%
8-10	47	21.1%
Pretreatment PSA		
PSA < 4	10	4.5%
4 ≥ PSA < 10	121	54.3%
10 ≥ PSA < 20	62	27.8%
20 ≥ PSA	30	13.4%
Clinical T stage		
T1b	2	0.9%
T1c	141	63.2%
T2a	42	18.8%
T2b	15	6.7%
T2c	6	2.7%
T3	17	7.7%
Prognostic Group*		
Favorable	44	19.7%

Intermediate	106	47.5%
Poor	73	32.7%
Type of radiation		
3D conformal radiation + IMRT boost	111	49.8%
IMRT alone	97	43.5%
Pelvic RT + IMRT boost	15	6.7%
Adjuvant therapy		
Hormonal therapy	177	79.4%
No hormonal therapy	46	20.6%

* Favorable prognostic group was defined as having a T1-T2a, Gleason score 6, and PSA < 10. Intermediate risk was T2b-T2c, Gleason score 7, or PSA 10-20 ng/mL. High risk was defined as T3, Gleason score 8-10, or PSA > 20.

Figure 5. Biochemical Disease-Free Survival over time, stratified by cancer-risk group

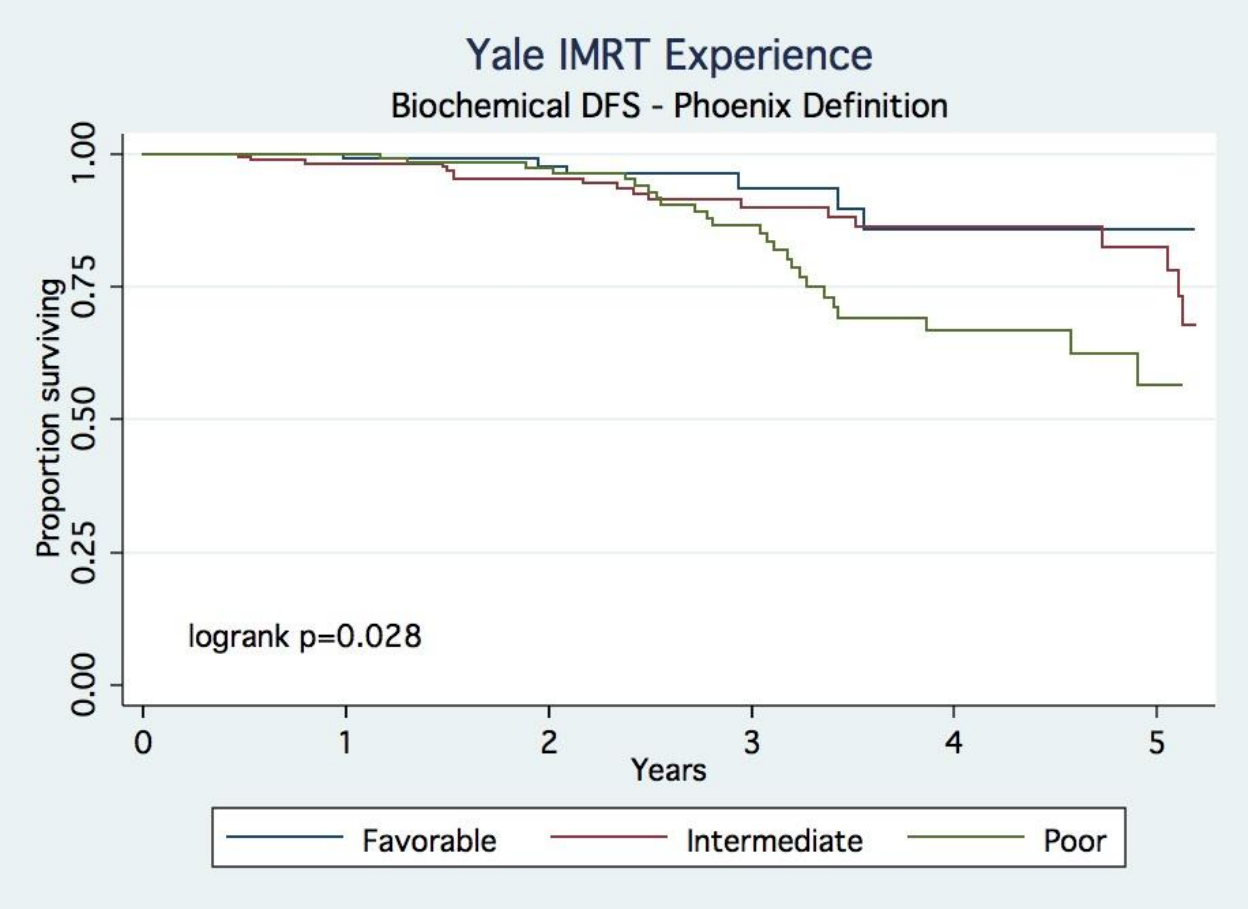

Table 4. Use of Adjuvant Therapy and Pelvic Therapy by prognostic group

	Number Receiving Adjuvant Hormone Therapy (percent)	**Odds Ratio – Likelihood of Receiving Adjuvant Hormone Therapy [95% CI]****	**P value****	**Number Receiving Pelvic RT**	**Odds Ratio – Likelihood of Receiving Pelvic RT [95% CI]****	**P value****
Prognostic group						
Favorable (n=44)	13/44 (29.5%)	1*		0	***	
Intermediate (n=106)	93/106 (87.7%)	17.1 [7.1 – 40.7]	<0.001	2/106 (1.9%)	1*	
Poor (n=73)	71/73 (97.3%)	84.7 [18.0 – 397.8]	<0.001	13/73 (17.8%)	11.3 [2.5-51.6]	<0.001

*Reference values

** Calculated with logistic regression

*** Not calculated

Table 5. Univariable and multivariable survival analysis – risk of biochemical disease free survival (ASTRO-Phoenix Definition)

Category	Univariable Hazard Ratio [95% CI]	Univariable p-value****	Multivariable Hazard Ratio [95% CI]***	Multivariable p-value****
Race		0.68		
White	1*		1*	
Black	0.61 [0.24-1.56]		0.50 [0.20-1.29]	0.15
Hispanic	**		**	
Asian / Other / Unknown	**		**	
Gleason score		<0.0001		
6	1*			
7	0.94 [0.42-2.10]			
8-10	4.41 [2.02-9.63]			
Pretreatment PSA		0.091		
PSA < 4	1*			
4 ≥ PSA < 10	0.53 [0.15-1.83]			
10 ≥ PSA < 20	1.09 [0.31-3.77]			
20 ≥ PSA	1.33 [0.36 – 4.96]			
Clinical T stage		0.024		
T1c	1*			
T2a	1.04 [0.47-2.27]			
T2b	4.81 [2.13-10.9]			
T2c	1.06 [0.14-7.91]			
T3 – T4	1.50 [0.51-4.35]			
Prognostic Group		0.0020		

Favorable	1*		1*	
Intermediate	1.59 [0.54-4.75]		2.02 [0.58-7.08]	0.27
Poor	4.10 [1.42-11.88]		6.12 [1.63-23.01]	0.007
Type of radiation		0.188		
3D conformal radiation + IMRT boost	1*		1*	
IMRT alone	0.54 [0.27-1.07]		0.61 [0.30-1.23]	0.17
Pelvic RT + IMRT boost	0.70 [0.16-2.96]		0.45 [0.10-1.96]	0.29
Adjuvant therapy		0.41		
No Hormonal therapy	1*		1*	
Hormonal therapy	1.39 [0.62-3.12]		0.56 [0.21-1.54]	0.264

* Reference value

** Numbers too small to meaningfully calculate

*** Multivariable model included prognosis, adjuvant therapy yes/no, race, and type of RT. Gleason score, pretreatment PSA, and clinical T stage are taken into consideration for the prognosis, and so were not included separately in the multivariable model.

**** Calculated by Cox proportional hazards analysis

Table 6. Acute and late toxicity

	Acute Toxicity (From start of RT to end of RT + 60 days)	Late Toxicity (Toxicity that occurred > 60 days after completion of RT)
All	Grade-3 – 12.1% Grade-4 – 0.45%*	Grade-3 – 4.0% Grade-4 – 0.9%***
Genitourinary	Grade-2 – 30.0% Grade-3 – 7.6%** Grade-4 – 0%	Grade-2 – 3.6% Grade-3 – 0.45% Grade-4 – 0%
Gastrointestinal	Grade-2 – 12.1% Grade-3 – 2.7% Grade-4 – 0%	Grade-2 – 4.0% Grade-3 – 1.3% Grade-4 – 0%

* One patient had a cardiac event unrelated to radiotherapy.

** This includes 5 patients with urethral or testicular pain requiring at least one episode of narcotic use.

*** One patient had a cardiac event unrelated to radiotherapy, and one patient had abdominal pain unrelated to radiation therapy.

Table 7. High dose prostate irradiation - Toxicity

Author / Institution / Nature of study	**N**	**Dose**	**Type of radiation technique**	**GI or GU Acute Toxicity**	**GI or GU Late Toxicity**
Zelefsky et al. / MSKCC / Retrospective[13]	1100	All patients (64.8-86.4 Gy)	3DCRT + IMRT		GI Grade-3 – 1% GI Grade-4 – 0.1% GU Grade-3 – 1.5% GU Grade-4 – 0%
	61	81 Gy	3DCRT		GI Grade-2 – 12% GI Grade-2 – 2%
	189	81 Gy	IMRT		GI Grade-3 – 2% GI Grade-3 – 0.5%
	40	86.4 Gy	IMRT		GI Grade-2 – 5% GI Grade-3 – 0% GU Grade-2 – 20% GU Grade-3 – 0%

Zelefsky et al. / MSKCC / Retrospective[21]	561	81 Gy	IMRT		GI Grade-2 – 1.5% (Rectal bleeding) GI Grade-3 – <1% (Defined as rectal bleeding requiring 1 or more transfusions or 1 cauterization procedure) GI Grade-4 – 0% GU Grade 2 – 9% (Chronic urethritis requiring medication for symptom control) GU Grade-3 – 3% (Defined as urethral stricture requiring dilation)
Zelefsky et al. / MSKCC / Retrospective[21]	478	86.4 Gy	IMRT	GI Grade 2 – 8% GI Grade 3 – 0% GI Grade 4 – 0% GU Grade 2 – 22% GU Grade 3 – 0.6% GU Grade 4 – 0%	GI Grade 2 – 3% GI Grade 3 – 0.4% GI Grade 4 – 0% GU Grade 2 – 13% GU Grade 3 - <3% GU Grade 4 – 0%

Kuban et al. / MDACC / Prospective, Randomized[15]	150	70 Gy	3DCRT	Crude 10-year rate: GI Grade-3 – 1% GI Grade-4 – 0% GU Grade-3 – 5% GU Grade-4 – 0%	
	151	78 Gy	3DCRT	Crude 10-year rate: GI Grade-3 – 7% GI Grade-4 – 0% GU Grade-3 – 4% GU Grade-4 – 0%	
Zietman et al. / MGH and Loma Linda / Prospective, Randomized[14]	196	70.2 Gy	3DCRT + Proton	GI Grade-3: 1% GI Grade-4: 0% GU Grade-3: 1% GU Grade-4: 0%	GI Grade-3: 1% GI Grade-4: 0% GU Grade-3: 2% GU Grade-4: 0%
	195	79.2 Gy	3DCRT + Proton	GI Grade-3: 0% GI Grade-4: 0% GU Grade-3: 2% GU Grade-4: 0%	GI Grade-3: 1% GI Grade-4: 0% GU Grade-3: 1% GU Grade-4: 0%
Michalski et al. / RTOG 9406 / Prospective phase I-II[22]	112	68.4 Gy (1.8 Gy/Fx)	3DCRT	GI or GU Grade 3+:3-6%	
	300	73.8 Gy (1.8 Gy/Fx)	3DCRT	GI or GU Grade 3+: 2-4%	
	167	79.2 Gy (1.8 Gy/Fx)	3DCRT	GI or GU Grade 3+: 6%	

	256	74 Gy (2 Gy/Fx)	3DCRT	GI or GU Grade 3+: 7-9%	
	220	78 Gy (2 Gy/Fx)	3DCRT	GI or GU Grade 3+: 9-12%	
De Meerleer et al. / Belgium / Retrospective[20]	114	72-78 Gy*	IMRT	GI Grade-3: 0% GI Grade-4: 0% GU Grade-3: 7% GU Grade-4: 0%	
De Meerleer et al. / Belgium / Retrospective[17]	133	72-74 Gy**	IMRT		GI Grade-3: 1% GI Grade-4: 0% GU Grade-3: 3% GU Grade-4: 0%
Liauw et al./ University of Chicago/ Retrospective[24]	130	74-76 Gy***	IMRT	GI Grade-2:38% GI Grade-3:0% GI Grade-4:0% GU Grade-2: 45% GU Grade-3: 2% GU Grade-4: 0%	GI Grade-2: 9% GI Grade-3: 5% GI Grade-4: 0% GU Grade-2: 31% GU Grade-3: 6% GU Grade-4: 0%

Martin et al./University of Toronto/ Prospective[25]	92	60 Gy in 20 fractions over 4 weeks	IMRT Hypo-fractionated	GI Grade-2: 11% GI Grade-3: 1% GI Grade-4 0% GU Grade-2: 25% GU Grade-3: 0% GU Grade-4: 0%	Actuarial GI Grade-2: 5.1% GI Grade-3: 1.2% GI Grade-4 0% GU Grade-2: 10% GU Grade-3: 0% GU Grade-4: 0%
Raldow et al. (This study) / Yale School of Medicine / Retrospective	228	75.6 Gy	3D+ IMRT	GI Grade 2: 12.1% GI Grade 3: 2.7% GI Grade 4: 0% GU Grade 2: 30.0% GU Grade 3: 7.6% GU Grade 4: 0%	GI Grade 2: 4.0% GI Grade 3: 1.35% GI Grade 4: 0% GU Grade 2: 3.6% GU Grade 3: 0.45% GU Grade 4: 0%

* Dose reported here as maximum rectal dose, given in 36-38 fractions. Median prostate PTV dose was 74-78 Gy.

** Dose reported here as maximum rectal dose, given in 36-37 fractions. Median prostate PTV dose was 74-76 Gy.

***Of 130 patients, 36 low-risk patients were treated with 74 Gy; and 69 intermediate-risk and 25 high-risk patients were treated with 76 Gy

Table 8. High dose prostate irradiation – Outcomes

Author / Institution / Nature of study	N	Dose	Type of radiation technique	BDFS (Except where marked otherwise)		
				Favorable	Intermediate	Poor
Zelefsky et al. / MSKCC / Retrospective[13]	365	64.8 Gy – 70.2 Gy	3DCRT	[a]* 5 year - 77%	[a]* 5 year - 50%	[a]* 5 year - 21% (95% CI +/- 4%)
	193	75.6 Gy	3DCRT+ IMRT			[a]* 5 year - 43% (95% CI +/- 4%)
	65	81.0 Gy	3DCRT + IMRT			[a]* 5 year - 67% (95% CI +/- 4%)
Zelefsky et al. / MSKCC / Retrospective[21]	561	81 Gy	IMRT	[b]** 8 year – 89%	[b]** 8 year – 78%	[b]** 8 year – 67%
Zelefsky et al. / MSKCC / Retrospective[21]	478	86.4 Gy	IMRT	[b]** 5 year – 99%	[b]** 5 year – 79%	[b]** 5 year – 72%
Kuban et al. / MDACC / Prospective, Randomized[15]	150	70 Gy	3DCRT	[c]** 8 year – 63%	[c]** 8 year – 76%	[c]** 8 year – 26%
	151	78 Gy	3DCRT	[c]** 8 year – 88% (p=0.042)	[c]** 8 year – 86% (p=0.36)	[c]** 8 year – 63% (p=0.004)
Kupelian et al. / Multi-institutional / Retrospective[89]	1061	< 72 Gy	EBRT	[d]* 5 year – 75%	[d]* 5 year – 63%	[d]* 5 year – 38%
	264	≥ 72 Gy	EBRT	[d]* 5 year – 79% (p=0.359)	[d]* 5 year – 72% (p=0.026)	[d]* 5 year – 46% (p=0.126)

Kupelian et al. / Cleveland Clinic / Retrospective[85]	321	< 72 Gy	EBRT	[e]*** 8 year – 48%	[e]*** 8 year – 28%	
	307	≥ 72 Gy	EBRT	[e]*** 8 year - 86%	[e]*** 8 year – 61%	
Valicenti et al. / RTOG / Pooled results from prospective, randomized trials[19]	107	≤ 66 Gy	EBRT			[f]**** (Gleason 8-10) 5 year – 61% 10 year – 31%
	331	> 66 Gy	EBRT			[f]**** (Gleason 8-10) 5 year – 71% 10 year - 46% (p=0.041)
Hanks, et al. / Fox Chase / Retrospective[27]	34	< 72.5 Gy	3DCRT	[g]* 5 year – 77% (Favorable and PSA < 10)		
	191	≥ 72.5 Gy	3DCRT	[g]* 5 year – 89% (Favorable and PSA < 10) (p=0.11)		

	67 56	35	< 76 Gy	3D		[g]* 5 year – 70% (Unfavorable and PSA < 10) 5 year – 72% (Favorable and PSA 10 – 19.9)	[g]* 5 year – 51% (Unfavorable and PSA ≥ 10)
	46 52	36	≥ 76 Gy	3D		[g]* 5 year – 92% (Unfavorable and PSA < 10) (p=0.0092) 5 year – 86% (Favorable and PSA 10 – 19.9) (p=0.10)	[g]* 5 year – 82% (Unfavorable and PSA ≥ 10) (p=0.0054)
Zietman et al. / MGH and Loma Linda / Prospective, Randomized[14]	197		70.2 Gy	3D + Proton	[e]* 5 year – 60.1%	[e]* 5 year – 63.4%	
	195		79.2 Gy	3D + Proton	[e]* 5 year – 80.5% (p<0.001)	[e]* 5 year – 79.5% (p=0.03)	
De Meerleer / Belgium / Retrospective[20]	133		[h] 74-76 Gy	IMRT	* 5 year – 100%	* 5 year – 94%	* 5 year – 74%

Liauw et al./ University of Chicago/ Retrospective[24]	130	74-76 Gy	IMRT	[b]** 4 years- 97%	[b]** 4 years- 94%	[b]** 4 years- 87%
Martin et al./University of Toronto/ Prospective[25]	92	60 Gy in 20 fractions over 4 weeks	IMRT Hypo-fraction-ated	** 3-year – 100%	** 3-year – 85%	** 3-year – 71%
Valicenti et al. / RTOG 94-06 / Prospective[19]	920	≥ 73.8 Gy	3D CRT	RT alone 5 year – 85% RT + Hormone therapy (HRT) 5 year – 83%	RT alone 5 year – 82% RT + HRT 5 year – 76%	RT alone 5 year – 69% RT + HRT 5 year – 69% RT + Long term hormone therapy (LHRT) 5 year – 71%
Raldow et al. / Yale / Retrospective (Current study)	223	75.6 Gy	3D + IMRT	[b]** 5 year – 92.1%	[b]** 5 year – 83.5%	[b]** 5 year – 59.0%

* ASTRO definition

** Phoenix definition (PSA Nadir + 2)

*** Definition of failure is any PSA > 0.5 ng/mL that is not clearly decreasing

**** 5 and 10 year disease specific survival defined as death due to prostate cancer

[a] Favorable group was defined as having the following three indicators: (1) PSA ≤ 10, (2) Gleason Score ≤ 6, and (3) stage T1 to T2. Intermediate defined as the absence of one of the three indicators, and poor prognostic group defined as the absence of two or more indicators.

[b] Favorable defined as PSA < 10, Gleason score ≤ 6, and stage T1 to T2a, intermediate defined as clinical stage T2b or T2c, Gleason score of 7, or pretreatment PSA 10 to 20, and poor defined as clinical stage T3a or higher, Gleason score ≥ 8, or pretreatment PSA > 20 ng/ml.

[c] Favorable defined as PSA ≤ 10, Gleason Score ≤ 6, and stage T1 to T2a, poor defined as Gleason score ≥ 8, PSA > 20, or T3, and intermediate patients all others.

[d] Favorable defined as PSA ≤ 10, Gleason Score ≤ 6, and stage T1b to T2a, poor defined as Gleason Score 8-10 or PSA > 20, and intermediate patients all others. T1a and T3 patients were not included.

[e] Favorable defined as PSA ≤ 10, Gleason score ≤ 6, and stage T1 to T2a. Unfavorable is defined as all others.

[f] Unfavorable defined as Gleason score 8-10.

[g] Favorable defined as Gleason score ≤ 6, stage T1 – T2a, and no perineural invasion. Unfavorable is all others.

[h] Dose reported here as median prostate PTV dose.

Table 9. Comparison of biochemical relapse-free survival in the ART and observation arms as reported from the three randomized controlled trials.

	Follow-up	**bRFS in ART arm**	**bRFS in observation arm**	**Hazard ratio**	***p*-Value**
EORTC 22911[49]	5 years	Overall: 74%	Overall: 52.6%	0.48	$p < 0{\cdot}0001$
		Undetectable ($\leqslant$0.2 ng/mL) PSA: 78.8%	Undetectable ($\leqslant$0.2 ng/mL) PSA: 59.6%	0.50	$p < 0{\cdot}0001$
		Detectable PSA: 62.6%	Detectable PSA: 37.6%	0.46	$p < 0{\cdot}0001$
SWOG 8794[132]	10.6 years	Undetectable ($\leqslant$0.4 ng/mL) PSA: 65.1%	Undetectable ($\leqslant$0.4 ng/mL) PSA: 36%	0.43	$p<.001$
ARO96-02/AUO AP 09/95 [51]	5 years	Undetectable ($\leqslant$0.1 ng/mL) PSA: 72%	Undetectable ($\leqslant$0.1 ng/mL) PSA: 54%	0.53	$p = .0015$