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Overall survival and biochemical failure-free survival comparison of brachytherapy treatment options versus external beam radiation therapy for both low and intermediate-risk prostate cancer: A propensity-score matched analysis

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OVERALL SURVIVAL AND BIOCHEMICAL FAILURE-FREE SURVIVAL COMPARISON OF BRACHYTHERAPY TREATMENT OPTIONS VERSUS EXTERNAL BEAM RADIATION THERAPY FOR PROSTATE CANCER: A PROPENSITY SCORE MATCHED ANALYSIS

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ABSTRACT

Purpose: This study compares overall survival (OS) and biochemical failure-free survival (bFFS) in low- and intermediate-risk prostate cancer patients that received brachytherapy [low-dose-rate brachytherapy (LDR-BT) or high-dose-rate brachytherapy with external beam radiation therapy (HDR-BT+EBRT)] versus external beam radiation therapy (EBRT) alone.

Materials/Methods: Patient data was obtained from the ProCaRS database, which contains 7974 prostate cancer patients treated at four Canadian institutions. Propensity score (PS) matching was used to generate matched cohorts with balanced baseline prognostic factors.

Results/Conclusions: Final PS matches included two 1:1 intermediate-risk patient matches, LDR-BT vs. EBRT (total n = 254) and HDR-BT+EBRT vs. EBRT (total n=388), and a 4:1 (LDR-BT:EBRT) low-risk match (total n=400). Hazard ratios for OS were 0.79 (p=0.69), 0.64 (p=0.47), and 1.41 (p=0.50), respectively. Hazard ratios for bFFS were 0.22 (p=0.001), 0.48 (p=0.007), and 0.35 (p=0.004), respectively.

Conclusions: PS matching showed BT significantly improved bFFS but not OS in matched prostate cancer patients.

DEDICATION

This thesis is dedicated to my love,
Joanne ‘Hope’ Namedynski, my mother
Anne and my father Lindsay.

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LIST OF ABBREVIATIONS AND UNITS

ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
ASRR	Age Specific Reference Range
ASTRO	American Society for Therapeutic Radiology and Oncology
bFFS	Biochemical Failure-Free Survival
BPH	Benign Prostatic Hypertrophy
BT	Brachytherapy
BT+EBRT	Brachytherapy with External Beam Radiation Therapy
cGy	Centigray
CAB	Combined Androgen Blockade
CER	Comparative Effectiveness Research
CI	Confidence Interval
CT	Computed Tomography
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
EBM	Evidence Based Medicine
EBRT	External Beam Radiation Therapy
ED	Erectile Dysfunction
EQD_{2Gy}	Biologically Equivalent Dose of EBRT in 2 Gy Fractions
GI	Gastrointestinal
GU	Genitourinary
Gy	Gray
GUROC	Genitourinary Radiation Oncologists of Canada
HDR-BT	High Dose Rate Brachytherapy
HDR-BT+EBRT	High Dose Rate Brachytherapy with External Beam
I-125	Iodine 125
Ir-192	Iridium 192
IMRT	Intensity Modulated Radiation Therapy

LDR-BT	Low Dose Rate Brachytherapy
LHRH	Luteinizing Hormone Releasing Hormone
MRI	Magnetic Resonance Imaging
Ng/mL	Nanograms per Millilitre
Ng/dL	Nanograms per Decilitre
OS	Overall Survival
Pd-103	Palladium 103
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PS	Propensity Score
PSA	Prostate Specific Antigen
ProCaRS	Prostate Cancer Risk Stratification Database
RCT	Randomized Controlled Trial
RP	Radical Prostatectomy
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
TNM	Tumor Nodes Metastasis
TRUS	Trans-Rectal Ultrasound
TURP	Trans-Urethral Resection of the Prostate

1.0 Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy and is the third leading cause of cancer-related death in Canadian men (Canadian Cancer Society 2012). Primary radiation therapy (RT) treatment of prostate cancer has been shown to provide similar local control and survival benefits compared to surgical management for patients with localized disease (Thompson 2007). Treatment options for patients with low-risk prostatic disease include either conservative management through active surveillance, or definitive therapy via radical prostatectomy (RP), external beam radiation therapy (EBRT), or brachytherapy (BT). Increased risk of local recurrence and distant metastasis following single modality therapy for patients with intermediate- or high-risk prostate cancer has led to increased use of adjuvant hormone therapy accompanied by dose escalated RT regimens (Thompson 2007). Intensity modulated radiation therapy (IMRT) prescription doses of >80 Gy have been explored for patients at higher risk of disease recurrence. However, standard prescription doses from primary EBRT treatments tend to range from 70-80 Gy given in 1.8 to 2.0 Gy fractions (Washington 2004).

BT options available to men with prostate cancer include low dose rate brachytherapy (LDR-BT) and high dose rate brachytherapy (HDR-BT). Permanent seed LDR-BT is generally given as a monotherapy, while HDR-BT boost has been explored as concurrent therapy with EBRT (HDR-BT+EBRT) (Thompson 2007). Higher doses are achievable using highly conformal BT treatments compared to EBRT treatments, with total doses of ≥115Gy delivered using permanent seed LDR-BT implants (Nag 1999). Biologically equivalent dose (EQD_{2Gy}), which is a standardized equivalent EBRT dose given in 2 Gy fractions, has been used to describe the total combined dose given with HDR-BT+EBRT treatments (Morton 2011). Modern HDR-BT+EBRT treatments giving two fractions of 10 Gy HDR-BT with 45 Gy EBRT have an estimated total EQD_{2Gy} of 95 Gy (Morton 2011).

Currently, a lack of high quality randomized controlled trial (RCT) data on prostate cancer RT survival outcomes are available in the literature. No definitive RCT data exists directly comparing two or more RT treatments. As a result, comparative evidence has been predominately generated from observational data. However, RT survival comparisons in several of these non-experimental studies do not control for the effects of adjuvant hormone therapy and they tend to assess heterogeneous patient populations composed of low-, intermediate- and high-risk patients. Novel comparisons of the effectiveness of the different RT modalities available within each prostate cancer risk-stratum are warranted, specifically aimed at isolating the effects of RT in the absence of hormone therapy.

The goal of this study was to assess primary RT survival outcomes of overall survival (OS) and biochemical failure-free survival (bFFS) in individual prostate cancer risk categories. This study used propensity score (PS) matching analysis to control for the effects of baseline prognostic factors on survival as well as to create separate, unique cohorts of entirely low-risk and intermediate-risk patients for analyses. There were three matched comparisons made. LDR-BT was compared with EBRT in separate low-risk and intermediate-risk cohorts, while combination HDR-BT+EBRT was compared with EBRT in an intermediate-risk cohort only.

2.0 Prostate Cancer

2.1 Introduction

In Canada, prostate cancer is the most commonly diagnosed non-cutaneous cancer in men, with an estimated 26,500 new cases reported in 2012 (Canadian Cancer Society 2012). The incidence of prostate cancer has risen steadily since 1980, with the exception of two rapid rises in incidence, the first peaking in 1993 and the second in 2001. Increased early detection of prostate cancer due to intensified prostate specific antigen (PSA) screening has been linked to both peaks in prostate cancer incidence. The first peak in prostate cancer incidence, in 1993, coincided with the introduction of the PSA blood test, while the second peak, in 2001, occurred during a time of increased public awareness and promotion of PSA screening following the prostate cancer diagnosis of then Canadian Minister of Health, Allan Rock (Fradet 2009). Both sharp rises in prostate cancer incidence were followed by equally significant declines. Currently, the incidence of prostate cancer has remained relatively constant in Canada, with an estimated incidence of 121 per 100,000 men in 2012 (Canadian Cancer Society 2012).

In contrast to incidence, death from prostate cancer is less common. Prostate cancer has the third highest mortality rate among all cancers in Canadian men. In 2012, prostate cancer was estimated to account for roughly 10% of all cancer-related deaths in Canadian men (Canadian Cancer Society 2012). The lower yearly mortality rate relative to incidence rate is attributable to the generally slow growing nature of prostate cancer, with diagnoses predominantly occurring in men with early stage disease. Overall, prostate cancer has a good prognosis, with 5-year survival rates of >90% for low-risk patients (Rubin 2001). The trend in prostate cancer mortality has been relatively stable over time. More recently, there has been a slight decline in prostate cancer mortality at a rate of 4.3% per year, from 2001 to 2007 (Canadian Cancer Society 2012). Early detection and improvements in the quality of care are popular explanations for this recent decrease in prostate cancer mortality (Fradet 2009).

Prostate cancer incidence varies by geographical region, with the highest rates reported in North America and the lowest rates in Asia (Curado 2007). Reduced dietary fat intake commonly found in oriental cuisine is thought to be responsible for these lower prostate cancer incidence rates seen in Asian countries (Fleshner 2004). Aside from the obvious requirement of being male, there are numerous additional factors that can increase an individual's risk for developing prostate cancer. Increased age has been associated with prostate cancer risk, with the majority of patients presenting over the age of 60 (Rubin 2001). African American and Hispanic men are at higher risk than Caucasians for prostate cancer (Hoffman 2001), as are men with at least one familial relative diagnosed with the disease (Bratt 2002). Chemical exposure to tobacco as well as certain pesticides increases risk for prostate cancer, while exposure to antioxidants, such as genistein (soy beans), lycopene (tomatoes), and vitamin E, could potentially be protective (Damber 2008). Conventionally studied etiological factors, such as alcohol consumption, obesity and reduced physical activity, do not appear to increase risk for prostate cancer. Although benign prostatic hypertrophy (BPH) presents with similar symptoms as prostate cancer, no study has been able to show a causal association between BPH and the development of prostate cancer (Rubin 2001).

The natural history of disease progression for prostate cancer originates as a mutation occurring in normal human cells. Prostate cancer can develop locally from cells originating in prostatic tissues, or distantly, as a result of metastasis from cancers of the lung, skin, colon or lymphatic tissues. Prostate cancer spreads locally by invading surroundings tissues, specifically the seminal vesicles, bladder, rectum, and pelvic soft tissues. Distant spread of prostate cancer tends to follow a sequential pattern, beginning with regional dissemination predominantly to the pelvic lymph nodes. Regional spread is followed by distant metastasis, usually to the bone. Although prostate cancer is a slow growing malignancy, metastasis to the bone and other organs including the liver, lung and occasionally, the brain, can eventually result in death (Rubin 2001).

2.2 Clinical Detection and Diagnosis

Most men with prostate cancer are asymptomatic and are diagnosed by an elevated PSA blood test. PSA is a serine protease enzyme that is secreted by prostatic epithelial cells. The primary function of PSA is to keep semen in a fluidic state prior to ejaculation (Balk 2003). Trace levels of PSA are normally detectable in peripheral blood serum, with higher concentrations found in the prostatic lumen. Localized disease, such as prostate cancer or BPH, can cause an increased amount of PSA to leak out of the prostatic lumen into the peripheral blood stream. Standard PSA screening tests use a serum total PSA threshold of 4.0 ng/mL to indicate the need for further biopsy evaluation (Balk 2003). However, controversy exists over the specificity of this PSA threshold, as aggressive, organ confined, prostate cancer is diagnosed in roughly 50% of individuals with low levels of serum PSA, ranging from 0 to 4ng/mL (Schröder 2000).

Additional methods have been proposed to help improve the accuracy of PSA screening. One such method uses age-specific reference ranges (ASRRs) to account for rising PSA levels as men age. The recommended PSA serum concentration using ASRRs starts from 0 to 2.5 ng/mL, for younger men aged 40 to 49 years and increases up to a maximum range of 0 to 6.5 ng/mL, for older men aged 70 and above (Oesterling 1993). There are two main theoretical advantages of using ASRRs. The first advantage is that ASRRs innately diagnose an increased number of prostate cancers in younger men. This means that a higher number of men, who are likely to require some form of interventional therapy, are properly identified. The second advantage of ASRRs is that fewer diagnoses are made in older men who are unlikely to die of their disease. This reduces the number of unnecessary biopsies and additional investigations in older individuals (Crawford 1999).

There are additional approaches to improving PSA measurement accuracy. One approach is to standardize PSA blood concentration relative to the prostate volume, also known as the PSA density. This technique attempts to differentiate benign elevated PSA levels from those caused by prostate cancer (Benson 1994). Measuring the change in

PSA over time, or PSA velocity, has also been identified as a means of screening for prostate cancer. A PSA velocity showing a yearly increase of 0.75 ng/mL is the most common criteria indicating a positive test result (Kadmon 1996). Limitations of PSA velocity are that it requires previous knowledge of PSA measurements and is unable to account for natural fluctuations in PSA serum concentration over time (Kadmon 1996). The PSA found in prostate cancer cells tends to avoid inactivation via proteolytic cleavage. This results in a lower fraction of free-PSA, or inactivated PSA, relative to total PSA in the peripheral blood. The fraction of free-PSA to total PSA can be measured and is known as the PSA index. A PSA index $\leq$25% in patients with total PSA measurements ranging from 4-10 ng/mL has been shown to increase risk for prostate cancer (Catalona 1998).

Controversy exists regarding the overall benefit of PSA screening for prostate cancer in otherwise healthy men. Although, PSA screening has increased the number of men diagnosed with early stage, low-risk prostate cancer, it has not been found to significantly reduce prostate cancer-specific mortality or all-cause mortality in men (Andriole 2009). In fact, over diagnosis from PSA screening can increase the morbidity for men, including increased stress and anxiety over the need for more invasive tests and treatments. One recent European randomized trial containing 162,243 men estimated that 1410 men would need to be PSA screened to prevent one death from prostate cancer (Schröder 2009).

In addition to screening, PSA testing can be used on follow-up examination to monitor efficacy of primary therapy. Elevated PSA has long been established as an indicator for clinical relapse following RP or RT (Kuriyama 1981). As low levels of PSA are normally detectable following RT, there have been multiple definitions for a rising PSA used to indicate treatment failure. The most current Radiation Therapy Oncology Group (RTOG) and American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical failure following primary RT is a PSA rise of 2 ng/mL, or more, above the nadir, or the lowest recorded PSA value (Roach 2006). This definition replaced the previous RTOG-ASTRO recommendation of three consecutive

rises in PSA after the nadir as indicative of biochemical failure (Roach 2006). Neither of these definitions accounts for the benign rises in PSA (also known as 'PSA bounce') that has been documented following BT radiation in prostate cancer patients (Mehta 2013). Current studies on PSA bounce have been unable to identify the etiology of this phenomenon (Chira 2013, Mehta 2013).

Besides PSA screening, clinical detection of prostate cancer can occur as a result of other investigations. One common presentation of prostate cancer is an abnormal nodular growth found on digital rectal examination (DRE). Although the specificity and sensitivity of using DRE alone to accurately diagnose prostate cancer has been questioned (Byar 1972), the combination of patient history, serum PSA measurement, and DRE are commonly used to assess prostate cancer risk and help shape biopsy decision making (Rubin 2001). In rare instances, a prostate cancer diagnosis can occur following transurethral resection of the prostate (TURP) for urinary obstructive symptoms. However, pre-existing urinary obstructive symptoms have not been found to be associated with decreased survival among men with prostate cancer (Brawn 1994). Trans-rectal ultrasound (TRUS) guided biopsy is performed for definitive diagnosis of prostate cancer in the instance of elevated PSA or abnormal DRE. Other routine tests such as chest x-ray, bone scans and computerized tomography (CT) scans or magnetic resonance imaging (MRI), are not involved in the diagnosis of prostate cancer, but are instead used for staging disease (Rubin 2001).

2.3 Classification and Histopathology

The prostate is made of both glandular and non-glandular tissues that are contained within the prostatic capsule. The glandular tissues are classified into three major zones, the peripheral zone, central zone and transitional zone. Each classified zone has unique histological architecture and function. The peripheral zone accounts for 70% of the glandular tissue and is the most common site for development of multifocal prostate carcinomas. The central zone is a conical shaped structure that makes up roughly 25% of the glandular tissue and is relatively resistant to prostate cancers and

other prostatic diseases. Finally, the transitional zone, which makes up the remaining 5%-10% of the glandular tissue, is the site most associated with the development of BPH (McNeal 1988).

Histologically, adenocarcinoma accounts for roughly 95% of all clinically diagnosed prostate cancers, most commonly originating in the peripheral zone. Additional histological subtypes that can occur within the prostate include: small cell (anaplastic) carcinoma, lymphoma, sarcoma, basal cell carcinoma, and transitional cell carcinoma (Rubin 2001). The most widely used histologic grading system for prostate cancer was first introduced by Gleason and Mellinger (Gleason 1974), and is called the Gleason score. A discrete value ranging from 1 to 5 is used in the creation of the Gleason score, with higher values indicating increasing degree of malignancy of histologic pattern. The total Gleason score is the sum of the two most common histologic patterns, resulting in a discrete numerical value ranging from 2 to 10. Prostate cancer patients with higher Gleason scores tend to have a poorer prognosis, as Gleason score is correlated with both pathological staging and survival (Rubin 2001).

2.4 Prostate Cancer Staging

The most commonly used prostate cancer staging system is the American Joint Committee on Cancer (AJCC), TNM classification system. TNM is an acronym that describes the size and extent of the primary tumor (T), spread to regional lymph nodes (N) and distant metastasis (M). Once histological finding of prostate cancer is confirmed, TNM classification can be used to both clinically and pathologically stage the disease. Clinical staging for prostate cancer occurs prior to the delivery of any definitive therapy, using information from several preliminary diagnostic tests, such as serum PSA level, DRE, and imaging. Alternatively, pathological staging is performed following surgical resection of the prostate, seminal vessels and pelvic lymph nodes with histological examination of the resected specimens for involvement with prostate cancer. Clinical and pathological staging is used to assess the extent of the disease and aid in treatment decision-making (Fleming 1997).

Several revisions to the AJCC TNM staging definitions for prostate cancer have occurred since their creation in 1977. The most dramatic change occurred in 1997, where the T-stage category T2 from the "T" portion of the TNM staging, went from three subcategories to two subcategories (Fleming 1997). Implementation of the 1997 TNM system ended in 2002, when the AJCC guidelines were changed back to their original definitions (Greene 2002). This major change in T-staging for patients treated from the years 1997 to 2002 is problematic in prostate cancer research, as comparisons between studies using different TNM definitions can be challenging. The current TNM staging system implemented in 2010 by the AJCC (Edge 2009) is shown in Tables 1 and 2.

Table 1: AJCC TNM clinical and pathological staging definitions.

Primary Tumor (T)

Clinical

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Clinically inapparent tumor neither palpable nor visible by imaging
    T1a: Tumor incidental histologic finding in 5% or less of tissue resected
    T1b: Tumor incidental histologic finding in more than 5% of tissue resected
    T1c: Tumor identified by needle biopsy (for example, because of elevated PSA)
T2: Tumor confined within prostate
    T2a: Tumor involves one-half of one lobe or less
    T2b: Tumor involves more than one-half of one lobe but not both lobes
    T2c: Tumor involves both lobes
T3: Tumor extends through the prostate capsule
    T3a: Extracapsular extension (unilateral or bilateral)
    T3b: Tumor invades seminal vesicles(s)
T4: Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Pathologic (pT)

pT2: Organ confined
    pT2a: Unilateral, one-half of one side or less
    pT2b: Unilateral, involving more than one-half of side but not both sides
    pT2c: Bilateral disease
pT3: Extraprostatic extension
    pT3a: Extraprostatic extension or microscopic invasion of bladder neck
    pT3b: Seminal vesicle invasion
pT4: Invasion of rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)

Clinical

NX: Regional lymph nodes were not assessed
N0: No regional lymph node metastasis
N1: Metastasis in regional lymph node(s)

Pathologic

pNX: Regional nodes not sampled
pN0: No positive regional nodes
pN1: Metastases in regional node(s)

Distant Metastasis (M)

M0: No distant metastasis
M1: Distant metastasis
- M1a: Nonregional lymph node(s)
- M1b: Bone(s)
- M1c: Other site(s) with or without bone disease

Table 2: AJCC prostate cancer anatomical stage/prognostic groupings.

Stage I

T1a-T1c, N0, M0, PSA < 10, Gleason ≤ 6
T2a, N0, M0, PSA < 10, Gleason ≤ 6
T1-2a, N0, M0, *PSA X, $^{\beta}$Gleason X

Stage IIA

T1a-T1c, N0, M0, PSA < 20, Gleason = 7
T1a-T1c, N0, M0, 10 ≤ PSA < 20, Gleason ≤ 6
T2a, N0, M0, 10 ≤ PSA < 20, Gleason ≤ 6
T2a, N0, M0, PSA < 20, Gleason = 7
T2b, N0, M0, PSA < 20, Gleason ≤ 7
T2b, N0, M0, *PSA X, $^{\beta}$Gleason X

Stage IIB

T2c, N0, M0, any PSA, any Gleason
T1-T2, N0, M0, PSA ≥ 20, any Gleason
T1-T2, N0, M0, any PSA, Gleason ≥ 8

Stage III

T3a-T3b, N0, M0, any PSA, any Gleason

Stage IV

T4, N0, M0, any PSA, any Gleason
Any T, N1, M0, any PSA, any Gleason
Any T, any N, M1, any PSA, any Gleason

*PSA X = PSA not assessed
$^{\beta}$ Gleason X = Gleason not assessed

2.5 Risk Stratification and Treatment Options

Historically, prostate cancer patients have been grouped into three prognostic risk categories, low-, intermediate- and high-risk. The three risk categories are used to predict risk of disease recurrence and metastasis as well as tailor therapy (Rubin 2001). The combination of serum PSA, Gleason score and T-stage are the most universally accepted prognostic factors used to stratify patient risk, with all three prognostic factors being independently associated with increased risk of disease progression (Partin 1997). Although there is currently a debate whether updating the Genitourinary Radiation Oncologists of Canada (GUROC) three-category, risk-stratification system for prostate cancer is warranted, the current consensus requirements remain unchanged (Lukka 2001, Rodrigues 2012). Table 3 shows the current GUROC consensus requirements for prostate cancer, three-category risk stratification (Lukka 2001) and the most commonly used treatment options for patients in each risk category (Keyes 2013, Rubin 2001, Thompson 2007).

As highlighted in Table 3, there is a wide range of treatment options available to prostate cancer patients in each risk category. Currently, there are three primary treatment modalities that are used with curative intent for men with prostate cancer, RP, EBRT and BT (Thompson 2007). All three treatments can be used alone, for patients with clinically localized disease, or they can be used in combination with other therapies for locally advanced, high-risk patients. Due to the slow growing nature of prostate cancer, active surveillance, or the process of observing a patient until their disease reaches a critical stage before providing therapy, is a unique option available to low-risk patients. Although observation is an attractive option for older men with low-risk cancer, it is not suitable for those in the intermediate- or high-risk categories, as these individuals have disease generally requiring intervention (Keyes 2013). In the case of metastatic disease, patients usually are no longer given primary therapies with curative intent. Androgen deprivation therapy (ADT) is a hormone therapy predominantly used alone or in combination with small doses of radiation to palliate patients with metastatic prostate cancer. ADT can also be used in the adjuvant setting for patients with locally confined

disease (Rubin 2001). Although the decision on treatment modality primarily depends on patient risk category, other factors such as the patient age, comorbid conditions, and personal preference can determine treatment choice (Keyes 2013, Rubin 2001, Thompson 2007).

Table 3: GUROC consensus requirements and treatment options by prostate cancer risk.

Risk Category	GUROC Consensus	Standard Treatment Options
Low	Must have all of the following: • PSA ≤ 10 ng/mL • Gleason Score ≤ 6 • Stage T2a or less	Observation (active surveillance or watchful waiting); Radical prostatectomy +/- nerve sparing; External beam radiation only; Brachytherapy only
Intermediate	Must have all of the following if not low-risk: • PSA ≤ 20ng/mL • Gleason Score < 8 • Stage T1/T2	Radical prostatectomy +/- lymphadenectomy; External beam radiation +/- ADT; Brachytherapy +/- ADT; External beam radiation + brachytherapy +/- ADT
High	Must have at least one of the following: • PSA > 20ng/mL • Gleason Score ≥ 8 • Stage ≥ T3a	Prostatectomy +/- lymphadenectomy + External beam radiation + ADT; External beam radiation only + ADT; External beam radiation + brachytherapy + ADT; ADT only

Abbreviations: ADT = androgen deprivation therapy; PSA= prostate specific antigen; GUROC= Genitourinary Radiation Oncologists of Canada

2.6 Surgical Management of Prostate Cancer

RP has been established as an appropriate monotherapy for treatment of clinically localized prostate cancer (Thompson 2007). RP involves complete removal of the prostate gland, seminal vesicles and part of the vas deferens. Commonly, RP is performed using an open retropubic or perineal incision, with both techniques yielding similar recurrence rates and survival (Lance 2001). Due to high rates of impotency and incontinence associated with RP, a nerve-sparing surgical technique can be performed on men with favorable tumor and patient characteristics. This technique has been found to yield desirable results in men, with up to 70% reporting returned potency following surgery (Catalona, 1999). The overall improvement of symptoms from nerve-sparing surgery depends on patient selection. The lowest rates of impotency following RP reported in the literature tend to include younger, healthier men, with less advanced disease (Talcott 1997). Pelvic lymphadenectomy is generally performed concurrently with RP in patients at high risk for nodal spread (Rubin 2001). An advantage of RP over other treatment options is that complete removal of the prostate gland will result in cure when disease is truly localized. However, when disease has spread outside of the prostate gland, additional therapies must be considered to reduce risk of recurrence (Thompson 2007).

There are a number of acute and chronic side effects from RP that can impact patient quality of life. Erectile dysfunction (ED) is common in men following RP, with varying degrees of severity. Factors that can influence the severity of ED include: whether nerve-sparing surgery was used, patient age, the patient's ability to achieve and maintain erections prior to surgery, and the use of ED medications such as Sildenafil (Viagra) following surgery (Kundu 2004, Stanford 2000, Walsh 2000). Urinary incontinence, urethral stricture, rectal pain and rectal incontinence are additional complications that can occur following RP (Benoit 2000). Short-term morbidities from the surgical procedure are rare, but include myocardial infarction, thrombosis, wound infection and death (Shabbir 2005).

2.7 Radiation Therapy Management of Prostate Cancer

2.7.1 Introduction

RT is the therapeutic delivery of ionizing radiation with the aim of reducing or eliminating disease. The biological mechanism of how the radiation dose is deposited in the tissue is quite complex. On the cellular level, charged particles (protons and electrons) and uncharged particles (photons and neutrons) excite water molecules, which create secondary reactive molecules called free radicals. These free radicals damage the deoxyribonucleic acid (DNA) within the cell, leading to apoptosis, or cell death. Because radiation damages both cancer cells and normal cells, there is a constant trade-off between delivering adequate dose to the tumor target and attempting to spare the surrounding tissues. Cells that are actively dividing are known to be more sensitive to radiation than slower growing cells. This feature of radiation allows it to be very effective in treating cancers with high rates of growth. Additionally, dose fractionation (partitioning of dose) and ensuring adequate tissue oxygenation take advantage of the radiobiology of tumor cells and have been shown to improve the therapeutic effect of RT treatments (Washington 2004).

With respect to RT management of prostate cancer, EBRT and BT are standard treatment options (Rubin 2001). No definitive randomized controlled trial data exists directly comparing either RT treatment modality to RP with respect to patient important outcomes. Observational data have demonstrated that both EBRT and BT provide local control and survival benefits similar to RP in men with regionally localized prostate cancer (Thompson 2007). Two large observational studies suggest both BT and EBRT are superior to RP with respect to ED and urinary incontinence, but inferior in preventing bowel toxicities (Martin 2008, Resnick 2013).

Higher doses of radiation have been shown to improve probability of cure following RT treatment for prostate cancer (Washington 2004). However, the incidence

of gastrointestinal (GI) and genitourinary (GU) side effects increases when higher volumes of the pelvis are irradiated. Possible acute GI side effects from RT treatments include proctitis, diarrhea, abdominal cramps, rectal bleeding and fecal incontinence. GU side effects include cystitis, frequency, dysuria, hematuria, urethral stricture and loss of potency or ED. EBRT can cause irritation to the skin in the treatment field, ranging from mild erythema and pruritus, to dry or moist desquamation. Rectal injury is uncommon from TRUS-guided BT, although it can occur. Fatigue is also a common side effect for men receiving RT treatments for prostate cancer (Rubin 2001).

2.7.2 External Beam Radiation Therapy (EBRT)

EBRT has been established as a form of radiation therapy delivery that provides excellent local control and relatively low risk of long-term morbidity for prostate cancer patients. EBRT uses high-energy photons that penetrate tissue and deliver radiation dose to the tumor target. EBRT machines deliver focused beams of radiation at different angles so that the highest dose reaches the tumor, while shielding is used to spare surrounding tissues. Currently, there is no consensus on what standard EBRT dose prescription, treatment technique or fractionation schedule should be used to treat prostate cancer. A typical EBRT treatment course for a prostate cancer patient involves daily treatments given over approximately 6 to 8 weeks. In cases where there is a high probability of local or regional spread, whole pelvis EBRT is generally given, with doses of 46-50 Gy prescribed to the pelvic lymph nodes and 54-56 Gy to the seminal vesicles (Washington 2004).

The development of 3D conformal and IMRT treatment planning and delivery techniques has allowed higher doses to be delivered to patients with improved accuracy. One randomized controlled trial containing 393 patients with low- to intermediate-risk prostate cancer found conformal EBRT doses of 79 Gy reduced PSA biochemical recurrence by >15% compared to doses of ≤70 Gy ($p < 0.001$). However, there was no statistically significant difference in overall survival or long-term side effects between the groups at 5-years (Zeitman 2005). Long-term follow-up of another randomized trial with

low- to high-risk patients found similar results, with a high dose of 78 Gy leading to non-failure rates of 70% compared to 64% in the 70 Gy group at 6-years ($p < 0.03$) (Pollack 2002). Currently, there is a lack of quality evidence to indicate whether dose escalation is beneficial for low-risk prostate cancer patients. Observational data and subgroup analysis from a randomized controlled trial have found doses >70 Gy to significantly reduce biochemical recurrence in men with PSA > 10ng/mL, but not in those with PSA < 10ng/mL (Hanks 1998, Pollack 2002).

As a single modality therapy, EBRT can be used to treat patients with low-, intermediate- and high-risk of recurrence. An advantage of EBRT over RP is that it can be prescribed for patients who are unfit for surgery (Rubin 2001). Post-operative RT to the pelvic lymph nodes and prostate bed following RP has become a frequently prescribed treatment of high-risk prostate cancer. One large, European randomized controlled trial, found immediate post-operative RT improves biochemical progression-free survival (hazard ratio = 0.49; 95% CI, 0.41-0.59) at > 10-years in patients with high-risk prognostic features (capsular perforation, positive surgical margins, or seminal vesicle invasion) compared to delayed management (Bolla 2012). A separate American randomized trial with 425 men, with a median follow-up of 10.5 years, reported significantly reduced PSA relapse (hazard ratio = 0.43; 95% CI, 0.31-0.58) and disease recurrence (hazard ratio = 0.62; 95% CI, 0.46-0.82) with postoperative EBRT compared to observation, but found no statistically significant difference in overall survival (Thompson 2006). Additionally, EBRT can be used to treat bone metastases originating from prostate cancer. Single fraction EBRT doses of 8 Gy have been shown to be equally effective at relieving pain symptoms from metastatic bone lesions compared to multiple fraction doses (20 Gy in 5 fractions or 30 Gy in 10 fractions), with roughly 60% of patients experiencing relief of their pain (Sze 2004).

2.7.3 Brachytherapy (BT)

The second radiation therapy option available to prostate cancer patients is BT. The term brachytherapy originates from the Greek word "brachys" meaning "short distance" therapy (Devlin 2007). For prostate cancer patients, BT involves the surgical implantation of small radioactive sources (seeds) in and around the prostate. These radioactive sources decay creating alpha, beta and gamma particles, which ionize cellular molecules (including DNA), depositing dose similar to EBRT (Beltas 2007). BT is a highly conformal therapy; meaning the radiation dose delivered is tightly confined to the cancer target, with surrounding tissues only receiving relatively low doses. The conformal dose achievable with BT can be attributed to the short-range radiation produced by the implanted sources, which have a steep dose fall-off with distance (Khan 2003). As a result, BT can achieve higher doses to the tumor target compared to EBRT and still adequately spare the surrounding tissues (Washington 2004).

For prostate cancer, TRUS guided LDR-BT can be used alone as a single modality treatment or to boost radiation dose to the primary tumor following EBRT. LDR-BT treatments usually involve a one-day, outpatient surgical procedure, where radioactive sources are permanently implanted within the prostate bed (Keyes 2013). This is one advantage of LDR-BT, as the time commitment for patients is much less than EBRT. Postoperative recovery following LDR-BT is quick in comparison to RP, with the potential for patients to undergo spinal, instead of general anesthetic (Keyes 2013). The effective treatment time for LDR-BT, or the time it takes for the permanent LDR-BT sources to fully decay and deposit the total dose, can last up to 9 months depending on the radioactive isotope used (Ling 1992).

Commercially available iodine-125 (I-125) and palladium-103 (Pd-103) are the most common radioisotopes used for LDR-BT. Standard minimum prescription doses of 144 Gy for I-125 and 115-120 Gy for Pd-103 are recommended by the American Brachytherapy Society for permanent seed LDR-BT (Nag 1999). An additional isotope, cesium-131, has also been explored for LDR-BT monotherapy use in the United States,

with a prescribed dose of 115 Gy (Kehwar 2009). For radiation boost following 40 to 50 Gy EBRT, LDR-BT doses of 100-110 Gy I-125 and 80-90 Gy Pd-103 are recommended (Nag 1999). Studies have shown that patients with favorable risk factors treated with either I-125 or Pd-103 LDR-BT have biochemical free recurrence rates >90% at 5-years (Blasko, 2000; Grimm 2001). No association has been found between radioisotope type and BT treatment efficacy (Merrick 2001, Rodrigues 2013).

HDR-BT is an additional radiation therapy technique available to men with prostate cancer. HDR-BT differs from LDR-BT with respect to the treatment delivery process and overall treatment time. HDR-BT sources have a higher dose per unit time than LDR-BT sources. As a result, HDR-BT treatments are usually delivered in multiple fractions to allow for optimal normal tissue repair (Nag 1994). Handling of HDR-BT sources can be dangerous due to the potential of rapid overexposure. The invention of automated devices that insert and remove the HDR-BT sources remotely (referred to as afterloading units), have allowed physicians to safely perform HDR-BT treatments from outside the treatment room (Henschke 1963). Prior to prostate HDR-BT treatment delivery, the patient is placed under epidural or spinal anesthesia, while temporary catheter tubes are surgically implanted throughout the target volume. Following patient recovery, CT imaging is used to create an optimized treatment plan, accounting for the location of the implanted catheters, while maximizing dose to the target volume and limiting dose to the surrounding tissues. During HDR-BT treatment delivery, radiation dose is delivered as the HDR-BT source “dwells” inside the patient at computer calculated points along the implanted catheters. These pre-calculated dwell points are planned so that they optimize radiation dose uniformity throughout the target volume (Slessinger 2010). Although the treatment time required for HDR-BT delivery via remote afterloading units can vary depending on the total dose prescribed and source strength, it generally lasts approximately 10 to 20 minutes (Keyes 2013). For an average size prostate, the use of 15 to 20 implanted catheters has been found to provide adequate tumor dose coverage for HDR-BT treatments (Charra-Brunaud 2003).

Iridium-192 (Ir-192) is the most common radioisotope used in HDR-BT. Prostate HDR-BT is predominantly used concurrently with EBRT to boost dose to the primary tumor in men with intermediate- to high-risk disease. Original HDR-BT boost treatment regimens developed in the 1980's gave two Ir-192 HDR-BT treatments of 15 Gy each, following 40-50 Gy pelvic RT (Nag 1994). More modern HDR-BT treatments tend to have lower doses of either 10 Gy fractions delivered over two treatments with concurrent 45 Gy EBRT, or a single 15 Gy HDR-BT treatment given with 37.5 Gy EBRT (Morton 2011). In general, HDR-BT+EBRT dose regimens reported in the literature have estimated EQD_{2Gy} doses 25% to 50% higher than standard fraction, 74 Gy EBRT (Fowler 2005, Morton 2011). Monotherapy HDR-BT has been shown to have similar biochemical control as LDR-BT with potentially reduced urinary and rectal toxicities in low-risk patients (Grills 2004). However, more studies are required to determine the full utility of monotherapy HDR-BT in the treatment of prostate cancer.

2.8 Additional Treatment Options

2.8.1 Observation (Active Surveillance/Watchful Waiting)

Evidence from autopsy series estimates roughly 20-30% of men over the age of 70 years old will have asymptomatic, undiagnosed prostate cancer (Sanchez-Chapado 2003; Stamatiou 2006). The use of PSA screening likely has increased the over diagnosis and over treatment of prostate cancers, especially in men with low-risk disease (Klotz 2013). In general, conservative management for patients with low-volume, low-risk prostate cancer is provided using active surveillance protocols. Recommendations for patients under active surveillance are to perform serial PSA tests, DRE exams and annual biopsy while they are followed (Klotz 2013). A positive test result from a rising PSA or evidence of histological progression initiates decision on definitive, curative therapy. This differs from watchful waiting protocols, where patients are passively followed until clinical symptoms present, usually indicative of disseminated disease. Therefore, patients who receive watchful waiting tend to not undergo curative therapy because, by the time they are symptomatic, they have metastatic disease and so, instead, they are

palliated at the appropriate time. This is why active surveillance is preferred for individuals with low-risk prostate cancer, so that patients have the potential of being spared unnecessary morbidity from radical therapies, yet still preserving the chance for cure (Klotz 2012).

No randomized data exists comparing active surveillance to RP or RT in entirely low-risk patients. However, two recent RCTs have attempted to compare watchful waiting to RP in men with prostate cancer, yielding conflicting results (Bill-Axelson 2011, Wilt 2012). The first of these trials, named the Prostate Cancer Intervention Versus Observation (PIVOT) trial, contained 731 men diagnosed with prostate cancer from 1994 to 2002. Results from the PIVOT trial indicated that there was no OS difference between watchful waiting compared to RP with a reported hazard ratio of 0.88 (95% CI 0.71 to 1.08) (Wilt 2012). The results of the PIVOT trial were contradictory to the second trial, that found RP to be superior to watchful waiting, reporting a relative risk of death of 0.75 (95% CI 0.61 to 0.92) after 15-year follow-up of 695 prostate cancer patients (Bill-Axelson 2011). Both of these trials included patients with low-, intermediate- and high-risk prostate cancers, making it difficult to compare efficacy of observation versus RP in entirely low-risk patients. Lower level evidence from cohort studies suggest active surveillance provides acceptable treatment outcomes for low-risk patients. One Canadian, single arm cohort study found that out of 450 low-risk patients treated with active surveillance, 30% were upgraded to higher risk disease and given either RT or RP, with only 1% dying from prostate cancer during a 10-year follow-up (Klotz 2012). Due to the lack of evidence, common practice guidelines consider RP, EBRT, BT and active surveillance as equal options for patients with low-risk cancer, but not those in the higher risk categories (Keyes 2013, Rubin 2001).

2.8.2 Hormone Therapy

Hormone manipulation using ADT is the standard single modality therapy reserved for patients with metastatic prostate cancer (Loblaw 2007). The primary goal of ADT is to block the stimulating effects of testosterone (androgen) on the prostate gland

and cause the prostate cancer to regress. The testes produce over 90% of the total circulating testosterone, with the additional 5-10% produced by the adrenal glands (Rubin 2001). Reduction of testosterone produced by the testes can be achieved surgically, with bilateral orchiectomy, or medically, through the use of luteinizing hormone-releasing hormone (LHRH) agonists or antagonists that block the production of sex hormones. LHRH agonists have been found to lower testosterone levels below 50ng/mL, which is generally achievable through surgical castration. Therefore, both therapies are considered equally effective (Rubin 2001). The use of antiandrogens to reduce the remaining testosterone produced by the adrenal glands can be used in combination with the above-mentioned ADTs and is termed combined androgen blockade (CAB). However, single ADTs such as LHRH agonists and orchiectomy tend to be preferred over CAB due to the higher costs associated with CAB and the lack of evidence suggesting any survival benefits. Additionally, CAB can cause increased severity in patient side effects, such as decreased libido, fatigue, diarrhea and anemia (Eisenberger 1998).

In addition to the treatment of metastatic disease, ADT is used to treat men with non-metastatic prostate cancer. ADT given with definitive primary therapy, such as RP or RT, is recommended for men with locally advanced disease (Rubin 2001). Long-term follow-up of one randomized trial from the RTOG found that ADT with EBRT led to improved local-control and disease free-survival compared to EBRT alone in patients with T3-4 or N1 stage prostate cancer (Lawton 2001). In a separate RCT carried out jointly by the United States National Cancer Institute and the United Kingdom Medical Research Council, called the PR3 trial, demonstrated that the addition of ADT to RT provided improved OS compared with ADT alone after six-year follow-up of 1205 men, with a reported hazard ratio of 0.77 (95% CI 0.61 to 0.98, p=0.03) (Warde 2011). Another trial from the European Organization for Research and Treatment of Cancer found that the 5-year OS was 78% in patients receiving EBRT plus ADT for 3 years compared to 62% in the EBRT only arm ($p<0.001$). This study contained a cohort of 412 men with advanced stage, non-metastatic prostate cancer (Bolla 2002). Six-month androgen suppression following EBRT has been shown to provide similar improvements in survival in a randomized study of intermediate- to high-risk patients (D'Amico 2004).

Although the benefits of ADT use in the treatment of men with unfavorable prognostic features are well documented, there is no definitive evidence to indicate its effectiveness in clinically localized, low-risk prostate cancer. Observational data indicates that hormone therapy given with RT significantly reduces PSA biochemical recurrence in intermediate- and high-risk patients, but not in men with low-risk disease, when compared to RT alone (D'Amico 2000). Neoadjuvant ADT can be used to reduce tumor bulk prior to RT or surgery leading to improved local control, as well as identify patients with hormone sensitive prostate cancer (Lee 1999).

Roughly 10-20% of men do not respond to initial ADT management and are identified as having castration resistant disease (Rubin 2001, Tannock 2004). Given enough time, of the remaining men that do initially respond to ADT, the majority will eventually develop hormone refractory prostate cancer, manifesting symptoms of treatment failure. Many chemotherapy agents have been studied to help treat patients with castration resistant prostate cancer, of which taxane derivatives are the most effective (Tannock 2004). The addition of up-front chemotherapy to ADT management of hormone sensitive prostate cancer has shown no clinical benefit (Gravis 2013).

3.0 Comparative Effectiveness Research (CER)

3.1 Introduction

Comparative Effectiveness Research (CER) contrasts the advantages and/or disadvantages that are afforded to patients receiving different therapies. CER generates new evidence in the form of experimental or observational studies, or synthesizes evidence from previous studies through systematic review. The primary goal of CER is to improve the quality of care provided to patients by creating or compiling evidence, which can later be used to help guide clinical decision-making (Luce 2010).

Historically, the term CER gained popularity in the United States, through a government initiative to improve the quality and transparency of their comparative studies (Wilensky 2006, VanLare 2010). In Canada, the term CER is now becoming more frequently used and familiar with Canadian researchers when describing their comparative studies in multiple health care fields (Whicher 2009, Sun 2014). Commonly, the term Evidence-Based Medicine (EBM) has been used synonymously with CER, due to the similarities between terms. However, there are some differences between the definitions of EBM versus CER. For example, both EBM and CER are focused on evidence synthesis through systematic review, however, EBM is more focused on using this evidence to drive decision-making and create practice guidelines, while CER is more focused on improving the evidence created in the primary studies. Therefore, CER is more concerned with answering both the effectiveness and value questions of "does it work in a clinical setting?" and "is it worth it?" while EBM takes it once step further by answering the efficacy and clinical practice driven questions of "will it work?" and "should we our change practice?" (Luce 2010). As a result, CER shifts the focus towards the creation of quality primary evidence generation in experimental and observational studies, which is later used in the EBM decision-making process.

3.2 CER in Experimental Studies

RCTs are generally considered to be the gold standard in CER. A properly designed RCT allows researchers to compare different therapies, while also minimizing the effects of all known and unknown confounding variables, which are, on average, made equal following randomization. In oncology, RCTs have advanced the care for patients by enabling investigators to answer important questions regarding the efficacy of a particular therapy aimed at driving EBM decision-making. RCTs also provide insight into which subgroups of patients might benefit the most from treatment as well as allow for prospective follow-up of patient reported side effects aimed at improving quality of life. Pragmatic RCTs, or experimental studies that are implemented under routine clinical conditions, fall under the category of CER, as they typically compare the effectiveness of a drug or therapy compared to the alternative standard of care given to patients. Additionally, pragmatic RCTs tend to be focused on important outcomes instead of surrogate end points (Hahn 2012).

Although pragmatic RCTs are the foundation of CER, there are some limitations that can make RCTs in general less appealing to researchers. RCTs can be costly to conduct, may require a large number of patients to detect small differences in treatment effect, may take a long time to finish depending on patient accrual time and the outcomes investigated, and tend to have highly selected patient enrollment that may not be representative of actual clinical populations (Friedman 2010). Due to these limitations, obtaining evidence through other means, such as systematic reviews or observational studies, can become exceedingly valuable for policy makers (Hahn 2012).

3.3 CER in Observational Studies

3.3.1 Introduction

Although RCTs have long been considered the first choice for evidence generation in medicine, due to their high level of internal validity and ability to provide

the least biased estimates of risk, there are many instances where results from experimental studies are not indicative of real-life application. Observational studies are a source of evidence generation that can answer research questions that are less suited for an RCT. For example, observational studies can be more appropriate in instances of rare diseases, when it is unethical to randomly assign the intervention of interest, when it is impossible to randomize the factor of interest (eg. a genetic factor), or when it is impractical to assign the intervention (Friedman 2010). Additionally, observational studies have the advantage of being less costly and labor intensive to carry out than an experimental study and can provide initial evidence to support the implementation of a future RCT (Dreyer 2010).

In CER, observational studies play an important role in the generation of primary evidence for practice guideline construction and policy driven decision-making. The use of administrative data in observational studies has the advantage of being inexpensive to use, contains information on very large populations and provides information on outcomes requiring a longer follow-up time (Hershman 2012). However, limitations in observational studies exist, which if not properly accounted for can lead to erroneous results. The inability to randomly allocate patients to different therapies can lead to confounding, which occurs when there are imbalances between confounding variables among patient groups (Hershman 2012). A confounding variable is defined as a variable that is associated with the primary variable of interest (independent variable) and associated with the outcome of interest (dependent variable), but is not an intermediate variable in the causal pathway between the independent variable and dependent variable (Szklo 2014). Adjustment for confounding is very important, as an imbalance in confounders has the potential to change the magnitude or even direction of estimated treatment effect. However, a properly designed study using appropriate analytical methods can help reduce the confounding bias, or inaccurate estimates of the association between treatment and outcome that is caused by confounding variables (Hershman 2012).

3.3.2 Instrumental Variable Analysis

Instrumental variable analysis is an analytical approach that can be used in observational studies to overcome imbalances between confounding variables among treatment groups. An instrumental variable "C" estimates the effect of a separate independent variable "A" on the outcome variable "B" without requiring the measurement of any confounders that bias the effects of A on B. For C to be a true instrumental variable, it must satisfy the following assumptions: each patient's outcome is not affected by treatment status of other individuals, C is correlated with A, C is not directly or indirectly associated with B, and all effects of C on B are manifested through the effects of C on A (Angrist 1996). In theory, the use of an instrumental variable attempts to balance all known and unknown confounding variables by using a characteristic that influences the treatment a patient receives, but does not have any sway on outcome, therefore providing an unbiased means of measuring treatment effect. Thus, a well-chosen instrumental variable can balance unmeasured confounding in a non-experimental study in a way similar to that of an RCT (Rassen 2009). However, validating whether an instrumental variable is appropriate can be challenging, especially when there are unforeseen associations between the instrumental variable and outcome, or when the correlation between the instrumental variable and treatment assignment is weak (Armstrong 2012). Some common instrumental variables found in the literature include: rates of treatment use by region, physician prescription preferences, distance from hospital or treatment facility, density of health care providers by geographical area, health care provider costs, and changes in health care infrastructure (Hershman 2012).

3.3.3 Regression-Based Modeling

Multivariable regression modeling is a traditional analytical approach used in observational studies to account for confounding bias. Regression-based modeling allows investigators to estimate the association between a treatment and outcome, while keeping other covariates in the model constant (Szklo 2014). As long as the number of outcomes of interest in the study sample is large, regression modeling using either, linear

regression for continuous outcomes, or logistic regression for binary outcomes, has the advantage of adjusting for a substantial number of confounding variables. Additionally, advanced, multi-level modeling techniques are able to adjust for correlated observations, when clustering of patient outcomes occurs within single institutions in multi-institutional studies (Armstrong 2012). However, there are some limitations to regression-based models, some of which include: they do not account for confounders which are not included in the model, they are unable to provide accurate estimates of association when there is insufficient overlap among covariates between treatment groups, and they are bound by the assumptions of the regression model chosen (Vittinghoff 2012).

3.3.4 Matching

Matching is another analytical tool used to control for the influences of confounding variables. Although matching is predominately used in case-control studies, it has also been used in cohort studies in oncology to control for multiple prognostic factors pertaining to survival (Coen 2012, Khor 2013, Pickle 2010, Szklo 2014). There are many different types of matching techniques that have been developed. Matching directly on an individual-by-individual basis is the most common, where subjects are matched so that both individuals have the same baseline-measured covariates. Direct individual matches are generally made based on both categorical variables (eg. male vs. female) and continuous variables using cutoff ranges (eg. age $\leq$ 65 years, or > 65 years) (Szklo 2014). Frequency matching is another common technique found in comparative studies, where matched patients are selected based on the distribution of covariates in each group (Szklo 2014). Minimum Euclidean distance measure matching is a more complex technique that has been developed to match patients. Matching using minimum Euclidean distance measures is based on the distance two subjects are apart in their combination of covariates represented in a standardized score (Smith 1977). An example of a simple match using minimum Euclidean distance measures is shown in Figure 1, where patient matches (group #1 and groups #2) are considered based on the covariates of age and PSA concentration in a two-dimensional diagram. Minimum distance

matching can be expanded to include multiple variables in ‘n’ dimensional space (Szklo 2014).

There are many advantages and disadvantages in using matching compared to other analytical techniques. For example, results from matched designs are easily interpretable and are able to provide balance in confounding baseline prognostic factors within the treatment groups. Additionally, matching allows for an increase in statistical power when strong confounders are used to create the matches (Szklo 2014). However, matching does have several disadvantages, some of which include: reduced sample size when matches are made based on a large number of variables, association and interaction assessment between variables used in the matching process is no longer possible, highly selected matched cohorts can lead to a reduction in the external validity, and possible loss of statistical efficiency when variables used to match subjects are not strongly correlated with exposure or outcome (Thompson 1982, Szklo 2014).

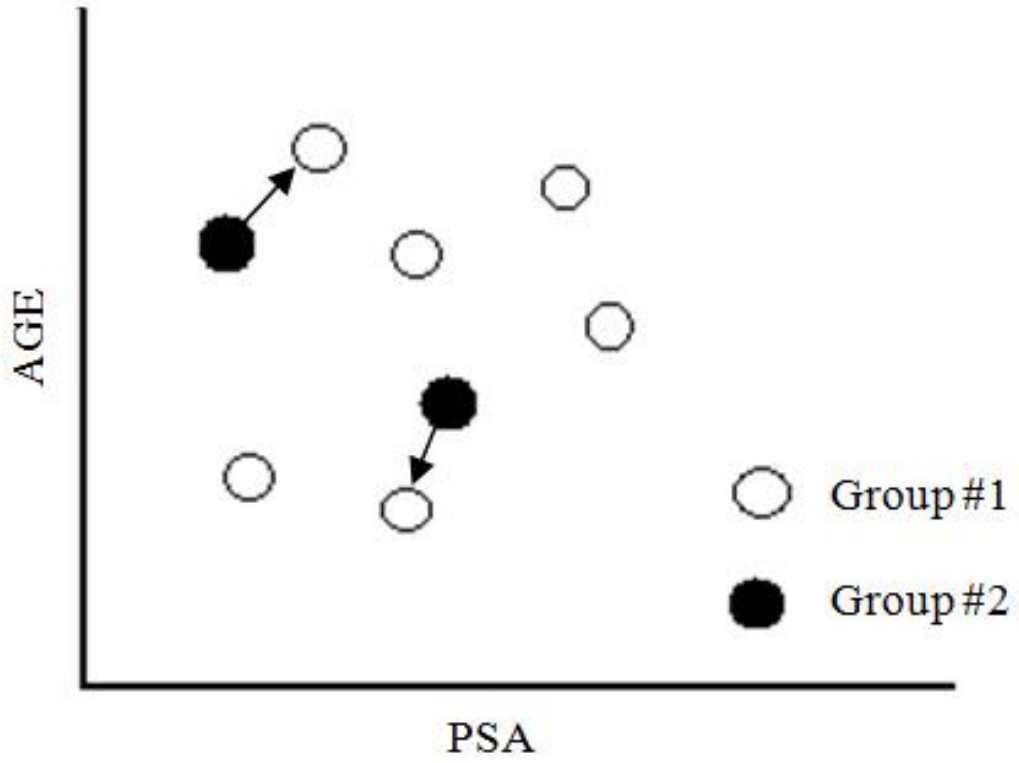


Fig. 1. Diagram demonstrating matching according to minimum distance method.

3.3.5 Propensity Score (PS) Matched Analysis

Propensity score (PS) matching is an analytical tool that has been used in observational studies to account for the effects of confounding. Similar to minimum distance matching, subjects are matched based on having a similar score (known as their propensity score), which is the estimated probability that an individual would receive a particular treatment given their specific combination of baseline covariates (Rosenbaum 1983). Multivariable logistic regression modeling is used to generate the PS for each patient, with treatment assignment as the dependent variable regressed on baseline prognostic factors found to impact the outcome of interest (Austin 2007). Matching based on correctly specified propensity score models has been demonstrated to provide balance in baseline prognostic factors in groups of patients receiving different therapies in a wide range of settings (Rubin 1996). Once PS matching is completed and adequate balance in baseline prognostic factors is achieved, investigators can then compare differences in the occurrence of outcomes between treatment groups. Popular in oncology, PS matching has been used in a variety of oncology research, including studies on cancers of the lung, breast, colon, brain, and prostate (Chen 2011, Ganz 2011, Khor 2013, O'Conner 2011, Rodrigues 2013, Verstegen 2013, Wong 2006). Similar to other matching techniques, PS matching has the advantage of being an active attempt at balancing baseline prognostic factors in groups of patients that can yield a high-level of internal validity in an observational study. However, PS matching has the disadvantage of only being able to provide balance in known confounders that are included in the PS model. Thus, balance in confounders, that are either unknown to the investigator or are unavailable to be included in the PS model, cannot be achieved in a PS matched study like it could be in a RCT (Armstrong 2012).

3.4 CER in Prostate Cancer Radiation Therapy Literature

As was previously discussed, experimental studies are regarded as the highest form of evidence generation in the CER literature. To date, a relatively small number of RCTs exist that have aimed to generate evidence comparing treatment outcomes in

prostate cancer. There are a number of relatively small RCTs comparing surgery to other treatment options, including two RCTs comparing RP vs. watchful waiting (Bill-Axelson 2005, Wilt 2012), an RCT comparing RP vs. BT (Gilberti 2009) and an RCT comparing RP vs. EBRT (Paulson 1982). Additionally, there are several RCTs that compare differences within a single radiation therapy modality, including studies comparing different EBRT dose fractionation sizes (Lukka 2005, Pollack 2006, Yeoh 2006), EBRT escalated doses (Kuban 2008, Peeters 2006, Zietman 2005), I-125 vs. Pd-103 BT implant sources (Merrick 2007), and BT+EBRT dose regimens (Wallner 2005). However, there is no definitive RCT data available that compares differences in effectiveness between two or more primary prostate cancer RT treatment modalities. No RCT exists that compares survival outcomes or side effects in EBRT vs. permanent implant BT treatments, or BT alone vs. combination BT+EBRT treatments. There is a single institutional RCT that compares outcomes of combination HDR-BT+EBRT vs. EBRT alone (Sathya 2005), however, due to some limitations, the evidence generated in this study can only be considered of lower quality.

In their study, Sathya et al compared 35 Gy Ir-192 permanent seed BT implants with adjuvant 40 Gy in 20 fractions EBRT to EBRT alone delivered to a total dose of 66 Gy in 33 fractions. A total of 138 patients treated at the Hamilton Regional Cancer Centre, Hamilton, ON, Canada, from 1992 to 1997 were adequately randomized to receive HDR-BT+EBRT (n=70) or EBRT only (n=68). OS and bFFS differences between groups were assessed with a median follow-up of 8 years. Results from this study indicated that HDR-BT+EBRT led to statistically significantly improved bFFS compared to EBRT alone (hazard ratio=0.42; p=0.024), but there was a non-statistically significant difference in OS (hazard ratio=1.36; p=0.54).

There were several study limitations in the RCT by Sathya et al. Intention-to-treat was violated, as 19 patients in the HDR-BT+EBRT group and 15 patients in the EBRT group were not included in the final analysis. Therefore, the balance of known and unknown confounders following randomization was no longer present in their final analysis. Additionally, the study had the limitation of being a relatively small, single

institutional study that included a combination of intermediate- and high-risk patients in their comparison. Subgroup analysis did show that HDR-BT+EBRT significantly improved bFFS in both intermediate- and high-risk subgroups, however this analysis was exploratory, making it difficult to assess whether this result is universal across all prostate cancer risk categories, including low-risk. Finally, EBRT dose was relatively low in this RCT at only 66 Gy. EBRT doses ≥ 72 Gy have been shown to improve survival outcomes for localized prostate cancer compared to lower doses (Kupelian 2000).

There are two active RCTs that potentially could improve the quality of evidence directly comparing RT treatment options. One of these trials, named the Effectiveness of Prostate Cancer Treatments, or the E-PROSTCaT trial (http://www.clinicaltrials.gov - #NCT01492751), compares quality of life measures and survival outcomes in prostate cancer patients treated with RP, EBRT or LDR-BT. However, results of the E-PROSTCaT trial are not expected until at least 2015. The other trial (#NCT00063882), sponsored by the RTOG (RTOG trial #0232) and the National Cancer Institute, compares EBRT+BT vs. BT alone in intermediate-risk patients, with results expected in 2017. Both of these trials are in the data analysis stage and are no longer recruiting patients. An additional trial was proposed by the British Columbia Cancer Agency to compare EBRT vs. LDR-BT (#NCT00407875), however, this trial was terminated due to low patient accrual.

Low patient accrual is one plausible explanation as to why RCTs comparing prostate cancer therapies are nonexistent in the literature. Differences between the various prostate cancer treatment modalities are known to impact final treatment choice (Rubin 2001). Radiation treatments are less invasive than surgery. Several studies have demonstrated that the risk of GU or GI side effects are not universal across surgical or RT treatment options (Martin 2008, Resnick 2013, Rubin 2001). The risk of impotency has been identified as a strong indicator for treatment choice in young, sexually active men, with the majority finding it difficult to consent to receiving a therapy that might increase their risk of losing potency (Rubin 2001). Additionally, the time commitment for patients receiving primary radiation can be quite different depending on treatment

chosen. For example, dose escalated IMRT treatment delivery can last over 8-weeks in duration, while permanent BT implantation is delivered on a single day, outpatient basis (Washington 2004, Keyes 2013). Thus, the advantages and disadvantages of each therapy could theoretically reduce the number of patients who are willing to enter a trial that randomizes them into receiving one RT treatment over another, as patients usually have strong preferences in their treatment selection (Rubin 2001).

Although the available RCT generated CER comparing outcomes from two or more RT modalities is quite sparse, a large number of observational comparative studies exist in the literature. Thirty-seven observational CER studies directly comparing prostate cancer primary RT outcomes were identified upon literature review, 29 of which were retrospective studies (Abel-Waheb 2008, Aoki 2009, Beyer 2000, Burdick 2009, Coen 2012, D'Amico 1998, da Silva Franca 2010, Deutsch 2010, Eade 2008, Elliot 2007, Gelbium 2000, Goldner 2012, Gondi 2007, Huang 2010, Klein 2009, Khor 2013, Krestin 2000, Kupelian 2004, Nieder 2008, Ojha 2010, Pe 2009, Pickles 2010, Pinkawa 2010, Vassil 2010, Wong 2009, Zelefsky 1999, Zelefsky 2008, Zelefsky 2011, Zhou 2009) and eight were prospective studies (Davis 2001, Ferrer 2008, Joseph 2008, Kalakota 2010, Lee 2001, Lev 2009, Smith 2009, Talcott 2003). Methods used to adjust for confounding included various forms of regression modeling in 30 studies (Abel-Wahab 2008, Aoki 2009, Beyer 2000, Burdick 2009, D'Amico 1998, d Silva Franca 2010, Deutsch 2010, Eade 2008, Elliot 2007, Ferrer 2008, Gelbium 2000, Goldner 2012, Gondi 2007, Huang 2010, Kalakota 2010, Klein 2009, Kupelian 2004, Nieder 2008, Ojha 2010, Pe 2009, Pinkawa 2010, Smith 2009, Talcott 2003, Vassil 2010, Wong 2009, Zelefsky 1999, Zelefsky 2008, Zelefsky 2011, Zhou 2009) and matching in four studies (Coen 2012, Khor 2013, Krestin 2000, Pickles 2010). No study on primary radiation outcomes involved the use of instrumental variable analysis, and three studies reported unadjusted results, making no effort to account for confounding variables (Davis 2001, Joseph 2008, Lee 2001). A summary of these observational studies on primary RT outcomes as well as the RCT by Santhya et al are shown in Appendix I. A description of the literature search strategy for CER articles directly comparing primary RT outcomes is described in Appendix II.

With respect to survival outcomes, biochemical failure was assessed in the highest number of observational studies, totaling 20 (Beyer 2000, Burdick 2009, Coen 2012, D'Amico 1998, da Silva Franca 2010, Deutsch 2010, Eade 2008, Goldner 2012, Gondi 2007, Klein 2009, Khor 2013, Krestin 2000, Kupelian 2004, Pe 2009, Pickles 2010, Pinkawa 2010, Vassil 2010, Wong 2009, Zelefsky 1999, Zelefsky 2011). However, a number of limitations in the bFFS comparisons existed in these studies. For example, different biochemical failure definitions were used, including the original RTOG-ASTRO definition of three consecutive PSA rises following nadir (Roach 2006) in four studies (Gondi 2007, Krestin 2000, Kupelian 2004, Zelefsky 1999), and the more currently accepted ASTRO-Phoenix definition of a PSA rise of 2ng/mL, or more, following nadir (Roach 2006) in 16 studies (Burdick 2009, Coen 2012, da Silva 2010, Deutsch 2010, Eade 2008, Goldner 2012, Gondi 2007, Klein 2009, Khor 2013, Pe 2009, Pickles 2010, Pinkawa 2010, Vassil 2010, Wong 2009, Zelefsky 2011). This made it difficult to compare results of biochemical failure in older studies compared to more modern ones. Biochemical failure was also included as part of a composite outcome, failure-free-survival (FFS), in one additional study, defined as the initiation of secondary therapy, positive biopsy post-treatment, PSA rise of 10 ng/dL or more even without three consecutive elevations, or development of metastasis (Beyer 2000). Additionally, follow-up was short in the majority of these studies, with only eight studies having a follow-up time ≥ 8-years (Beyer 2000, Burdick 2009, Coen 2012, Deutsch 2010, Goldner 2012, Klein 2009, Khor 2013, Zelefsky 2011). Only four of these studies with longer follow-up included patients from multiple cancer centres (Coen 2012, Deutsch 2010, Goldner 2012, Klein 2009) and only three studies accounted for differences in ADT use between treatment groups (Coen 2012, Klein 2009, Khor 2013).

One additional issue with the majority of observational studies using bFFS as their primary outcome (Burdick 2009, Coen 2012, da Silva Franca 2010, Deutsch 2010, Eade 2008, Goldner 2012, Gondi 2007, Klein 2009, Khor 2013, Krestin 2000, Kupelian 2004, Pe 2009, Pickles 2010, Pinkawa 2010, Vassil 2010, Wong 2009, Zelefsky 1999, Zelefsky 2011), was that comparisons were made in populations composed of mixed low,

intermediate and high-risk patients. This made it difficult to distinguish how PSA failure from the compared RTs would be affected within each prostate cancer risk category. There were only eight studies that assessed comparative cohorts made up of a singular prostate cancer risk category; five assessed entirely low-risk patients (Eade 2008, Goldner 2012, Pe 2009, Zelefsky 1999, Zelefsky 2011) and three assessed intermediate-risk patients (Gondi 2007, Klein 2009, Vassil 2010). Three of the five low-risk studies compared ASTRO-Phoenix bFFS differences in patients receiving LDR-BT vs. EBRT with ≥ 5-years of follow-up time (Goldner 2012, Pe 2009, Zelefsky 2011). In the low-risk studies by Goldner et al and Pe et al, both compared 74 Gy EBRT to 144 Gy I-125 permanent implant LDR-BT. Goldner et al reported no clinically significant difference in bFFS between groups, reporting 5-year survival percentages of 94% (LDR-BT, n=667) and 91% (EBRT, n=170), while Pe et al reported similar 5-year survival percentages of 96% (LDR-BT, n=171) vs. 95% (EBRT, n=189), p=0.70. The low-risk study by Zelefsky et al (2011) reported results of a comparison between high dose 81 Gy IMRT (n=448) vs. the same LDR-BT dose regimen of 144 Gy (n=281). Their results demonstrated a statistically significant difference in 5-year bFFS of 95% (LDR-BT) vs. 89% (EBRT), p=0.04. Although efforts were made to account for confounding, through Cox proportional hazard regression adjustment, in all of the low-risk prostate cancer studies comparing ASTRO-Phoenix defined bFFS, two of the studies did not account for differences in ADT use (Goldner 2012, Zelefsky 2011), and another study by Pe et al, reported results from their single institution with a relatively short median follow-up of 37 months in their BT cohort.

In the intermediate-risk studies that compared ASTRO-Phoenix bFFS, 144 Gy LDR-BT was compared to EBRT doses ranging from 70-80 Gy (Vassil 2010), or a singular dose prescription of 81 Gy (Klein 2009). Vassil et al reported a non-statistically significant difference in bFFS comparing LDR-BT (n=256) vs. EBRT (n=305) with a hazard ratio of 0.99 (95% CI 0.62-1.58, p=0.97). Similarly, Klein et al reported non-statistically significant bFFS 8-year actuarial percentages of 82% (LDR-BT, n=204) vs. 75% (EBRT, n=321), p>0.05. Again, attempts to account for confounding though Cox regression adjustment was performed in both studies, however, one of the studies made

the mistake of classifying the prostate cancer etiological factor 'race' as a prognostic factor in their adjustment (Vassil 2010). Race is known to be a risk factor for the development of prostate cancer, but is not known to impact treatment prognosis (Rubin 2001). Since race is thus not a classical confounding variable, as it is not associated with the outcome of interest, some authors feel that it should not be included in the regression model (Szklo 2014). Klein et al, accounted for the confounder ADT use in their study by eliminating all ADT patients, this was not done by Vassil et al. However, Klein et al did not report age differences between groups, and made no reference to adjusting for this strong confounder in their analysis.

Attempts to ascertain results comparing bFFS in separate risk categories were attempted in five studies through subgroup analyses (Coen 2012, Deutsch 2010, Khor 2013, Pickles 2010, Wong 2009). Beyond that cautious interpretation of subgroup analysis is universally recommended, due to the increased likelihood of chance findings (Friedman 2010), there were some additional limitations found in these exploratory analyses. For example, one study did not account for ADT (Deutsch 2010), while another study did not account for either ADT or age (Wong 2009). There were also some limitations in two additional matched studies, one using conventional 1:1 case-by-case matching (Pickles 2005) and the other using propensity score matching (Khor 2013). In their single institutional, Canadian study, Pickles et al compared bFFS in a cohort of low- and intermediate-risk patients, receiving either 145 Gy I-125 LDR-BT (n=139) or 52-72 Gy EBRT (n=139). Although matching did bring balance to comparison groups with respect to most of the important prognostic factors, including ADT, the confounding variable age was curiously not used in the matching process. This led to a >7 year median age gap between treatment groups. In their subgroup analysis, Pickles et al reported 5-year bFFS actuarial percentages of 94% (LDR-BT) vs. 88% (EBRT), $p<0.001$, for low-risk patients, and 100% (LDR-BT) vs. 78% (EBRT), $p=0.02$, for intermediate-risk patients, respectively. In another single institutional study from Australia, Khor et al compared 19.5 Gy Ir-192 with 46 Gy adjuvant EBRT (HDR-BT+EBRT) to 74 Gy EBRT alone using propensity score matched analysis (total n=688, matched ratio 1:1). Their cohort was comprised of intermediate- and high-risk patients, and PS matching was

performed based on the variables of age, ADT use and prostate cancer risk category. Results from subgroup analysis showed a statistically significant improvement in bFFS in the HDR-BT+EBRT compared to the EBRT patients with intermediate-risk disease (hazard ratio=0.44, 95% CI 0.28-0.70, p<0.001), but a non-statistically significant difference in the high-risk patients (hazard ratio=0.82, 95% CI 0.52-1.28).

The outcome of OS was assessed in a relatively low number of studies found in the literature (Coen 2012, Klein 2009, Zhou 2009, Wong 2009). Coen et al reported a non-statistically significant difference in OS (secondary outcome) between high dose protons with adjuvant EBRT vs. EBRT alone, with 8-year actuarial percentages of 93% vs. 96% (p=0.45). Zhou et al reported a significant difference between BT (n=664) and EBRT (n=876), with 5-year OS percentages of 82% and 72% (p<0.001), respectively. However, the type of BT (HDR or LDR) and source type (I-125, Pd-103, Ir-192) was not reported by Zhou et al, as well as total dose, fractionation schedule or ADT use. This made it difficult to decipher the exact comparison being made. Klein et al reported a borderline statistically significant difference in their LDR-BT vs. EBRT comparison of OS in entirely intermediate-risk patients, with 8-year actuarial percentages of 94% (LDR-BT) vs. 81% (EBRT).

There were a number of additional primary outcomes that were investigated in the prostate cancer CER RT literature, including late GI or GU side effects (Aoki 2009, Elliot 2007, Gelbium 2000, Kalakota 2010, Zelefsky 2008), patient reported quality of life (Davis 2001, Ferrer 2008, Huang 2010, Joseph 2008, Lee 2001, Lev 2009, Smith 2009, Talcott 2003) and secondary cancers (Abel-Waheb 2008, Nieder 2008, Ojha 2010). However, our CER study only focuses on overall survival and biological failure outcomes. For reference, the results from these studies are available in Appendix I.

Upon literature review, it was clear that the CER comparing primary RT survival outcomes is lacking. Most studies that were found compared primary RT survival outcomes in a mixture of low-, intermediate- and high-risk patients, with very few studies comparing treatment differences within one prostate cancer risk group. A short follow-

up time and poor adjustment for ADT use between comparative groups were also important limitations that were seen. The goal of this study is to help improve the quality of CER evidence by retrospectively comparing primary RT survival outcomes in separately matched prostate cancer risk groupings, in the absence of ADT use.

4.0 Research Study

4.1 Primary Study Objectives

1a) To compare overall survival rates between prostate cancer patients who received either external beam radiation alone or brachytherapy with or without adjuvant external beam radiation as their primary mode of treatment.

1b) To compare overall survival rates for propensity score matched low-risk prostate cancer patients that received external beam radiation alone or low dose rate brachytherapy.

1c) To compare overall survival rates for propensity score matched intermediate-risk prostate cancer patients that received external beam radiation alone or brachytherapy (low dose rate brachytherapy alone or high dose rate brachytherapy with adjuvant external beam radiation).

1d) To compare overall survival rates for propensity score matched high-risk prostate cancer patients that received external beam radiation alone or brachytherapy (low dose rate brachytherapy alone or high dose rate brachytherapy with adjuvant external beam radiation).

4.2 Secondary Study Objectives

2a) To compare biochemical failure-free survival rates between prostate cancer patients who received either external beam radiation alone or brachytherapy with or without adjuvant external beam radiation as their primary mode of treatment.

2b) To compare biochemical failure-free survival rates for propensity score matched low-risk prostate cancer patients that received external beam radiation alone or low dose rate brachytherapy.

2c) To compare biochemical failure-free survival rates for propensity score matched intermediate-risk prostate cancer patients that received external beam radiation alone or brachytherapy (low dose rate brachytherapy alone or high dose rate brachytherapy with adjuvant external beam radiation).

2d) To compare biochemical failure-free survival rates for propensity score matched high-risk prostate cancer patients that received external beam radiation alone or brachytherapy (low dose rate brachytherapy alone or high dose rate brachytherapy with adjuvant external beam radiation).

4.3 Study Hypothesis

The overall hypothesis of this study is that brachytherapy with or without adjuvant external beam radiation provides superior overall survival and biochemical-failure-free survival compared with external beam radiation alone as a primary treatment option for prostate cancer patients.

5.0 Methods

5.1 Summary of Methods

1. Conducted a literature review to obtain expert knowledge on prostate cancer radiation and propensity score matching methodology.

2. Established a theoretical casual framework for the mechanism of action of radiation treatment on survival by modeling a directed acyclic graph (DAG)

3. Performed ProCaRS database quality assurance to ensure patients were correctly risk-stratified.

4. Obtained low-, intermediate-, and high-risk study populations from the ProCaRS database using appropriate inclusion and exclusion criteria.

5. Selected preliminary comparison populations in each risk strata based on sample size.

6. Selected the covariates used to create the propensity score models for each comparison group based on literature review and availability in the ProCaRS database.

7. Performed propensity score matching on all final comparison populations.

8. Chose the best match for each comparison group based on an assessment of confounding covariate balance following propensity score matching.

9. Assessed overall survival and biochemical failure-free survival for each comparison using the Kaplan Meier method.

5.2 Case Definitions

The primary goal of this study was to determine whether BT treatment options were superior to EBRT in providing a survival benefit for prostate cancer patients. The exposure and outcome definitions used for this study are shown in Table 4.

Table 4: Exposure and outcome definitions.

Exposures (E):

E1) EBRT exposure definition:

- Any EBRT treatment given (3D conformal or IMRT) that met the minimum radiation dose requirements.
    - The minimum EBRT dose requirements are further described in section 5.5.
    - Possible radiation therapy treatments that fell under this category:
        - EBRT only.

E2) Brachytherapy exposure definition:

- Any primary RT treatment option that involved either LDR-BT or HDR-BT with or without EBRT.
- LDR-BT exposure was defined as any patient who underwent iodine-125 or palladium-103 permanent seed LDR-BT.
- HDR-BT was defined as any patient who received iridium-192 HDR-BT.
    - Minimum dose requirements for both LDR-BT and HDR-BT with or without EBRT are further described in section 5.5.
    - Possible radiation therapy treatments that fell under this category:
        - LDR-BT only.
        - HDR-BT + EBRT.
        - LDR-BT + EBRT.

Outcomes (O):

O1) Overall survival:

- The time from which a patient ends radiation treatment until death. Death could be from any cause.

O2) Biochemical failure-free survival:

- The time from which a patient ends radiation treatment until biochemical failure. Biochemical failure was defined using ASTRO-RTOG Phoenix II definition of a PSA rise by 2 ng/mL or more above the nadir PSA (Roach 2006). To eliminate the possibility of false positive biochemical failure in the BT group because of PSA bounce (Mehta 2013), a PSA of ≥ 0.5 ng/mL on last known follow-up was an additional requirement for biochemical failure in BT patients (Rodrigues 2013).

5.3 Theoretical Causal Framework/Directed Acyclic Graph (DAG)

A Directed Acyclic Graph (DAG), which is a visual representation of the possible causal mechanisms (including confounding) that can lead to the primary outcome of interest (Szklo 2014), was used to establish a causal framework for this study. The DAG model was used to visualize all probable associations that were thought to exist between the known confounding variables and both the primary independent and dependent variables. The visual representation of the causal mechanisms in the DAG model was used to establish which confounders were most appropriate to control for (Szklo 2014). Following literature review, five variables were identified as the strongest patient confounders of the association of prostate cancer radiation treatment and survival, age, T-stage, PSA concentration, Gleason total, and adjuvant hormone therapy use (see Section 2.0, "Prostate Cancer"). Age and hormone therapy were included in the DAG model individually, while T-stage, PSA concentration, and Gleason total were combined as 'tumor factors' for simplicity.

An additional variable identified as a confounder of surgical management of prostate cancer and survival, with the potential to be a confounder of prostate cancer RT outcomes, was the percentages of prostate cancer found in core biopsies (Hinkelammert 2013). The percentage of positive cores was added to the variable 'tumor factors' in the DAG model. Finally, the effect of treatment variation across centres ('treatment centre factors') and the effects of any changes in radiation therapy practice ('time trends'), which have both previously been shown to influence RT outcomes (Cooperberg 2010), were accounted for in the DAG model.

All backdoor paths in the DAG model, which are the possible causal pathways created between the primary independent variable and the dependent variable via their associations with known confounders, regardless of the direction of association (Szklo, 2014), were used to help determine which confounders were to be adjusted for in our analyses. The DAG representing the theoretical causal framework for the mechanism of action of radiation treatment on overall survival (OS) including all backdoor paths is shown in Figure 2.

The variables age, tumor factors, hormone therapy, treatment centre and time trends were all identified as confounders to be accounted for in this study. Controlling for these factors blocked all backdoor paths, including the ensured blocking of backdoor paths 1, 2, 5, 8 and 11 (Fig. 2). No colliders, or variables where two pathways meet (ie. 'variable a' → 'collider variable b' ← 'variable c'), were identified in the DAG model, meaning that all of the above variables could be adjusted for without introducing further bias, assuming there was no unknown confounding (Cole 2002).

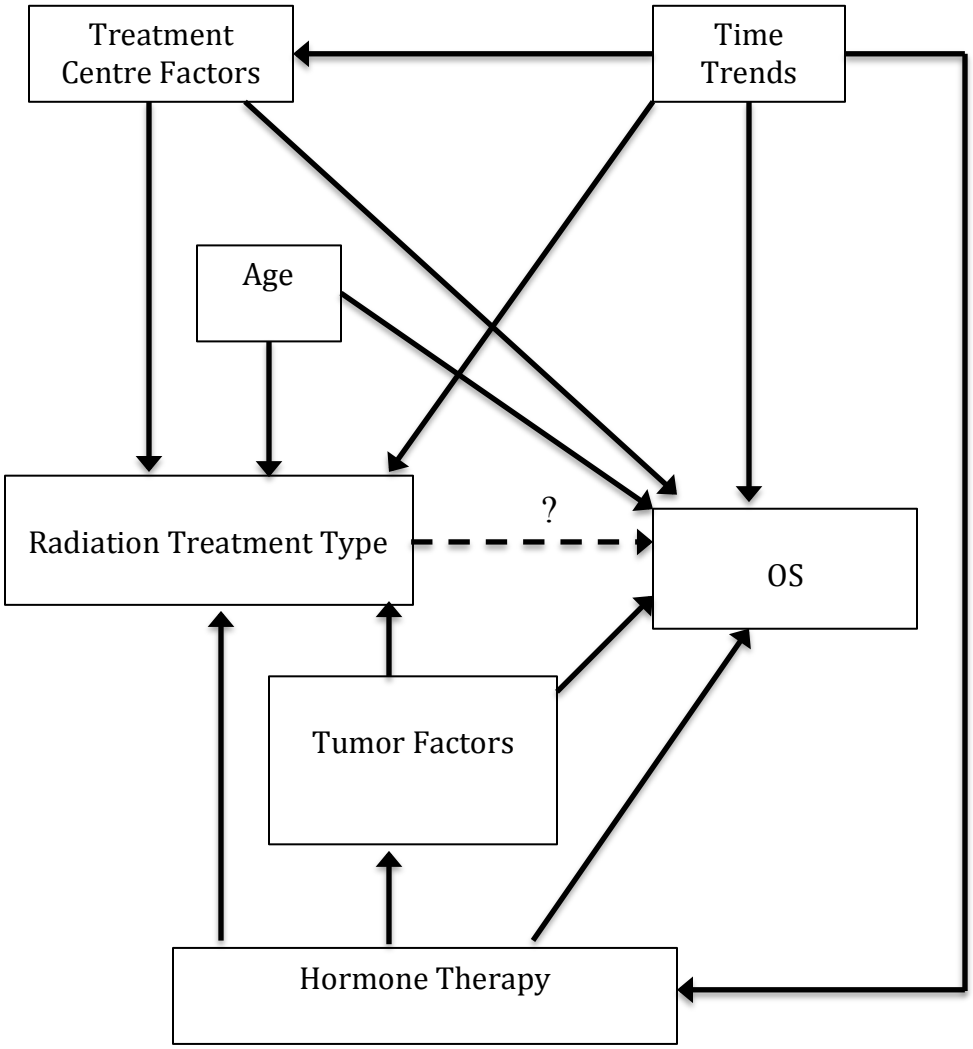


Fig. 2. Directed acyclic graph (DAG) for examining effects of radiation type on OS.

Possible Backdoor Paths:

1) Radiation Treatment Type ← Age → OS
2) Radiation Treatment Type ← Tumor Factors → OS
3) Radiation Treatment Type ← Tumor Factors ← Hormone Therapy → OS
4) Radiation Treatment Type ← Tumor Factors ← Hormone Therapy ← Time Trends → Treatment Centre Factors → OS
5) Radiation Treatment Type ← Hormone Therapy → OS
6) Radiation Treatment Type ← Hormone Therapy ← Time Trends → Treatment Centre Factors → OS
7) Radiation Treatment Type ← Hormone Therapy → Tumor Factors → OS
8) Radiation Treatment Type ← Treatment Centre → OS

9) Radiation Treatment Type ← Treatment Centre ← Time Trends → Hormone Therapy → OS
10) Radiation Treatment Type ← Treatment Centre ← Time Trends → Hormone Therapy → Tumor Factors → OS
11) Radiation Treatment Type ← Time Trends → OS
12) Radiation Treatment Type ← Time Trends → Hormone Therapy → OS
13) Radiation Treatment Type ← Time Trends → Hormone Therapy → Tumor Factors → OS

5.4 The Prostate Cancer Risk Stratification (ProCaRS) Database (Data Source)

Patient information from the Prostate Cancer Risk Stratification (ProCaRS) database was used as the data source for this study. The ProCaRS database contains primary RT outcome data on 7974 prostate cancer patients treated at four major cancer institutions (Princess Margaret Hospital, Toronto, Ontario, Canada; l'Université Laval, Quebec, Canada; McGill University, Montréal, Canada; and the British Columbia Cancer Agency, British Columbia, Canada) (Rodrigues 2013). Following a review of the most current guidelines for prostate cancer risk stratification (Rodrigues 2012), the creation of the ProCaRS database was sanctioned by the GUROC in an attempt to advance research in prostate cancer RT outcomes and methodology. Results from recursive partitioning risk stratification modeling using the ProCaRS data suggested that a six category prostate cancer risk stratification system, including categories of extreme-low-, low-, intermediate-low-, intermediate-high-, high- and extreme-high-risk, should replace the current GUROC three-category system of low-, intermediate- and high-risk (Rodrigues 2013). Multivariable Cox proportional hazard regression using ProCaRS data indicated that BT was a significant predictor in the outcome of bFFS (Rodrigues 2012). The results from this initial analysis led to the current study, using PS matched analysis to compare EBRT versus BT outcomes of OS and bFFS in homogenous cohorts of entirely low-risk, intermediate-risk and high-risk patients. For the purpose of this investigation, the previously described original GUROC three-category risk stratification system (Lukka 2001) was used to stratify patients into low-, intermediate- and high-risk categories prior to PS matching and analysis (see Section 2.5, Table 3 for the GUROC low-, intermediate- and high-risk category requirements).

All available variables in the ProCaRS database as well as brief descriptions are displayed in Appendix III.

5.5 Selection of Study Populations for Propensity Score Matches

5.5.1 Initial Patient Selection Process and Sample Size Assessment

The initial process used to select all RT treatment comparison groups prior to propensity score matching is outlined in Figure 3.

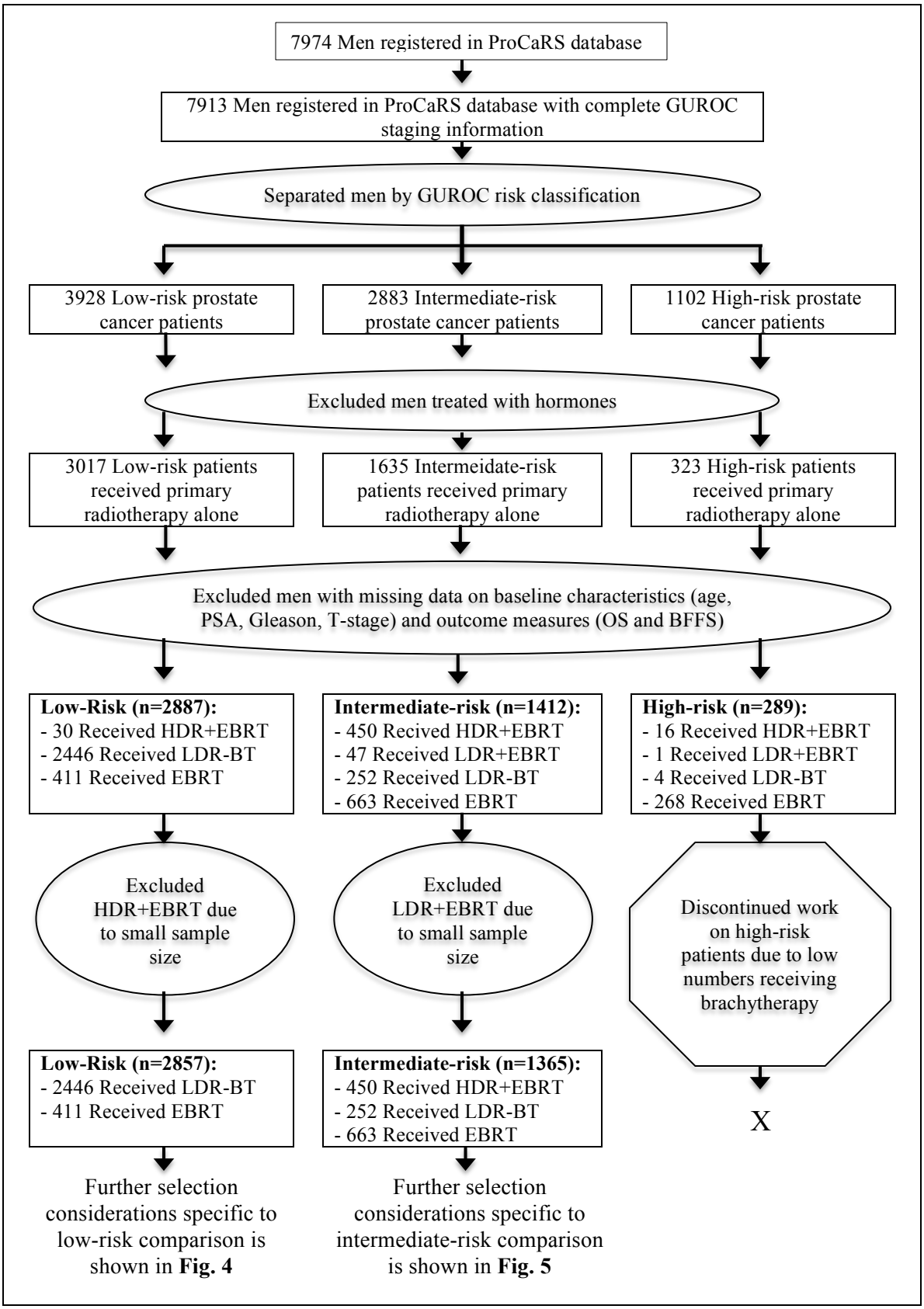


Fig. 3. Initial patient selection process.

Patients were separated by GUROC prostate cancer risk category into three homogenous groups of low-risk, intermediate-risk, or high-risk. Patients receiving hormone therapy were removed from the comparison groups, as ADT has been previously established as a strong confounder of prostate cancer RT survival outcomes (Bolla 2002, D'Amico 2004, Lawton 2001). Patients with missing data on important baseline characteristics including age, PSA concentration, Gleason total pattern and T-stage, as well as outcome data on OS and bFFS were excluded. This was done to ensure that all patients had data on the most important baseline variables and outcomes used in all propensity score models and matched analyses. Following these exclusions the total numbers of individuals receiving each RT treatment option was assessed. Adequate sample size was found in low-risk patients that received either LDR-BT (n=2446) or EBRT alone (n=411) and intermediate-risk patients who had HDR-BT+EBRT (n=450), LDR-BT (n=252), or EBRT alone (n=663). There were insufficient numbers of low-risk patients that received HDR-BT+EBRT (n=30) and intermediate-risk patients that received LDR-BT+EBRT (n=47); these patients were excluded prior to propensity score matching. Due to the lack of high-risk patients treated with any of the BT modalities (ie. HDR-BT or LDR-BT with or without EBRT), work on the high-risk patient population was abandoned. Before PS matching, some additional selection considerations for the low-risk and intermediate-risk patient populations were considered separately and are discussed in section 5.5.2 and 5.5.3, respectively. The SAS code used to create the initial patient populations shown in Figure 3 can be seen in Appendix V and Appendix VI.

5.5.2 Patient Selection for Low-Risk Propensity Score Match

The patient selection process for PS matching specific to the low-risk prostate cancer comparison is shown in Figure 4. The SAS coding for this selection process is shown in Appendix VI.

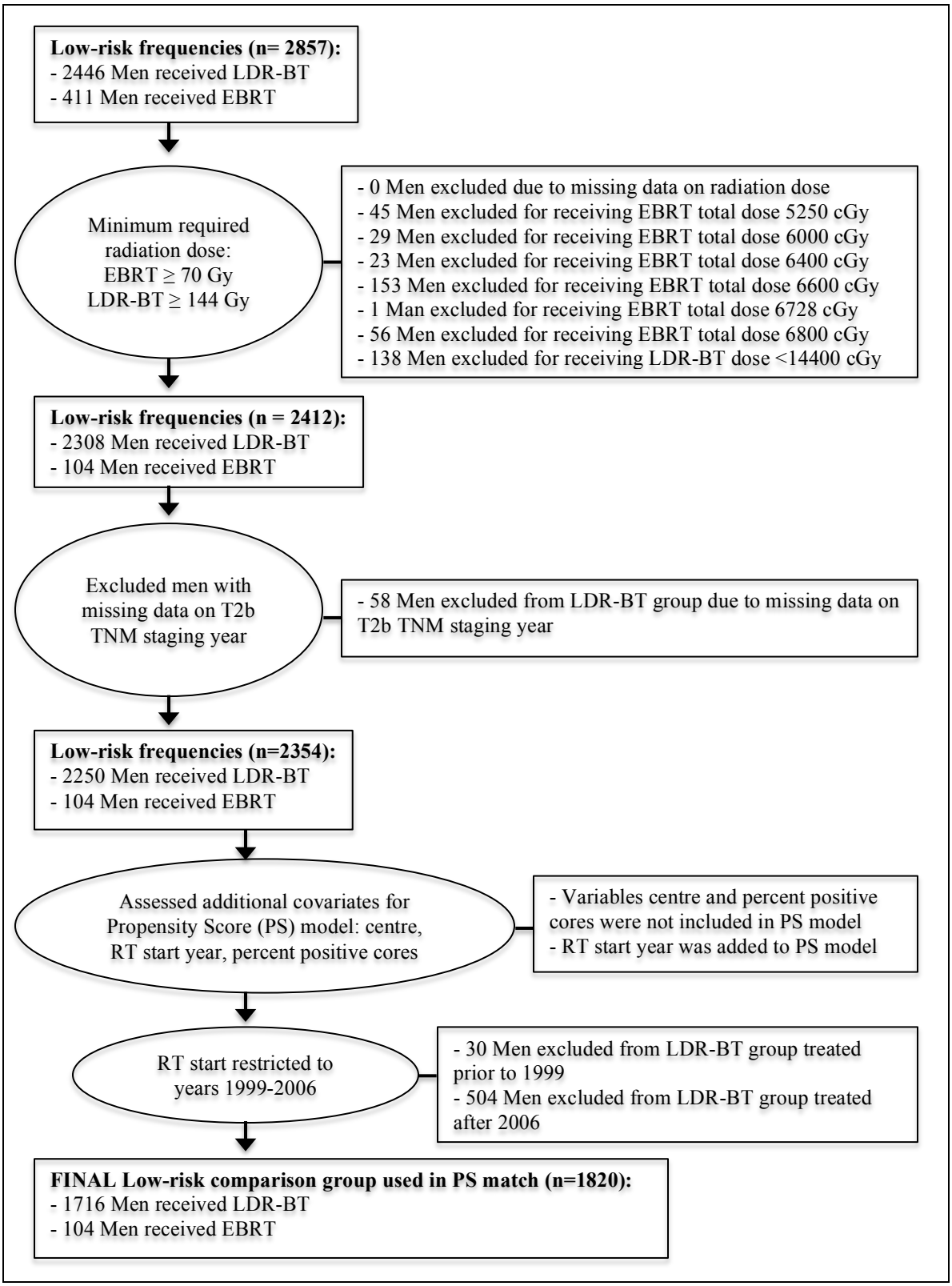


Fig. 4. Low-risk comparison group selection process (cont. from fig. 3).

Radiation Dose Considerations for Low-Risk Comparison:

To ensure a fair comparison was made between low-risk radiation treatment modalities, a minimum radiation dose requirement of 70 Gy for the EBRT group and 144 Gy for the LDR-BT group was required to be included in the PS match. These doses were chosen based on literature review. Currently, a debate exists as to whether the benefits of dose escalation in low-risk patients is as beneficial compared to intermediate or high-risk patients. Two randomized trials found in subgroup analysis that dose escalation up to 78 Gy provides a benefit in low-risk patients (Kuban 2008, Zietman 2005), while a separate trial found no significant difference between 68 Gy and 78 Gy in their subgroup analysis (Peeters 2006). Due to the lack of quality evidence to support EBRT doses exceeding 70 Gy for low-risk prostate cancer, a required EBRT dose of ≥ 70 Gy for all low-risk patients was chosen for this study. Additionally, the minimum dose of 144 Gy given with I-125 LDR-BT was chosen based on standard treatment recommendations (Nag 1999). Although a large number of patients that received EBRT doses < 70 Gy were excluded (n=307), the benefits of EBRT dose escalation on survival are well documented (Hanks 1999, Zelefsky 1998, Kupelian 2000). Therefore, a minimum EBRT dose of at least 70 Gy was required in this comparison group to ensure that an adequate EBRT dose was being compared to the higher doses given with LDR-BT. There were no patients eliminated from the low-risk population due to missing data on RT dose.

TNM Staging Considerations for Low-Risk Comparison:

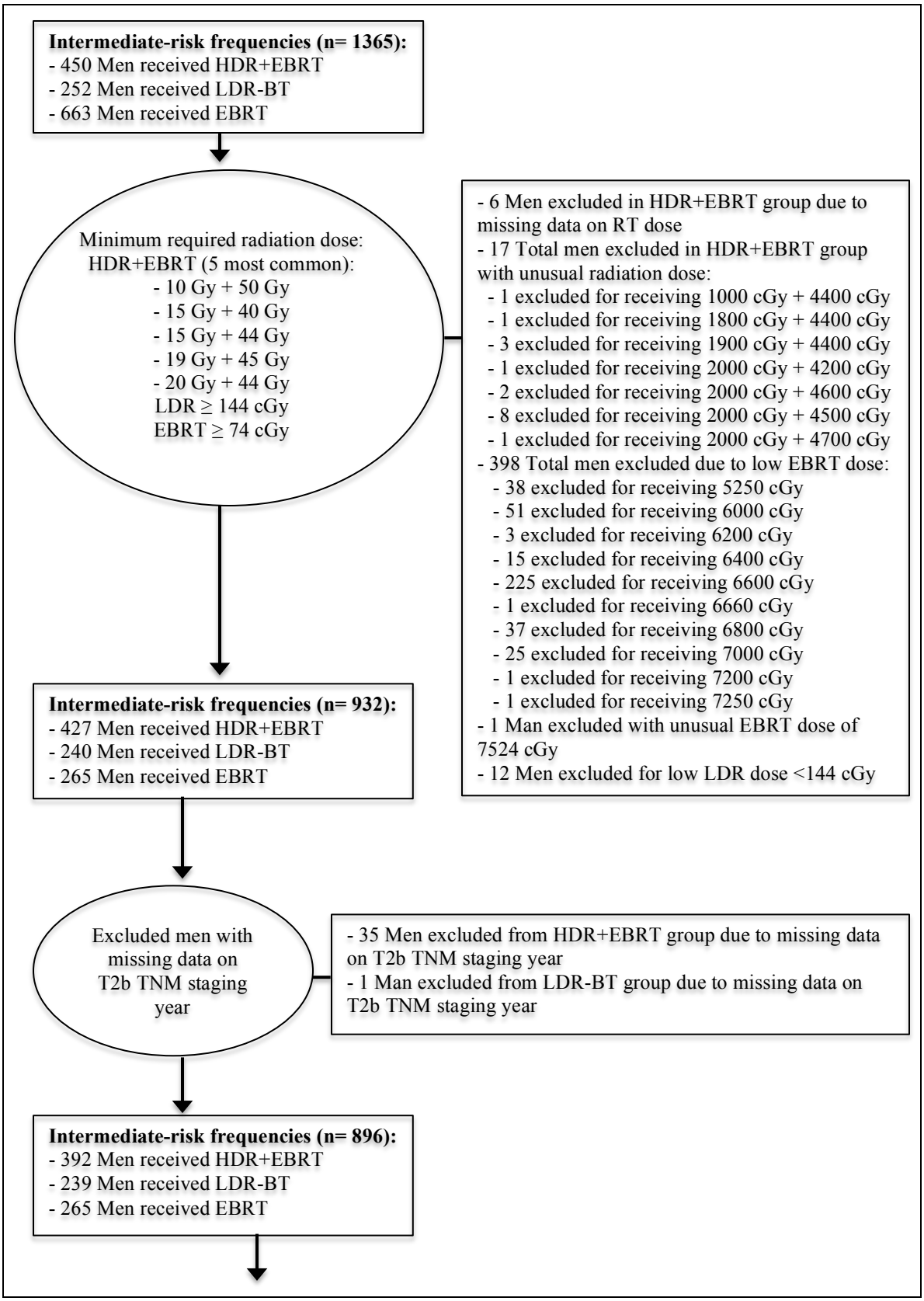
Low-risk patients with T2b T-stage with missing data on TNM staging year were removed prior to PS matching. This ensured that there were no patients with bilateral disease in the patient cohort, which would have categorized them as being intermediate-risk. Palpable bilateral disease is defined as T2b using the 1997 AJCC TNM staging definitions and T2c using the more current definitions adopted after 2002 (Fleming 1997, Greene 2002, Edge 2009). This excluded 58 men from the LDR-BT group.

Additional Variable Assessment for Low-Risk Propensity Score Model:

All variables used in the PS models were required for a patient to receive a PS and be used in the PS matches. An assessment was made whether including additional variables in the low-risk PS model would impact patient numbers available for PS matching. Some of the additional covariates considered for inclusion in the low-risk PS model prior to matching included: percent positive cores, treatment centre, and RT start year. The variable 'percent positive cores' was not included in the PS model, as this would have prevented 17 EBRT patients and 1078 LDR-BT patients from receiving a PS (roughly 16% and 48% of the remaining EBRT and LDR-BT populations, respectively). Additionally, the variable 'treatment centre' was also not included due to the distribution of RT treatment modalities provided by the various cancer centres. For example, cancer centres 1, 2 and 3 provided data on low-risk patients treated with LDR-BT, while only centres 1 and 2 gave data on EBRT. Therefore, if the variable 'treatment centre' was included in the PS model, all LDR-BT patients from cancer centre 3 (n=942) would receive no PS and could not be matched. Finally, RT start year was included in the PS model. Restricting RT start dates was viable because all low-risk EBRT treatments occurred during the years 1999-2006, with ample numbers of low-risk LDR-BT patients receiving treatment over that same timeframe. In total, 104 EBRT and 1716 LDR-BT patients made up the eventual population used for the low-risk PS match.

5.5.3 Patient Selection for Intermediate-Risk Propensity Score Matches

The patient selection process for PS matches specific to the intermediate-risk prostate cancer comparisons are shown in Figure 5. The SAS coding for this selection process is shown in Appendix V.


Intermediate-risk frequencies (n= 1365):
- 450 Men received HDR+EBRT
- 252 Men received LDR-BT
- 663 Men received EBRT
Minimum required radiation dose:
HDR+EBRT (5 most common):
- 10 Gy + 50 Gy
- 15 Gy + 40 Gy
- 15 Gy + 44 Gy
- 19 Gy + 45 Gy
- 20 Gy + 44 Gy
LDR ≥ 144 cGy
EBRT ≥ 74 cGy
- 6 Men excluded in HDR+EBRT group due to missing data on RT dose
- 17 Total men excluded in HDR+EBRT group with unusual radiation dose:
- 1 excluded for receiving 1000 cGy + 4400 cGy
- 1 excluded for receiving 1800 cGy + 4400 cGy
- 3 excluded for receiving 1900 cGy + 4400 cGy
- 1 excluded for receiving 2000 cGy + 4200 cGy
- 2 excluded for receiving 2000 cGy + 4600 cGy
- 8 excluded for receiving 2000 cGy + 4500 cGy
- 1 excluded for receiving 2000 cGy + 4700 cGy
- 398 Total men excluded due to low EBRT dose:
- 38 excluded for receiving 5250 cGy
- 51 excluded for receiving 6000 cGy
- 3 excluded for receiving 6200 cGy
- 15 excluded for receiving 6400 cGy
- 225 excluded for receiving 6600 cGy
- 1 excluded for receiving 6660 cGy
- 37 excluded for receiving 6800 cGy
- 25 excluded for receiving 7000 cGy
- 1 excluded for receiving 7200 cGy
- 1 excluded for receiving 7250 cGy
- 1 Man excluded with unusual EBRT dose of 7524 cGy
- 12 Men excluded for low LDR dose <144 cGy
Intermediate-risk frequencies (n= 932):
- 427 Men received HDR+EBRT
- 240 Men received LDR-BT
- 265 Men received EBRT
Excluded men with missing data on T2b TNM staging year
- 35 Men excluded from HDR+EBRT group due to missing data on T2b TNM staging year
- 1 Man excluded from LDR-BT group due to missing data on T2b TNM staging year
Intermediate-risk frequencies (n= 896):
- 392 Men received HDR+EBRT
- 239 Men received LDR-BT
- 265 Men received EBRT

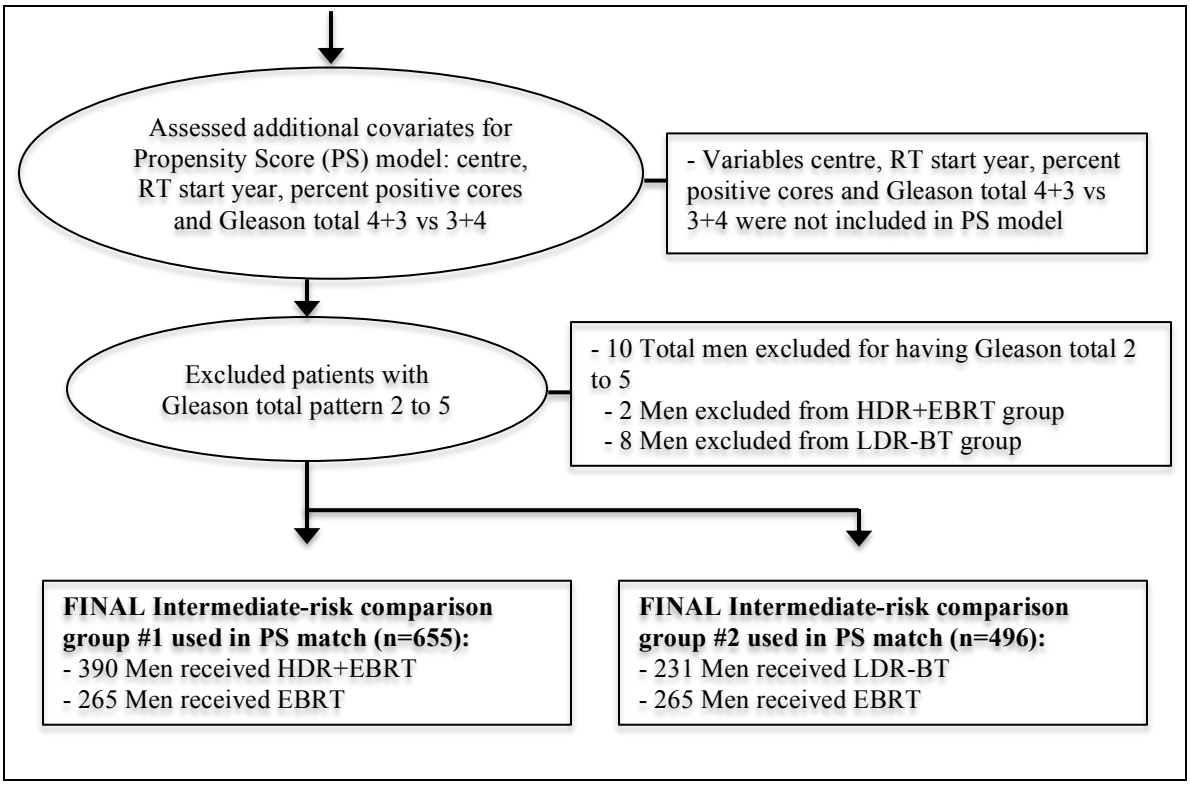


Fig. 5. Intermediate-risk comparison group selection process (cont. from fig. 3).

Radiation Dose Considerations for Intermediate-Risk Comparisons:

Similar to low-risk, a minimum radiation dose was required to be included in the intermediate-risk PS matches. LDR-BT minimum dose remained the same as in the low-risk cohort, at ≥ 144 Gy. Current literature suggests EBRT doses of at least 72 Gy provide improved survival outcomes for localized prostate cancer compared to lower doses (Kupelian 2000). The minimum EBRT dose chosen for this study was slightly higher than this recommendation, at ≥ 74 Gy because only two intermediate-risk patients received doses of at least 72 Gy but less than 74 Gy. This allowed for an increase in minimum dose and ensured that dose escalation was used for all EBRT patients in the intermediate-risk PS matches. HDR-BT+EBRT doses were limited to the five most common dose regimens found in the ProCaRS database (Fig 5). There were an additional six men removed from the HDR-BT+EBRT population due to missing data on RT dose.

TNM Staging Considerations for Intermediate-Risk Comparisons:

Intermediate-risk patients with T2b T-stage with missing data on TNM staging year were excluded prior to PS matching. This was done for similar reasons as in the low-risk category, to ensure that patients with T-stage T2b were correctly identified as having either unilateral or bilateral disease (Fleming 1997, Greene 2002, Edge 2009). There were 35 T2b staged men from the HDR-BT+EBRT group and a single T2b staged man from the LDR-BT group that were excluded because of missing data on TNM staging year.

Variable Assessment for Intermediate-Risk Propensity Score Models:

Again, similar to the low-risk cohort, the additional variables of treatment centre, RT start year, and percent positive cores were assessed for inclusion in the PS models. The variable 'treatment centre' was not included in the PS models for the same reason as in the low-risk cohort. For intermediate-risk patients, cancer centres 1 and 2 provided treatment data on LDR-BT and EBRT, cancer centre 3 on LDR-BT and HDR-BT+EBRT,

and centre 4 gave data exclusively on HDR-BT+EBRT. RT start year was not included in the PS models due to a wide range of years that each treatment modality was given, LDR-BT was given from the year 1994 to 2010, EBRT from 1999-2006, and HDR-BT+EBRT from 2001 to 2010. This precluded the possibility of restricting treatment year for the PS modeling. The percentage of positive cores was not included in the PS models due to a large proportion of men (310 in the HDR-BT+EBRT group, 70 in the LDR-BT group, and 26 in EBRT group) who had missing data on this variable.

Additionally, an assessment was made whether Gleason total 7 in the intermediate-risk cohort could be further subdivided into sub-patterns 3+4 vs. 4+3. Current evidence suggests that Gleason pattern 4+3 compared to Gleason pattern 3+4 can lead to a worse survival prognosis for men with prostate cancer (Wright 2009). Unfortunately, splitting Gleason 7 into two sub categories was not possible for the intermediate-risk PS modeling, as there were a large number of patients receiving BT with missing sub-pattern data (306 men in the HDR-BT+EBRT group and 59 in the LDR-BT group). Therefore, Gleason pattern 7 was kept as a single category in the intermediate-risk PS models.

Finally, following an assessment of the distribution of Gleason total pattern in the intermediate-risk patient population, it was discovered that all patients with Gleason totals of 2, 3, 4 or 5 received BT and not EBRT. These patients were removed prior to matching as including them would lead to difficulties in PS model convergence. This was due to the category of Gleason total 2 to 5 predicting 100% probability of receiving BT in the PS model. Thus, only patients with Gleason total 6 or 7 were included in the intermediate-risk matches.

5.6 Overview of Propensity Score Matching Methodology

Propensity score matching methodology described by Peter Austin (2007) in his systematic review entitled “Propensity-score matching in cardiovascular surgery literature from 2004 to 2006: A systematic review and suggestions for improvement”

was used as a general guideline for the PS methods used in this study. There were four steps involved in the PS matching and analysis in this study: i) creating PS model(s); ii) performing PS matching; iii) statistical assessment of covariates balance following matching; iv) estimating treatment effects.

5.6.1 Creation of Final Propensity Score Models

As was previously discussed, the PS for each patient was estimated indicating their probability of receiving a particular treatment based on a number of baseline variables in a PS model (Heinze 2011). Multivariable logistic regression modeling was used to create the PS models for this study. RT treatment designation was the dependent variable in the logistic models, while the confounders for RT treatment outcomes were the independent variables. The independent variables chosen for all PS models were chosen a priori and were all known to confound prostate cancer survival outcomes. This followed current theory that variables used in PS models should predict outcome and not necessarily treatment given (Brookhart 2006). Four out of the five main prognostic factors of prostate cancer radiation therapy were included in all PS models: age, T-stage, baseline PSA concentration and Gleason Total. Due to the requirement that patients must have data on all variables in the PS model to receive a PS, baseline data on all four of these variables were required throughout the patient inclusion process. The fifth main confounding factor of RT treatment and survival, hormone therapy, was accounted for by excluding all patients who received ADT from the cohorts prior to matching.

The prognostic factors of 'percent positive cores' and 'treatment centre' were not included in any of the PS models following initial sample size assessments. RT start year was included in the low-risk PS model, but not in the intermediate-risk models due to reasons previously mentioned in sections 5.5.2 and 5.5.3. All variables were included in the models as main effects with no interactions. Although interactions have been used in PS modeling, there is no current method of assessing the balance created in the combinations of variables following matching (Heinze 2011). The covariates age and baseline PSA were included as continuous variables in the PS models, while the

covariates T-stage, Gleason total and RT start year were included as categorical variables. In the low-risk comparison PS model, T-stage had two categories (any T1; T2), Gleason total had two categories (Gleason total 2 to 5 inclusive; Gleason total 6), and RT start year had eight categories (one for each year from 1999 to 2006). In the intermediate-risk PS models, T-stage had three categories (any T1; unilateral T2; bilateral T2) and Gleason total had two categories (Gleason total 6; Gleason total 7). The final PS model formulas with variable definitions for low-risk and intermediate-risk comparisons are shown in Table 5. The SAS code for low-risk PS model is shown in Appendix IX. The SAS codes for the intermediate-risk PS models are shown in Appendices VII and VIII.

Table 5: Propensity score models and variable definitions.

Low-risk model:

LDR-BT vs. EBRT:

$\text{Logit}\{\pi\} = \beta_0 + \beta_1\text{age} + \beta_2\text{PSA} + \beta_3\text{Tstage} + \beta_4\text{GleasonTotal} + \beta_5\text{RTStartYr2000} + \beta_6\text{RTStartYr2001} + \beta_7\text{RTStartYr2002} + \beta_8\text{RTStartYr2003} + \beta_9\text{RTStartYr2004} + \beta_{10}\text{RTStartYr2005} + \beta_{11}\text{RTStartYr2006}$

Where $\text{Logit}\{\pi\} = P(Y=1|\text{age, PSA, Tstage, GleasonTotal, RTStartYr})$, Y={1 if LDR-BT, 0 if EBRT only}

Age = {age in years}
PSA = {baseline PSA measured in ng/mL}
Tstage = {1 if baseline T-stage = T2, 0 if baseline T-staging = any T1}
GleasonTotal = {1 if Gleason total = 6, 0 if Gleason total = 2, 3, 4, or 5}
RTStartYr 2000 = {1 if RT Start occurred in 2000, 0 otherwise}
RTStartYr 2001 = {1 if RT Start occurred in 2001, 0 otherwise}
RTStartYr 2002 = {1 if RT Start occurred in 2002, 0 otherwise}
RTStartYr 2003 = {1 if RT Start occurred in 2003, 0 otherwise}
RTStartYr 2004 = {1 if RT Start occurred in 2004, 0 otherwise}
RTStartYr 2005 = {1 if RT Start occurred in 2005, 0 otherwise}
RTStartYr 2006 = {1 if RT Start occurred in 2006, 0 otherwise}

Intermediate-risk models:

LDR-BT vs. EBRT:

$\text{Logit}\{\pi\} = \beta_0 + \beta_1\text{age} + \beta_2\text{PSA} + \beta_3\text{TstageT2unilateral} + \beta_4\text{TstageT2bilateral} + \beta_5\text{GleasonTotal7}$

Where $\text{Logit}\{\pi\} = P(Y=1|\text{age, PSA, Tstage, GleasonTotal})$, Y={1 if LDR-BT, 0 if EBRT only}

Age = {age in years}
PSA = {baseline PSA measured in ng/mL}
TstageT2unilateral = {1 if unilateral T2 disease, 0 if any T1 or T2 bilateral disease}
TstageT2bilateral = {1 if bilateral T2 disease, 0 if any T1 or T2 unilateral disease}
GleasonTotal = {1 if Gleason total = 7, 0 if Gleason total = 6}

HDR-BT+EBRT vs. EBRT:

$\text{Logit}\{\pi\} = \beta_0 + \beta_1\text{age} + \beta_2\text{PSA} + \beta_3\text{TstageT2unilateral} + \beta_4\text{TstageT2bilateral} + \beta_5\text{GleasonTotal7}$

Where $\text{Logit}\{\pi\} = P(Y=1|\text{age, PSA, Tstage, GleasonTotal, RTStartYr})$, Y={1 if HDR-BT+EBRT, 0 if EBRT only}

Age = {age in years}
PSA = {baseline PSA measured in ng/mL}
TstageT2unilateral = {1 if unilateral T2 disease, 0 if any T1 or T2 bilateral disease}
TstageT2bilateral = {1 if bilateral T2 disease, 0 if any T1 or T2 unilateral disease}
GleasonTotal = {1 if Gleason total = 7, 0 if Gleason total = 6}

5.6.2 Propensity Score Matching

To ensure that optimal matches were achieved, several matches were attempted in each comparison group. Nearest-neighbor matching methodology also known as 'greedy matching' was used for all matches. This meant that each randomly selected EBRT patient was matched to the nearest BT patient based on patient 'score' regardless of whether that patient would be a better overall candidate for a different match (Austin 2007). Sampling was done without replacement, meaning once a patient was matched they were no longer available for future matches (Szklo 2014). An assessment of the total number of patients was performed prior to matching to determine what matching ratios would be attempted. One-to-one matches were explored prior to one-to-many matches. One-to-many matches were used only when there was sufficient sample size disparity between treatment groups (ie. if roughly a 1:2 ratio existed, a 1:2 match was explored). In the intermediate-risk comparisons, 1:2 matches were attempted with the slightly larger treatment group acting as the control or 'many' group. Due to the large number of BT patients available in the low-risk comparison group (n=1716), 1:2, 1:3, and 1:4 matches were explored with EBRT patients matched to multiple LDR-BT patients. A maximum ratio of 1:4 was chosen based on previous literature indicating matches with higher ratios beyond 1:4 are not usually attempted, as the gain in statistical power becomes insignificant (Silva 1999). Although one-to-one-to-one PS matching has been documented (Rassen 2013), the statistical methodology used to assess covariate balance in three-way PS matches is not fully developed, therefore 1:1:1 (EBRT:LDR-BT:HDR-BT+EBRT) matching in the intermediate-risk comparison grouping was not attempted.

A variety of caliper widths, or the range of PS values within which an acceptable match was allowed, were explored in this study. Caliper widths ranging from as low as 0.005 (Christakis 2003) to as high as 0.1 (Moss 2003) of a propensity score have been reported. In a Monte Carlo simulation study, a caliper of 0.2 of a standard deviation of the logit of the propensity score was shown to lead to improved covariate balance compared to other common caliper widths (Austin 2009). However, other recommendations have not yielded a consensus on which caliper size is most appropriate

for PS matching (Calideno 2008, Lunt 2013, Stuart 2010). For the matches in this study, the initial caliper used was 0.2 of a standard deviation of the logit of the propensity score. These initial matches were compared concurrently with additional matches on the propensity score scale, which included a tight, previously utilized, caliper width of 0.025 (Verstegen 2013), a moderate caliper width of 0.05, and a generous caliper width of 0.1. An assessment of the covariate balance and sample size was made to determine which matches were to be used in the final analyses. The SAS codes used to generate the final matches were based on a previously described SAS code (Coca-Perralillon 2006) and are shown in Appendices VII, VIII and IX.

5.6.3 Statistical Assessment of Covariate Balance After Matching

Following PS matching, the balance created in each match was assessed statistically by comparing the standardized difference in the matched variables. The advantage of using the standardized difference to assess balance over significance testing is that the standardized difference is unaffected by sample size or power (Heinze 2011). The formula used to calculate the standardized difference for continues variable was

$$d = \frac{100(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{(s^2_{\text{treatment}} + s^2_{\text{control}})/2}} \quad (1)$$

Additionally, for dichotomous variables, the standardized difference formula used was

$$d = \frac{100(p_T - p_C)}{\sqrt{(p_T(1-p_T) + p_C(1-p_C))/2}} \quad (2)$$

For formula (1), $\bar{x}_{\text{treatment}}$ and $\bar{x}_{\text{control}}$ indicate the mean of the continuous variable in 'treated' and 'control' subjects, while the $s^2_{\text{treatment}}$ and s^2_{control} denote their variances. In formula (2), for a dichotomous variable, the p_T and p_C are the proportion of treated and control patients, respectively (Heinze 2011). For this study, the recommended standardized difference cut-point of >0.10 (Austin 2007) was used to indicate significant imbalance in the baseline covariates. The use of the standardized difference statistic was chosen based on recommendations that a proper statistical test of balance should not be effected by sample size and is related to the sample population not a theoretical one,

which are not features of standard p-value testing (Imai 2008). Previously described SAS code (Faries 2010) was used to generate the standardized differences assessing covariate balance in each treatment comparison and is shown in Appendix X.

The choice of which matches were used in the final analyses were based on the following criteria:

1. Following matching all variables used in the PS model must have a standardized difference <0.10.
2. One-to-one matches were assessed prior to one-to-many matches.
3. A match must be identified in each comparison group having the 'best' distribution of balance among all variables.
4. Side-by-side box plots and five number summaries of continuous variables in each matched cohort must be similar on visual inspection.
5. If two or more matches were found to have similar balance in a comparison group, the match with the highest number of variables with the lowest standardized difference was chosen (indicating a tighter match).
6. If two or more matches were found to have comparable balance in all variables, then the match with the larger sample size was chosen.
7. If no suitable match was found (with standardized difference <0.10 in all matched variables) using the original calipers of 0.2 of a standard deviation of the logit of the propensity score, or 0.025, 0.05 or 0.1 of a propensity score, in either one-to-one matches or one-to-many matches, then a tighter caliper match was performed starting with a caliper of 0.01 of a propensity score.

Selection of the Final Match for Analysis in Low-risk LDR-BT vs. EBRT Cohort:

A summary of the sample sizes created using different matching criteria for the low-risk LDR-BT vs. EBRT cohort is shown in Table 6. For the low-risk cohort comparing LDR-BT to EBRT, 1:1 matches did not achieve balance (standardized

difference <0.10) in PSA, Gleason total or RT start year, regardless of the caliper size used. The matches using ratios (EBRT:LDR-BT) of 1:2 and 1:3 did not bring balance to RT start year. However, balance was achieved in 1:4 matches using a caliper width of 0.2 of a standard deviation of the logit of the propensity score and a caliper width of 0.025 of a propensity score. Due to the similar balance produced in both of these matches, the 0.2 of a standard deviation of the logit of the propensity score match using a 1:4 ratio (EBRT:LDR-BT) was chosen for final analysis based on a slightly larger sample size (n=400). Tables 7-10 give examples of the balance produced using different caliper widths in the low-risk LDR-BT vs. EBRT matches.

Table 6: Sample size based on propensity score matching in low-risk cohort (pre-match n=1820).

Caliper	**Ratio (LDR:EBRT)**	**Total N**
0.025	1:1	206
0.025	2:1	282
0.025	3:1	332
0.025	4:1	395
0.05	1:1	206
0.05	2:1	294
0.05	3:1	384
0.05	4:1	410
0.1	1:1	208
0.1	2:1	300
0.1	3:1	376
0.1	4:1	425
0.2*1SDevLogit	1:1	206
0.2*1SDevLogit	2:1	294
0.2*1SDevLogit	3:1	340
0.2*1SDevLogit	4:1	400

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; SDev = standard deviation

Table 7: Baseline characteristics of variables used in low-risk propensity score match (pre-match n=1820) [1:1 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 1 LDR : 1 EBRT **Total N = 206**			**Caliper:** 0.025 **Ratio:** 1 LDR : 1 EBRT **Total N = 206**			**Caliper:** 0.1 **Ratio:** 1 LDR : 1 EBRT **Total N = 208**		
VARIABLE	**LDR n = 103**	**EBRT n = 103**	***S.D.***	**LDR n = 103**	**EBRT n = 103**	***S.D.***	**LDR n = 104**	**EBRT n = 104**	***S.D.***
****Age*** – mean ± SDev	68.6 ± 6.5	68.8 ± 6.4	0.031	68.6 ± 6.5	68.9 ± 6.6	0.043	68.7 ± 6.5	69.0 ± 6.6	0.038
****Baseline PSA*** – mean ± SDev	6.42 ± 1.9	6.07 ± 2.4	**0.165**	6.42 ± 1.9	6.04 ± 2.4	**0.180**	6.43 ± 1.9	6.06 ± 2.4	**0.177**
***Gleason Total** – n(%)									
2-5	4(3.9)	7(6.8)	**0.130**	4(3.9)	7(6.8)	**0.130**	4(3.9)	7(6.7)	**0.129**
6	99(96.1)	96(93.2)		99(96.1)	96(93.2)		100(96.2)	97(93.3)	
****T Stage*** – n(%)									
T1	63(61.2)	61(59.2)	0.040	63(61.2)	60(58.3)	0.059	64(61.5)	61(58.7)	0.059
T2	40(38.8)	42(40.8)		40(38.8)	43(41.8)		40(38.5)	43(41.4)	
****RT Start Year*** – n(%)									
1999	5(4.9)	8(7.8)	**0.120**	5(4.9)	7(6.8)	0.083	5(4.8)	8(7.7)	**0.119**
2000	19(18.5)	18(17.5)	0.025	19(18.5)	18(17.5)	0.025	19(18.3)	18(17.3)	0.025
2001	4(3.9)	5(4.9)	0.048	4(3.9)	5(4.9)	0.047	4(3.9)	5(4.8)	0.047
2002	28(27.2)	27(26.2)	0.022	28(27.2)	28(27.2)	0.000	28(26.9)	28(26.9)	0.000
2003	28(27.2)	28(27.2)	0.000	28(27.2)	28(27.2)	0.000	29(27.9)	28(26.9)	0.022
2004	11(10.7)	7(6.8)	**0.138**	11(10.7)	7(6.8)	**0.137**	11(10.6)	7(6.7)	**0.137**
2005	4(3.9)	6(5.8)	0.090	4(3.9)	6(5.8)	0.090	4(3.9)	6(5.8)	0.090
2006	4(3.9)	4(3.9)	0.000	4(3.9)	4(3.9)	0.000	4(3.9)	4(3.9)	0.000

*Abbreviations***:** EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**

Grey Box = Variable with S.D > 0.10.

Table 8: Baseline characteristics of variables used in low-risk propensity score match (pre-match n=1820) [1:2 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 2 LDR : 1 EBRT **Total N = 294**			**Caliper:** 0.025 **Ratio:** 2 LDR : 1 EBRT **Total N = 282**			**Caliper:** 0.1 **Ratio:** 2 LDR : 1 EBRT **Total N = 300**		
VARIABLE	**LDR n = 196**	**EBRT n = 98**	***S.D.***	**LDR n = 188**	**EBRT n = 94**	***S.D.***	**LDR n = 200**	**EBRT n = 100**	***S.D.***
****Age*** – mean ± SDev	68.5 ± 6.0	68.5 ± 6.4	0.011	68.2 ± 5.8	68.2 ± 6.4	0.004	68.6 ± 6.0	68.6 ± 6.0	0.000
****Baseline PSA*** – mean ± SDev	6.01 ± 2.0	5.95 ± 2.4	0.067	6.01 ± 2.0	5.87 ± 2.4	0.085	6.12 ± 2.0	6.00 ± 2.4	0.053
***Gleason Total** – n(%)									
2-5	13(6.6)	7(7.1)	0.020	13(6.9)	7(7.5)	0.021	14(7.0)	7(7.0)	0.000
6	183(93.4)	91(92.9)		175(93.1)	87(92.6)		186(93.0)	93(93.0)	
****T Stage*** – n(%)									
T1	116(59.2)	58(59.2)	0.000	113(60.1)	55(58.5)	0.033	119(59.5)	59(59.0)	0.010
T2	80(40.8)	40(40.8)		75(39.9)	39(41.5)		81(40.5)	41(41.0)	
****RT Start Year*** – n(%)									
1999	16(8.2)	8(8.2)	0.000	15(8.0)	7(7.5)	0.020	17(8.5)	8(8.0)	0.018
2000	30(15.3)	18(18.4)	0.082	26(13.8)	17(18.1)	**0.116**	30(15.0)	18(18.0)	0.081
2001	6(3.1)	5(5.1)	**0.103**	6(3.2)	5(5.3)	**0.106**	6(3.0)	5(5.0)	**0.102**
2002	50(25.5)	26(26.5)	0.023	47(25.0)	24(25.5)	0.012	53(26.5)	26(26.0)	0.011
2003	55(28.1)	24(24.5)	0.081	55(29.3)	24(25.5)	0.084	55(27.5)	26(26.0)	0.033
2004	19(9.7)	7(7.1)	0.092	19(10.1)	7(7.5)	0.094	19(9.5)	7(7.0)	0.091
2005	11(5.6)	6(6.1)	0.023	11(5.9)	6(6.4)	0.022	11(5.5)	6(6.0)	0.021
2006	9(4.6)	4(4.1)	0.025	9(4.8)	4(4.3)	0026	9(4.5)	4(4.0)	0.025

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**

Grey Box = Variable with S.D > 0.10.

Table 9: Baseline characteristics of variables used in low-risk propensity score match (pre-match n=1820) [1:3 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 3 LDR : 1 EBRT **Total N = 340**			**Caliper:** 0.025 **Ratio:** 3 LDR : 1 EBRT **Total N = 332**			**Caliper:** 0.1 **Ratio:** 3 LDR : 1 EBRT **Total N = 376**		
VARIABLE	**LDR n = 255**	**EBRT n = 85**	***S.D.***	**LDR n = 249**	**EBRT n = 83**	***S.D.***	**LDR n = 282**	**EBRT n = 94**	***S.D.***
****Age*** – mean ± SDev	67.3 ± 5.6	67.3 ± 6.0	0.007	67.2 ± 5.7	67.1 ± 6.0	0.007	67.8 ± 5.6	68.1 ± 6.2	0.051
****Baseline PSA*** – mean ± SDev	6.02 ± 2.0	5.86 ± 2.4	0.086	6.03 ± 2.1	5.86 ± 2.4	0.079	6.11 ± 2.0	5.95 ± 2.4	0.074
***Gleason Total** – n(%)									
2-5	15(5.9)	6(7.1)	0.048	15(6.0)	6(7.2)	0.049	17(6.0)	6(6.4)	0.015
6	240(94.1)	79(92.9)		234(94.0)	77(92.8)		265(94.0)	88(93.6)	
****T Stage*** – n(%)									
T1	151(59.2)	52(61.2)	0.040	148(59.4)	52(62.7)	0.066	112(39.7)	38(40.4)	0.014
T2	104(40.8)	33(38.8)		101(40.6)	31(37.4)		170(60.3)	56(59.6)	
****RT Start Year*** – n(%)									
1999	17(6.7)	6(7.1)	0.016	16(6.4)	7(8.4)	0.077	21(7.5)	6(6.4)	0.042
2000	30(11.8)	14(16.5)	**0.136**	30(12.1)	13(15.7)	**0.104**	38(13.5)	16(17.0)	**0.101**
2001	12(4.7)	5(5.9)	0.053	12(4.8)	5(6.0)	0.053	12(4.3)	5(5.3)	0.050
2002	66(25.9)	21(24.7)	0.027	60(24.1)	19(22.9)	0.028	76(27.0)	24(25.5)	0.032
2003	76(29.8)	22(25.9)	0.088	77(30.9)	22(26.5)	0.098	81(28.7)	26(27.7)	0.024
2004	26(10.2)	7(8.2)	0.068	26(10.4)	7(8.4)	0.069	26(9.2)	7(7.5)	0.064
2005	15(5.9)	6(7.1)	0.047	15(6.0)	6(7.2)	0.049	15(5.3)	6(6.4)	0.045
2006	13(5.1)	4(4.7)	0.018	13(5.2)	4(4.8)	0.018	13(4.6)	4(4.3)	0.017

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**

Grey Box = Variable with S.D > 0.10.

Table 10: Baseline characteristics of variables used in low-risk propensity score match (pre-match n=1820) [1:4 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 4 LDR : 1 EBRT **Total N = 400**			**Caliper:** 0.025 **Ratio:** 4 LDR : 1 EBRT **Total N = 395**			**Caliper:** 0.1 **Ratio:** 4 LDR : 1 EBRT **Total N = 425**		
VARIABLE	**LDR n = 320**	**EBRT n = 80**	***S.D.***	**LDR n = 316**	**EBRT n = 79**	***S.D.***	**LDR n = 340**	**EBRT n = 85**	***S.D.***
****Age*** – mean ± SDev	66.9 ± 5.4	66.9 ± 5.9	0.012	66.9 ± 5.4	66.8 ± 5.9	0.022	67.3 ± 5.4	67.3 ± 6.0	0.009
****Baseline PSA*** – mean ± SDev	5.89 ± 2.1	5.86 ± 2.4	0.013	5.87 ± 2.1	5.84 ± 2.5	0.011	5.89 ± 2.1	5.84 ± 2.4	0.021
***Gleason Total** – n(%)									
2-5	19(5.9)	6(7.5)	0.062	19(6.0)	6(7.6)	0.063	20(5.9)	6(7.1)	0.048
6	301(94.1)	74(92.5)		297(94.0)	73(92.4)		320(94.1)	79(92.9)	
****T Stage*** – n(%)									
T1	185(57.8)	49(61.3)	0.070	181(57.3)	48(60.8)	0.071	196(57.7)	51(60.0)	0.048
T2	135(42.2)	31(38.8)		135(42.7)	31(39.2)		144(42.4)	34(40.0)	
****RT Start Year*** – n(%)									
1999	19(5.9)	6(7.5)	0.062	18(5.7)	6(7.6)	0.076	22(6.5)	6(7.1)	0.023
2000	42(13.1)	12(15.0)	0.054	41(13.0)	12(15.2)	0.064	48(14.1)	16(18.8)	**0.127**
2001	20(6.3)	5(6.3)	0.000	20(6.3)	5(6.3)	0.000	20(5.9)	5(5.9)	0.000
2002	77(24.1)	18(22.5)	0.037	75(23.7)	18(22.8)	0.023	79(23.2)	19(22.4)	0.021
2003	94(29.4)	22(27.5)	0.042	94(29.8)	21(26.5)	0.070	103(30.3)	22(25.9)	0.098
2004	31(9.7)	7(8.8)	0.032	31(9.8)	7(8.9)	0.033	31(9.1)	7(8.2)	0.031
2005	19(5.9)	6(7.5)	0.062	19(6.0)	6(7.6)	0.062	19(5.6)	6(7.1)	0.060
2006	18(5.6)	4(5.0)	0.029	18(5.7)	4(5.1)	0.028	18(5.3)	4(4.7)	0.027

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**

Grey Box = Variable with S.D > 0.10.

Selection of the Final Match for Analysis in Intermediate-risk LDR-BT vs. EBRT Cohort:

A summary of the sample sizes created using various matching criteria for the intermediate-risk LDR-BT vs. EBRT cohort is shown in Table 11. One-to-one matches in the LDR-BT vs. EBRT cohort using all original caliper widths including our tightest calipers of 0.2 of a standard deviation of the logit of the propensity score as well as a width of 0.025 of a propensity score were unable to balance the variable T-stage to within a standardized difference of 0.10. Two-to-one (EBRT:LDR-BT) matches were also unable to bring balance to T-stage, or balance the variables of baseline PSA or Gleason total. However, an appropriate match was found when a 1:1 match with a tighter caliper of 0.01 of a propensity score was used (n=254). This match was chosen for final analysis in the intermediate-risk LDR-BT vs. EBRT cohort. Tables 12 and 13 give examples of the balance produced using different caliper widths in the intermediate-risk LDR-BT vs. EBRT matches.

Table 11: Sample size based on propensity score matching in intermediate-risk LDR-BT vs. EBRT cohort (pre-match n=496).

Caliper	**Ratio (LDR:EBRT)**	**Total N**
0.01	1:1	254
0.025	1:1	260
0.025	1:2	207
0.05	1:1	264
0.05	1:2	216
0.10	1:1	278
0.10	1:2	225
0.2*1SDevLogit	1:1	268
0.2*1SDevLogit	1:2	219

*Abbreviations***:** EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; SDev = standard deviation

Table 12: Baseline characteristics of variables used in intermediate-risk LDR-BT vs. EBRT propensity score match (pre-match n=496) [1:1 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 1 LDR : 1 EBRT **Total N = 268**			**Caliper:** 0.025 **Ratio:** 1 LDR : 1 EBRT **Total N = 260**			**Caliper:** 0.1 **Ratio:** 1 LDR : 1 EBRT **Total N = 278**		
VARIABLE	**LDR n = 134**	**EBRT n = 134**	***S.D.***	**LDR n = 130**	**EBRT n = 130**	***S.D.***	**LDR n = 139**	**EBRT n = 139**	***S.D.***
***Age** – mean ± SDev	68.8 ± 6.4	68.5 ± 6.1	0.050	68.9 ± 6.4	68.5 ± 6.1	0.060	68.8 ± 6.3	68.6 ± 6.1	0.037
***Baseline PSA** – mean ± SDev	7.77 ± 2.9	7.89 ± 3.9	0.035	7.79 ± 3.0	7.78 ± 3.8	0.004	7.66 ± 3.0	7.82 ± 3.8	0.047
***Gleason Total** – n(%)									
6	34(25.4)	32(23.9)	0.035	32(24.6)	29(22.3)	0.055	37(26.6)	33(23.7)	0.066
7	100(74.6)	102(76.1)		98(75.4)	101(77.7)		102(73.4)	106(76.3)	
***T Stage** – n(%)									
Any T1	58(43.3)	58(43.3)	0.000	56(43.1)	55(42.3)	0.016	60(43.2)	60(43.2)	0.000
Low T2	57(42.5)	64(47.8)	**0.105**	56(43.1)	63(48.5)	**0.108**	58(41.7)	67(48.2)	**0.130**
High T2	19(14.2)	12(9.0)	**0.164**	18(13.9)	12(9.2)	**0.149**	21(15.1)	12(8.6)	**0.201**

*Abbreviations***:** EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**
Grey Box = Variable with S.D > 0.10.

Table 13: Baseline characteristics of variables used in intermediate-risk LDR-BT vs. EBRT propensity score match (pre-match n=496) [Exploratory Matches].

	Caliper: 0.01 **Ratio:** 1 LDR : 1 EBRT **Total N = 254**			**Caliper:** 0.2*1SDevLogit **Ratio:** 1 LDR : 2 EBRT **Total N = 219**			**Caliper:** 0.025 **Ratio:** 1 LDR : 2 EBRT **Total N = 207**		
VARIABLE	**LDR n = 127**	**EBRT n = 127**	***S.D.***	**LDR n = 73**	**EBRT n = 146**	***S.D.***	**LDR n = 69**	**EBRT n = 138**	***S.D.***
***Age** – mean ± SDev	68.7 ± 6.6	68.5 ± 6.1	0.029	71.4 ± 5.7	71.9 ± 4.1	0.093	71.4 ± 5.8	71.9 ± 4.3	**0.107**
***Baseline PSA** – mean ± SDev	7.87 ± 3.0	7.70 ± 3.8	0.050	7.92 ± 2.8	8.64 ± 3.9	**0.210**	7.87 ± 2.8	8.77 ± 3.8	**0.270**
***Gleason Total** – n(%)									
6	30(23.6)	27(21.3)	0.057	4(5.5)	25(17.1)	**0.374**	44(63.8)	95(68.8)	**0.495**
7	97(76.4)	100(78.7)		69(94.5)	121(82.8)		25(36.2)	43(31.2)	
***T Stage** – n(%)									
Any T1	56(44.1)	53(41.7)	0.048	27(37.0)	46(31.5)	**0.116**	25(36.2)	43(31.2)	**0.108**
Low T2	56(44.1)	62(48.8)	0.095	39(53.4)	83(56.9)	0.070	37(53.6)	81(58.7)	**0.102**
High T2	15(11.8)	12(9.5)	0.077	7(9.6)	17(11.6)	0.067	7(10.1)	14(10.1)	0.000

*Abbreviations***:** EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**
Grey Box = Variable with S.D > 0.10.

Selection of Final Match for Intermediate-risk HDR-BT+EBRT vs. EBRT Cohort:

A summary of the sample sizes created by the various matching criteria for the intermediate-risk HDR-BT+EBRT vs. EBRT cohort is displayed in Table 14. Matches in the intermediate-risk HDR-BT+EBRT vs. EBRT cohort using a 1:1 ratio and caliper widths of 0.2 of a standard deviation of the logit of the propensity score and widths of 0.025 and 0.1 on the propensity score scale were able to balance all variables used in the match (standardized difference <0.10). Out of these three 1:1 matches, the match using the 0.2 of a standard deviation of the logit of the propensity score was determined to be the closest match as it had the lowest standardized difference values in all but one variable (Gleason total). This match (n=388) was chosen for the HDR-BT+EBRT vs. EBRT final analysis. Exploratory matches using 1:2 ratios did not produce acceptable matches. Tables 15 and 16 give examples of the balance produced using different caliper widths in the intermediate-risk HDR-BT+EBRT vs. EBRT matches.

Table 14: Sample size based on propensity score matching in intermediate-risk HDR-BT+EBRT vs. EBRT cohort (pre-match n=655).

Caliper	**Ratio (HDR:EBRT)**	**Total N**
0.025	1:1	382
0.025	2:1	258
0.05	1:1	390
0.05	2:1	282
0.10	1:1	406
0.10	2:1	291
0.2*1SDevLogit	1:1	388
0.2*1SDevLogit	2:1	273

*Abbreviations***:** EBRT = external beam radiation therapy; HDR = high dose rate brachytherapy with adjuvant external beam radiation; SDev = standard deviation

Table 15: Baseline characteristics of variables used in intermediate-risk HDR-BT+EBRT vs. EBRT propensity score match (pre-match n=655) [1:1 Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 1 HDR : 1 EBRT **Total N = 388**			**Caliper:** 0.025 **Ratio:** 1 HDR : 1 EBRT **Total N = 382**			**Caliper:** 0.1 **Ratio:** 1 HDR : 1 EBRT **Total N = 406**		
VARIABLE	**HDR n = 194**	**EBRT n = 194**	***S.D.***	**HDR n = 191**	**EBRT n = 191**	***S.D.***	**HDR n = 203**	**EBRT n = 203**	***S.D.***
****Age*** – mean ± SDev	69.2 ± 5.0	69.2 ± 5.5	0.006	69.0 ± 5.3	68.9 ± 5.6	0.026	69.1 ± 5.3	69.2 ± 5.7	0.020
****Baseline PSA*** – mean ± SDev	8.92 ± 4.0	8.62 ± 4.1	0.074	8.91 ± 4.0	8.60 ± 4.2	0.074	8.95 ± 4.0	8.61 ± 4.1	0.084
***Gleason Total** – n(%)									
6	27(13.9)	30(15.5)	0.044	27(14.1)	29(15.2)	0.030	28(13.8)	32(15.8)	0.056
7	167(86.1)	164(84.5)		164(85.9)	162(84.8)		175(86.2)	171(84.2)	
****T Stage*** – n(%)									
Any T1	92(47.4)	92(47.4)	0.000	90(47.1)	88(46.1)	0.021	98(48.3)	95(46.8)	0.030
Low T2	90(46.4)	89(45.9)	0.010	89(46.6)	90(47.1)	0.011	92(45.3)	93(45.8)	0.010
High T2	12(6.2)	13(6.7)	0.021	12(6.3)	13(6.8)	0.021	13(6.4)	15(7.4)	0.039

*Abbreviations***:** EBRT = external beam radiation therapy; HDR= high dose rate brachytherapy with adjuvant external beam radiation therapy; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**
Grey Box = Variable with S.D > 0.10.

Table 16: Baseline characteristics of variables used in intermediate-risk HDR-BT+EBRT vs. EBRT propensity score match (pre-match n=655) [Exploratory Matches].

	Caliper: 0.2*1SDevLogit **Ratio:** 2 HDR: 1 EBRT **Total N = 273**			**Caliper:** 0.025 **Ratio:** 2 HDR : 1 EBRT **Total N = 258**			**Caliper:** 0.2*1SDevLogit **Ratio:** 1 HDR: 2 EBRT **Total N = 141**		
VARIABLE	**HDR n = 182**	**EBRT n = 91**	***S.D.***	**HDR n = 172**	**EBRT n = 86**	***S.D.***	**HDR n =47**	**EBRT n = 94**	***S.D.***
****Age*** – mean ± SDev	65.6 ± 4.9	65.3 ± 4.8	0.067	65.4 ± 5.2	64.8 ± 5.1	**0.114**	73.0 ± 3.9	73.5 ± 3.0	**0.146**
****Baseline PSA*** – mean ± SDev	8.33 ± 3.8	8.82 ± 4.1	**0.125**	8.38 ± 3.8	8.83 ± 4.2	**0.114**	9.76 ± 4.3	8.73 ± 4.5	**0.234**
***Gleason Total** – n(%)									
6	14(7.7)	9(9.9)	0.078	12(7.0)	9(10.5)	**0.124**	16(34.0)	23(24.5)	**0.212**
7	168(92.3)	82(90.1)		160(93.0)	77(89.5)		31(66.0)	71(75.5)	
****T Stage*** – n(%)									
Any T1	126(69.2)	59(64.8)	0.094	124(72.1)	57(66.3)	**0.126**	9(19.2)	16(17.0)	0.055
Low T2	52(28.6)	29(31.9)	0.072	46(26.7)	27(31.4)	**0.103**	28(59.6)	60(63.8)	0.088
High T2	4(2.2)	3(3.3)	0.078	2(1.2)	2(2.3)	0.089	10(21.3)	18(19.2)	0.053

Abbreviations: EBRT = external beam radiation therapy; HDR = high dose rate brachytherapy with adjuvant external beam radiation therapy; PSA = prostate specific antigen; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures.**
Grey Box = Variable with S.D > 0.10.

5.6.4 Estimating Treatment Effects (Statistical Analysis)

Once final matches were obtained in each of the compared cohorts, Kaplan-Meier survival curves stratified by treatment group (EBRT vs. BT option) were generated for OS and bFFS. The Kaplan-Meier curves were created for both pre-matches and post-matches. The log-rank test was used to assess whether a significant difference in OS or bFFS existed in the pre-match cohorts. Due to the lack of independence in the PS matched cohorts, Cox proportional hazard regression adjusted for clustering (stratified by matched pairs) was used to generate the reported p-value, instead of the log-rank test. Both visual tests and global tests for violation of the proportionality assumption in the Cox regression models were performed on each of the final PS matched cohorts. Visual testing for violation of proportionality included Log-Minus-Log survival plots and Schoenfeld residual plots, while global testing included the Suprmum-Kolmogorov test (based on 1000 replications) and the Schoenfeld test. If there was indication of a violation of the proportionality assumption in either the visual tests (ie. a lack of parallelism on the Log-Minus-Log survival plot or bending of the Schoenfeld residual plot), or global tests (ie. significance in either the Suprmum-Kolmogorov or Schoenfeld test), then an extended Cox model was explored by adding a time dependent covariate [Radiation type*Log(Survival)]. If the addition of the time dependent covariate was significant ($p<0.05$) to the Cox model, then the extended Cox regression p-value using the likelihood ratio test (with 2 degrees of freedom under the null) was reported. If the addition of the time dependent variable was not significant, the p-value from the original Cox regression adjusted for clustering was reported. In the event that results from model testing were inconclusive, we compared results from both adjusted and extended Cox models in sensitivity analysis. If results from sensitivity analysis using both models were comparable, then the extended Cox regression p-value was reported. The survival difference in all PS matches was tested against the null hypothesis of no difference between groups at the 5% level of significance. The statistical methods used in this study follow current consensus for appropriate propensity score matched survival analysis (Austin, 2007, Kleinbaum 2012). The SAS code used to create the Kaplan-Meier curves, the adjusted and extended Cox-models, the model assumption tests, and the significance

tests are shown in Appendix XI. The visual plots and results from the global tests are shown in Appendix XII. The extended Cox-modeling shown in Appendix XI was achieved using a previously described SAS code (Kleinbaum 2012).

5.7 Power and Sample Size Considerations

The sample sizes for each comparison was determined through the PS match selection process and was not considered prior to matching. The statistical power to detect survival differences in each cohort was considered once the best matches with adequate covariate balance were chosen. A range in the statistical power for each match was calculated using SAS 9.3 statistical software. For all power calculations, sample size was fixed and an alpha of 0.05 was used. In the low-risk comparison, the 4:1 (LDR-BT:EBRT) match was accounted for in the power calculation. Based on the hypothesis of this study, that in all comparisons the BT treatment options were expected to be superior to EBRT, ranges in statistical power for each cohort assumed BT would have a lower hazard than EBRT. Statistical power was calculated using 5-year and ≥7-year bFFS actuarial percentages for prostate cancer patients treated with EBRT found in the literature. Low-risk and intermediate-risk, 5-year bFFS percentages ranged from 84% (Goldner 2012) to 95% (Pe 2009) and 74% (Wong 2009) to 86% (Vassil 2010), respectively. The 7- to 10-year bFFS percentages following EBRT ranged from 75% (Pickles 2010) to 89% (Zelefsky 2011) for low-risk and 75% (Klein 2009) to 81% (Kupelian 2004) for intermediate-risk patients. The power calculations used in this study were based on non-matched designs, thus the reported power may actually be under estimating the true power. A minimum hazard ratio of at least 0.40 in favor of LDR-BT was required for statistical power ≥ 0.8 in the low-risk LDR-BT vs. EBRT comparison and a hazard ratio of 0.35 in favor of LDR-BT in the intermediate-risk comparison. A hazard ratio of at least 0.45 in favor of HDR-BT+EBRT was required in the HDR-BT+EBRT vs. EBRT comparison. Table 17 shows the estimated range in hazard ratios required for statistical power of at least 0.8 in all comparisons. The SAS code used for the power calculations is shown in Appendix XIII.

Table 17: Hazard ratio required for statistical power of 0.8 using literature EBRT bFFS percentages.

Comparison	Sample size	5-year EBRT bFFS%	7-to-10 year EBRT bFFS%	HR range for power ≥ 0.8
Low-risk: LDR-BT vs. EBRT	*400	95% - 84%	89% - 75%	0.25 - 0.40
Intermediate-risk: LDR-BT vs. EBRT	254	86% - 74%	81% - 75%	0.30 - 0.35
Intermediate-risk: HDR-BT+EBRT vs. EBRT	388	86% - 74%	81% - 75%	0.40 - 0.45

Abbreviations: EBRT = external beam radiation therapy; HDR-BT+EBRT = high dose rate brachytherapy with adjuvant external beam radiation therapy; HR = hazard ratio; LDR-BT = low dose rate brachytherapy

*4:1 (LDR-BT:EBRT) match

6.0 Results

6.1 Descriptive Statistics of Propensity Score Matches

PS matching brought adequate balance to all variables used in each of the PS models. The baseline characteristics of age, PSA, Gleason total and T-stage had standardized differences <0.10 in all matches as well as RT start year in the low-risk match. However, PS matching was unable to bring balance to many of the variables not included in the PS models. In the low-risk, 4:1 (LDR-BT:EBRT) PS match (n=400), the variables of 'percent positive cores' and 'treatment centre' were not balanced (standardized difference > 0.1). Similarly, in the intermediate-risk matches, the variables of percent positive cores, treatment year, and treatment centre were unbalanced. In intermediate-risk matches, Gleason pattern 4+3 vs. 3+4 was balanced in the 1:1 HDR-BT vs. EBRT match (n=388) but not in the 1:1 LDR-BT vs. EBRT match (n=254).

Median follow-up time was varied in the PS matched cohorts. For the low-risk match, patients that received LDR-BT had a median follow-up of 82 months, while EBRT patients had a median follow-up of 87 months. In the intermediate-risk, HDR-BT+EBRT vs. EBRT cohort, HDR-BT+EBRT patients had a median follow-up of 32 months, and EBRT patients had a median follow-up of 81.5 months. Finally, in the intermediate-risk LDR-BT vs. EBRT match, LDR-BT patients had a median follow-up of 49 months, while EBRT patients had a median follow-up of 83 months. The descriptive statistics with standardized differences for all patients (low-risk and intermediate-risk) prior to matching as well as following PS matching are shown in summary Tables 18-20.

Table 18: Baseline characteristics for all low-risk patients (n=1820) and patients matched on propensity scores (n=400), stratified by treatment type (LDR-BT vs. EBRT).

	All Patients N=1820				**Matched Patients N= 400** **Caliper:** 0.2*1SDevLogit **Ratio:** 4 LDR : 1 EBRT			
VARIABLE	**LDR + EBRT n = 1820**	**LDR n = 1716**	**EBRT n = 104**	***S.D.***	**LDR + EBRT n = 400**	**LDR n = 320**	**EBRT n = 80**	***S.D.***
***Age** – mean ± SDev, median, (min – max)	63.32 ± 7.07 63.00 (43.00 – 84.00)	62.97 ± 6.96 63.00 (43.00 – 83.00)	68.98 ± 6.59 70.00 (51.00 – 84.00)	0.886	66.93 ± 5.49 68.00 (51.00 – 80.00	66.94 ± 5.39 68.00 (51.00 – 79.00)	66.87 ± 5.91 67.00 (51.00 – 80.00)	0.012
***Baseline PSA** – mean ± SDev, median, (min – max)	5.44 ± 2.12 5.40 (0.26 – 10.00)	5.40 ± 2.10 5.34 (0.30 – 10.00)	6.06 ± 2.36 6.23 (0.26 – 10.00)	0.295	5.88 ± 2.14 5.90 (0.26 – 10.00)	5.89 ± 2.06 5.90 (0.50 – 9.80)	5.86 ± 2.44 5.92 (0.26 – 10.00)	0.013
***Gleason Total** – n(%)								
2-5	136 (7.5)	129 (7.5)	7 (6.7)	0.031	25 (6.3)	19 (5.9)	6 (7.5)	0.062
6	1684(92.5)	1587(92.5)	97 (93.3)		375 (93.7)	301 (94.1)	74 (92.5)	
***T Stage** – n(%)								
T1	1112(61.1)	1051(61.3)	61 (58.7)	0.053	234 (58.5)	185 (57.8)	49 (61.3)	0.070
T2	708 (38.9)	665 (38.8)	43 (41.4)		166 (41.5)	135 (42.2)	31 (38.8)	
***RT Start Year** – n(%)								
1999	67 (3.7)	59 (3.4)	8 (7.7)	0.186	25 (6.3)	19 (5.9)	6 (7.5)	0.062
2000	138 (7.6)	120 (7.0)	18 (17.3)	0.320	54 (13.5)	42 (13.1)	12 (15.0)	0.054
2001	197 (10.8)	192 (11.2)	5 (4.8)	0.237	25 (6.3)	20 (6.3)	5 (6.3)	0.000
2002	236 (13.0)	208 (12.1)	28 (26.9)	0.380	95 (23.8)	77 (24.1)	18 (22.5)	0.037
2003	312 (17.1)	284 (16.6)	28 (26.9)	0.254	116 (29.0)	94 (29.4)	22 (27.5)	0.042
2004	314 (17.3)	307 (17.9)	7 (6.7)	0.345	38 (9.5)	31 (9.7)	7 (8.8)	0.032
2005	275 (15.1)	269 (15.7)	6 (5.8)	0.324	25 (6.3)	19 (5.9)	6 (7.5)	0.062
2006	281 (15.4)	277 (16.1)	4 (3.9)	0.419	22 (5.5)	18 (5.6)	4 (5.0)	0.029
Percent Positive Cores – n(%)								
<50%	860 (80.1)	800 (81.1)	60 (69.0)	0.282	189 (76.5)	147 (80.3)	42 (65.6)	0.336
>50%	214 (19.9)	187 (19.0)	27 (31.0)		58 (23.5)	36 (19.7)	22 (34.4)	
[Missing]	[746]	[729]	[17]		[153]	[137]	[16]	
Treatment Centre – n(%)								
1	536 (29.5)	495 (28.9)	41 (39.4)	0.224	124 (31.0)	91 (28.4)	33 (41.3)	0.271
2	687 (37.8)	624 (36.4)	63 (60.6)	0.500	170 (42.5)	123 (38.4)	47 (58.8)	0.415
3	597 (32.8)	597 (34.8)	0 (0)	1.033	106 (26.5)	106 (33.1)	0 (0)	1.000

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; LDR+EBRT = total cohort of low dose rate brachytherapy and external beam patients; PSA = prostate specific antigen; RT = radiation therapy; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures (if NO asterisk(*) shown, then not used in propensity-score model).**

Table 19: Baseline characteristics for all patients (n=496) and patients matched on propensity scores (n=254), stratified by treatment type in intermediate-risk LDR-BT vs. EBRT comparison.

	All Patients N=496				**Matched Patients N = 254 Caliper:** 0.01 **Ratio:** 1 LDR : 1 EBRT			
VARIABLE	**LDR + EBRT n = 496**	**LDR n = 231**	**EBRT n = 265**	***S.D.***	**LDR + EBRT n = 254**	**LDR n = 127**	**EBRT n = 127**	***S.D.***
***Age** – mean ± SDev, median, (min – max)	68.31 ± 6.82 69.00 (45.00 – 83.00)	65.88 ± 7.24 67.00 (46.00 – 83.00)	70.42 ± 5.64 71.00 (45.00 – 82.00)	0.700	68.63 ± 6.33 69.00 (45.00 – 83.00)	68.72 ± 6.56 69.00 (46.00 – 83.00)	68.54 ± 6.12 69.00 (45.00 – 82.00)	0.029
***Baseline PSA** – mean ± SDev, median, (min – max)	8.24 ± 3.94 7.46 (0.46 – 19.97)	7.49 ± 3.39 7.00 (0.46 – 18.00)	8.89 ± 4.26 7.83 (1.13 – 19.97)	0.361	7.78 ± 3.40 7.12 (1.30 – 18.00)	7.87 ± 2.99 7.41 (1.30 – 18.00)	7.70 ± 3.77 6.80 (1.48 – 17.00)	0.050
***Gleason Total** – n(%)								
6	146 (29.4)	95 (41.1)	51 (19.3)	0.491	57 (22.4)	30 (23.6)	27 (21.3)	0.057
7	350 (70.6)	136 (58.9)	214 (80.8)		197 (77.6)	97 (76.4)	100(78.7)	
***T Stage** – n(%)								
Any T1	212 (42.7)	110 (47.6)	102 (38.5)	0.185	109 (42.9)	56 (44.1)	53 (41.7)	0.048
Low T2	211 (42.5)	79 (34.2)	132 (49.8)	0.320	118 (46.5)	56 (44.1)	62 (48.8)	0.095
High T2	73 (14.7)	42 (18.2)	31 (11.7)	0.183	27 (10.6)	15 (11.8)	12 (9.5)	0.077
Percent Positive Cores – n(%)								
<50%	240 (59.0)	119 (70.8)	121 (50.6)	0.423	140 (62.8)	77 (72.6)	63 (53.9)	0.398
>50%	167 (41.0)	49 (29.2)	118 (49.4)		83 (37.2)	29 (27.4)	54 (46.2)	
[Missing]	[89]	[63]	[26]		[31]	[21]	[10]	
Gleason Pattern – n(%)								
3+3	110 (24.8)	59 (33.2)	51 (19.3)	0.320	47 (20.0)	20 (18.5)	27 (21.3)	0.069
3+4	251 (56.7)	100 (56.2)	151 {57.0)	0.016	145 (61.7)	73 (67.6)	72 (56.7)	0.226
4+3	82 (18.5)	19 (10.7)	63 (23.8)	0.352	43 (18.3)	15 (13.9)	28 (22.1)	0.214
[Missing]	[53]	[53]	[0]		[19]	[19]	[0]	
RT Start Year - n (%)								
1996	1 (0.2)	1 (0.4)	0 (0)	0.093	0 (0)	0 (0)	0 (0)	0.000
1997	2 (0.4)	2 (0.9)	0 (0)	0.132	0 (0)	0 (0)	0 (0)	0.000
1998	0 (0)	0 (0)	0 (0)	0.000	0 (0)	0 (0)	0 (0)	0.000
1999	16 (3.2)	11 (4.8)	5 (1.9)	0.161	3 (1.2)	2 (1.6)	1 (0.8)	0.073
2000	23 (4.6)	6 (2.6)	17 (6.4)	0.185	12 (4.7)	2 (1.6)	10 (7.9)	0.300
2001	47 (9.5)	13 (5.6)	34 (12.8)	0.251	23 (9.1)	3 (2.4)	20 (15.8)	0.480
2002	94 (19.0)	13 (5.6)	81 (30.6)	0.685	41 (16.1)	6 (4.7)	35 (27.6)	0.653
2003	80 (16.1)	16 (6.9)	64 (24.2)	0.489	35 (13.8)	5 (3.9)	30 (23.6)	0.596
2004	44 (8.9)	19 (8.2)	25 (9.4)	0.043	24 (9.5)	12 (9.5)	12 (9.5)	0.000
2005	56 (11.3)	33 (14.3)	23 (8.7)	0.177	33 (13.0)	23 (18.1)	10 (7.9)	0.308
2006	72 (14.5)	56 (24.2)	16 (6.0)	0.525	59 (23.2)	50 (39.4)	9 (7.1)	0.827
2007	15 (3.0)	15 (6.5)	0 (0)	0.373	5 (2.0)	5 (3.9)	0 (0)	0.286
2008	20 (4.0)	20 (8.7)	0 (0)	0.435	11 (4.3)	11 (8.7)	0 (0)	0.436

2009	15 (3.0)	15 (6.5)	0 (0)	0.373	3 (1.2)	3 (2.4)	0 (0)	0.220
2010	11 (2.2)	11 (4.8)	0 (0)	0.316	5 (2.0)	5 (3.9)	0 (0)	0.286
Treatment Centre – n(%)								
1	130 (26.2)	93 (40.3)	37 (14.0)	0.619	83 (32.7)	65 (51.2)	18 (14.2)	0.859
2	313 (63.1)	85 (36.8)	228 (86.0)	1.173	152 (59.8)	43 (33.9)	109 (85.8)	1.250
3	53 (10.7)	53 (22.9)	0 (0)	0.777	19 (7.5)	19 (15.0)	0 (0)	0.593

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; LDR+EBRT = total cohort of low dose rate brachytherapy and external beam patients; PSA = prostate specific antigen; RT = radiation therapy; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures (if NO asterisk(*) shown, then not used in propensity-score model).**

Table 20: Baseline characteristics for all patients (n=655) and patients matched on propensity scores (n=388), stratified by treatment type in intermediate-risk HDR-BT+EBRT vs. EBRT comparison.

	All Patients N=655				**Matched Patients N=388** **Caliper:** 0.2*1SDevLogit **Ratio:** 1 HDR : 1 EBRT			
VARIABLE	**Total Sample n = 655**	**HDR+ EBRT n = 390**	**EBRT n = 265**	***S.D.***	**Total Sample n = 388**	**HDR+ EBRT n = 194**	**EBRT n = 194**	***S.D.***
****Age*** – mean ± SDev, median, (min – max)	67.59 ± 6.62 69.00 (45.00 – 82.00)	65.66 ± 6.55 66.00 (47.00 – 81.00)	70.42 ± 5.64 71.00 (45.00 – 82.00)	0.779	69.19 ± 5.25 70.00 (55.00 – 82.00)	69.20 ± 5.03 70.00 (57.00 – 81.00)	69.17 ± 5.48 70.00 (55.00 – 82.00)	0.006
****Baseline PSA*** – mean ± SDev, median, (min – max)	8.51 ± 4.06 7.41 (0.37 – 19.97)	8.26 ± 3.91 7.23 (0.37 – 19.96)	8.89 ± 4.26 7.83 (1.13 – 19.97)	0.155	8.77 ± 4.06 7.79 (1.00 – 19.76)	8.92 ± 4.01 8.00 (1.00 – 19.76)	8.62 ± 4.13 7.60 (1.48 – 19.60)	0.074
***Gleason Total** – n(%) 6 7	 93 (14.2) 562 (85.8)	 42 (10.8) 348 (89.2)	 51 (19.3) 214 (80.8)	 0.239	 57 (14.7) 331 (85.3)	 27 (13.9) 167 (86.1)	 30 (15.5) 164 (84.5)	 0.044
****T Stage*** – n(%) Any T1 Low T2 High T2	 344 (52.5) 263 (40.2) 48 (7.3)	 242 (62.1) 131 (33.6) 17 (4.4)	 102 (38.5) 132 (49.8) 31 (11.7)	 0.485 0.334 0.273	 184 (47.4) 179 (46.1) 25 (6.4)	 92 (47.4) 90 (46.4) 12 (6.2)	 92 (47.4) 89 (45.9) 13 (6.7)	 0.000 0.010 0.021
Percent Positive Cores – n(%) <50% >50% [Missing]	 173 (53.9) 148 (46.1) [334]	 52 (63.4) 30 (36.6) [308]	 121 (50.6) 118 (49.4) [26]	 0.260	 121 (54.5) 101 (45.5) [166]	 30 (62.5) 18 (37.5) [146]	 91 (52.3) 83 (47.7) [20]	 0.207
Gleason Pattern – n(%) 3+3 3+4 4+3 [Missing]	 65 (18.5) 202 (57.6) 84 (23.9) [304]	 14 [16.3) 51 (59.3) 21 (24.4) [304]	 51 (19.3) 151 (57.0) 63 (23.8) [0]	 0.078 0.047 0.015	 39 (15.9) 145 (59.2) 61 (24.9) [143]	 9 (17.7) 29 (56.9) 13 (25.5) [143]	 30 (15.5) 116 (59.8) 48 (24.7) [0]	 0.059 0.060 0.017
RT Start Year – n(%) 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010	 5 (0.8) 17 (2.6) 44 (6.7) 102 (15.6) 84 (12.8) 54 (8.2) 50 (7.6) 47 (7.2) 55 (8.4) 98 (15.0) 73 (11.2) 26 (4.0)	 0 (0) 0 (0) 10 (2.6) 21 (5.4) 20 (5.1) 29 (7.4) 27 (6.9) 31 (8.0) 55 (14.1) 98 (25.1) 73 (18.7) 26 (6.7)	 5 (1.9) 17 (6.4) 34 (12.8) 81 (30.6) 64 (24.2) 25 (9.4) 23 (8.7) 16 (6.0) 0 (0) 0 (0) 0 (0) 0 (0)	 0.196 0.370 0.392 0.694 0.559 0.072 0.066 0.075 0.573 0.819 0.679 0.378	 4 (1.0) 15 (3.9) 31 (8.0) 74 (19.1) 50 (12.9) 36 (9.3) 35 (9.0) 28 (7.2) 25 (6.4) 50 (12.9) 28 (7.2) 12 (3.1)	 0 (0) 0 (0) 6 (3.1) 12 (6.2) 12 (6.2) 16 (8.3) 15 (7.7) 18 (9.3) 25 (12.9) 50 (25.8) 28 (14.4) 12 (6.2)	 4 (2.1) 15 (7.7) 25 (12.9) 62 (32.0) 38 (19.6) 20 (10.3) 20 (10.3) 10 (5.2) 0 (0) 0 (0) 0 (0) 0 (0)	 0.205 0.409 0.367 0.694 0.408 0.071 0.090 0.160 0.544 0.833 0.581 0.363

Treatment Centre – (n%)								
1	37 (5.7)	0 (0)	37 (14.0)	0.570	35 (9.0)	0 (0)	35 (18.0)	0.664
2	228 (34.8)	0 (0)	228 (86.0)	3.511	159 (41.0)	0 (0)	159 (82.0)	3.014
3	303 (46.3)	303 (77.7)	0 (0)	2.640	142 (36.6)	142 (73.2)	0 (0)	2.337
4	87 (13.3)	87 (22.3)	0 (0)	0.758	52 (13.4)	52 (26.8)	0 (0)	0.856

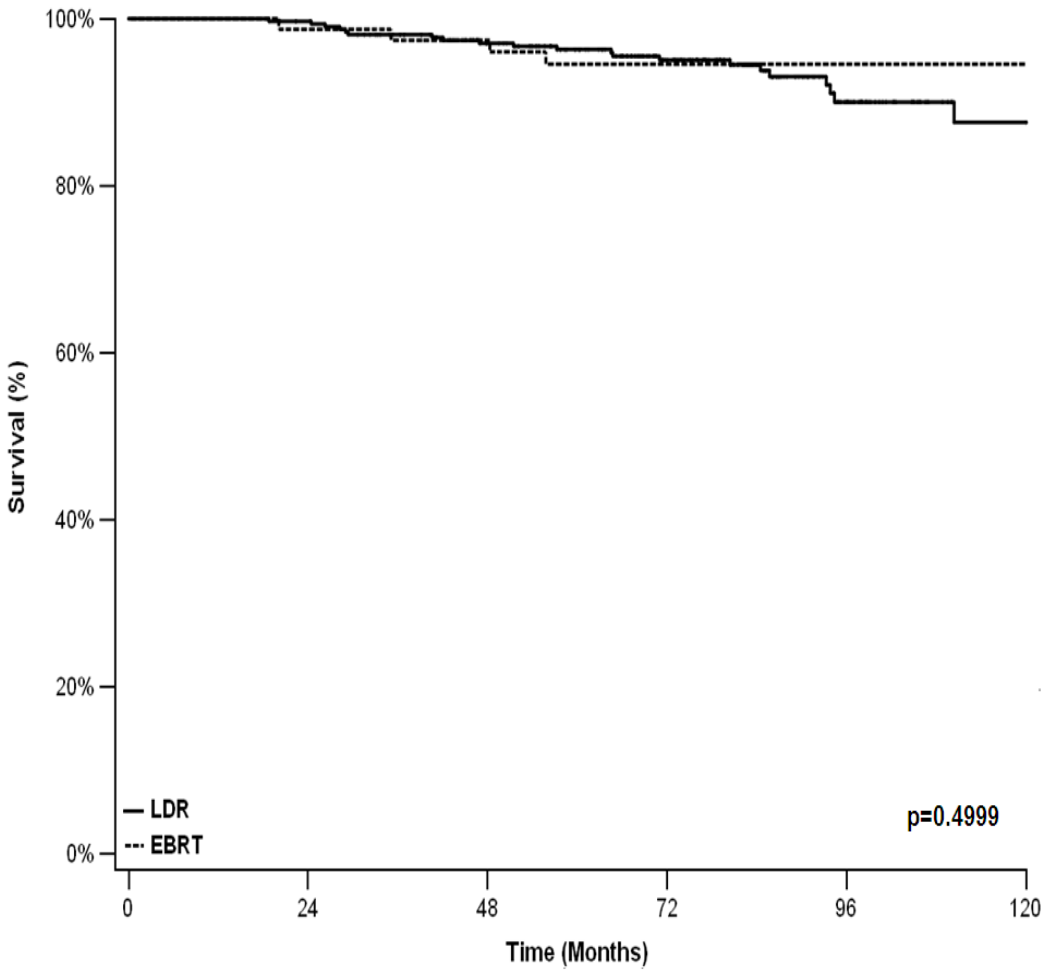
*Abbreviations***:** EBRT = external beam radiation therapy; HDR+EBRT = high dose rate brachytherapy with external beam radiation therapy; PSA = prostate specific antigen; RT = radiation therapy; S.D. = standardized difference; SDev = standard deviation

***Variable(s) used in propensity-score computation procedures (if NO asterisk(*) shown, then not used in propensity-score model).**

6.2 Survival Outcomes

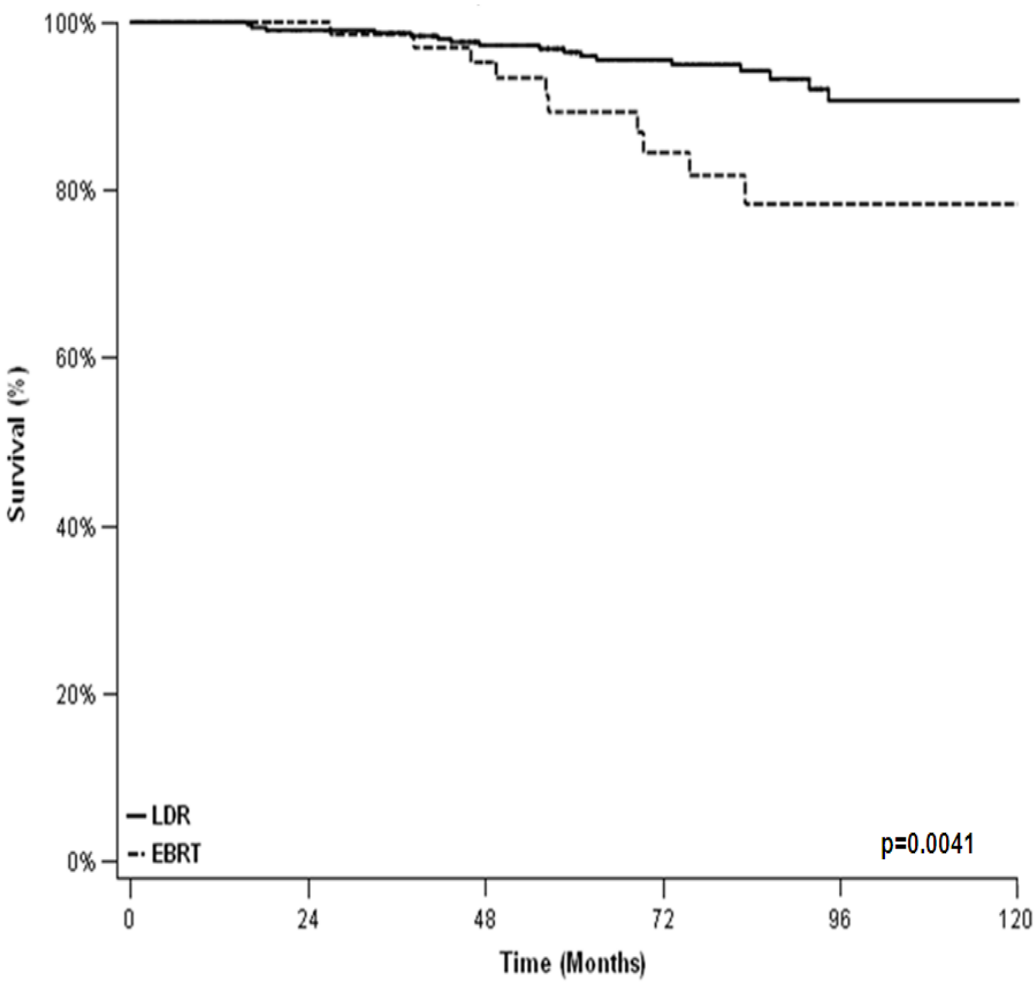
Low-Risk LDR-BT vs. EBRT Match:

Kaplan-Meier curves comparing both OS and bFFS for LDR-BT and EBRT in low-risk PS matched prostate cancer patients are shown in Figures 6 and 7. No significant difference was found comparing OS in the low-risk LDR-BT vs. EBRT match (hazard ratio = 1.41, 95% CI 0.52-3.86, p = 0.50). The 5-year and 10-year actuarial percentages for OS were 96% and 88% for LDR-BT patients and 95% and 95% for EBRT patients, respectively. However, LDR-BT was associated with a statistically significant improvement in bFFS when compared with EBRT (hazard ratio = 0.35, 95% CI 0.17-0.71, p=0.004). The 5-year and 10-year actuarial percentages for bFFS were 96% and 91% in the LDR-BT group and 89% and 78% in the EBRT group, respectively. In total, 17 (5.3%) LDR-BT patients and 10 (12.5%) EBRT patients experienced a biochemical failure, while 21 (6.6%) LDR-BT patients and 4 (5%) EBRT patients died.



Patients at Risk						
LDR	320	314	271	206	79	16
EBRT	80	77	70	52	26	5

Fig. 6. Overall survival for low-risk patients in LDR-BT vs. EBRT comparison group following propensity score match.

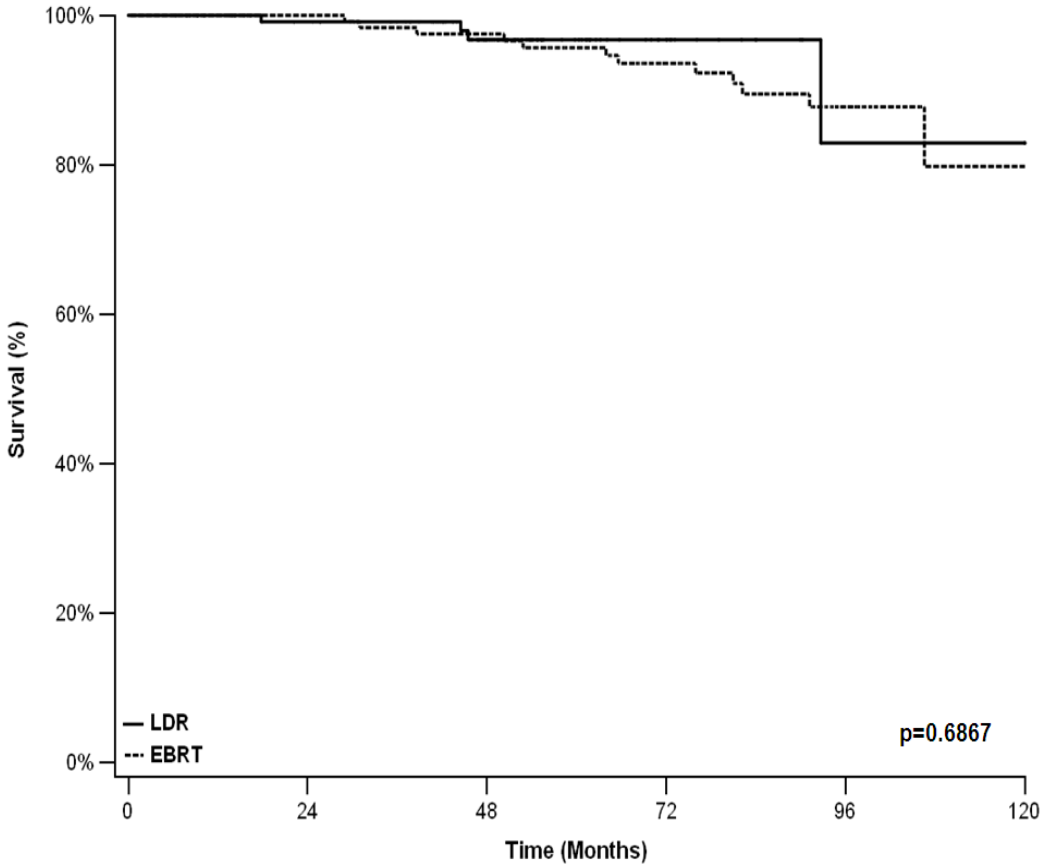


Patients at Risk						
LDR	320	305	251	173	59	7
EBRT	80	71	52	34	7	0

Fig. 7. Biochemical failure-free survival for low-risk patients in LDR-BT vs. EBRT comparison group following propensity score match.

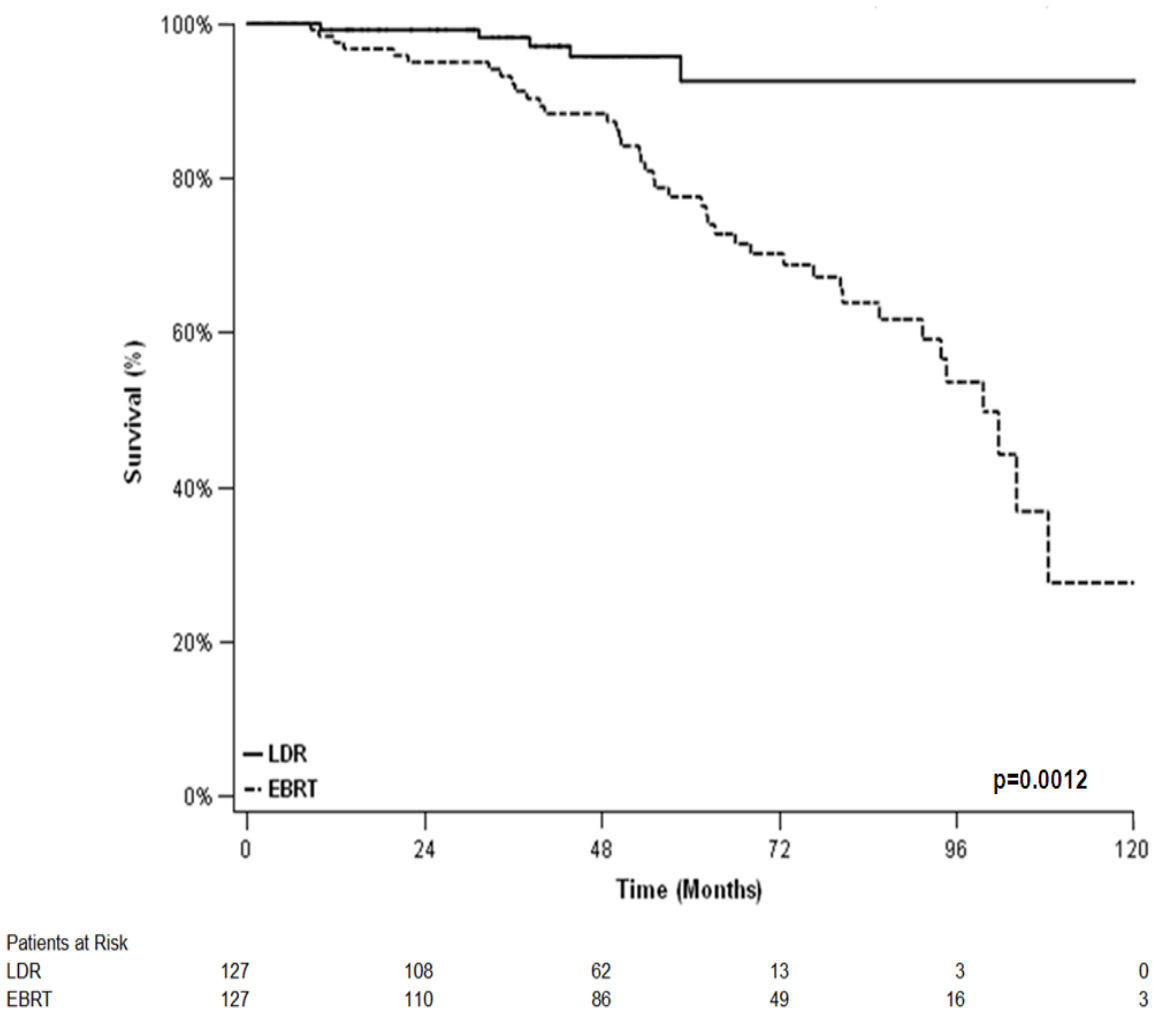
Intermediate-Risk LDR-BT vs. EBRT Match:

Kaplan-Meier curves comparing both OS and bFFS for LDR-BT and EBRT in intermediate-risk PS matched prostate cancer patients are shown in Figures 8 and 9. No significant difference was found comparing OS in the intermediate-risk LDR-BT vs. EBRT match (hazard ratio = 0.79, 95% CI 0.24-2.53, p = 0.69). The 5-year and 10-year actuarial percentages for OS were 97% and 83% for LDR-BT patient and 96% and 80% for EBRT patients, respectively. LDR-BT was associated with a statistically significant improvement in bFFS when compared with EBRT (hazard ratio = 0.22, 95% CI 0.09-0.50, p=0.001). The 5-year and 10-year actuarial percentages for bFFS were 93% and 93% in the LDR-BT group and 78% and 28% in the EBRT group, respectively. In total, 5 (3.9%) LDR-BT patients and 41 (32.3%) EBRT patients experienced a biochemical failure, while 4 (3.1%) LDR-BT patients and 12 (9.4%) EBRT patients died.



Patients at Risk						
LDR	127	112	69	19	5	2
EBRT	127	123	110	77	32	6

Fig. 8. Overall survival for intermediate-risk patients in LDR-BT vs. EBRT comparison group following propensity score match.

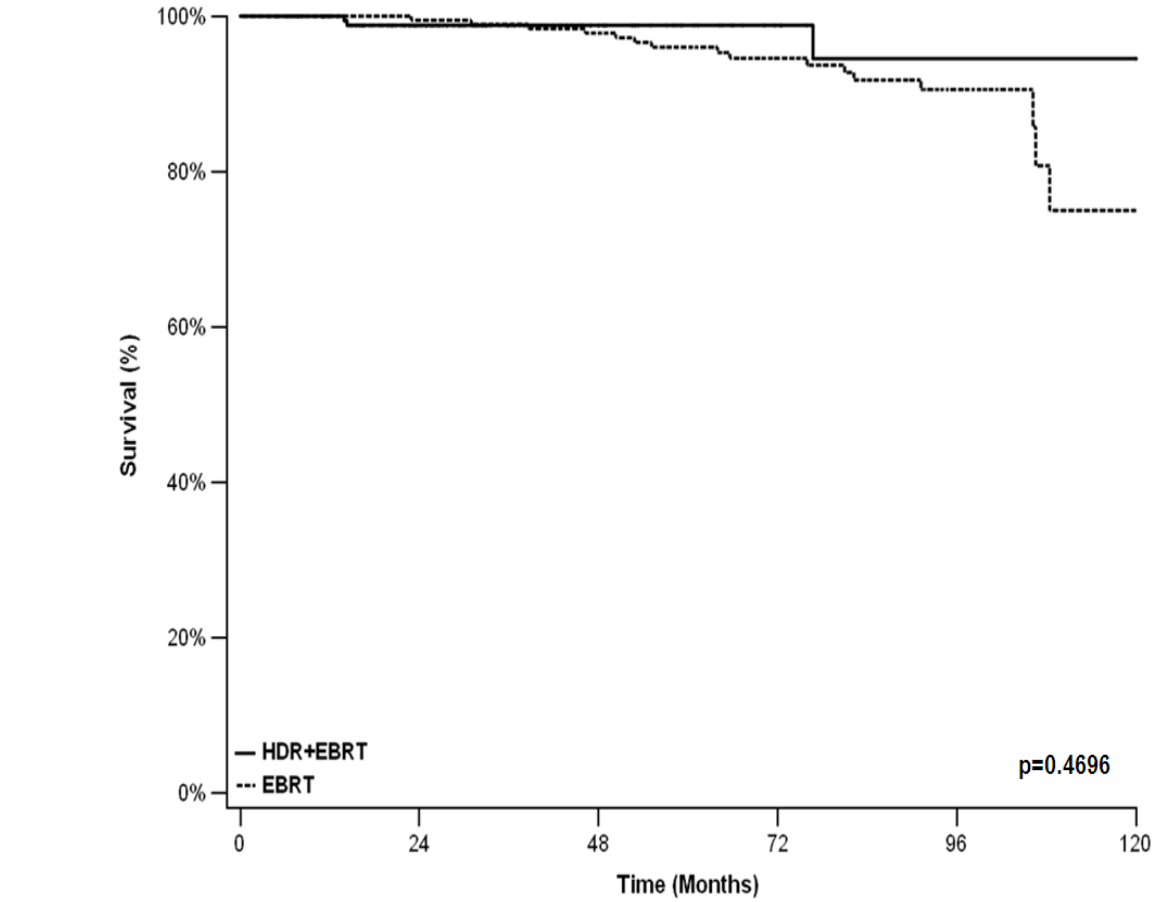


Patients at Risk						
LDR	127	108	62	13	3	0
EBRT	127	110	86	49	16	3

Fig. 9. Biochemical failure-free survival for intermediate-risk patients in LDR-BT vs. EBRT comparison group following propensity score match.

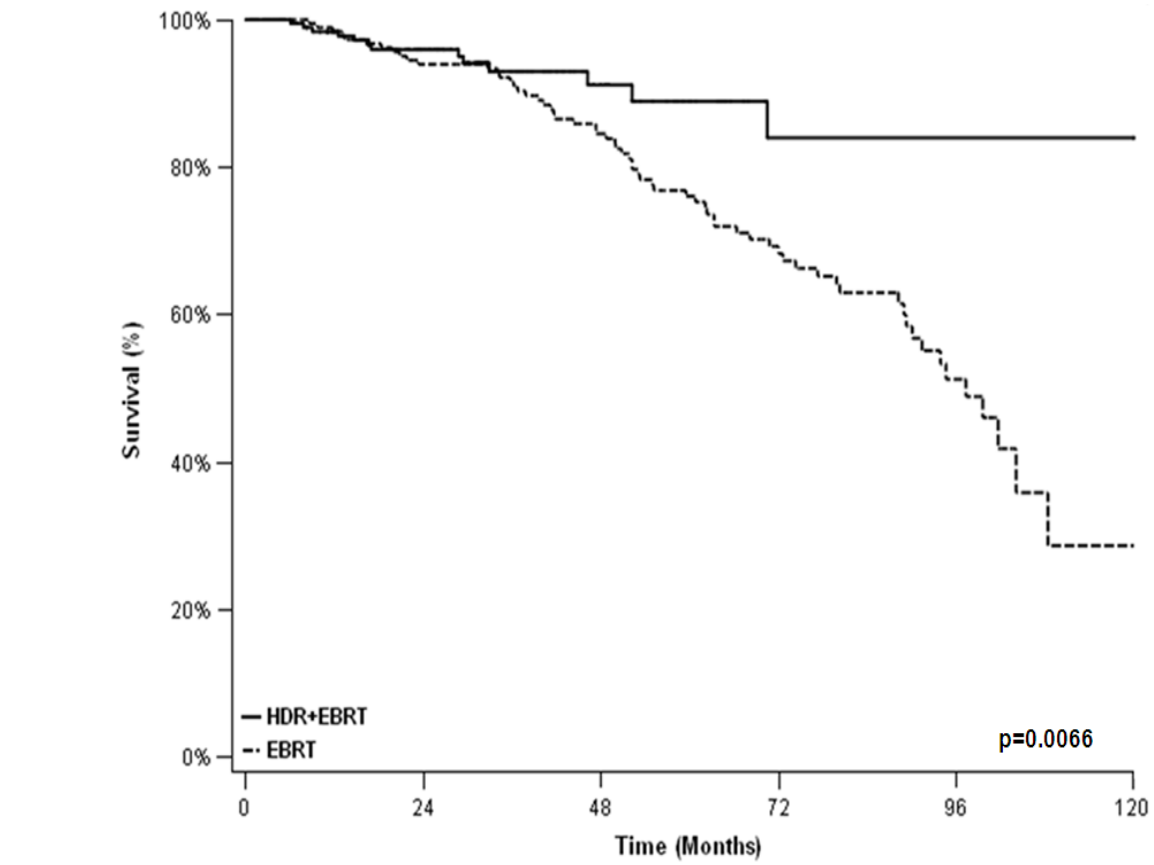
Intermediate-Risk HDR-BT+EBRT vs. EBRT Match:

Kaplan-Meier curves comparing both OS and bFFS for HDR-BT+EBRT and EBRT in intermediate-risk PS matched prostate cancer patients are shown in Figures 10 and 11. No significant difference was found comparing OS in the intermediate-risk HDR-BT+EBRT vs. EBRT match (hazard ratio = 0.64, 95% CI 0.20-2.13, p = 0.47). The 5-year and 10-year actuarial percentages for OS were 99% and 95% for HDR-BT+EBRT patients and 96% and 75% for EBRT patients, respectively. HDR-BT+EBRT was associated with a statistically significant improvement in bFFS when compared with EBRT (hazard ratio = 0.48, 95% CI 0.26-0.89, p=0.007). The 5-year and 10-year actuarial percentages for bFFS were 89% and 84% in the HDR-BT+EBRT group and 76% and 29% in the EBRT group, respectively. In total, 13 (6.7%) HDR-BT+EBRT patients and 64 (33.0%) EBRT patients experienced a biochemical failure, while 3 (1.5%) HDR-BT+EBRT patients and 16 (8.2%) EBRT patients died.



Patients at Risk						
HDR+EBRT	194	132	52	27	4	0
EBRT	194	187	170	115	51	11

Fig. 10. Overall survival for intermediate-risk patients in HDR-BT+EBRT vs. EBRT comparison group following propensity score match.

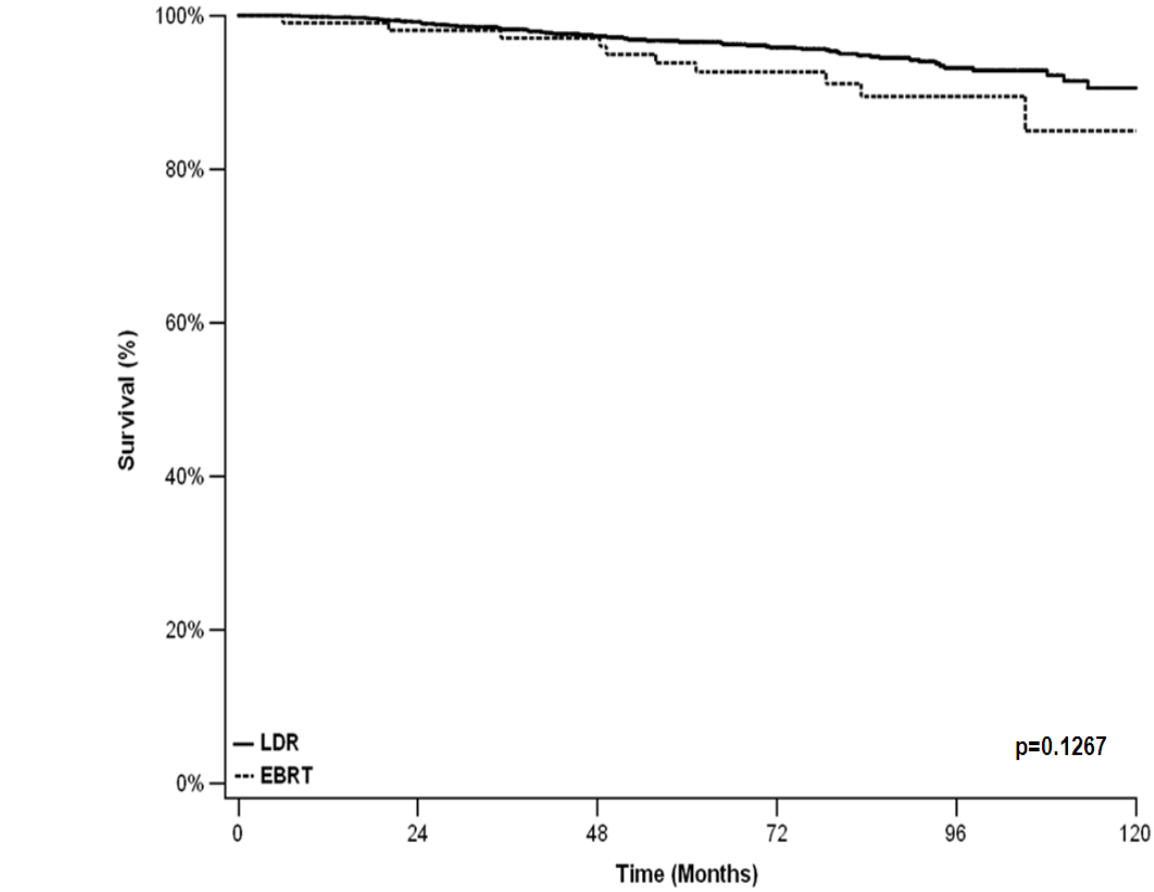


Patients at Risk						
HDR+EBRT	194	128	45	16	2	0
EBRT	194	167	126	70	24	3

Fig. 11. Biochemical failure-free survival for intermediate-risk patients in HDR-BT+EBRT vs. EBRT comparison group following propensity score match.

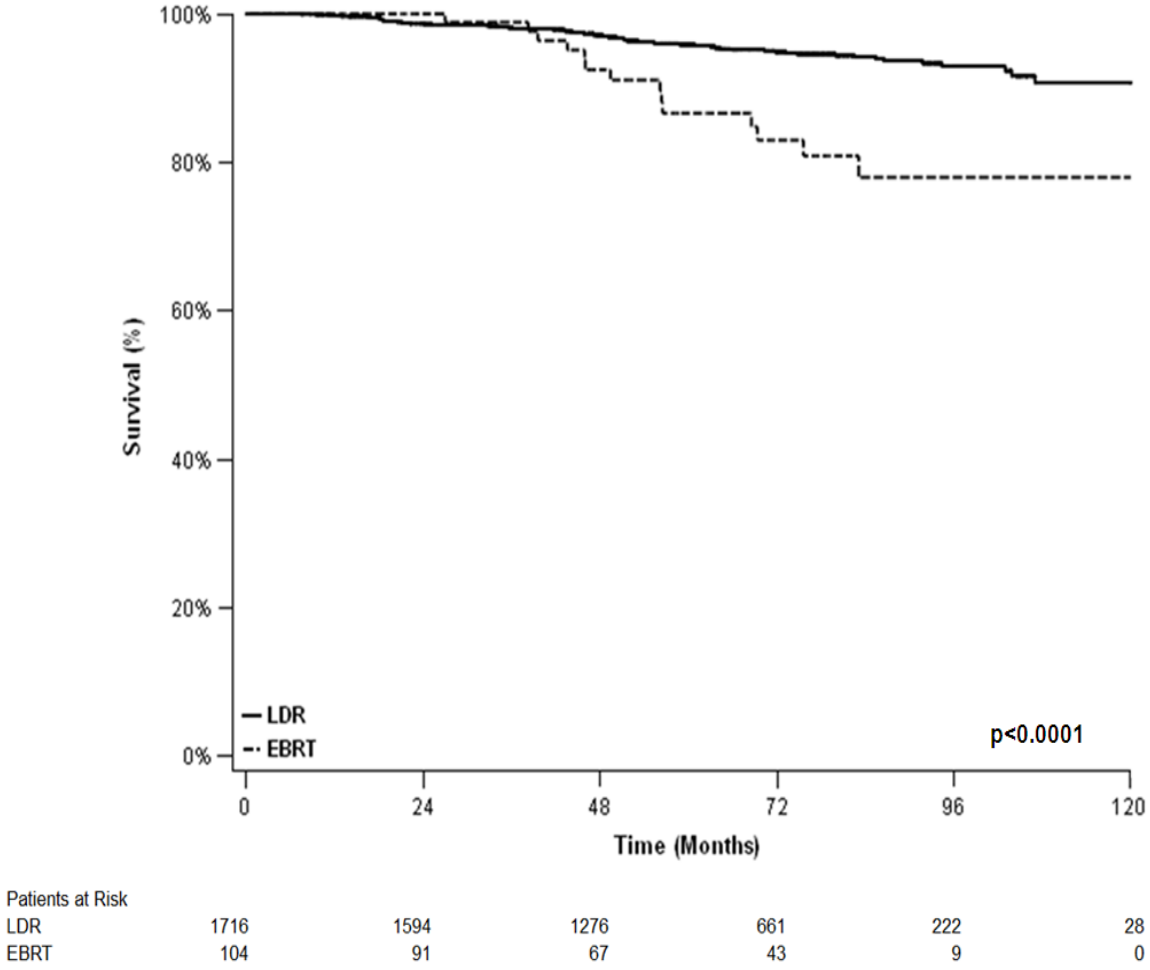
6.3 Pre-Match Versus Post-Match Comparison

Kaplan-Meier survival curves showing differences in OS and bFFS in pre-matched cohorts are shown in Figures 12-17. The hazard ratio for pre-matched OS was 0.60 (95% CI 0.31-1.16, p=0.13) for the low-risk cohort, 1.07 (95% CI 0.49-2.32, p=0.87) for the intermediate-risk LDR-BT vs. EBRT cohort, and 0.36 (95% CI 0.10-1.27, p=0.10) for the intermediate risk HDR-BT+EBRT vs. EBRT cohort. The hazard ratio for pre-matched bFFS was 0.31 (95% CI 0.18-0.55, p<0.0001) for the low-risk cohort, 0.19 (95% CI 0.10-0.36, p<0.0001) for the intermediate-risk LDR-BT vs. EBRT cohort, and 0.52 (95% CI 0.34-0.80, p=0.003) for the HDR-BT+EBRT vs. EBRT cohort.



Patients at Risk						
LDR	1716	1656	1400	804	310	53
EBRT	104	99	92	68	32	5

Fig. 12. Overall survival for low-risk patients in LDR-BT vs. EBRT comparison group prior to propensity score matching.



Patients at Risk						
LDR	1716	1594	1276	661	222	28
EBRT	104	91	67	43	9	0

Fig. 13. Biochemical failure-free survival for low-risk patients in LDR-BT vs. EBRT comparison group prior to propensity score matching.

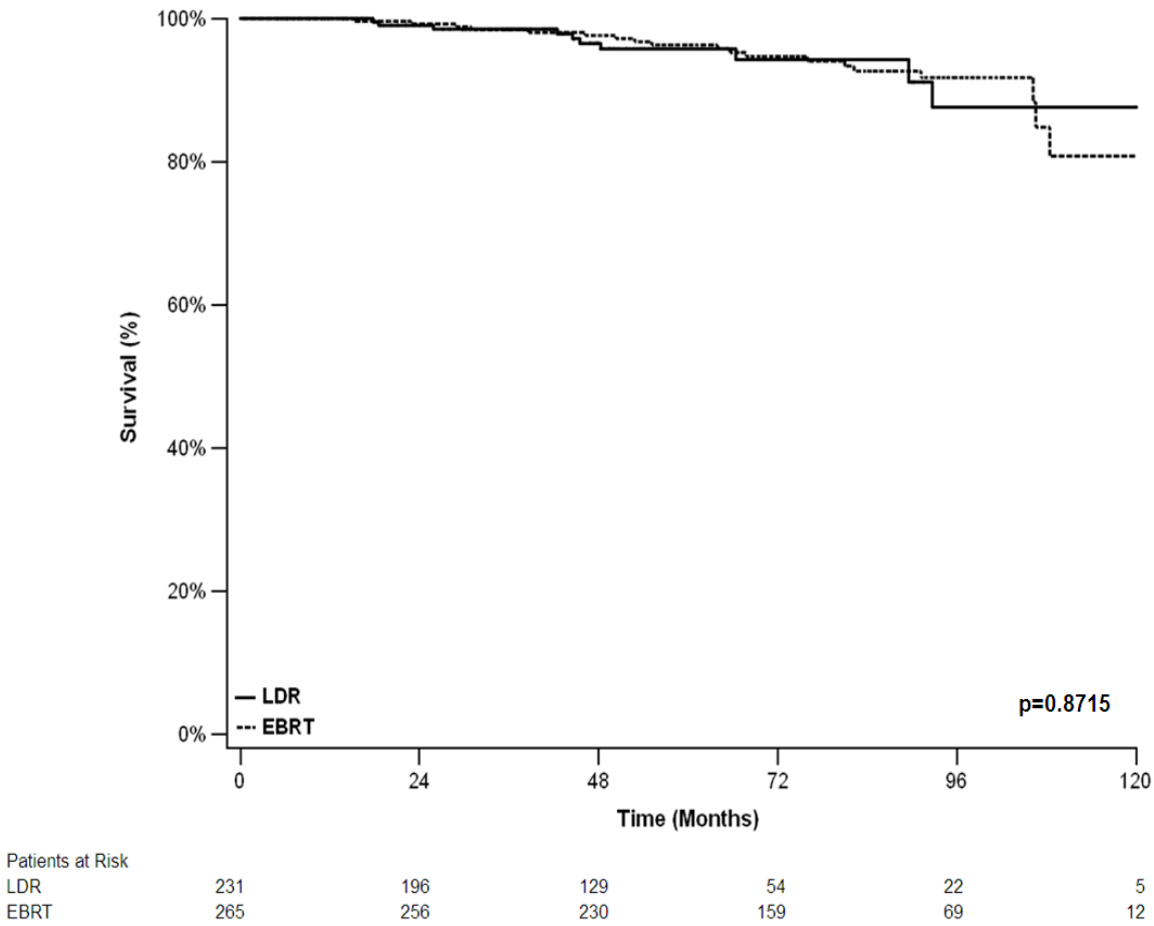
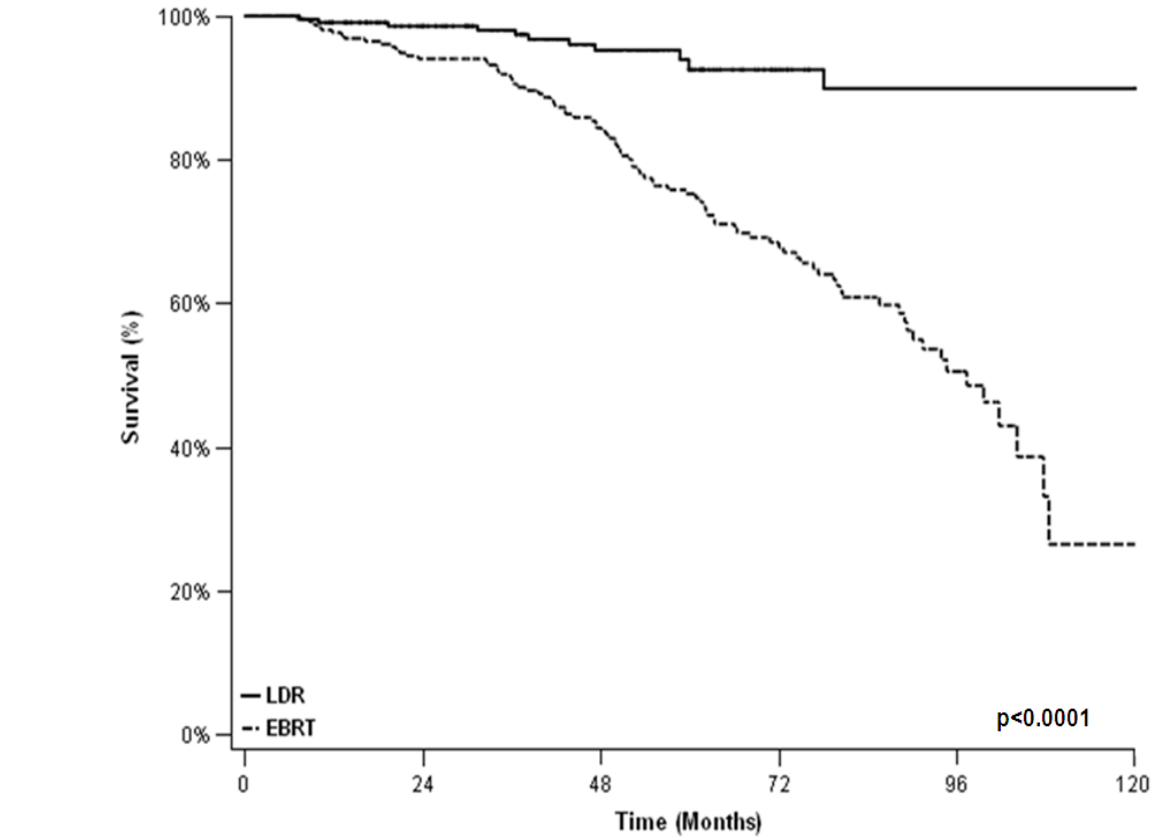
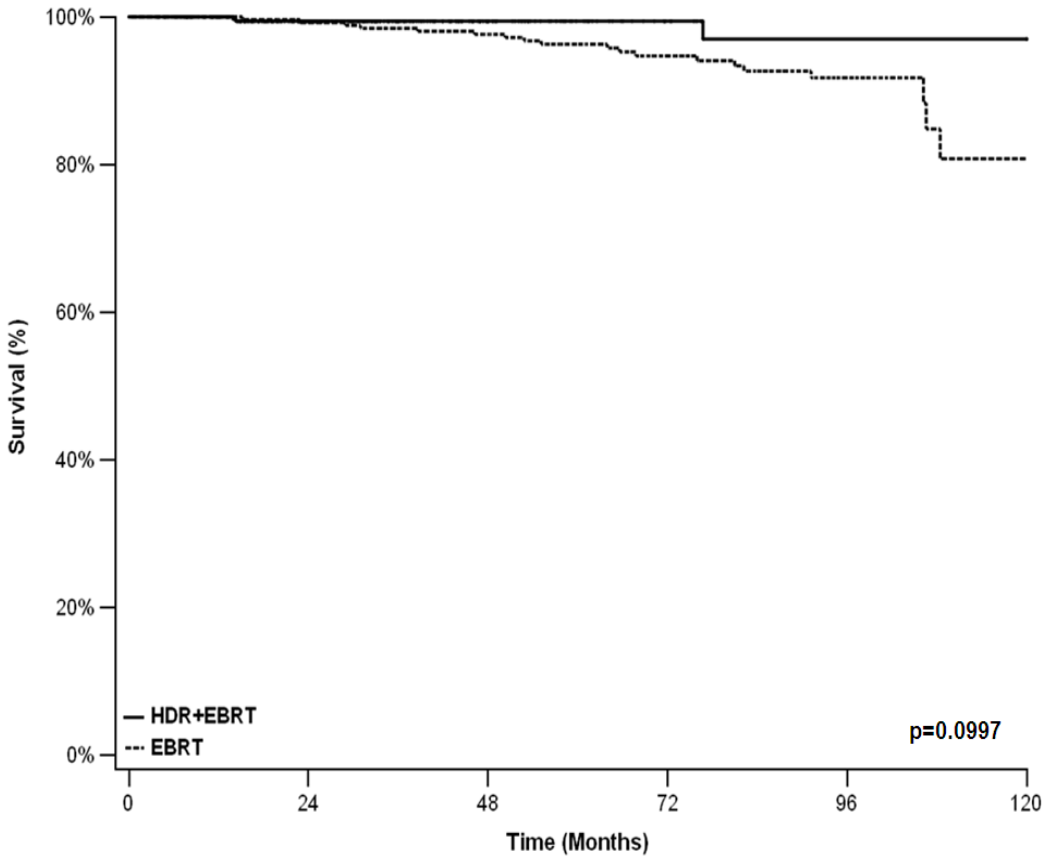


Fig. 14. Overall survival for intermediate-risk patients in LDR-BT vs. EBRT comparison group prior to propensity score matching.



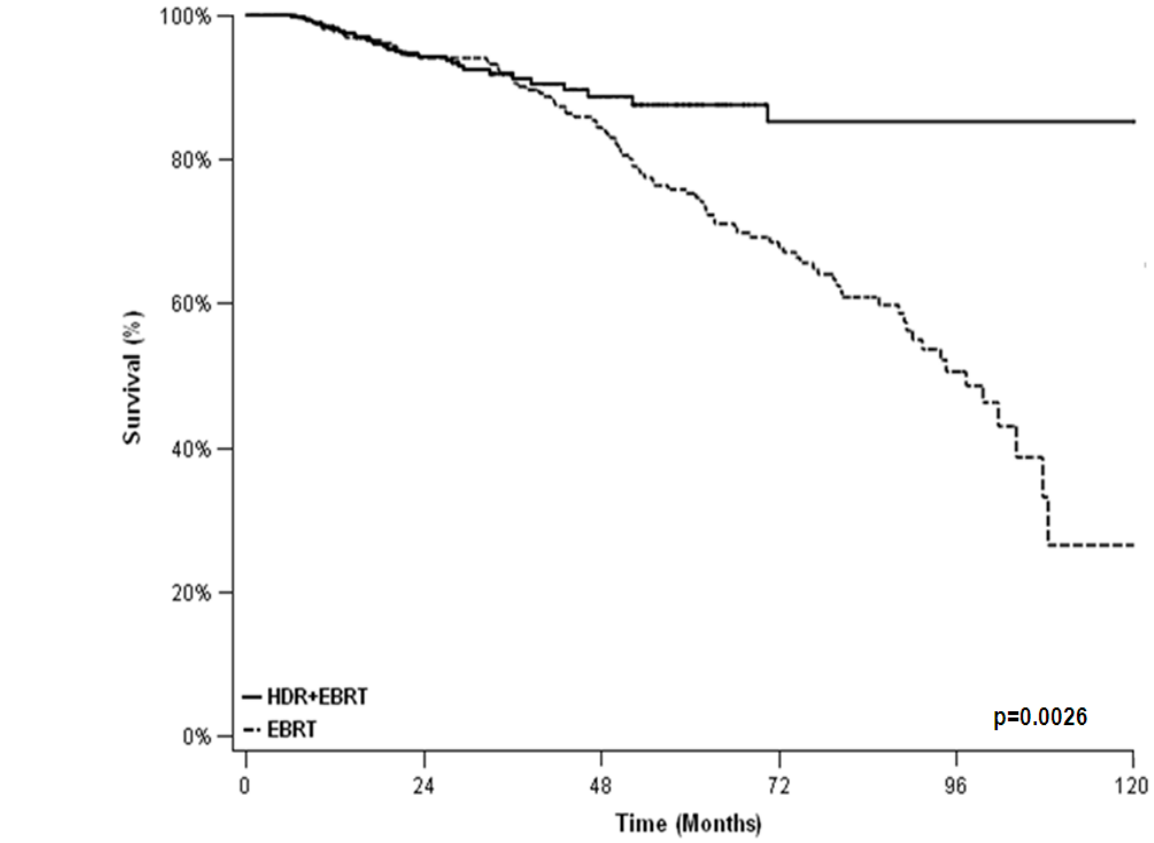
Patients at Risk						
LDR	231	188	118	43	15	3
EBRT	265	231	175	97	29	3

Fig. 15. Biochemical failure-free survival for intermediate-risk patients in LDR-BT vs. EBRT comparison group prior to propensity score matching.



Patients at Risk						
HDR+EBRT	390	255	94	47	6	0
EBRT	265	256	230	159	69	12

Fig. 16. Overall survival for intermediate-risk patients in HDR-BT+EBRT vs. EBRT comparison group prior to propensity score matching.



Patients at Risk						
HDR+EBRT	390	244	84	33	3	0
EBRT	265	231	175	97	29	3

Fig. 17. Biochemical failure-free survival for intermediate-risk patients in HDR-BT+EBRT vs. EBRT comparison group prior to propensity score matching.

7.0 Discussion

7.1 Survival Outcomes Assessment

Propensity score matched analysis demonstrated no difference in OS comparing BT options to EBRT in any of the comparison groups (LDR-BT vs. EBRT or HDR-BT+EBRT vs. EBRT in low-risk or intermediate-risk matches) (Fig. 6, 8 and 10). This matched analysis successfully adjusted for the baseline prognostic factors of age, PSA, Gleason total score and T-stage, which are the primary factors used to risk-stratify patients and tailor their radiation therapy (Keyes 2013, Rubin 2001, Thompson 2007). Prospective randomized data comparing OS in intermediate- to high-risk patients receiving combination BT with EBRT vs. EBRT alone have reported 5-year actuarial percentages of 94% vs. 92%, respectively (Santhya 2005). Our PS matched analysis reported 5-year OS percentages of 99% HDR-BT+EBRT vs. 96% EBRT (p=0.47) in the intermediate-risk cohort (Fig. 10). Similarly, observational data reporting on intermediate-risk LDR-BT vs. EBRT found no statistically significant OS difference with 5-year actuarial percentages of 94% vs. 94% (Klein 2009). Our results comparing LDR-BT vs. EBRT in intermediate-risk patients found a similar 5-year OS result of 97% vs. 96% (p=0.69), respectively (Fig. 8). Results from observational studies show that OS for prostate cancer patients with favorable-risk disease is very high, with 5-year actuarial percentages reported at 97% (Wong 2009). Results from our study showed no statistically significant OS difference in the low-risk matched cohort with survival rates of 96% LDR-BT vs. 95% EBRT (p=0.50) (Fig. 6).

A statistically significant difference in biochemical failure was found in both low-risk and intermediate-risk matched cohorts comparing LDR-BT vs. EBRT, with BT providing superior bFFS in both cases (Fig. 7 and 9). Observational studies comparing ASTRO Phoenix defined bFFS as their primary outcome have reported similar results when comparing LDR-BT to EBRT. In strictly low-risk comparisons, literature reported 5-year bFFS actuarial percentages of ≥ 94% for LDR-BT were constantly higher than EBRT compared values, ranging from 84% to 95% (Goldner 2012, Pe 2009, Pickles

2010, Wong 2009). Results from our matched analysis of LDR-BT vs. EBRT in the low-risk cohort demonstrated 5-year bFFS percentages of 96% LDR-BT vs. 89% EBRT (p=0.004) (Fig. 7). Previously reported CER on entirely intermediate-risk patients comparing LDR-BT vs. EBRT have also reported improved bFFS in direct comparisons (Klein 2009, Pickles 2010, Vassil 2010, Wong 2009). The results from our matched study are agreeable with the literature, with a hazard ratio of 0.22 (95% CI 0.09-0.50, p=0.001) favoring BT in the intermediate-risk LDR-BT vs. EBRT compared cohort (Fig. 9).

In the combination HDR-BT+EBRT vs. EBRT PS matched, intermediate-risk comparison, statistically significant improvement in bFFS was observed in the HDR-BT+EBRT group. The 5-year bFFS percentages were 89% in the HDR-BT+EBRT group and 76% in the EBRT group, respectively (p=0.007) (Fig. 11). Our results agree with other CER directly comparing HDR-BT+EBRT vs. EBRT in strictly intermediate-risk patients, which have reported similar results that favor combination therapy (Khor 2013, Deutsch 2010). However, the results from one of these studies using Cox regression modeling for confounding adjustment, reported results on intermediate-risk in subgroup analysis but did not account for differences in ADT use between groups (Deutsch 2010). Results from our study on intermediate-risk HDR-BT+EBRT vs. EBRT patients was obtained from a homogenous intermediate-risk cohort that received no ADT use. Isolating the effect of radiation therapy alone on survival without hormone assistance was an advantage of our study over a large proportion of comparative RT outcome studies available.

Visually, in both intermediate-risk comparisons, no apparent difference in biochemical failure was observed until ≥3-years, at which point a sharp drop off in bFFS was noted in the EBRT cohorts (Fig. 9 and 11). This visual trend was similar in the low-risk comparison, where no observable difference in bFFS was seen until roughly 4-years post treatment (Fig. 7). The need for PSA to reach nadir prior to any indication of biochemical failure using the ASTRO-RTOG Phoenix II definition (Roach 2006) is a likely explanation for this visual trend. The time to reach PSA nadir following RT has

been demonstrated to take as long as 3-years (Shi 2013), which would agree with our results, where larger frequencies of biochemical failures were not present until roughly 3-years after RT treatment was given. These results demonstrate the importance of having follow-up times of at least 5-years to adequately assess PSA failure following RT in patients with prostatic cancer. Another interesting discovery was that although a larger proportion of EBRT patients experienced biochemical failure, this did not correlate to a poorer overall survival probability. A possible explanation for this discrepancy between biochemical failure and survival in the EBRT cohorts may be a result of salvage therapy. This would agree with current studies on BT salvage following EBRT, which have demonstrated adequate biochemical control at 5-years (Vargas 2014, Yamada 2013).

Upon literature review, only one other CER study directly comparing BT versus EBRT treatment survival outcomes was found that used PS matched analysis for confounding adjustment. In their study, Khor et al matched 344 EBRT with 344 HDR-BT+EBRT patients with intermediate- and high-risk disease, reporting a bFFS hazard ratio of 0.44 (95% CI 0.28-0.70, $p<0.001$), favoring combination therapy in intermediate-risk subgroup analysis. However, in this study ADT use was only effectively balanced between treatment groups in their primary match, which included both intermediate-risk and high-risk patients. Therefore, among other factors included in their PS match model, ADT use in the intermediate-risk cohort was no longer balanced and may have confounded their subgroup analysis. Results from our analysis of intermediate-risk HDR-BT+EBRT vs. EBRT showed a bFFS hazard ratio of 0.48 (95% CI 0.26-0.89, $p=0.007$) (Fig. 11) in favor of combination HDR-BT+EBRT. Additionally, our results are from a matched, strictly intermediate-risk cohort that had balanced baseline prognostic factors with no ADT use in either group.

When comparing pre-matched, unadjusted survival curves to PS matched curves, some differences were observed. For example, in the pre-match low-risk cohort, a slight visual difference in OS with borderline significance favoring LDR-BT was present (Fig. 12). This borderline visual difference in OS was no longer present in the low-risk PS matched curve (Fig. 6). Visual comparison of additional pre-match to post-match curves

provided similar results. In the intermediate-risk HDR-BT+EBRT vs. EBRT comparison, OS is borderline statistically significant pre-match (Fig. 16) but not following PS matching (Fig. 10). Although reduced sample size in the matched cohorts compared to the original pre-matched population could explain this change in statistical significance, under visual inspection, survival between treatment groups appears to become more similar after PS matching. This visual trend is also noticeable in the pre-match and post-match bFFS curves in the intermediate-risk LDR-BT vs. EBRT cohort (Fig. 9 and 15) with a slight reduction in strength of difference between groups post-match. These results demonstrate that PS matching can be an effective tool at removing imbalances in baseline prognostic factors that impact survival and can provide results with a reduced amount of bias.

To our knowledge, this was the first multi-institutional Canadian study comparing primary BT vs. EBRT survival outcomes in separate prostate cancer risk groups using PS matched analysis. Through retrospective data analysis, we were able to obtain results of biochemical failure and overall survival of patients treated at four major cancer institutions in Canada, with over 10-years of follow-up data. Another advantage of this study was that it controlled for the phenomenon of PSA bounce, or the benign spike in PSA measurement that can occur following BT treatment (Mehta 2013). An attempt to control for PSA bounce was either not mentioned or attempted in most comparative studies found in the literature. In an exploratory analysis, we created additional Kaplan Meier curves that did not factor in PSA bounce in the matched cohorts and compared them to the original survival curves (see Appendix IV). Under visual inspection of the bFFS curves, when PSA bounce was not accounted for, EBRT appeared to be initially protective compared with BT options over the first 1 to 3 years, until BT eventually became superior. This initial protective effect of EBRT is no longer present when PSA bounce was factored into the biochemical survival analysis (Fig. 7, 9 and 11). This demonstrates the potential effect PSA bounce can have on biochemical outcome analysis in prostate cancer, specifically when assessing PSA failures from BT treatments within the first few years of follow-up.

7.2 Study Limitations

1. Data Source: A major limitation to this study was that results were from a secondary analysis that was not originally planned during the creation of the ProCaRS database. As a result, our analysis was restricted to the data originally present in the ProCaRS database. Outcome data was restricted to survival and biochemical failure only. There was no information on acute or late side effects available in the database, including data on GI or GU toxicities, impotency, or any measurement on patient reported quality of life. Information on these additional patient important outcomes would have strengthened this study by allowing a more in depth assessment of the mortality and morbidity associated with the various RT treatments.

2. Sample Size: Matching was restricted to patients with complete data for all variables included in the PS models (logistic regression models) and based on specific sets of exclusion criteria used to create homogenous comparison groups. This resulted in a reduction in sample size and power in our matched comparisons.

3. Confounding Variable Selection: Variable eligibility for inclusion in PS models was restricted to those readily available in the database and of sufficient level of completeness. For example, information on both percent positive core biopsy and Gleason 7 sub-pattern (3+4 vs. 4+3) was generally incompletely entered and could not be controlled for in our analysis. The variation in RT management of prostate cancer across different treatment centres could potentially impact outcomes (Cooperberg 2010), however, the method of data collection from the various cancer institutions made it impossible to include a 'treatment centre' variable in the PS models.

4. Comparisons: Again, due to limitations in available data, no RT modality comparisons were made with high-risk prostate cancer patients. Additionally, there were no comparisons of the RT treatments to conservative management strategies (watchful waiting or active surveillance) or radical prostatectomy.

7.3 Future Work

Given the completion of this CER study on prostate cancer outcomes, and the effort expended in creating the ProCaRS database containing RT data on roughly 8000 patients, additional uses for this database could be explored. A potential retrospective study aimed at exploring the relationship between biochemical failure and overall survival is warranted. Identifying patient characteristics that best predict survival following biochemical failure would help investigators better understand the relationship between these two important patient outcomes. Additionally, identifying the importance of ADT use in LDR-BT patients could be explored to better understand the impact of hormone therapy in this patient population.

With respect to future work in the field of prostate cancer CER, expansion of the ProCaRS database to include more patients treated with higher doses of EBRT (>78 Gy) with more modern techniques, such as image guided IMRT, would allow for higher quality comparisons of BT versus dose escalated IMRT treatments. Incorporating outcome data on acute and late toxicities, impotency and patient reported quality of life into the ProCaRS database would also be beneficial. Exploring patient toxicities as well as other side effects from compared therapies could strengthen the quality of comparisons made between treatment groups. Additionally, integrating information on health care costs into the ProCaRS database would enable economic assessment. This could allow for a more complete understanding of strengths and weaknesses between therapies and ultimately aid decision-making by health policy makers. Finally, improving the volume of high-risk patients in the ProCaRS database could allow for RT outcome comparisons to be made in this patient population that, as yet, were not achievable.

Potential randomized phase III trials comparing both survival and side effect outcomes in patients receiving BT or EBRT could be explored. Results from our study indicate that BT treatments appear to lead to fewer treatment failures in low-risk and intermediate-risk patients. However, confirmation of the overall benefit of BT compared

to EBRT from a treatment effectiveness standpoint that includes both survival and side-effect data is not yet fully understood.

7.4 Conclusions

Propensity score matched analysis showed BT options significantly improved bFFS in low- and intermediate-risk prostate cancer patients after 10-years of follow-up, but did not lead to statistically significant improvements in OS. The comparisons made demonstrated that LDR-BT led to relatively fewer treatment failures than EBRT in both low-risk and intermediate-risk patients. Combination HDR-BT+EBRT was also found to have a superior benefit in reducing biochemical failures compared with EBRT in men with intermediate-risk prostate cancer. The results of this study add to an increasing amount of evidence favoring BT over EBRT with respect to biochemical control in the treatment of localized prostate cancer. Assuming this research question is still of interest to the radiation oncology community, our results also provide preliminary evidence for implementation of an RCT comparing RT survival outcomes of BT vs. EBRT in low-risk, intermediate-risk and potentially high-risk prostate cancer patients.

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Appendix I

Summary of CER Articles on Primary RT Outcomes

Appendix I: Summary of CER Articles on Primary RT Outcomes.

Author	Date	Study Type	Confounder Adjustment	Comparison (n per treatment)	RT Dose (Tx)	% Prostate Cancer Risk Groups per treatment
Abel-Wahab et al	2008	Retrospective	Cox PH Regression	BT (10214) vs. EBRT (28225) vs. BT+EBRT (9078)	NR	NR
Aoki et al	2009	Retrospective	Cox PH Regression	LDR-BT (252) vs. LDR-BT+EBRT (44)	LDR-BT: 144 Gy I-125 vs. LDR-BT+EBRT: 110 Gy I-125 + 44-46 Gy EBRT	LDR-BT: (Low=65%;Int=33 %;High=2%) vs. LDR-BT+EBRT: (Int=75%;High=25 %)
Beyer et al	2000	Retrospective	Cox PH Regression	LDR-BT (595) vs. EBRT (1527)	LDR-BT: 120 Gy Pd-103 or 160 Gy I-125 vs. EBRT: 66 Gy	NR
Burdick et al	2009	Retrospective	Cox PH Regression	LDR-BT (127) vs. EBRT (268)	LDR-BT: 144 Gy I-125 vs. EBRT: 70 Gy	NR
Coen et al	2012	Retrospective	Individual 1:1 Case Match	Proton + EBRT (141) vs. LDR-BT (141)	Proton + EBRT: 20 Gy to 29 Gy Proton EBRT + 50 Gy Photon EBRT vs. LDR-BT: 145 Gy I-125 or 115 Gy Pd-103	Proton EBRT: (Low=80%;Int=20 %) vs. LDR-BT: (Low=84%;Int=16 %)
D'Amico et al	1998	Retrospective	Cox PH Regression	LDR-BT (218) vs. EBRT (766)	LDR-BT: 115 Gy Pd-103 vs. EBRT: 66-72 Gy	LDR-BT: (low=56%;int=23% ;high=20%) vs. EBRT: (low=29%;int=31% ;high=40%)
da Silva Franca et al	2010	Retrospective	Cox PH Regression	LDR-BT (72) vs. LDR-BT+EBRT (24)	LDR-BT: 145 Gy I-125 vs. LDR-BT+EBRT: 110 Gy I-125 + 45 Gy EBRT	LDR-BT: (Int=64%;High=36 %) vs. LDR-BT+EBRT: (Int=29%;High=71 %)
Davis et al	2001	Prospective	None	LDR-BT (142) vs. EBRT (222)	LDR-BT: 115 Gy Pd-103 vs. EBRT: 70 Gy	NR

Deutsch et al	2010	Retrospective	Cox PH Regression	EBRT (470) vs. HDR-BT+EBRT (160)	EBRT: 86 Gy vs. HDR-BT+EBRT: 21 Gy Ir-192 + 50 Gy EBRT	EBRT: (Low=21%;Int=40 %;High=39%) vs. HDR-BT+EBRT: (Low=14%;Int=71 %;High=15%)
Eade et al	2008	Retrospective	Cox PH Regression	LDR-BT (158) vs. EBRT (216)	LDR-BT: 145-166 Gy I-125 vs. EBRT: 70-78 Gy	100% low
Elliot et al	2007	Retrospective	Cox PH Regression	BT (799) vs. EBRT (645)	NR	NR
Ferrer et al	2008	Prospective	GEE	LDR-BT (275) vs. EBRT (205)	LDR-BT: 144 Gy I-125 vs. EBRT: 74 Gy	LDR-BT: (Low=88%;Int=11 %:High=1%) vs. EBRT: (Low=48%;Int=34 %;High=18%)
Gelbium et al	2000	Retrospective	Cox PH Regression	LDR-BT (685) vs. LDR-BT+EBRT (140)	LDR-BT: 144 Gy I-125 or 120 Gy Pd-103 vs. LDR-BT+EBRT: 100 Gy I-125 or 90 Gy Pd-103 + 41-45 Gy EBRT	NR
Goldner et al	2012	Retrospective	Cox PH Regression	LDR-BT (667) vs. 70 Gy EBRT (82) vs. 74 Gy EBRT (170)	LDR-BT: 144 Gy I-125 vs. EBRT: 70 Gy vs. EBRT: 74 Gy	100% low-risk patients
Gondi et al	2007	Retrospective	Cox PH Regression	LDR-BT or LDR-BT+EBRT ± ADT (72) vs. EBRT+ADT (84) vs. EBRT only (141)	LDR-BT or LDR-BT+EBRT ± ADT: 145 Gy I-125 or 120 Gy Pd-103 or 110 Gy I-125 + 45 Gy EBRT or 90 Gy Pd-103 + 45 Gy EBRT vs. EBRT+ADT: 66-70 Gy + ADT vs. EBRT: 66-70 Gy	100% Intermediate-risk patients
Huang et al	2010	Retrospective	Regression	BT (219) vs. EBRT (154)	NS	BT: (Low=65%;Int=27 %;High=7%) vs. EBRT: (Low=25%;Int=38 %;High=37%)

Joseph et al	2008	Prospective	None	EBRT (111) vs. HDR-BT+EBRT (23)	EBRT: 66-70 Gy vs. HDR-BT+EBRT: 17 Gy Ir-192 + 40 Gy EBRT	NR - all int/high-risk
Kalakota et al	2010	Prospective	Cox PH Regression	LDR-BT (62) vs. LDR-BT+EBRT (48)	LDR-BT: 144 Gy I-125 vs. LDR-BT+EBRT: 108 Gy I-125 + 45 Gy EBRT	NR
Klein et al	2009	Retrospective	Cox PH Regression	LDR-BT (204) vs. EBRT (321)	LDR-BT: 144 Gy I-125 vs. EBRT: 81 Gy	100% Intermediate-risk patients
Khor et al	2013	Retrospective	Propensity Score Match	EBRT (344) vs. HDR-BT+EBT (344)	EBRT: 74 Gy vs. HDR-BT+EBRT: 19.5 Gy Ir-192 + 46 Gy EBRT	EBRT: (Int=59%;High=41 %) vs. HDR-BT+EBRT: (Int=59%;High=41 %)
Krestin et al	2000	Retrospective	Individual 1:1 Case Match	EBRT (161) vs. HDR+EBRT (161)	EBRT: 66 Gy vs. HDR-BT+EBRT: 16-21 Gy Ir-192 + 46 Gy EBRT	NR
Kupelian et al	2004	Retrospective	Cox PH Regression	LDR-BT (950) vs. EBRT≥72Gy (301) vs. EBRT<72Gy (484) vs. LDR-BT+EBRT (222)	LDR-BT: 144 Gy I-125 or 136 Gy Pd-103 vs. EBRT≥72Gy: 72-82 Gy vs. EBRT<72Gy 63-70 Gy vs. LDR-BT+EBRT: 108 Gy I-125 + 41 Gy EBRT or 102 Gy Pd-103 + 45 Gy EBRT	NR - T1/T2 disease
Lee et al	2001	Prospective	None	LDR-BT (44) vs. EBRT (23)	LDR-BT: 144 Gy I-125 vs. EBRT: 70-72 Gy	LDR-BT: (100% low/int) vs. EBRT: (low/int/<10%high)
Lev et al	2009	Prospective	Regression	LDR-BT+EBRT (61) vs. HDR-BT+EBRT (49)	NR	NR
Nieder et al	2008	Retrospective	Cox PH Regression	BT (22889) vs. EBRT (93059) vs.	NR	NR

				BT+EBRT (17956)		
Ojha et al	2010	Retrospective	Cox PH Regression	BT (20259) vs. EBRT (41986)	NR	NR
Pe et al	2009	Retrospective	Cox PH Regression	LDR-BT (171) vs. EBRT (189)	LDR-BT: 145 Gy I-125 vs. EBRT: 74 Gy	100% low-risk patients
Pickles et al	2010	Retrospective	Individual 1:1 Case Match	LDR-BT (139) vs. EBRT (139)	LDR-BT: 145 Gy I-125 vs. EBRT: 52-72 Gy	LDR-BT: (Low=77%;Int=23 %) vs. EBRT: (Low=77%;Int=23 %)
Pinkawa et al	2010	Retrospective	Cox PH Regression	LDR-BT (94) vs. EBRT (135) vs. HDR-BT+EBRT (66)	LDR-BT: 145 Gy I-125 vs. EBRT: 70 Gy vs. HDR-BT+EBRT: 18 Gy Ir-192 + 50 Gy	LDR-BT: (Low=65%;Int=35 %) vs. EBRT: (Low=27%;Int=24 %;High=49%) vs. HDR-BT+EBRT (Low=35%;Int=26 %;High=39%)
Santhya et al	2005	RCT	Cox PH Regression	HDR-BT+EBRT (51) vs. EBRT (53)	HDR-BT+EBRT: 35 Gy BT + 40 Gy EBRT vs. EBRT: 66 Gy	HDR-BT+EBRT: (int=41%;high=59 %) vs. EBRT: (int=40%;high=60 %)
Smith et al	2009	Prospective	Regression	LDR-BT (58) vs. HDR-BT (47) vs. EBRT (123)	NR	NR
Talcott et al	2003	Prospective	Regression	BT (80) vs. EBRT (182)	NR	BT: (Low=35%;Int=32 %;High=33%;unkn own=4%) vs. EBRT: (Low=55%;Int=22 %;High=23%;Unkn own=7%)
Vassil et al	2010	Retrospective	Cox PH Regression	LDR-BT (256) vs. EBRT (305)	LDR-BT: 144 Gy I-125 vs. EBRT: 70-80 Gy	100% Intermediate-risk patients

Wong et al	2009	Retrospective	Cox PH Regression	LDR-BT (225) vs. 3D-CRT (270) vs. IMRT (314) vs. LDR-BT+EBRT (44)	LDR-BT: 144 Gy I-125 or 120 Pd-103 vs. 3D-CRT: 66-71 Gy vs. IMRT: 75-77 Gy vs. LDR-BT_EBRT) 110 Gy I-125 or 90 Gy Pd-103 + 45 Gy 3D-CRT	LDR-BT: (Low=70%;Int=26%;High=9%) vs. 3D-CRT: (Low=44%;Int=41%;High=15%); vs. IMRT: (Low=35%;Int=48%;High=17%) vs. LDR-BT+EBRT (Low=32%;Int=52%;High=16%)
Zelefsky et al	1999	Retrospective	Cox PH Regression	LDR-BT (145) vs. EBRT (137)	LDR-BT: 144 Gy I-125 vs. EBRT: 65-81 Gy	100% low-risk patients
Zelefsky et al	2008	Retrospective	Cox PH Regression	LDR-BT (127) vs. LDR-BT+EBRT (216)	LDR-BT: 144 Gy I-125 vs. LDR-BT+EBRT: 110 Gy I-125 + 50 Gy EBRT	LDR-BT: (Low=28%;Int=64%;High=8%) vs. LDR-BT+EBRT: (Low=88%;Int=12%)
Zelefsky et al	2011	Retrospective	Cox PH Regression	LDR-BT (448) vs. EBRT (281)	LDR-BT: 144 Gy I-125 vs. EBRT: 81 Gy	100% low-risk patients
Zhou et al	2009	Retrospective	Cox PH Regression	BT (644) vs. EBRT (876)	NR	NR

Appendix I: Continued.

Author	ADT use?	Primary Outcome	Reported Result of Primary Outcome	Secondary Outcomes	Reported Result of Secondary Outcome (s)	Country	Multi-centred ?
Abel-Wahab et al	NR	Secondary Cancer Incidence >5 years	Actuarial percentages > 5 years: 4.7% (BT) vs. 10.3% (EBRT) vs. 5.7% (BT+EBRT), p<0.001	No	N/A	USA	Y
Aoki et al	No - ADT patients excluded	Late Grade 2 GI toxicity (rectal bleeding)	9.1% (LDR-BT) vs. 36% (LDR-BT+EBRT), p <0.01	No	N/A	Japan	N
Beyer et al	Yes - Mixed use in both groups	FFS	Actuarial percentages > 5 years: 71% (LDR-BT) vs. 69% (EBRT), p=0.91	No	N/A	USA	N

Burdick et al	Yes - Mixed use in both groups	bFFS (Phoenix)	Actuarial percentages @ 5 years: 88% (95% CI 80-95%) LDR-BT vs. 84% (95% CI 78-91%) EBRT	No	N/A	USA	N
Coen et al	No - ADT patients excluded	bFFS (Phoenix)	Actuarial percentages @ 8 years: 92% (Proton EBRT) vs. 84% (LDR-BT), p=0.44[log-rank]	OS	Actuarial percentages @ 8 years: 93% (Proton EBRT) vs. 96% (LDR-BT), p=0.45[log-rank]	USA	Y
D'Amico et al	Yes - used in LDR-BT group	PSAF	Relative Risk not reported; showed no significant difference in low-risk (p=0.3), int-risk (p=0.6), or high-risk (0.5)	No	N/A	USA	Y
da Silva Franca et al	Yes - Mixed use in both groups	bFFS (Phoenix)	Actuarial percentages @ 5 years: 96% (LDR-BT) vs. 72% (LDR-BT+EBRT)	No	N/A	Brazil	Y
Davis et al	Yes - Mixed use in both groups	SF-36	Reported a variety of results from SF-36 questionnaire	No	N/A	USA	N
Deutsch et al	Yes - Mixed in both groups	bFFS (Phoenix)	Actuarial percentages @ 5 years: 82% (EBRT) vs. 98% (HDR-BT+EBRT), p<0.001	No	N/A	USA	Y
Eade et al	No - ADT patients excluded	bFFS (Phoenix)	Actuarial percentages @ 4 years: 99% (LDR-BT) vs. 93% (EBRT), p=0.09	Late Grade 2 or higher GI/GU toxicity	Actuarial percentages @ 4 years: GI: 7.8% (LDR-BT) vs. 2.4% (EBRT), p=0.03; GU: 19.2% (LDR-BT) vs. 3.5% (EBRT), p<0.001	USA	N
Elliot et al	Yes - Mixed use in both groups	Urethral Stricture Incidence	Actuarial percentages at 4 years: 1.8% (BT) vs. 1.7% (EBRT), p=NS	No	N/A	USA	Y
Ferrer et al	Yes - Mixed use in both groups	EPIC	EBRT led to significantly worse bowel (p<0.001), sexual (p<0.01), and hormonal (p<0.01) function than LDR-BT	No	N/A	Spain	Y

Gelbium et al	Yes - Mixed in both groups	Late Grade 2 or higher GI toxicity	Actuarial percentages @ 4 years: 6.9% (LDR-BT) vs. 7.8%, p=NR	No	N/A	USA	N
Goldner et al	Yes- Mixed in all groups	bFFS (Phoenix)	Actuarial percentages @ 5 years: 94% (LDR-BT) vs. 91% (74 Gy EBRT) vs. 84% (70 Gy EBRT), p<0.01	No	N/A	Austria	Y
Gondi et al	Yes - Mixed in LDR-BT group	bFFS (ASTRO1)	Actuarial percentages @ 5 years: 88% (LDR-BT or LDR-BT+EBRT ± ADT) vs. 60% (EBRT+ADT) vs. 49% (EBRT only), p<0.001	bFFS (Phoenix)	Actuarial percentages @ 5 years: 81% (LDR-BT or LDR-BT+EBRT ± ADT) vs. 85% (EBRT+ADT) vs. 64% (EBRT only), p=0.014	USA	N
Huang et al	NS	SF-36	Primary Treatment was significant predictor of SF-36 scoring of urinary, bowel and sexual function (all p<0.001)	No	N/A	USA	Y
Joseph et al	NR	FACT-P	Overall FACT-P scores @ 1 year: 98 (EBRT) vs. 95 (HDR-BT+EBRT), p=0.67	No	N/A	Canada	Y
Kalakota et al	Yes - Mixed use in both groups	Late Grade 2 GI toxicity	Actuarial percentages @ 4 years: 91% (LDR-BT) vs. 82% (LDR-BT+EBRT), p=0.30	No	N/A	USA	Y
Klein et al	No - ADT patients excluded	bFFS (Phoenix)	Actuarial percentages @ 5 and 8 years: 82% and 82% (LDR-BT) vs. 80% and 75% (EBRT), p=NS	RFS, OS	Actuarial percentages for RFS @ 5 and 8 years: 97% and 81% (LDR-BT) vs. 95% and 90% (EBRT), p=0.02; Actuarial percentages for OS @ 5 and 8 years: 94% and 94% (LDR-BT) vs. 93% and 81% (EBRT), p=0.05	USA	Y
Khor et al	Yes - Equal use in both tx groups	bFFS (Phoenix)	Hazard Ratio for HDR-BT+EBRT vs. EBRT = 0.59 (95% CI 0.43-0.81, p<0.01)	No	N/A	Australia	N

Krestin et al	NR	bFFS (ASTRO1)	Actuarial percentages @ 5 years: 44% (EBRT) vs. 67% (HDR-BT+EBRT)	No	N/A	USA	N
Kupelian et al	Yes - Mixed use in all groups	bFFS (ASTRO1)	Actuarial percentages @ 5 and 7 years: 83% and 76% (LDR-BT) vs. 81% and 81% (EBRT) vs. 51% and 48% (EBRT) vs. 77% and 77% (LDR-BT+EBRT); When EBRT<72 Gy removed, no significant difference between treatment groups	No	N/A	USA	Y
Lee et al	Yes - Mixed use in both groups	FACT-P	Reported a variety of results from the FACT-P questionnaire	No	N/A	USA	N
Lev et al	NR	HQoL	RT treatment not a significant predictor of HQoL	No	N/A	USA	Y
Nieder et al	NR	Secondary Cancer	No significant difference between treatment groups	No	N/A	USA	Y
Ojha et al	NR	Secondary Cancer	HR = 1.68 (p=NS) favors BT	No	N/A	USA	Y
Pe et al	No - ADT patients excluded	bFFS (Phoenix)	Actuarial percentages @ 5 years: 96% (LDR-BT) vs. 95% (EBRT), p=0.70	No	N/A	USA	N
Pickles et al	Yes - Equal use in both tx groups	bFFS(Phoenix)	Actuarial percentages @ 5 and 7 years: 95% and 95% (LDR-BT) vs. 85% and 75% (EBRT), p<0.001	No	N/A	Canada	N
Pinkawa et al	Yes - Mixed used in all groups	bFFS (Phoenix)	Hazard Ratios: LDR-BT vs. EBRT: 0.5 (95% CI 0.3-0.8, p<0.01); HDRT-BT+EBRT vs. EBRT: 0.6 (95% CI 0.4-0.97, p=0.04)	No	N/A	Germany	N
Santhya et al	Yes, Mixed use in both groups	OS	HR = 1.36 (p=0.54) favors EBRT	BCF, GI/GU toxicity	BCF: HR=0.42 (p=0.02), favors HDR-BT+EBRT; GI/GU toxicity: p=NS	Canada	No

Smith et al	Yes - Mixed used in all groups	HQoL	Reported on a variety of results from their HQoL questionnaire	No	N/A	Australia	Y
Talcott et al	Yes - Mixed use in both groups	SF-36	Reported on a variety of results from SF-36 questionnaire	No	N/A	USA	Y
Vassil et al	Yes - Mixed use in both groups	bFFS (Phoenix)	LDR-BT vs. EBRT HR = 0.99 (95% CI 0.62-1.58, p=0.97)	No	N/A	USA	Y
Wong et al	Yes - Mixed use in all groups	bFFS (Phoenix)	Actuarial percentages @ 5 years: 94% (LDR-BT) vs. 74% (3D-CRT) vs. 87% (IMRT) vs. 94% (LDR-BT+EBRT), p<0.001	OS	Actuarial percentages @ 5 years: 97% (LDR-BT) vs. 97% (EBRT) vs. 97% (LDR-BT+EBRT), p=NR	USA	N
Zelefsky et al	Yes - Mixed use in all groups	bFFS (ASTRO1)	Actuarial percentages @ 5 years: 88% (LDR-BT) vs. 82% (EBRT), p=0.09	Urethral stricture incidence	Actuarial percentages @ 5 years: 12% (LDR-BT) vs. 2% (EBRT), p<0.01	USA	N
Zelefsky et al	Yes - Mixed in both groups	Late Grade 2 GI/GU toxicity	Hazard Ratios for LDR-BT vs. LDR-BT+EBRT: Grade 2 GI Toxicity: 8.9 (p<0.001); Grade 2 GU Toxicity: 2.3 (p<0.01)	No	N/A	USA	Y
Zelefsky et al	Yes- Mixed use in both groups	bFFS (Phoenix)	Actuarial percentages @ 7 years: 95% (LDR-BT) vs. 89% (EBRT), p=0.04	No	N/A	USA	N
Zhou et al	NR	OS	Actuarial percentages @ 7 years: 82% (BT) vs. 72% (EBRT), p<0.001	DSS	Actuarial percentages @ 7 years: 97% (BT) vs. 94% (EBRT), p<0.001	USA	Y

Appendix I: Continued.

Author	Mean/Median Follow-Up (months)	Total Follow-Up Time (Years)	Mean/Median Age of Patients (Years)	Independent, low-, intermediate-, high-risk assessment?
Abel-Wahab et al	40 (BT) vs. 64 (EBRT) vs. 46 (BT+EBRT)	16 years	67 (BT) vs. 71 (EBRT) vs. 68 (BT+EBRT)	No
Aoki et al	NR	>3 years	68 (LDR-BT) vs. 71 (LDR-BT+EBRT)	No

Beyer et al	51 (LDR-BT) vs. 41 (EBRT)	8 years	74 for both	No
Burdick et al	54 (LDR-BT) vs. 54 (EBRT)	10 years	70 (LDR-BT) vs. 69.5 (EBRT)	No
Coen et al	103 (Proton EBRT) vs. 89 (LDR-BT)	>10 years	67 (Proton EBRT) vs. 65 (LDR-BT)	No significant difference in bFFS (Phoenix) in low-risk (p=0.74) or intermediate-risk (p=0.21)
D'Amico et al	41 (LDR-BT) vs. 38 (EBRT)	5 years	NR	Yes - see primary outcome results
da Silva Franca et al	105 (LDR-BT) vs. 60 (LDR-BT+EBRT)	5 Years	66 (LDR-BT) vs. 68 (LDR-BT+EBRT)	No
Davis et al	22 (LDR-BT) vs. 30 (EBRT)	NR	67 (LDR-BT) vs. 69 (EBRT)	No
Deutsch et al	53 (EBRT) 47 (HDR-BT+EBRT)	> 8 Years	68 (EBRT) vs. 65 (HDR-BT+EBRT)	Actuarial percentages @ 5 years: Low-risk: 98% (EBRT) vs. 100% (HDR-BT+EBRT), p=0.71; Intermediate-risk: 84% (EBRT) vs. 100% (HDR-BT+EBRT), p<0.001; High-risk: 71% (EBRT) vs. 93% (HDR-BT+EBRT), p=0.23
Eade et al	48 (LDR-BT) vs. 43 (EBRT)	4 years	65 (LDR-BT) vs. 68 (EBRT)	No
Elliot et al	32 (BT) vs. 32 (EBRT)	4 years	NR	No
Ferrer et al	24 (LDR-BT) vs. 24 (EBRT)	2 years	67 (LDR-BT) vs. 69 (EBRT)	No
Gelbium et al	48 for all patients	>4 years	NR	No
Goldner et al	44 (LDR-BT) vs. 41 (74 Gy EBRT) vs. 81 (70 Gy EBRT)	10 years	64 (LDR-BT) vs. 71 (EBRT)	N/A - all low-risk patients
Gondi et al	34 for all patients	5 years	NR	No
Huang et al	NR	4 Years	NR	No
Joseph et al	12 for all patients	1 year	69 (EBRT) vs. 69 (HDR-BT+EBRT)	No
Kalakota et al	41 for all patients	4 years	65 (LDR-BT) vs. 63 (LDR-BT+EBRT)	No
Klein et al	39 (LDR-BT) vs. 58 (EBRT)	>8 years	NR	N/A - all intermediate-risk patients
Khor et al	68 (EBRT) vs. 61 (HDR-BT+EBRT)	10 years	69 (EBRT) vs. 67 (HDR-BT+EBRT)	Hazard Ratios for HDR-BT+EBRT vs. EBRT: Intermediate-risk: 0.44 (95% CI 0.28-0.70, p<0.001); High-risk: 0.82 (95% CI 0.52-1.28, p=0.38)
Krestin et al	30 (EBRT) vs. 30 (HDR-BT+EBRT)	6 years	74 (EBRT) vs. 69 (HDR-BT+EBRT)	No

Kupelian et al	47 (LDR-BT) vs. 49 (EBRT≥72Gy) vs. 75 (EBRT<72Gy) vs. 46 LDR-BT+EBRT	7 Years	70 (LDR-BT) vs. 68 (EBRT≥72Gy) vs. 70 (EBRT<72Gy) vs. 69 LDR-BT+EBRT	No
Lee et al	12 (BT) vs. 12 (EBRT)	1 Year	67 (LDR-BT) vs. 69 (EBRT)	No
Lev et al	12 for all patients	1 Year	67 (LDR-BT+EBRT) vs. 68 (HDR-BT+EBRT)	No
Nieder et al	49 for all patients	>10 years	NR	No
Ojha et al	46 (BT) vs. 67 (EBRT)	>10 years	67 (BT) vs. 71 (EBRT)	No
Pe et al	37 (BT) vs. 51 (EBRT)	7 years	65 (LDR-BT) vs. 70 (EBRT)	N/A - all low-risk patients
Pickles et al	68 (LDR-BT) vs. 67 (EBRT)	7 years	64 (LDR-BT) vs. 71 (EBRT) (*did not match on age)	Actuarial percentages @ 5 years: Low-risk: 94% (LDR-BT) vs. 88% (EBRT), p<0.001; Int-risk: 100% (LDR-BT) vs. 78% (EBRT), p=0.02
Pinkawa et al	76 (BT) vs. 67 (EBRT)	5 years	69 (LDR-BT) vs. 71 (EBRT) vs. 72 (HDR-BT+EBRT)	No
Santhya et al	NR	10 years	65 HDR-BT+EBRT vs. 66 EBRT	BCF favors HDR-BT+EBRT in both Int-risk and High-risk; Int-risk: HR=0.30 (p=0.03); High-risk: HR=0.47(p=0.03)
Smith et al	NR	3 years	60 (LDR-BT) vs. 62 (HDR-BT) vs. 64 (EBRT)	No
Talcott et al	24 (BT) vs. 24 (EBRT)	2 Years	65 (BT) vs. 69 (EBRT)	No
Vassil et al	65 for all patients	5 years	69 (LDR-BT) vs. 68 (EBRT)	N/A - all intermediate-risk patients
Wong et al	49 (LDR-BT) vs. 62 (3D-CRT) vs. 56 (IMRT) vs. 63 (LDR-BT+EBRT)	5 years	NR	Actuarial percentages @ 5 years: Low-risk: 97% (LDR-BT) vs. 92% (3D-CRT) vs. 93% (IMRT) vs. 100% (LDR-BT+EBRT), p=0.30; Intermediate-risk: 94% (LDR-BT) vs. 74% (3D-CRT) vs. 88% (IMRT) vs. 94% (LDR-BT+EBRT), p<0.001; High-risk: 50% (LDR-BT) vs. 55% (3D-CRT) vs. 76% (IMRT) vs. 100% (LDR-BT+EBRT), p=0.18
Zelefsky et al	24 (LDR-BT) vs. 36 (EBRT)	> 7 Years	68 (LDR-BT) vs. 64 (EBRT)	N/A - all low-risk patients
Zelefsky et al	30 for all patients	NR	NR	No

Zelefsky et al	77 (LDR-BT) vs. 76 (EBRT)	8 years	65 (LDR-BT) vs. 66 (EBRT)	N/A - all low-risk patients
Zhou et al	NR	7 years	NR	NR

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; BCF = biochemical or clinical failure: a PSA failure or clinical failure or death; bFFS(ASTRO1) = biochemical relapse-free survival, American Society for Therapeutic Radiology and Oncology definition: three consecutive rising PSA levels after nadir; bFFS(Phoenix) = biochemical failure-free survival, American Society for Therapeutic Radiology and Oncology Phoenix definition: a PSA level of 2ng/mL or more than nadir; BT = brachytherapy of unknown type; BT+EBRT = brachytherapy of unknown type with adjuvant external beam radiation therapy; DSS = disease specific survival: date from therapy to prostate cancer death; EBRT = external beam radiation therapy; EPIC = Expanded Prostate Cancer Index Composite Questionnaire: a 50 item instrument created at the University of California to assess prostate cancer patient reported urinary, bowel, sexual, and hormonal functioning; FACT-P= Functional Assessment of Cancer Therapy-Prostate: a 12 item questionnaire specifically designed to measure quality of life in prostate cancer patients; FFS = failure free survival: initiation of secondary therapy, positive biopsy post-treatment, PSA rise of 10 ng/dL or more even without three consecutive elevations, development of metastasis; GEE = generalized estimating equation modeling; Grade 2 GI Toxicity = Radiation Therapy Oncology Group defined grade 2 gastrointestinal side effect which includes any symptom of moderate nature requiring medical therapy eg. rectal bleeding requiring suppositories; Grade 2 GU Toxicity = Radiation Therapy Oncology Group defined grade 2 genitourinary side effects which includes any symptom of moderate nature requiring medical therapy eg. urinary urgency or dysuria; HDR-BT = high dose rate brachytherapy; HDR-BT+EBRT = high dose rate brachytherapy with adjuvant external beam radiation therapy; HQoL = health quality of life; IMRT = intensity modulated radiation therapy; LDR-BT = low dose rate brachytherapy; LDR-BT+EBRT = low dose rate brachytherapy with adjuvant external beam radiation therapy; N/A = Not Applicable; NR = not reported; NS = none significant; OS = overall survival: date from therapy to death from any cause; PSAF = prostate specific antigen failure = a patient must have 3 consecutive rising PSA values each obtained at least 3 months apart; RFS = recurrence free survival: date from treatment until clinically diagnosed recurrence under radiography or biopsy; SF-36 = Medical Outcomes Study 36-Item Short Form Questionnaire: contains 36 items covering eight dimensions of health related quality of life including physical function, pain, general health, vitality, social, emotional, and mental health; Tx = treatment group;

Appendix II

Literature Search Strategy for CER Articles Comparing Different RT Modalities

Appendix II: Literature Search Strategy for CER Studies Comparing Primary RT Modalities

The literature search for CER articles directly comparing primary RT modalities was conducted using the electronic databases of Pubmed, MEDLINE (OVID), Cochrane Library, EMBASE, and Google Scholar; also the clinical trials registry at 'www.clinicaltrials.gov' was searched to identify any potential RCTs. The search period was from January 1, 1996 to December 2013 and was limited to English publications. The following key terms were used in combination to search the databases: prostate, prostate cancer, cancer, comparative effectiveness, brachytherapy, external beam radiation therapy, external beam radiotherapy, versus, randomized trial, radiation therapy or radiotherapy, high-dose rate, low-dose rate, intensity modulated radiation therapy, survival, biochemical failure, PSA failure, toxicity, impotency, secondary cancer, and quality of life. Relevant studies were also searched for in review articles or on reference lists of identified articles. The relevant RT guideline websites such as the RTOG and the European Organization for Research and Treatment of Cancer were checked for systematic reviews and randomized trials. All articles included in this review required a sample size ≥30 patients and must have directly compared at least two RT treatment modalities with respect to the outcomes of overall survival, biochemical or PSA failure, late toxicities or side effects, or patient reported outcomes.

Appendix III

ProCaRS Variable List and Descriptions

PROCARS: Variable List (Last Updated December 2, 2013)

#	Variable	Description
1	ID	Patient ID Number: Centre-XX (e.g. BCCA-1012)
2	ID2	Patient ID Number: 1, 2, 3,...,7973, 7974 [For Sorting Purposes Only]
3	ID_PMH	Patients included in PMH cohorts only
4	PMH_9907	Patients included in PMH Trial #9907 cohort only
5	Centre	Centre: 1, 2, 3, 4
6	Centrex	Centre: Description
7	Cohort_7cat	Cohort (7 categories): BCCA, PMH LDR, PMH Dose Escalation, PMH Trial #9907, Laval LDR, Laval HDR+EBRT, McGill
8	Age	Age
9	BasePSA	Baseline PSA (ng/mL)
10	BasePSA_ROUND	Baseline PSA (ng/mL) **ROUNDED TO NEAREST WHOLE NUMBER**
11	Tstage	T-Stage: '4', '8' and '12' corresponding to Tstage '2', '3' and '4' coded as MISSING **IGNORE**
12	Tstage_CRU	T-Stage: '4', '8' and '12' corresponding to Tstage '2', '3' and '4' RETAINED **IGNORE**
13	Tstage_CORR	T-Stage (including Sub-Type): n = 7839 (frequency missing = 135)
14	Tstage_CORR_4cat	T-Stage (excluding Sub-Type): n = 7839 (frequency missing = 135)
15	Tstage_CORR_4catx	T-Stage (excluding Sub-Type): n = 7860 (frequency missing = 114)
16	TNMyear	TNM Year
17	GleasonPattern	Gleason Pattern: 1, 2, 3,...24, 25
18	GleasonPattern_CORR	Gleason Pattern: 1+1, 1+2...5+4, 5+5
19	GleasonMajor	Gleason Major: 1st number in pattern **DO NOT USE**
20	GleasonMajor_CORR	Gleason Major: Re-derived based on FIRST number in Gleason Pattern **CORRECTED**
21	GleasonMinor	Gleason Minor: 2nd number in pattern **DO NOT USE**
22	GleasonMinor_CORR	Gleason Minor: Re-derived based on SECOND number in Gleason Pattern **CORRECTED**
23	GleasonTotal	Total Gleason Score: Add 2 numbers in pattern **DO NOT USE**
24	GleasonTotal_CORR	Total Gleason Score: Re-derived based on corrected Gleason Major and Minor **CORRECTED**
25	GleasonTotal_CORR_4cat	Total Gleason Score (4 categories): (1) 2-5, (2) 6, (3) 7, (4) 8-10
26	Cores_total	Biopsy Cores: Total Number
27	Cores_pos	Biopsy Cores: Number of cores containing any cancer
28	Cores_neg	Biopsy Cores: Number of cores NOT containing any cancer
29	Cores_rejected	Biopsy Cores: Number of cores rejected
30	PosCores_Percent	Biopsy Cores: Percent of Positive Cores
31	PosCores_ge50pct	Biopsy Cores: Positive Cores: (1) $\geq$ 50 % , (0) < 50%
32	Bilateral_biopsy_pos	Bilateral Biopsy Status: 0, 1, 8, 9

PROCARS: Variable List (Last Updated December 2, 2013)

#	Variable	Description
33	Bilat_Biopsy_Status_CORR	Bilateral Biopsy Status: No, Yes, Unknown, N/A
34	Hormones	Hormones: (1) Yes, (0) No
35	HormStart	Hormones: Start Date
36	HormEnd	Hormones: End Date
37	AdjHT_months	Adjuvant Hormone Therapy (Months): ZEROs coded as MISSING
38	AdjHT_months_OLD	Adjuvant Hormone Therapy (Months): ZEROs kept as ZEROs (for modeling)
39	RTStart	RT Start Date
40	RTStart_Year	RT Start Year
41	RTStart_Year_4cat	RT Start Year (4 categories): (1) 1994-1999, (2) 2000-2002, (3) 2003-2005, (4) 2006-2010
42	RTEnd	RT End Date
43	RTdays	Number of Days of RT
44	EBRT	EBRT: (1) Yes, (0) No
45	EBRT_Dose	EBRT Dose (cGy)
46	EBRT_Dose_GT70	EBRT Dose: (1) > 70 Gy, (0) ≤ 70 Gy
47	EBRT_Dose_GT70x	EBRT Dose Label
48	EBRT_Fractions	EBRT: Number of Fractions
49	EBRT_FractionDose	EBRT: Dose per Fraction (cGy)
50	EBRT_BED_Gy	EBRT Biologic Equivalent Dose (Gy)
51	LDR	LDR: Low Dose Rate Brachytherapy
52	LDR_Dose	
53	LDR_Fractions	
54	HDR	HDR: High Dose Rate Brachytherapy
55	HDR_Dose	
56	HDR_Fractions	
57	Brachy	Brachytherapy: (1) Yes, (0) No
58	Radiation_Type	Radiation Type: Brachy + EBRT, Brachy only, EBRT only
59	Radiation_Type_5cat	Radiation Type (5 categories): Brachy(LDR) only, Brachy(HDR) only, EBRT only, Brachy(LDR) + EBRT, Brachy(HDR) + EBRT
60	LocalRelapse	Clin/Path confirmed Local Relapse
61	LocalRelapseDate	Date of Local Relapse
62	PostRTHormStart	Salvage Hormone Therapy Start Date
63	Dead	Dead: (1) Dead, (0) Alive
64	Dead_5yr	Dead (≤ 5 years): (1) Dead, (0) Alive
65	Status	
66	StatDate	
67	Survival_months	Survival in MONTHS
68	Surmon	

PROCARS: Variable List (Last Updated December 2, 2013)

#	Variable	Description
69	AliveDate	
70	DeathDate	Date of Death
71	DeathCause	
72	CauseofDeath	Cause of Death
73	CauseofDeath_CORR	
74	CauseofDeath_CORRx	Denominator = 7974
75	Date_data_pulled	
76	Notes	
77	PSADT2	
78	PSAvelocity	
79	PSADT	
80	npsa	
81	BrachyAINorm	
82	rownames	
83	Amico	AMICO Classification: Low, Intermediate, High
84	GUROC	GUROC Classification: Low, Intermediate, High
85	GUROC2	GUROC2 Classification: 1, 2, 3
86	GUROC_OLD	**UNCORRECTED VERSION (For Earlier Manuscript(s))**
87	GUROC2_OLD	**UNCORRECTED VERSION (For Earlier Manuscripts(s))**
88	CAPSURE	CAPSURE Classification: Low, Intermediate, High
89	EAU	EAU Classification: Low, Intermediate, High
90	NICE	NICE Classification: Low, Intermediate, High
91	AUA	AUA Classification: Low, Intermediate, High
92	NCCN	NCCN Classification: Very Low, Low, Intermediate, High, Very High
93	NCCN_5cat	NCCN_5cat: 1, 2, 3, 4, 5
94	ESMO	ESMO Classification: Low, Intermediate, High
95	George	George Classification: Low, Intermediate, High
96	GeorgeII	GeorgeII Classification: Low, Intermediate, High
97	procars_6cat	PROCARS 6 Classification: A, B, C, D, E, F
98	procars_6catx	PROCARS 6 Classification: Extr Low, Low, Inter Low, Inter High, High, Extr High
99	procars_5cat	PROCARS 5 Classification: AB, C, D, E, F
100	procars_5catx	PROCARS 5 Classification: Low, Inter Low, Inter High, High, Extr High
101	procars_4cat	PROCARS 4 Classification: AB, C, DE, F
102	procars_4catx	PROCARS 4 Classification: Low, Inter Low, Inter High, High
103	Simplified	
104	Time	

PROCARS: Variable List (Last Updated December 2, 2013)

#	Variable	Description
105	CRS	Prostate Cancer Death (aka Cancer-Related/Specific Survival): (1) Yes, (0) No (Equivalent to "CRStatus")
106	CRS_5yr	Prostate Cancer Death (≤ 5 years): (1) Yes, (0) No
107	CRStatus	
108	CRS_months	Cancer-Related/Specific Survival in MONTHS
109	CRTime	
110	AIBFStat	
111	AIBFTime	
112	AIBFFSStat	
113	AIBFFSTime	
114	AIBFFS2Stat	
115	AIBFFS2Time	
116	AIHSTBFStat	
117	AIHSTBFTime	
118	AIHSTBFFSStat	
119	AIHSTBFFSTime	
120	AIHSTBFFS2Stat	
121	AIHSTBFFS2Time	
122	PhBFStat	
123	PhBFTime	
124	PhBFFSStat	
125	PhBFFSTime	
126	BFFS2	Biochemical Failure (aka Biochemical-Failure-Free Survival): (1) Yes, (0) No (Equivalent to "PhBFFS2Stat" - Phoenix Version #2)
127	BFFS2_5yr	Biochemical Failure (≤ 5 years): (1) Yes, (0) No
128	PhBFFS2Stat	
129	BFFS2_months	Biochemical-Failure-Free Survival in MONTHS
130	PhBFFS2Time	
131	BFFS2_months_5yr	Biochemical-Failure-Free Survival in MONTHS (corresponds with "BFFS2_5yr")
132	BFFS2_to_CRS_months	Time (months) from Biochemical Failure (BFFS2) to Prostate Cancer Death (CRS)
133	BFFS2_CORR	Biochemical Failure CORRECTED for PSA bounce (Brachytherapy patients with NO post-RT hormone therapy meeting previous ASTRO II Phoenix definition censored if LAST PSA ≤ 0.5 ng/mL).
134	BFFS2_CORR_months	Biochemical-Failure-Free Survival CORRECTED in MONTHS
135	PSA_Bounce	PSA Bounce (assessed for brachytherapy patients with NO post-RT hormone therapy and ASTRO II BF): (1) LAST PSA ≤ 0.5 ng/mL, (0) LAST PSA > 0.5 ng/mL [opposite to BFFS2_CORR]

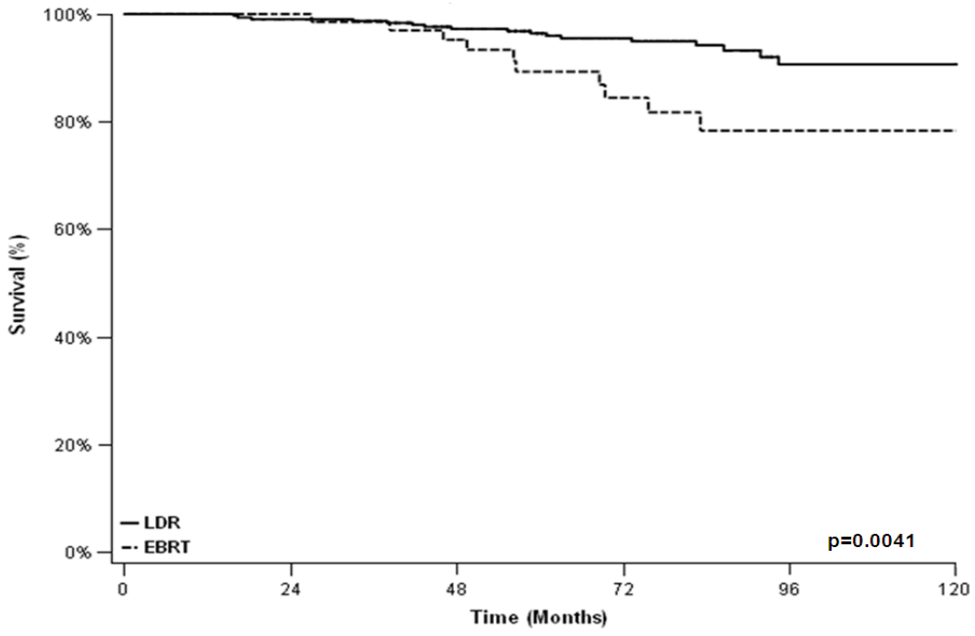
PROCARS: Variable List (Last Updated December 2, 2013)

#	Variable	Description
136	Nadir_PSA	Nadir PSA (ng/mL)
137	Nadir_Months	Time-to-Nadir in MONTHS

Appendix IV

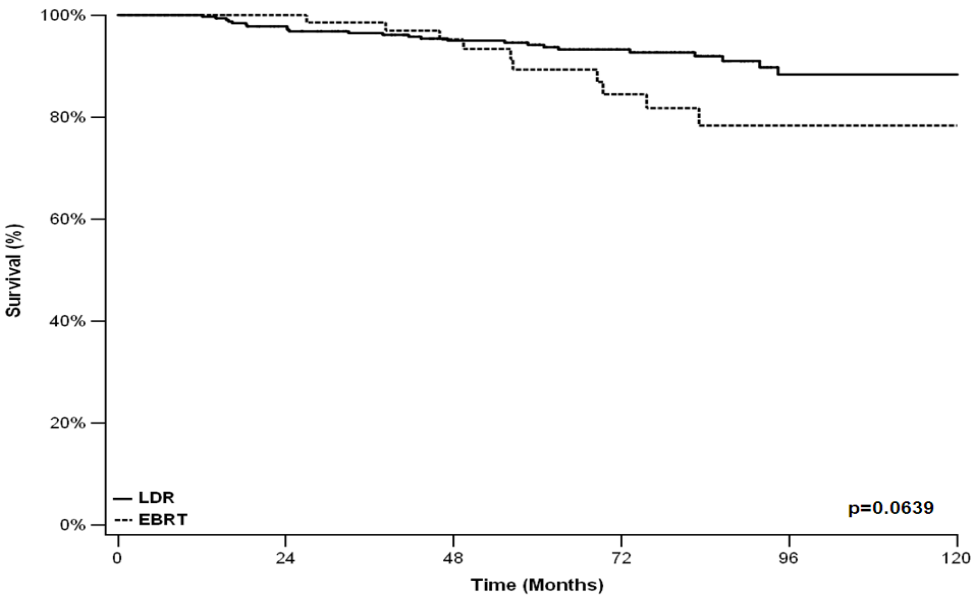
Kaplan Meier Curves of bFFS with and Without Accounting for PSA Bounce

Low-risk bFFS Match with or Without Accounting for PSA Bounce:



Patients at Risk						
LDR	320	305	251	173	59	7
EBRT	80	71	52	34	7	0

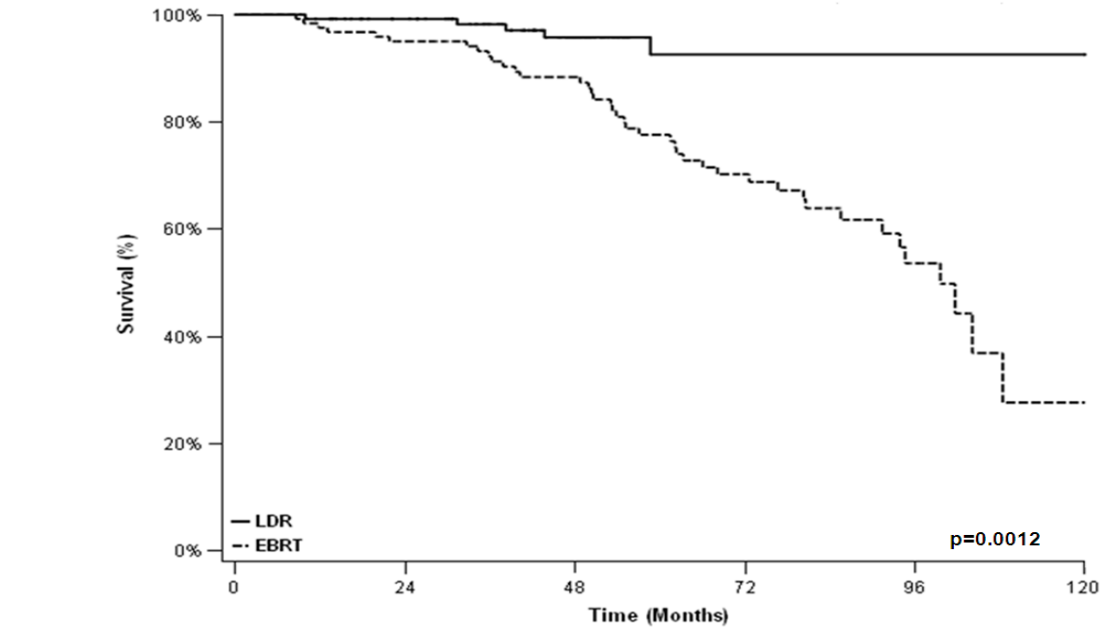
(Accounting for PSA Bounce)



Patients at Risk						
LDR	320	301	244	167	57	6
EBRT	80	71	52	34	7	0

(Not Accounting for PSA Bounce)

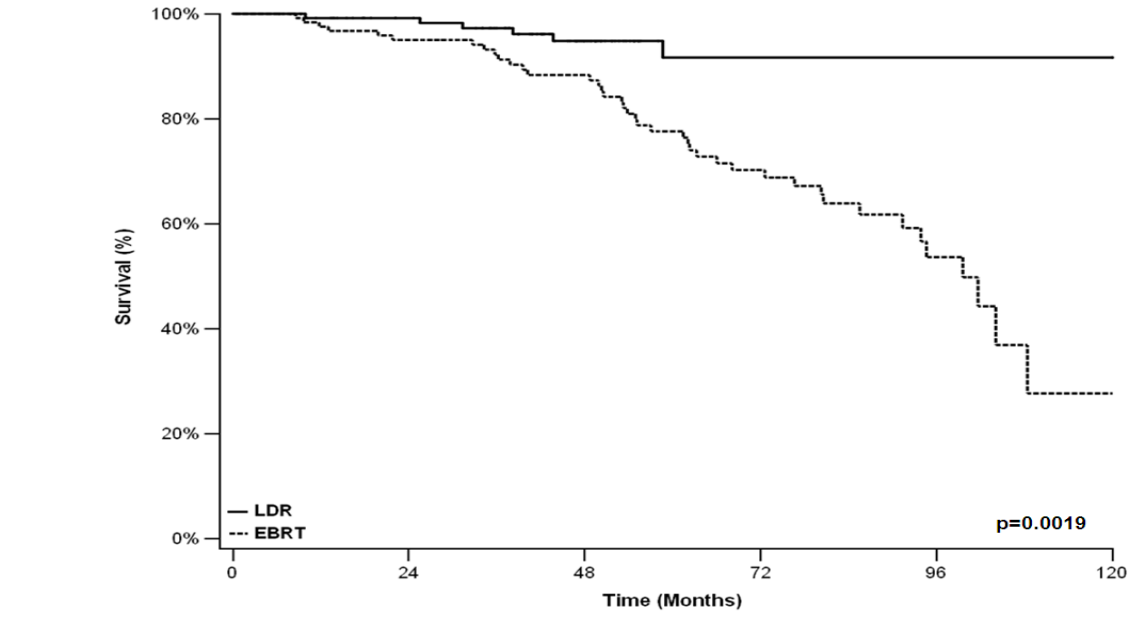
Intermediate-risk LDR-BT vs. EBRT Match with or Without Accounting for PSA Bounce:



Patients at Risk

LDR	127	108	62	13	3	0
EBRT	127	110	86	49	16	3

(Accounting for PSA bounce)

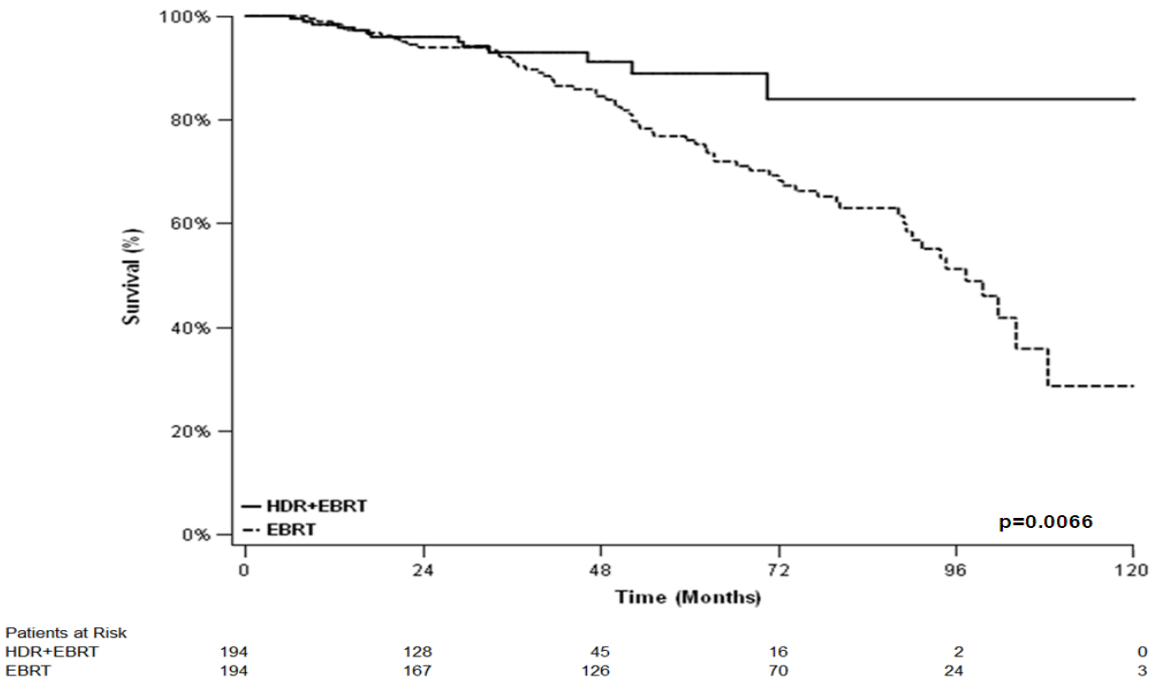


Patients at Risk

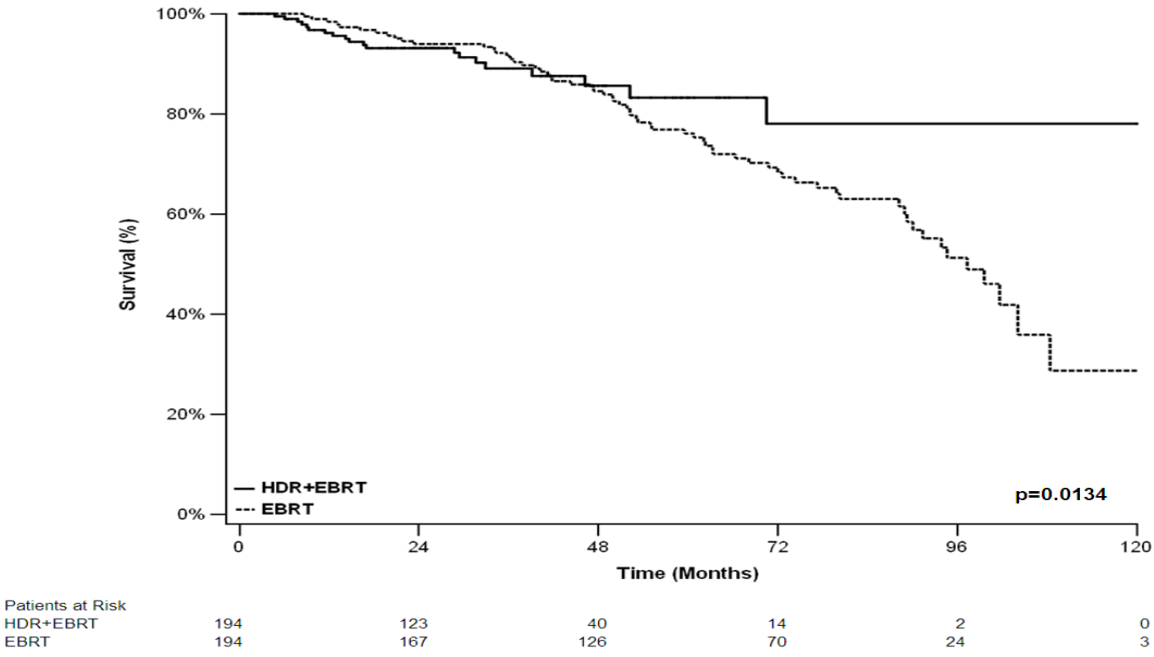
LDR	127	108	61	13	3	0
EBRT	127	110	86	49	16	3

(Not Accounting for PSA Bounce)

Intermediate-risk HDR-BT+EBRT vs. EBRT Match with or Without Accounting for PSA Bounce:



(Accounting for PSA Bounce)



(Not Accounting for PSA Bounce)

Appendix V

SAS Code for Intermediate-Risk Cohort Selection

SAS Code for Selection Process (Intermediate-Risk):

```
libname thesis 'P:\Graham\Thesis';
data Procars_Interm_Risky;
set thesis.procars_final_03dec2013;
where GUROC = 'Interm';
/*Adjust for T-Stage year, Remove Gleason total 2to5*/
if TNMyear = '0' and Tstage_CORR = '2b' then delete;
if GleasonTotal_CORR_4Cat = '1_2to5' then delete;
if Tstage_CORR = '2b' and TNMyear = '1997' then Tstage_3cat = '3';
if Tstage_CORR = '2b' and TNMyear = '2002' then Tstage_3cat = '2';
if Tstage_CORR = '2b' and TNMyear = '1992' then Tstage_3cat = '2';
if Tstage_CORR = '2a' then Tstage_3cat = '2';
if Tstage_CORR = '2c' then Tstage_3cat = '3';
if Tstage_CORR = '1a' or Tstage_CORR = '1b' or Tstage_CORR = '1c' then Tstage_3cat = '1';
run;
proc freq data=procars_interm_risky;
tables Radiation_Type_5cat /list;
run;
```

Create T-Stage and Gleason Pattern Variables for Standardized Difference Testing:

```
data thesis.procars_interm_risk;
set procars_interm_risky;
if Tstage_3cat = 1 then Tstage_T1 = 1;
if Tstage_3cat = 2 or Tstage_3cat = 3 then Tstage_T1 = 0;
if Tstage_3cat = 2 then Tstage_LowT2 = 1;
if Tstage_3cat = 1 or Tstage_3cat = 3 then Tstage_LowT2 = 0;
if Tstage_3cat = 3 then Tstage_HighT2 = 1;
if Tstage_3cat = 1 or Tstage_3cat = 2 then Tstage_HighT2 = 0;
if GleasonTotal_CORR_4cat = "2_6" then GleasonTotal_7 = 0;
if GleasonTotal_CORR_4cat = "3_7" then GleasonTotal_7 = 1;
if GleasonPattern_CORR = "3+4" then GleasonPattern_CORRx3plus4 = 1;
if GleasonPattern_CORR = "4+3" or GleasonPattern_CORR = "3+3" or GleasonPattern_CORR = "." then
GleasonPattern_CORRx3plus4 = 0;
if GleasonPattern_CORR = "4+3" then GleasonPattern_CORRx4plus3 = 1;
if GleasonPattern_CORR = "3+4" or GleasonPattern_CORR = "3+3" or GleasonPattern_CORR = "." then
GleasonPattern_CORRx4plus3 = 0;
if GleasonPattern_CORR = "3+3" then GleasonPattern_CORRx3plus3 = 1;
if GleasonPattern_CORR = "3+4" or GleasonPattern_CORR = "4+3" or GleasonPattern_CORR = "." then
GleasonPattern_CORRx3plus3 = 0;
run;

proc freq data=thesis.procars_interm_risk;
table GleasonTotal_7*GleasonTotal_CORR_4cat Tstage_T1*Tstage_3cat Tstage_LowT2*Tstage_3cat
Tstage_HighT2*Tstage_3cat/list;
run;
```

Initial Selection of intermediate-risk cohort, including ensuring patients have info on outcomes, important baseline factors, adequate RT dose and NO hormones:

```
libname thesis 'P:\Graham\Thesis';
data thesis.Interm_Risk_PS;
set thesis.Procars_Interm_Risk;
if Tstage = '.' then delete;
```

```
if Age = '.' then delete;
if BasePSA = '.' then delete;
if GleasonTotal_CORR = '.' then delete;
if Dead = '.' then delete;
if Survival_months = '.' then delete;
if BFFS2_months = '.' then delete;
if BFFS2 = '.' then delete;
if Radiation_Type_5cat = 'EBRT_only' and EBRT_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and HDR_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(LDR)_only' and LDR_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_only' or Radiation_Type_5cat = 'Brachy(LDR)_and_EBRT' then
delete;
if Radiation_Type_5cat = 'EBRT_only' and EBRT_Dose < 7400 then delete;
if Radiation_Type_5cat = 'EBRT_only' and EBRT_Dose = 7524 then delete;
if Radiation_Type_5cat = 'Brachy(LDR)_only' and LDR_Dose < 14400 then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4400 and HDR_Dose = 1000
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4400 and HDR_Dose = 1800
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4400 and HDR_Dose = 1900
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4200 and HDR_Dose = 2000
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4500 and HDR_Dose = 2000
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4600 and HDR_Dose = 2000
then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' and EBRT_Dose = 4700 and HDR_Dose = 2000
then delete;
where hormones = 0;
run;
proc freq data=thesis.Interm_Risk_PS;
tables Radiation_Type_5cat Radiation_Type_5cat*Centre Radiation_Type_5cat*RTStart_year/list;
```

Appendix VI

SAS Code for Low-Risk Cohort Selection

SAS Code for Selection Process (Low-Risk):

```
libname thesis 'P:\Graham\Thesis';
data Procars_Low_Risky;
set thesis.procars_final_03dec2013;
if GUROC = 'Low';
/*Adjust for T-Stage Year, Restrict RT-Start Year*/
if TNMyear = '0' and Tstage_CORR = '2b' then delete;
if RTStart_Year < 1999 then delete;
if RTStart_Year > 2006 then delete;
if Tstage_CORR = '2b' and TNMyear = '1997' then Tstage_3cat = '3';
if Tstage_CORR = '2b' and TNMyear = '2002' then Tstage_3cat = '2';
if Tstage_CORR = '2b' and TNMyear = '1992' then Tstage_3cat = '2';
if Tstage_CORR = '2a' then Tstage_3cat = '2';
if Tstage_CORR = '2c' then Tstage_3cat = '3';
if Tstage_CORR = '1a' or Tstage_CORR = '1b' or Tstage_CORR = '1c' then Tstage_3cat = '1';
run;
proc freq data=Procars_Low_Risky;
tables Tstage_CORR*TNMyear*Tstage_3cat/list;
run;
```

Create T-Stage, Gleason Total, RT-Start Year and Treatment Centre Variables for Standardized Difference Testing:

```
data thesis.Procars_Low_Risk;
set Procars_Low_Risky;
if Tstage_3cat = 1 then Tstage_T1 = 1;
if Tstage_3cat = 2 or Tstage_3cat = 3 then Tstage_T1 = 0;
if Tstage_3cat = 2 then Tstage_LowT2 = 1;
if Tstage_3cat = 1 or Tstage_3cat = 3 then Tstage_LowT2 = 0;
if Tstage_3cat = 3 then Tstage_HighT2 = 1;
if Tstage_3cat = 1 or Tstage_3cat = 2 then Tstage_HighT2 = 0;
if GleasonTotal_CORR_4cat = "1_2to5" then GleasonTotal_6 = 0;
if GleasonTotal_CORR_4cat = "2_6" then GleasonTotal_6 = 1;
if RTStart_Year = 1999 then RTStart_Year_1999 = 1;
if RTStart_Year > 1999 then RTStart_Year_1999 = 0;
if RTStart_Year = 2000 then RTStart_Year_2000 = 1;
if RTStart_Year > 2000 then RTStart_Year_2000 = 0;
if RTStart_Year < 2000 then RTStart_Year_2000 = 0;
if RTStart_Year = 2001 then RTStart_Year_2001 = 1;
if RTStart_Year > 2001 then RTStart_Year_2001 = 0;
if RTStart_Year < 2001 then RTStart_Year_2001 = 0;
if RTStart_Year = 2002 then RTStart_Year_2002 = 1;
if RTStart_Year > 2002 then RTStart_Year_2002 = 0;
if RTStart_Year < 2002 then RTStart_Year_2002 = 0;
if RTStart_Year = 2003 then RTStart_Year_2003 = 1;
if RTStart_Year > 2003 then RTStart_Year_2003 = 0;
if RTStart_Year < 2003 then RTStart_Year_2003 = 0;
if RTStart_Year = 2004 then RTStart_Year_2004 = 1;
if RTStart_Year > 2004 then RTStart_Year_2004 = 0;
if RTStart_Year < 2004 then RTStart_Year_2004 = 0;
if RTStart_Year = 2005 then RTStart_Year_2005 = 1;
if RTStart_Year > 2005 then RTStart_Year_2005 = 0;
if RTStart_Year < 2005 then RTStart_Year_2005 = 0;
if RTStart_Year = 2006 then RTStart_Year_2006 = 1;
```

```
if RTStart_Year > 2006 then RTStart_Year_2006 = 0;
if RTStart_Year < 2006 then RTStart_Year_2006 = 0;
if centre = 1 then centre1 = 1;
if centre = 2 or centre = 3 then centre1 = 0;
if centre = 2 then centre2 = 1;
if centre = 1 or centre = 3 then centre2 = 0;
if centre = 3 then centre3 = 1;
if centre = 2 or centre = 1 then centre3 = 0;
run;

proc freq data=thesis.Procars_Low_Risk;
table GleasonTotal_6*GleasonTotal_CORR_4cat Tstage_T1*Tstage_3cat Tstage_LowT2*Tstage_3cat
Tstage_HighT2*Tstage_3cat/list;
run;
```

Initial Selection of low-risk cohort, including ensuring patients have info on outcomes, important baseline factors, adequate RT dose and NO hormones:

```
Title 'Low Risk Propensity Score';
libname thesis 'P:\Graham\Thesis';
data thesis.Low_Risk_PS;
set thesis.Procars_Low_Risk;
if Tstage = '.' then delete;
if Age = '.' then delete;
if BasePSA = '.' then delete;
if GleasonTotal_CORR = '.' then delete;
if Dead = '.' then delete;
if Survival_months = '.' then delete;
if BFFS2_months = '.' then delete;
if BFFS2 = '.' then delete;
if Radiation_Type_5cat = 'EBRT_only' and EBRT_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(LDR)_only' and LDR_Dose = '.' then delete;
if Radiation_Type_5cat = 'Brachy(HDR)_only' or Radiation_Type_5cat = 'Brachy(LDR)_and_EBRT' or
Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' then delete;
if Radiation_Type_5cat = 'EBRT_only' and EBRT_Dose < 7000 then delete;
if Radiation_Type_5cat = 'Brachy(LDR)_only' and LDR_Dose < 14400 then delete;
where Hormones = 0;
run;
proc freq data=thesis.Low_Risk_PS;
tables Radiation_Type_5cat*Hormones EBRT_Dose*Radiation_Type_5cat LDR_Dose
Radiation_Type_5cat/list;
run;
```

Appendix VII

SAS Code for PS Model and Matching Intermediate-risk LDR-BT vs. EBRT

Code for LDR-BT vs. EBRT Intermediate-risk PS match:

```
Title 'Intermediate Risk EBRT vs. LDR';
libname thesis 'P:\Graham\Thesis';
Data Thesis.IR_PS_EBRTvsLDR;
set thesis.Interm_Risk_PS;
if Radiation_Type_5cat = 'Brachy(HDR)_and_EBRT' then delete;
if Radiation_Type_5cat = 'EBRT_only' then Tx = 0;
if Radiation_type_5cat = 'Brachy(LDR)_only' then Tx = 1;
/*Create RT Start Year and Treatment Centre Variables for Standardized Difference Testing*/
if RTStart_Year = 1996 then RTStart_Year_1996 = 1;
if RTStart_Year > 1996 then RTStart_Year_1996 = 0;
if RTStart_Year = 1997 then RTStart_Year_1997 = 1;
if RTStart_Year > 1997 then RTStart_Year_1997 = 0;
if RTStart_Year < 1997 then RTStart_Year_1997 = 0;
if RTStart_Year = 1998 then RTStart_Year_1998 = 1;
if RTStart_Year > 1998 then RTStart_Year_1998 = 0;
if RTStart_Year < 1998 then RTStart_Year_1998 = 0;
if RTStart_Year = 1999 then RTStart_Year_1999 = 1;
if RTStart_Year > 1999 then RTStart_Year_1999 = 0;
if RTStart_Year < 1999 then RTStart_Year_1999 = 0;
if RTStart_Year = 2000 then RTStart_Year_2000 = 1;
if RTStart_Year > 2000 then RTStart_Year_2000 = 0;
if RTStart_Year < 2000 then RTStart_Year_2000 = 0;
if RTStart_Year = 2000 then RTStart_Year_2000 = 1;
if RTStart_Year > 2000 then RTStart_Year_2000 = 0;
if RTStart_Year < 2000 then RTStart_Year_2000 = 0;
if RTStart_Year = 2001 then RTStart_Year_2001 = 1;
if RTStart_Year > 2001 then RTStart_Year_2001 = 0;
if RTStart_Year < 2001 then RTStart_Year_2001 = 0;
if RTStart_Year = 2002 then RTStart_Year_2002 = 1;
if RTStart_Year > 2002 then RTStart_Year_2002 = 0;
if RTStart_Year < 2002 then RTStart_Year_2002 = 0;
if RTStart_Year = 2003 then RTStart_Year_2003 = 1;
if RTStart_Year > 2003 then RTStart_Year_2003 = 0;
if RTStart_Year < 2003 then RTStart_Year_2003 = 0;
if RTStart_Year = 2004 then RTStart_Year_2004 = 1;
if RTStart_Year > 2004 then RTStart_Year_2004 = 0;
if RTStart_Year < 2004 then RTStart_Year_2004 = 0;
if RTStart_Year = 2005 then RTStart_Year_2005 = 1;
if RTStart_Year > 2005 then RTStart_Year_2005 = 0;
if RTStart_Year < 2005 then RTStart_Year_2005 = 0;
if RTStart_Year = 2006 then RTStart_Year_2006 = 1;
if RTStart_Year > 2006 then RTStart_Year_2006 = 0;
if RTStart_Year < 2006 then RTStart_Year_2006 = 0;
if RTStart_Year = 2007 then RTStart_Year_2007 = 1;
if RTStart_Year > 2007 then RTStart_Year_2007 = 0;
if RTStart_Year < 2007 then RTStart_Year_2007 = 0;
if RTStart_Year = 2008 then RTStart_Year_2008 = 1;
if RTStart_Year > 2008 then RTStart_Year_2008 = 0;
if RTStart_Year < 2008 then RTStart_Year_2008 = 0;
if RTStart_Year = 2009 then RTStart_Year_2009 = 1;
if RTStart_Year > 2009 then RTStart_Year_2009 = 0;
if RTStart_Year < 2009 then RTStart_Year_2009 = 0;
if RTStart_Year = 2010 then RTStart_Year_2010 = 1;
```

```
if RTStart_Year > 2010 then RTStart_Year_2010 = 0;
if RTStart_Year < 2010 then RTStart_Year_2010 = 0;
if centre = 1 then centre1 = 1;
if centre = 2 or centre = 3 then centre1 = 0;
if centre = 2 then centre2 = 1;
if centre = 1 or centre = 3 then centre2 = 0;
if centre = 3 then centre3 = 1;
if centre = 2 or centre = 1 then centre3 = 0;
run;
proc freq data=Thesis.IR_PS_EBRTvsLDR;
tables Tstage_CORR*tx GleasonTotal*tx Radiation_Type_5cat*tx GleasonTotal_CORR_4cat*tx
Tstage_3cat*tx /list;
run;
```

Create PS model for LDR vs. EBRT Intermediate-risk match:

```
proc logistic descending data=Thesis.IR_PS_EBRTvsLDR;
  class GleasonTotal_CORR_4cat (param=ref ref="2_6");
  class Tstage_3cat (param=ref ref="1");
    model Tx = Age BasePSA GleasonTotal_CORR_4cat Tstage_3cat/lackfit rsquare;
  output out=Propensity_Scores predprobs=Individual;
run;
```

Create 1:1 and 2:1 PS matches for LDR vs. EBRT intermediate-risk match – Caliper 0.01:

```
data thesis.Pscores_IR_EBRTvsLDR;
  set Propensity_Scores;
  Pscore=IP_1;
  drop _from_ _into_ IP_0 IP_1;
run;

proc sort data=Thesis.Pscores_IR_EBRTvsLDR;
  by ID2;
run;

data Brachy_LDR_pscores_C1;
  set Thesis.Pscores_IR_EBRTvsLDR;
  where Tx=1;
  Brachy_LDR_ID=ID2;
  Brachy_LDR_Pscore=Pscore;
  keep Brachy_LDR_ID Brachy_LDR_Pscore;
run;
data EBRT_pscores_C1;
  set Thesis.Pscores_IR_EBRTvsLDR;
  where Tx=0;
  EBRT_ID=ID2;
  EBRT_Pscore=Pscore;
  keep EBRT_ID EBRT_Pscore;
run;
```

```
/*============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 1 ========*/
/*=================== Caliper = 0.01 =========================*/
/*============================================================*/

data Matched_C025_W1(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w1);
   length ebrt_pscore 8;
          length EBRT_ID 8;
          if _N_= 1 then do;
    declare hash h(dataset: "EBRT_pscores_C1", ordered: 'no');
    declare hiter iter('h');
    h.defineKey('EBRT_ID');
           h.defineData('EBRT_Pscore', 'EBRT_ID');
    h.defineDone();
                    call missing(EBRT_ID, EBRT_Pscore);
   end;
   set Brachy_LDR_pscores_C1;
   retain BestDistance 99;
   rc= iter.first();
   if (rc=0) then BestDistance= 99;
   do while (rc= 0);
    if (Brachy_LDR_Pscore - 0.01) <= EBRT_Pscore <= (Brachy_LDR_Pscore + 0.01) then do;
      ScoreDistance= abs(Brachy_LDR_Pscore - EBRT_Pscore);
    if ScoreDistance < BestDistance then do;
      BestDistance= ScoreDistance;
      EBRT_ID_matched= EBRT_ID;
      Brachy_LDR_ID_matched= Brachy_LDR_ID;
      C025_w1=1;
     end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
     output;
       rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;

/*============================================================*/
/*======== Remove EBRT Patients Selected in Wave 1 ===========*/
/*============================================================*/

data C025_W1_EBRT_ID;
 set Matched_C025_W1;
 EBRT_ID=EBRT_ID_matched;
 keep EBRT_ID C025_w1;
run;

proc sort data=C025_W1_EBRT_ID;
 by EBRT_ID;
run;

data C025_W2_EBRT_pscores;
 merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
      C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
 by EBRT_ID;
```

```
   if EBRT_pscores_C1;
run;

data C025_W2_EBRT_pscoresB;
  set C025_W2_EBRT_pscores;
  if C025_w1=1 then delete;
run;

/*============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 2 ==================*/
/*================== Caliper = 0.01 ============================*/
/*============================================================*/


data Matched_C025_W2(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w2);
length EBRT_ID 8;
length EBRT_pscore 8;
     if _N_ = 1 then do;
     declare hash h(dataset: "C025_W2_EBRT_pscoresB", ordered: 'no');
     declare hiter iter('h');
     h.defineKey('EBRT_ID');
     h.defineData('EBRT_pscore', 'EBRT_ID');
     h.defineDone();
                call missing(EBRT_ID, EBRT_pscore);
   end;
   set Brachy_LDR_pscores_C1;
   retain BestDistance 99;
   rc= iter.first();
   if (rc=0) then BestDistance= 99;
   do while (rc= 0);
    if (Brachy_LDR_pscore - 0.01) <= EBRT_pscore <= (Brachy_LDR_pscore + 0.01) then do;
      ScoreDistance= abs(Brachy_LDR_pscore - EBRT_pscore);
    if ScoreDistance < BestDistance then do;
      BestDistance= ScoreDistance;
      EBRT_ID_matched= EBRT_ID;
      Brachy_LDR_ID_matched= Brachy_LDR_ID;
      C025_w2=1;
    end;
   end;
   rc= iter.next();
   if (rc~= 0) and BestDistance~= 99 then do;
    output;
      rc1= h.remove(key: EBRT_ID_matched);
   end;
   end;
run;

/*============================================================*/
/*====== Remove EBRT Patients Selected in Wave 1 or 2 ================*/
/*============================================================*/

data C025_W2_EBRT_ID;
  set Matched_C025_W2;
  EBRT_ID=EBRT_ID_matched;
  keep EBRT_ID C025_w2;
run;
```

```
proc sort data=C025_W2_EBRT_ID;
  by EBRT_ID;
run;

data C025_W3_EBRT_pscores;
  merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
        C025_W2_EBRT_ID (in=C025_W2_EBRT_ID)
        C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
  by EBRT_ID;
    if EBRT_pscores_C1;
run;


/*============================================================*/
/*============= Re-Import Matched ID Datasets ================*/
/*============================================================*/

data Matched_C025_W1_F;
  set Matched_C025_W1;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID1=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

data Matched_C025_W2_F;
  set Matched_C025_W2;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID2=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

/*============================================================*/
/*======== Merge Datasets and Fix Variable Order ============*/
/*============================================================*/

data Matched_C025;
  merge Matched_C025_W1_F (in=Matched_C025_W1_F)
        Matched_C025_W2_F (in=Matched_C025_W2_F)

;
  by Brachy_LDR_ID;
    if Matched_C025_W1_F;
run;

data Matched_C025B;
  retain Brachy_LDR_ID
         EBRT_ID1 C025_W1
         EBRT_ID2 C025_w2
  set Matched_C025;
run;

/*============================================================*/
/*========== Re-Import Updated ID Matched Flags ==============*/
/*============================================================*/
```

```
data matched_C025B_F;
  set matched_C025B;
run;

*Caliper=0.025, 1:1;
data C025_1to1;
  set matched_C025B_F;
  if C025_w1=1; C025_1to1=1;
  pair = _N_;
run;
data C025_1to1_Brachy_LDR;
  set C025_1to1;
  ID2=Brachy_LDR_ID;
  keep ID2 C025_1to1 pair;
run;
data C025_1to1_EBRT1;
  set C025_1to1;
  ID2=EBRT_ID1;
  keep ID2 C025_1to1 pair;
run;
data C025_1to1x;
  set C025_1to1_Brachy_LDR
      C025_1to1_EBRT1;
run;
proc sort data=C025_1to1x;
  by ID2;
run;


data IR_PS_EBRTvsLDR;
set Thesis.IR_PS_EBRTvsLDR;
run;
data C025_EBRT_LDR_IR;
  merge C025_1to1x (in=C025_1to1x)
        IR_PS_EBRTvsLDR (in=IR_PS_EBRTvsLDR);
  by ID2;
    if C025_1to1x;
run;
```

Appendix VIII

SAS code for PS Model and Matching Intermediate-risk HDR-BT+EBRT vs. EBRT

Code for HDR-BT+EBRT vs. EBRT Intermediate-risk PS match:

```
Title 'Intermediate Risk: EBRT vs. HDR+EBRT';
libname thesis 'P:\Graham\Thesis';
Data Thesis.IR_PS_EBRTvsHDRandEBRT;
set thesis.Interm_Risk_PS;
if Radiation_Type_5cat = 'Brachy(LDR)_only' then delete;
if Radiation_Type_5cat = 'EBRT_only' then Tx = 0;
if Radiation_type_5cat = 'Brachy(HDR)_and_EBRT' then Tx = 1;
/*Create RT Start Year and Treatment Centre Variables for Standardized Difference Analysis*/
if RTStart_Year = 1996 then RTStart_Year_1996 = 1;
if RTStart_Year > 1996 then RTStart_Year_1996 = 0;
if RTStart_Year = 1997 then RTStart_Year_1997 = 1;
if RTStart_Year > 1997 then RTStart_Year_1997 = 0;
if RTStart_Year < 1997 then RTStart_Year_1997 = 0;
if RTStart_Year = 1998 then RTStart_Year_1998 = 1;
if RTStart_Year > 1998 then RTStart_Year_1998 = 0;
if RTStart_Year < 1998 then RTStart_Year_1998 = 0;
if RTStart_Year = 1999 then RTStart_Year_1999 = 1;
if RTStart_Year > 1999 then RTStart_Year_1999 = 0;
if RTStart_Year < 1999 then RTStart_Year_1999 = 0;
if RTStart_Year = 2000 then RTStart_Year_2000 = 1;
if RTStart_Year > 2000 then RTStart_Year_2000 = 0;
if RTStart_Year < 2000 then RTStart_Year_2000 = 0;
if RTStart_Year = 2000 then RTStart_Year_2000 = 1;
if RTStart_Year > 2000 then RTStart_Year_2000 = 0;
if RTStart_Year < 2000 then RTStart_Year_2000 = 0;
if RTStart_Year = 2001 then RTStart_Year_2001 = 1;
if RTStart_Year > 2001 then RTStart_Year_2001 = 0;
if RTStart_Year < 2001 then RTStart_Year_2001 = 0;
if RTStart_Year = 2002 then RTStart_Year_2002 = 1;
if RTStart_Year > 2002 then RTStart_Year_2002 = 0;
if RTStart_Year < 2002 then RTStart_Year_2002 = 0;
if RTStart_Year = 2003 then RTStart_Year_2003 = 1;
if RTStart_Year > 2003 then RTStart_Year_2003 = 0;
if RTStart_Year < 2003 then RTStart_Year_2003 = 0;
if RTStart_Year = 2004 then RTStart_Year_2004 = 1;
if RTStart_Year > 2004 then RTStart_Year_2004 = 0;
if RTStart_Year < 2004 then RTStart_Year_2004 = 0;
if RTStart_Year = 2005 then RTStart_Year_2005 = 1;
if RTStart_Year > 2005 then RTStart_Year_2005 = 0;
if RTStart_Year < 2005 then RTStart_Year_2005 = 0;
if RTStart_Year = 2006 then RTStart_Year_2006 = 1;
if RTStart_Year > 2006 then RTStart_Year_2006 = 0;
if RTStart_Year < 2006 then RTStart_Year_2006 = 0;
if RTStart_Year = 2007 then RTStart_Year_2007 = 1;
if RTStart_Year > 2007 then RTStart_Year_2007 = 0;
if RTStart_Year < 2007 then RTStart_Year_2007 = 0;
if RTStart_Year = 2008 then RTStart_Year_2008 = 1;
if RTStart_Year > 2008 then RTStart_Year_2008 = 0;
if RTStart_Year < 2008 then RTStart_Year_2008 = 0;
if RTStart_Year = 2009 then RTStart_Year_2009 = 1;
if RTStart_Year > 2009 then RTStart_Year_2009 = 0;
if RTStart_Year < 2009 then RTStart_Year_2009 = 0;
if RTStart_Year = 2010 then RTStart_Year_2010 = 1;
if RTStart_Year > 2010 then RTStart_Year_2010 = 0;
```

```
if RTStart_Year < 2010 then RTStart_Year_2010 = 0;
if centre = 1 then centre1 = 1;
if centre = 2 or centre = 3 or centre = 4 then centre1 = 0;
if centre = 2 then centre2 = 1;
if centre = 1 or centre = 3 or centre = 4 then centre2 = 0;
if centre = 3 then centre3 = 1;
if centre = 2 or centre = 1 or centre = 4 then centre3 = 0;
if centre = 4 then centre4 = 1;
if centre = 3 or centre = 2 or centre = 1 then centre4 = 0;
run;
proc freq data=Thesis.IR_PS_EBRTvsHDRandEBRT;
tables Tstage_CORR*tx GleasonTotal*tx Radiation_Type_5cat*tx GleasonTotal_CORR_4cat*tx
Tstage_3cat*tx /list;
run;
```

Create PS model for HDR+EBRT vs EBRT Intermediate-risk match:

```
proc logistic descending data=Thesis.IR_PS_EBRTvsHDRandEBRT;
  class GleasonTotal_CORR_4cat (param=ref ref="2_6");
  class Tstage_3cat (param=ref ref="1");
    model Tx = Age BasePSA GleasonTotal_CORR_4cat Tstage_3cat/lackfit rsquare;
  output out=Propensity_Scores predprobs=Individual xbeta=logitps;
run;
proc means data=Propensity_Scores std;
run;
```

Create 1:1 and 2:1 PS matches for HDR+EBRT vs EBRT intermediate-risk match – Caliper - 1STD[logit]*(0.2):

```
data thesis.Pscores_IR_EBRTvsHDR;
  set Propensity_Scores;
  Pscore=logitps;
  drop _from_ _into_ IP_0 IP_1;
run;

proc sort data=Thesis.Pscores_IR_EBRTvsHDR;
  by ID2;
run;

data Brachy_LDR_pscores_C1;
  set Thesis.Pscores_IR_EBRTvsHDR;
  where Tx=0;
  Brachy_LDR_ID=ID2;
  Brachy_LDR_Pscore=Pscore;
  keep Brachy_LDR_ID Brachy_LDR_Pscore;
run;
data EBRT_pscores_C1;
  set Thesis.Pscores_IR_EBRTvsHDR;
  where Tx=1;
  EBRT_ID=ID2;
  EBRT_Pscore=Pscore;
  keep EBRT_ID EBRT_Pscore;
run;
```

```
/*================================================================*/
/*==== Caliper Matching (Without Replacement): Wave 1 ============*/
/*================== Caliper =1STD[logit]*(0.2)====================*/
/*================================================================*/

data Matched_C025_W1(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w1);
   length ebrt_pscore 8;
          length EBRT_ID 8;
          if _N_= 1 then do;
    declare hash h(dataset: "EBRT_pscores_C1", ordered: 'no');
    declare hiter iter('h');
    h.defineKey('EBRT_ID');
           h.defineData('EBRT_Pscore', 'EBRT_ID');
    h.defineDone();
                    call missing(EBRT_ID, EBRT_Pscore);
   end;
   set Brachy_LDR_pscores_C1;
   retain BestDistance 99;
   rc= iter.first();
   if (rc=0) then BestDistance= 99;
   do while (rc= 0);
    if (Brachy_LDR_Pscore - (1.0143704*0.2)) <= EBRT_Pscore <= (Brachy_LDR_Pscore +
(1.0143704*0.2)) then do;
      ScoreDistance= abs(Brachy_LDR_Pscore - EBRT_Pscore);
    if ScoreDistance < BestDistance then do;
      BestDistance= ScoreDistance;
      EBRT_ID_matched= EBRT_ID;
      Brachy_LDR_ID_matched= Brachy_LDR_ID;
      C025_w1=1;
     end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
     output;
       rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;

/*================================================================*/
/*======== Remove EBRT Patients Selected in Wave 1 ===============*/
/*================================================================*/

data C025_W1_EBRT_ID;
 set Matched_C025_W1;
 EBRT_ID=EBRT_ID_matched;
 keep EBRT_ID C025_w1;
run;

proc sort data=C025_W1_EBRT_ID;
 by EBRT_ID;
run;

data C025_W2_EBRT_pscores;
 merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
       C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
```

```
  by EBRT_ID;
    if EBRT_pscores_C1;
run;

data C025_W2_EBRT_pscoresB;
  set C025_W2_EBRT_pscores;
  if C025_w1=1 then delete;
run;



/*=============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 2 ==========*/
/*============== Caliper 1STD[logit]*(0.2)=====================*/
/*=============================================================*/


data Matched_C025_W2(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w2);
length EBRT_ID 8;
length EBRT_pscore 8;
      if _N_= 1 then do;
      declare hash h(dataset: "C025_W2_EBRT_pscoresB", ordered: 'no');
      declare hiter iter('h');
      h.defineKey('EBRT_ID');
      h.defineData('EBRT_pscore', 'EBRT_ID');
      h.defineDone();
                    call missing(EBRT_ID, EBRT_pscore);
    end;
    set Brachy_LDR_pscores_C1;
    retain BestDistance 99;
    rc= iter.first();
    if (rc=0) then BestDistance= 99;
    do while (rc= 0);
      if (Brachy_LDR_pscore – (1.0143704*0.2) <= EBRT_pscore <= (Brachy_LDR_pscore +
(1.0143704*0.2) then do;
        ScoreDistance= abs(Brachy_LDR_pscore - EBRT_pscore);
      if ScoreDistance < BestDistance then do;
        BestDistance= ScoreDistance;
        EBRT_ID_matched= EBRT_ID;
        Brachy_LDR_ID_matched= Brachy_LDR_ID;
        C025_w2=1;
      end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
      output;
        rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;

/*=============================================================*/
/*====== Remove EBRT Patients Selected in Wave 1 or 2 ==========*/
/*=============================================================*/

data C025_W2_EBRT_ID;
```

```
 set Matched_C025_W2;
 EBRT_ID=EBRT_ID_matched;
 keep EBRT_ID C025_w2;
run;

proc sort data=C025_W2_EBRT_ID;
 by EBRT_ID;
run;

data C025_W3_EBRT_pscores;
 merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
      C025_W2_EBRT_ID (in=C025_W2_EBRT_ID)
      C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
 by EBRT_ID;
  if EBRT_pscores_C1;
run;


/*============================================================*/
/*============= Re-Import Matched ID Datasets ================*/
/*============================================================*/

data Matched_C025_W1_F;
 set Matched_C025_W1;
 Brachy_LDR_ID=Brachy_LDR_ID_matched;
 EBRT_ID1=EBRT_ID_matched;
 drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

data Matched_C025_W2_F;
 set Matched_C025_W2;
 Brachy_LDR_ID=Brachy_LDR_ID_matched;
 EBRT_ID2=EBRT_ID_matched;
 drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

/*============================================================*/
/*======== Merge Datasets and Fix Variable Order ============*/
/*============================================================*/

data Matched_C025;
 merge Matched_C025_W1_F (in=Matched_C025_W1_F)
      Matched_C025_W2_F (in=Matched_C025_W2_F)
;
 by Brachy_LDR_ID;
  if Matched_C025_W1_F;
run;

data Matched_C025B;
 retain Brachy_LDR_ID
       EBRT_ID1 C025_W1
       EBRT_ID2 C025_w2
 set Matched_C025;
run;
```

```
/*============================================================*/
/*========== Re-Import Updated ID Matched Flags ==============*/
/*============================================================*/

data matched_C025B_F;
  set matched_C025B;
run;

Caliper=1STDlogit*0.2, 1:1;
data C025_1to1;
  set matched_C025B_F;
  if C025_w1=1; C025_1to1=1;
  pair = _N_;
run;
data C025_1to1_Brachy_LDR;
  set C025_1to1;
  ID2=Brachy_LDR_ID;
  keep ID2 C025_1to1 pair;
run;
data C025_1to1_EBRT1;
  set C025_1to1;
  ID2=EBRT_ID1;
  keep ID2 C025_1to1 pair;
run;
data C025_1to1x;
  set C025_1to1_Brachy_LDR
      C025_1to1_EBRT1;
run;
proc sort data=C025_1to1x;
  by ID2;
run;

data IR_PS_EBRTvsHDR;
set Thesis.IR_PS_EBRTvsHDRandEBRT;
run;
data C025_EBRT_HDR_IR;
  merge C025_1to1x (in=C025_1to1x)
        IR_PS_EBRTvsHDR (in=IR_PS_EBRTvsHDR);
  by ID2;
    if C025_1to1x;
run;
```

Appendix IX

SAS Code for PS Model and Matching Low-risk LDR-BT vs. EBRT

Code for LDR vs. EBRT Low-risk PS match:

```
libname thesis 'P:\Graham\Thesis';
Data Thesis.LR_PS_EBRTvsLDR;
set thesis.Low_Risk_PS;
if Radiation_Type_5cat = 'EBRT_only' then Tx = 0;
if Radiation_type_5cat = 'Brachy(LDR)_only' then Tx = 1;
run;
proc freq data=Thesis.LR_PS_EBRTvsLDR;
tables Tstage_CORR*tx GleasonTotal*tx Radiation_Type_5cat*tx GleasonTotal_CORR_4cat*tx
Tstage_3cat*tx /list;
Title 'Low Risk Propensity Score Match EBRT vs LDR';
run;
```

Create PS model for LDR vs EBRT Low-risk match:

```
proc logistic descending data=Thesis.LR_PS_EBRTvsLDR;
   class GleasonTotal_CORR_4cat (param=ref ref="2_6");
   class Tstage_3cat (param=ref ref="1");
   class RTStart_Year (param=ref ref="1999");
    model Tx = Age BasePSA GleasonTotal_CORR_4cat Tstage_3cat RTStart_Year/lackfit rsquare;
  output out=Propensity_Scores predprobs=Individual xbeta=logitps;
run;
```

Create 1:1, 2:1, 3:1 and 4:1 (LDR:EBRT) PS matches for LDR vs EBRT Low-risk match – Caliper - 1STD[logit]*(0.2):

```
data Thesis.LR_PS_EBRTvsLDR;
  set Propensity_Scores;
  Pscore=logitps;
  drop _from_ _into_ IP_0 IP_1;
run;

proc sort data=Thesis.LR_PS_EBRTvsLDR;
  by ID2;
run;

data Brachy_LDR_pscores_C1;
  set Thesis.LR_PS_EBRTvsLDR;
  where Tx=0;
  Brachy_LDR_ID=ID2;
  Brachy_LDR_Pscore=Pscore;
  keep Brachy_LDR_ID Brachy_LDR_Pscore;
run;
data EBRT_pscores_C1;
  set Thesis.LR_PS_EBRTvsLDR;
  where Tx=1;
  EBRT_ID=ID2;
  EBRT_Pscore=Pscore;
  keep EBRT_ID EBRT_Pscore;
run;
```

```
/*============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 1 ========*/
/*============= Caliper = 1STD[logit]*(0.2)===================*/
/*============================================================*/

data Matched_C025_W1(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w1);
   length ebrt_pscore 8;
          length EBRT_ID 8;
          if _N_= 1 then do;
    declare hash h(dataset: "EBRT_pscores_C1", ordered: 'no');
    declare hiter iter('h');
    h.defineKey('EBRT_ID');
           h.defineData('EBRT_Pscore', 'EBRT_ID');
    h.defineDone();
                    call missing(EBRT_ID, EBRT_Pscore);
   end;
   set Brachy_LDR_pscores_C1;
   retain BestDistance 99;
   rc= iter.first();
   if (rc=0) then BestDistance= 99;
   do while (rc= 0);
    if (Brachy_LDR_Pscore - (1.1565042*0.2)) <= EBRT_Pscore <= (Brachy_LDR_Pscore +
(1.1565042*0.2)) then do;
      ScoreDistance= abs(Brachy_LDR_Pscore - EBRT_Pscore);
     if ScoreDistance < BestDistance then do;
      BestDistance= ScoreDistance;
      EBRT_ID_matched= EBRT_ID;
      Brachy_LDR_ID_matched= Brachy_LDR_ID;
      C025_w1=1;
     end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
     output;
       rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;

/*============================================================*/
/*======== Remove EBRT Patients Selected in Wave 1 ===========*/
/*============================================================*/

data C025_W1_EBRT_ID;
 set Matched_C025_W1;
 EBRT_ID=EBRT_ID_matched;
 keep EBRT_ID C025_w1;
run;

proc sort data=C025_W1_EBRT_ID;
 by EBRT_ID;
run;

data C025_W2_EBRT_pscores;
 merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
       C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
```

```
  by EBRT_ID;
    if EBRT_pscores_C1;
run;

data C025_W2_EBRT_pscoresB;
  set C025_W2_EBRT_pscores;
  if C025_w1=1 then delete;
run;

/*=============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 2 ==========*/
/=========== Caliper = 1STD[logit]*(0.2) ======================*/
/*=============================================================*/


data Matched_C025_W2(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w2);
length EBRT_ID 8;
length EBRT_pscore 8;
      if _N_= 1 then do;
      declare hash h(dataset: "C025_W2_EBRT_pscoresB", ordered: 'no');
      declare hiter iter('h');
      h.defineKey('EBRT_ID');
      h.defineData('EBRT_pscore', 'EBRT_ID');
      h.defineDone();
                    call missing(EBRT_ID, EBRT_pscore);
    end;
    set Brachy_LDR_pscores_C1;
    retain BestDistance 99;
    rc= iter.first();
    if (rc=0) then BestDistance= 99;
    do while (rc= 0);
      if (Brachy_LDR_pscore - (1.1565042*0.2)) <= EBRT_pscore <= (Brachy_LDR_pscore +
(1.1565042*0.2)) then do;
        ScoreDistance= abs(Brachy_LDR_pscore - EBRT_pscore);
      if ScoreDistance < BestDistance then do;
        BestDistance= ScoreDistance;
        EBRT_ID_matched= EBRT_ID;
        Brachy_LDR_ID_matched= Brachy_LDR_ID;
        C025_w2=1;
      end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
      output;
        rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;

/*=============================================================*/
/*====== Remove EBRT Patients Selected in Wave 1 or 2 ==========*/
/*=============================================================*/

data C025_W2_EBRT_ID;
  set Matched_C025_W2;
  EBRT_ID=EBRT_ID_matched;
```

```
  keep EBRT_ID C025_w2;
run;

proc sort data=C025_W2_EBRT_ID;
  by EBRT_ID;
run;

data C025_W3_EBRT_pscores;
  merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
        C025_W2_EBRT_ID (in=C025_W2_EBRT_ID)
        C025_W1_EBRT_ID (in=C025_W1_EBRT_ID);
  by EBRT_ID;
    if EBRT_pscores_C1;
run;


data C025_W3_EBRT_pscoresB;
  set C025_W3_EBRT_pscores;
  if C025_w1=1 or C025_w2=1 then delete;
run;

/*=============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 3 ==========*/
/*========== Caliper = 1STD[logit]*(0.2) ======================*/
/*=============================================================*/


data Matched_C025_W3(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w3);
length EBRT_ID 8;
length EBRT_pscore 8;
      if _N_= 1 then do;
      declare hash h(dataset: "C025_W3_EBRT_pscoresB", ordered: 'no');
      declare hiter iter('h');
      h.defineKey('EBRT_ID');
      h.defineData('EBRT_pscore', 'EBRT_ID');
      h.defineDone();
                    call missing(EBRT_ID, EBRT_pscore);
    end;
    set Brachy_LDR_pscores_C1;
    retain BestDistance 99;
    rc= iter.first();
    if (rc=0) then BestDistance= 99;
    do while (rc= 0);
      if (Brachy_LDR_pscore - (1.1565042*0.2)) <= EBRT_pscore <= (Brachy_LDR_pscore +
(1.1565042*0.2)) then do;
        ScoreDistance= abs(Brachy_LDR_pscore - EBRT_pscore);
      if ScoreDistance < BestDistance then do;
        BestDistance= ScoreDistance;
        EBRT_ID_matched= EBRT_ID;
        Brachy_LDR_ID_matched= Brachy_LDR_ID;
        C025_w3=1;
      end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
      output;
```

```
      rc1= h.remove(key: EBRT_ID_matched);
   end;
   end;
run;


/*============================================================*/
/*====== Remove EBRT Patients Selected in Wave 1 or 2 or 3 ===========*/
/*============================================================*/

data C025_W3_EBRT_ID;
 set Matched_C025_W3;
 EBRT_ID=EBRT_ID_matched;
 keep EBRT_ID C025_w3;
run;

proc sort data=C025_W3_EBRT_ID;
 by EBRT_ID;
run;

data C025_W4_EBRT_pscores;
 merge EBRT_pscores_C1 (in=EBRT_pscores_C1)
      C025_W2_EBRT_ID (in=C025_W2_EBRT_ID)
      C025_W1_EBRT_ID (in=C025_W1_EBRT_ID)
                  C025_W3_EBRT_ID (in=C025_W3_EBRT_ID);
 by EBRT_ID;
   if EBRT_pscores_C1;
run;


data C025_W4_EBRT_pscoresB;
 set C025_W4_EBRT_pscores;
 if C025_w1=1 or C025_w2=1 or C025_w3 then delete;
run;
/*============================================================*/
/*==== Caliper Matching (Without Replacement): Wave 4 ================*/
/*========== Caliper = 1STD[logit]*(0.2)  ============================*/
/*============================================================*/


data Matched_C025_W4(keep= EBRT_ID_matched Brachy_LDR_ID_matched C025_w4);
length EBRT_ID 8;
length EBRT_pscore 8;
     if _N_ = 1 then do;
     declare hash h(dataset: "C025_W4_EBRT_pscoresB", ordered: 'no');
     declare hiter iter('h');
     h.defineKey('EBRT_ID');
     h.defineData('EBRT_pscore', 'EBRT_ID');
     h.defineDone();
                call missing(EBRT_ID, EBRT_pscore);
   end;
   set Brachy_LDR_pscores_C1;
   retain BestDistance 99;
   rc= iter.first();
   if (rc=0) then BestDistance= 99;
   do while (rc= 0);
```

```
     if (Brachy_LDR_pscore - (1.1565042*0.2)) <= EBRT_pscore <= (Brachy_LDR_pscore +
(1.1565042*0.2)) then do;
       ScoreDistance= abs(Brachy_LDR_pscore - EBRT_pscore);
      if ScoreDistance < BestDistance then do;
       BestDistance= ScoreDistance;
       EBRT_ID_matched= EBRT_ID;
       Brachy_LDR_ID_matched= Brachy_LDR_ID;
       C025_w4=1;
      end;
    end;
    rc= iter.next();
    if (rc~= 0) and BestDistance~= 99 then do;
     output;
       rc1= h.remove(key: EBRT_ID_matched);
    end;
    end;
run;
/*============================================================*/
/*============= Re-Import Matched ID Datasets ================*/
/*============================================================*/

data Matched_C025_W1_F;
  set Matched_C025_W1;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID1=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

data Matched_C025_W2_F;
  set Matched_C025_W2;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID2=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

data Matched_C025_W3_F;
  set Matched_C025_W3;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID3=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

data Matched_C025_W4_F;
  set Matched_C025_W4;
  Brachy_LDR_ID=Brachy_LDR_ID_matched;
  EBRT_ID4=EBRT_ID_matched;
  drop Brachy_LDR_ID_matched EBRT_ID_matched;
run;

/*============================================================*/
/*======== Merge Datasets and Fix Variable Order ============*/
/*============================================================*/

data Matched_C025;
  merge Matched_C025_W1_F (in=Matched_C025_W1_F)
        Matched_C025_W2_F (in=Matched_C025_W2_F)
```

```
                    Matched_C025_W3_F (in=Matched_C025_W3_F)
                    Matched_C025_W4_F (in=Matched_C025_W4_F);

 by Brachy_LDR_ID;
  if Matched_C025_W1_F;
run;

data Matched_C025B;
 retain Brachy_LDR_ID
       EBRT_ID1 C025_W1
       EBRT_ID2 C025_w2
                    EBRT_ID3 C025_w3
                    EBRT_ID4 C025_w4;

 set Matched_C025;
run;

/*============================================================*/
/*========== Re-Import Updated ID Matched Flags ==============*/
/*============================================================*/

data matched_C025B_F;
 set matched_C025B;
run;

*Caliper=0.02logit, 1:1;
data C025_1to1;
 set matched_C025B_F;
 if C025_w1=1; C025_1to1=1;
 pair = _N_;
run;
data C025_1to1_Brachy_LDR;
 set C025_1to1;
 ID2=Brachy_LDR_ID;
 keep ID2 C025_1to1 pair;
run;
data C025_1to1_EBRT1;
 set C025_1to1;
 ID2=EBRT_ID1;
 keep ID2 C025_1to1 pair;
run;
data C025_1to1x;
 set C025_1to1_Brachy_LDR
    C025_1to1_EBRT1;
run;
proc sort data=C025_1to1x;
 by ID2;
run;

*Caliper=0.2logit, 1:2;
data C025_1to2;
 set matched_C025B;
 if C025_w1=1 and C025_w2=1;
 C025_1to2=1;
 pair = _N_;
run;
```

```
data C025_1to2_Brachy_LDR;
  set C025_1to2;
  ID2=Brachy_LDR_ID;
  keep ID2 C025_1to2 pair;
run;
data C025_1to2_EBRT1;
  set C025_1to2;
  ID2=EBRT_ID1;
  keep ID2 C025_1to2 pair;
run;
data C025_1to2_EBRT2;
  set C025_1to2;
  ID2=EBRT_ID2;
  keep ID2 C025_1to2 pair;
run;
data C025_1to2x;
  set C025_1to2_Brachy_LDR
      C025_1to2_EBRT1
      C025_1to2_EBRT2;
run;
proc sort data=C025_1to2x;
  by ID2;
run;
*Caliper=0.2logit, 1:3;
data C025_1to3;
  set matched_C025B;
  if C025_w1=1 and C025_w2=1 and C025_w3=1;
  C025_1to3=1;
  pair = _N_;
run;

data C025_1to3_Brachy_LDR;
  set C025_1to3;
  ID2=Brachy_LDR_ID;
  keep ID2 C025_1to3 pair;
run;
data C025_1to3_EBRT1;
  set C025_1to3;
  ID2=EBRT_ID1;
  keep ID2 C025_1to3 pair;
run;
data C025_1to3_EBRT2;
  set C025_1to3;
  ID2=EBRT_ID2;
  keep ID2 C025_1to3 pair;
run;
data C025_1to3_EBRT3;
  set C025_1to3;
  ID2=EBRT_ID3;
  keep ID2 C025_1to3 pair;
run;
data C025_1to3x;
  set C025_1to3_Brachy_LDR
      C025_1to3_EBRT1
      C025_1to3_EBRT2
```

```
            C025_1to3_EBRT3;
run;
proc sort data=C025_1to3x;
  by ID2;
run;
*Caliper=0.2logit, 1:4;
data C025_1to4;
  set matched_C025B;
  if C025_w1=1 and C025_w2=1 and C025_w3=1 and C025_w4=1;
  C025_1to4=1;
  pair = _N_;
run;
data C025_1to4_Brachy_LDR;
  set C025_1to4;
  ID2=Brachy_LDR_ID;
  keep ID2 C025_1to4 pair;
run;
data C025_1to4_EBRT1;
  set C025_1to4;
  ID2=EBRT_ID1;
  keep ID2 C025_1to4 pair;
run;
data C025_1to4_EBRT2;
  set C025_1to4;
  ID2=EBRT_ID2;
  keep ID2 C025_1to4 pair;
run;
data C025_1to4_EBRT3;
  set C025_1to4;
  ID2=EBRT_ID3;
  keep ID2 C025_1to4 pair;
run;
data C025_1to4_EBRT4;
  set C025_1to4;
  ID2=EBRT_ID4;
  keep ID2 C025_1to4 pair;
run;
data C025_1to4x;
  set C025_1to4_Brachy_LDR
     C025_1to4_EBRT1
     C025_1to4_EBRT2
            C025_1to4_EBRT3
            C025_1to4_EBRT4;
run;
proc sort data=C025_1to4x;
  by ID2;
run;
data LR_PS_EBRTvsLDR;
set Thesis.LR_PS_EBRTvsLDR;
run;
data C025_EBRT_LDR_LR;
  merge C025_1to4x (in=C025_1to4x)
       LR_PS_EBRTvsLDR (in=LR_PS_EBRTvsLDR);
  by ID2;
    if C025_1to4x;
run;
```

Appendix X

SAS Code for Standardized Difference Testing

Standardized Difference Testing:

Intermediate-risk LDR vs EBRT Match:

```
proc sort data=C025_EBRT_LDR_IR;
by Tx;
run;

/*== Macro for computing standardized difference for continuous variables ===*/

%macro cont(var=,label=);
proc means mean stddev data=C025_EBRT_LDR_IR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean stddev) mean = mean stddev=stddev;
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
s_0 = stddev;
keep mean_0 S_0;
run;

data Brachy;
set outmean;
if Tx = 1;
mean_1 = mean;
s_1 = stddev;
keep mean_1 s_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;
d = (mean_1 - mean_0)/sqrt((s_1*S_1 + S_0*s_0)/2);
d = round(abs(d),0.00001);
label = &label;
keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend cont;

/*== Macro for computing standardized difference for categorical variables ===*/

%macro binary(var=,label=);
proc means mean data=C025_EBRT_LDR_IR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean) mean = mean;
```

```
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
keep mean_0;
run;

data Brachy;
set outmean;
if Tx = 1;
mean_1 = mean;
keep mean_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;

d = (mean_1 - mean_0)/sqrt((mean_1*(1-mean_1) + mean_0*(1-mean_0))/2);
d = round(abs(d),0.0001);

label = &label;

keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend binary;

%cont(var=age,label="Age");
%cont(var=BasePSA,label="Baseline PSA ng/mL");

%binary(var=Tstage_T1,label="Any T1");
%binary(var=Tstage_LowT2,label="Low T2");
%binary(var=Tstage_HighT2,label="High T2");
%binary(var=GleasonTotal_7,label="Gleason Total 7 vs 6");
%binary(var=PosCores_ge50pct,label="Percent Positive Cores > 50");
%binary(var=GleasonPattern_CORRx3plus3,label="Gleason Pattern 3+3");
%binary(var=GleasonPattern_CORRx3plus4,label="Gleason Pattern 3+4");
%binary(var=GleasonPattern_CORRx4plus3,label="Gleason Pattern 4+3");
%binary(var=RTStart_Year_1996;,label="RT Start YR 1996");
%binary(var=RTStart_Year_1997;,label="RT Start YR 1997");
%binary(var=RTStart_Year_1998;,label="RT Start YR 1998");
%binary(var=RTStart_Year_1999;,label="RT Start YR 1999");
%binary(var=RTStart_Year_2000;,label="RT Start YR 2000");
%binary(var=RTStart_Year_2001;,label="RT Start YR 2001");
%binary(var=RTStart_Year_2002;,label="RT Start YR 2002");
%binary(var=RTStart_Year_2003;,label="RT Start YR 2003");
%binary(var=RTStart_Year_2004;,label="RT Start YR 2004");
%binary(var=RTStart_Year_2005;,label="RT Start YR 2005");
%binary(var=RTStart_Year_2006;,label="RT Start YR 2006");
%binary(var=RTStart_Year_2007;,label="RT Start YR 2007");
```

```
%binary(var=RTStart_Year_2008;,label="RT Start YR 2008");
%binary(var=RTStart_Year_2009;,label="RT Start YR 2009");
%binary(var=RTStart_Year_2010;,label="RT Start YR 2010");
%binary(var=centre1;,label="Centre 1");
%binary(var=centre2;,label="Centre 2");
%binary(var=centre3;,label="Centre 3");
proc print data=standiff;
title "Standard Difference in Matched Sample";
run;

proc freq data=C025_EBRT_LDR_IR;
table RTStart_Year*tx centre*tx PosCores_ge50pct*tx GleasonPattern_CORR*tx Tstage_3cat*tx
GleasonTotal_7*Tx Tstage_T1*Tx Tstage_LowT2*Tx Tstage_HighT2*tx/list chisq;
run;
proc freq data=C025_EBRT_LDR_IR;
table PosCores_ge50pct*tx GleasonPattern_CORR*Tx GleasonTotal_CORR /missprint;
run;
data BrachyC025_Age_PSA;
set C025_EBRT_LDR_IR;
where Tx = 1;
run;
proc means data=brachyC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in Brachytherapy Group';
run;

data EBRTC025_Age_PSA;
set C025_EBRT_LDR_IR;
where tx = 0;
run;
proc means data=EBRTC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in EBRT Group';
run;

proc ttest data=C025_EBRT_LDR_IR;
class tx;
var age basePSA;
run;

Proc means data=C025_EBRT_LDR_IR N mean median std max min;
var age basePSA;
run;

data Thesis.Final_LDRvsEBRT_Int_PS;
set C025_EBRT_LDR_IR;
Survival_Years = Survival_Months/12;
BFFS2_Years = BFFS2_months/12;
CRS_Years = CRS_months/12;
run;
```

Intermediate-risk HDR+EBRT vs EBRT Match:

```
proc sort data=C025_EBRT_HDR_IR;
```

```
by Tx;
run;

/*== Macro for computing standardized difference for continuous variables ===*/

%macro cont(var=,label=);
proc means mean stddev data=C025_EBRT_HDR_IR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean stddev) mean = mean stddev=stddev;
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
s_0 = stddev;
keep mean_0 S_0;
run;

data Brachy;
set outmean;
if Tx = 1;
mean_1 = mean;
s_1 = stddev;
keep mean_1 s_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;
d = (mean_1 - mean_0)/sqrt((s_1*S_1 + S_0*s_0)/2);
d = round(abs(d),0.00001);
label = &label;
keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend cont;

/*== Macro for computing standardized difference for categorical variables ===*/

%macro binary(var=,label=);
proc means mean data=C025_EBRT_HDR_IR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean) mean = mean;
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
keep mean_0;
```

```
run;

data Brachy;
set outmean;
if Tx = 1;
mean_1 = mean;
keep mean_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;

d = (mean_1 - mean_0)/sqrt((mean_1*(1-mean_1) + mean_0*(1-mean_0))/2);
d = round(abs(d),0.0001);

label = &label;

keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend binary;

%cont(var=age,label="Age");
%cont(var=BasePSA,label="Baseline PSA ng/mL");

%binary(var=Tstage_T1,label="Any T1");
%binary(var=Tstage_LowT2,label="Low T2");
%binary(var=Tstage_HighT2,label="High T2");
%binary(var=GleasonTotal_7,label="Gleason Total 7 vs 6");
%binary(var=PosCores_ge50pct,label="Percent Positive Cores > 50");
%binary(var=GleasonPattern_CORRx3plus3,label="Gleason Pattern 3+3");
%binary(var=GleasonPattern_CORRx3plus4,label="Gleason Pattern 3+4");
%binary(var=GleasonPattern_CORRx4plus3,label="Gleason Pattern 4+3");
%binary(var=RTStart_Year_1996;,label="RT Start YR 1996");
%binary(var=RTStart_Year_1997;,label="RT Start YR 1997");
%binary(var=RTStart_Year_1998;,label="RT Start YR 1998");
%binary(var=RTStart_Year_1999;,label="RT Start YR 1999");
%binary(var=RTStart_Year_2000;,label="RT Start YR 2000");
%binary(var=RTStart_Year_2001;,label="RT Start YR 2001");
%binary(var=RTStart_Year_2002;,label="RT Start YR 2002");
%binary(var=RTStart_Year_2003;,label="RT Start YR 2003");
%binary(var=RTStart_Year_2004;,label="RT Start YR 2004");
%binary(var=RTStart_Year_2005;,label="RT Start YR 2005");
%binary(var=RTStart_Year_2006;,label="RT Start YR 2006");
%binary(var=RTStart_Year_2007;,label="RT Start YR 2007");
%binary(var=RTStart_Year_2008;,label="RT Start YR 2008");
%binary(var=RTStart_Year_2009;,label="RT Start YR 2009");
%binary(var=RTStart_Year_2010;,label="RT Start YR 2010");
%binary(var=centre1;,label="Centre 1");
%binary(var=centre2;,label="Centre 2");
%binary(var=centre3;,label="Centre 3");
%binary(var=centre4;,label="Centre 4");
```

```
proc print data=standiff;
title "Standard Difference in Matched Sample";
run;

proc freq data=C025_EBRT_HDR_IR;
table GleasonPattern_CORR*Tx PosCores_ge50pct*tx /missprint;
run;

proc freq data=C025_EBRT_HDR_IR;
table RTStart_Year*tx centre*tx PosCores_ge50pct*tx GleasonPattern_CORR*tx
PosCores_ge50pct*centre GleasonPattern_CORR*centre Tstage_3cat*tx GleasonTotal_7*Tx
Tstage_T1*Tx Tstage_LowT2*Tx Tstage_HighT2*tx/list chisq missprint;
run;

data BrachyC025_Age_PSA;
set C025_EBRT_HDR_IR;
where Tx = 1;
run;
proc means data=brachyC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in Brachytherapy Group';
run;

data EBRTC025_Age_PSA;
set C025_EBRT_HDR_IR;
where tx = 0;
run;
proc means data=EBRTC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in EBRT Group';
run;
Proc means data=C025_EBRT_HDR_IR N mean median std max min;
var age basePSA;
run;
proc ttest data=C025_EBRT_HDR_IR;
class tx;
var age basePSA;
run;

data Thesis.Final_HDRplusEBRTvsEBRT_Int_PS;
set C025_EBRT_HDR_IR;
Survival_Years = Survival_Months/12;
BFFS2_Years = BFFS2_months/12;
CRS_Years = CRS_months/12;
run;
```

Low-risk LDR vs EBRT Match:

```
proc sort data=C025_EBRT_LDR_LR;
by Tx;
run;
```

/*== Macro for computing standardized difference for continuous variables ===*/

```
%macro cont(var=,label=);
proc means mean stddev data=C025_EBRT_LDR_LR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean stddev) mean = mean stddev=stddev;
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
s_0 = stddev;
keep mean_0 S_0;
run;

data Brachy;
set outmean;
if Tx = 1;
mean_1 = mean;
s_1 = stddev;
keep mean_1 s_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;
d = (mean_1 - mean_0)/sqrt((s_1*S_1 + S_0*s_0)/2);
d = round(abs(d),0.00001);
label = &label;
keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend cont;
```

/*== Macro for computing standardized difference for categorical variables ===*/

```
%macro binary(var=,label=);
proc means mean data=C025_EBRT_LDR_LR noprint;
var &var;
by Tx;
output out=outmean (keep = Tx mean) mean = mean;
run;

data EBRT;
set outmean;
if Tx = 0;
mean_0 = mean;
keep mean_0;
run;

data Brachy;
set outmean;
if Tx = 1;
```

```
mean_1 = mean;
keep mean_1;
run;

data newdata;
length label $ 25;
merge EBRT Brachy;

d = (mean_1 - mean_0)/sqrt((mean_1*(1-mean_1) + mean_0*(1-mean_0))/2);
d = round(abs(d),0.0001);

label = &label;

keep d label;
run;

proc append data=newdata base=standiff force;
run;

%mend binary;

%cont(var=age,label="Age");
%cont(var=BasePSA,label="Baseline PSA ng/mL");

%binary(var=Tstage_T1,label="Any T1");
%binary(var=Tstage_LowT2,label="Low T2");
%binary(var=GleasonTotal_6,label="Gleason Total 6 vs 2to5");
%binary(var=RTStart_Year_1999,label="RT Start Year 1999");
%binary(var=RTStart_Year_2000,label="RT Start Year 2000");
%binary(var=RTStart_Year_2001,label="RT Start Year 2001");
%binary(var=RTStart_Year_2002,label="RT Start Year 2002");
%binary(var=RTStart_Year_2003,label="RT Start Year 2003");
%binary(var=RTStart_Year_2004,label="RT Start Year 2004");
%binary(var=RTStart_Year_2005,label="RT Start Year 2005");
%binary(var=RTStart_Year_2006,label="RT Start Year 2006");
%binary(var=PosCores_ge50pct,label="Percent Positive Cores > 50");
%binary(var=centre1,label="Treatment Centre 1");
%binary(var=centre2,label="Treatment Centre 2");
%binary(var=centre3,label="Treatment Centre 3");


proc print data=standiff;
title "Standard Difference in Matched Sample";
run;

proc freq data=C025_EBRT_LDR_LR;
table centre*tx PosCores_ge50pct*tx RTStart_Year*tx Tstage_3cat*tx GleasonTotal_6*Tx Tstage_T1*Tx
Tstage_LowT2*Tx Tstage_HighT2*tx/list chisq;
run;
proc freq data=C025_EBRT_LDR_LR;
table PosCores_ge50pct*tx /missprint;
run;

data BrachyC025_Age_PSA;
set C025_EBRT_LDR_LR;
where Tx = 1;
```

```
run;
proc means data=brachyC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in Brachytherapy Group';
run;

data EBRTC025_Age_PSA;
set C025_EBRT_LDR_LR;
where tx = 0;
run;
proc means data=EBRTC025_Age_PSA N mean median std max min;
var age basePSA;
Title 'Mean AGE and BASELINE PSA in EBRT Group';
run;

proc ttest data=C025_EBRT_LDR_LR;
class tx;
var age basePSA;
run;

proc datasets lib=work nolist;
delete C025_1to1 C025_1to1x C025_1to1_Brachy_LDR C025_1to1_EBRT1 C025_1to2 C025_1to2x
C025_1to2_Brachy_LDR C025_1to2_EBRT1 C025_1to2_EBRT2 C025_1to3 C025_1to3x
C025_1to3_EBRT1 C025_1to3_EBRT2;
run;

proc means data=C025_EBRT_LDR_LR N mean median std max min;
var age basePSA;
run;

data Thesis.Final_LDRvsEBRT_LOW_PS;
set C025_EBRT_LDR_LR;
Survival_Years = Survival_Months/12;
BFFS2_Years = BFFS2_months/12;
CRS_Years = CRS_months/12;
run;
```

Appendix XI

SAS Code for Kaplan Meier Curves, Cox Adjusted and Extended Models (Time Dependent Covariate Models), and Model Assumption Tests (Visual and Global Tests)

OS Comparison Intermediate-risk LDR vs EBRT PS Matched Cohort:

```
ods graphics on;
libname thesis 'P:\Graham\Thesis';
Title "Intermediate Risk: LDR vs EBRT (Propensity Score Match)";
proc lifetest data=Thesis.Final_LDRvsEBRT_INT_PS outsurv=S_INT_LDRvsEBRT_PS maxtime=120
notable
plots=(survival(atrisk=0 to 120 by 24));
time Survival_Months*Dead(0);
label Survival_Months = 'Time (Months)';
strata Radiation_Type_5cat / group=pair;
run;
```

/*Creating Kaplan Meier Curves*/

```
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "LDR" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.survival_INT_LDR;
plot SURVIVAL*Survival_Months = Radiation_Type_5cat /
vaxis=axis1 haxis=axis2 legend=legend1;
format survival percent12.;
run;
```

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum Test*/

```
proc phreg data=Thesis.Final_LDRvsEBRT_INT_PS covs(aggregate);
class Radiation_Type_5cat (param=ref ref="EBRT_only");
model Survival_Months*Dead(0) = Radiation_Type_5cat /rl;
id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT ressch=Radiation_Type_5cat;
run;
```

/*Log of Negative Log of Estimated Survival Visual Test*/

```
proc lifetest data=Thesis.Final_LDRvsEBRT_INT_PS notable maxtime=120
  plots=(lls);
  time Survival_Months*Dead(0);
  strata Radiation_Type_5cat;
  label Survival_Months = 'Time (Months)';
  survival out=out1;
run;
```

```
/*Schoenfeld Residual Plot*/
proc sgplot data=outRT;
loess x=Survival_Months y=Radiation_Type_5cat2;
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT;
var Radiation_Type_5cat2;
with Survival_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for OS Using Extended Cox PH Model*/
data TDC_LDRvsEBRT_INT2;
  set Thesis.Final_LDRvsEBRT_INT_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(LDR)_only" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_LDRvsEBRT_INT2;
class Radiation_Type_Num (param=ref ref="1");
model Survival_months*Dead(0) = Radiation_Type_Num RT5cat_Log_Surv/rl;
RT5cat_Log_Surv=Radiation_Type_Num*LOG(Survival_months);
run;
```

BFFS Comparison Intermediate-risk LDR vs EBRT PS Matched:

```
proc lifetest data=Thesis.Final_LDRvsEBRT_INT_PS  notable outsurv=BFFS_INT_LDRvsEBRT_PS
maxtime=120
  plots=(survival(atrisk=0 to 120 by 24));
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat / test=logrank;
  label BFFS2_CORR_months = 'Time (Months)';
run;
proc lifetest data=Thesis.Final_LDRvsEBRT_INT_PS  notable outsurv=BFFS_INT_LDRvsEBRT_PS
maxtime=120
  plots=(survival(atrisk=0 to 120 by 24));
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat / group=pair;
  label BFFS2_CORR_months = 'Time (Months)';
run;

/*Creating Kaplan Meier Curves*/
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
```

```
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "LDR" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.bff_INT_LDR;
plot SURVIVAL*bffs2_CORR_Months = Radiation_Type_5cat /
vaxis=axis1 haxis=axis2 legend=legend1;
format survival percent12.;
run;

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum
Test*/
proc phreg data=Thesis.Final_LDRvsEBRT_INT_PS covs(aggregate);
class Radiation_Type_5cat (param=ref ref="EBRT_only");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_5cat /rl;
id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT2 ressch=Radiation_Type_5cat;
run;

/*Log of Negative Log of Estimated Survival Visual Test*/
proc lifetest data=Thesis.Final_LDRvsEBRT_INT_PS notable maxtime=120
  plots=(lls);
time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat;
  label BFFS2_CORR_months = 'Time (Months)';
survival out=out2;
run;

/*Schoenfeld Residual Plot*/
proc sgplot data=outRT2;
loess x=BFFS2_CORR_Months y=Radiation_Type_5cat2;
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT2;
var Radiation_Type_5cat2;
with BFFS2_CORR_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for BFFS Using Extended Cox PH Model */
data TDC_LDRvsEBRT_INT1;
  set Thesis.Final_LDRvsEBRT_INT_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(LDR)_only" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_LDRvsEBRT_INT1;
class Radiation_Type_Num (param=ref ref="1");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_Num RT5cat_Log_BFFS2/rl;
RT5cat_Log_BFFS2=Radiation_Type_Num*LOG(BFFS2_CORR_months);
run;

ods graphics off;
```

OS Comparison Intermediate-risk HDR+EBRT vs EBRT PS Matched Cohort:

```
ods graphics on;
libname thesis 'P:\Graham\Thesis';
Title "Intermediate Risk: HDR+EBRT vs EBRT (Propensity Score Match)";
proc lifetest data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS outsurv=S_INT_HDRvsEBRT_PS
maxtime=120 notable
plots=(survival(atrisk=0 to 120 by 24));
time Survival_Months*Dead(0);
label Survival_Months = 'Time (Months)';
strata Radiation_Type_5cat / group=pair;
run;

/*Creating Kaplan Meier Curves*/
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "HDR+EBRT" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.survival_INT_HDR;
plot SURVIVAL*Survival_Months = Radiation_Type_5cat /
vaxis=axis1 haxis=axis2 legend=legend1;
format survival percent12.;
run;

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum
Test*/
proc phreg data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS covs(aggregate);
class Radiation_Type_5cat (param=ref ref="EBRT_only");
model Survival_Months*Dead(0) = Radiation_Type_5cat / rl;
id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT ressch=Radiation_Type_5cat;
run;

/*Log of Negative Log of Estimated Survival Visual Test*/
proc lifetest data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS notable maxtime=120
  plots=(lls);
time Survival_Months*Dead(0);
label Survival_Months = 'Time (Months)';
strata Radiation_Type_5cat;
survival out=out1;
run;
```

```
/*Schoenfeld Residual Plot*/
proc sgplot data=outRT;
loess x=Survival_Months y=Radiation_Type_5cat2;
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT;
var Radiation_Type_5cat2;
with Survival_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for OS Using Extended Cox PH Model*/
data TDC_HDRvsEBRT_INT;
  set Thesis.Final_HDRplusEBRTvsEBRT_INT_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(HDR)_and_EBRT" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_HDRvsEBRT_INT;
class Radiation_Type_Num (param=ref ref="1");
model Survival_months*Dead(0) = Radiation_Type_Num RT5cat_Log_Surv/rl;
RT5cat_Log_Surv=Radiation_Type_Num*LOG(Survival_months);
run;
```

BFFS Comparison Intermediate-risk HDR+EBRT vs EBRT PS Matched Cohort:

```
proc lifetest data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS  notable
outsurv=BFFS_INT_HDRvsEBRT_PS maxtime=120
  plots=(survival(atrisk=0 to 120 by 24));
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat / group=pair;
  label BFFS2_CORR_months = 'Time (Months)';
run;

/*Creating Kaplan Meier Curves*/
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "HDR+EBRT" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.bff_INT_HDR;
plot SURVIVAL*bffs2_CORR_Months = Radiation_Type_5cat /
```

```
vaxis=axis1 haxis=axis2 legend=legend1;
format survival percent12.;
run;

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum Test*/
proc phreg data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS covs(aggregate);
class Radiation_Type_5cat (param=ref ref="EBRT_only");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_5cat /rl;
id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT2 ressch=Radiation_Type_5cat;
run;

/*Log of Negative Log of Estimated Survival Visual Test*/
proc lifetest data=Thesis.Final_HDRplusEBRTvsEBRT_INT_PS notable maxtime=120
  plots=(lls);
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat;
  label BFFS2_CORR_months = 'Time (Months)';
  survival out=out2;
run;

/*Schoenfeld Residual Plot*/
proc sgplot data=outRT2;
loess x=BFFS2_CORR_Months y=Radiation_Type_5cat2;
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT2;
var Radiation_Type_5cat2;
with BFFS2_CORR_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for BFFS Using Extended Cox PH Model*/
data TDC_HDRvsEBRT_INT;
  set Thesis.Final_HDRplusEBRTvsEBRT_INT_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(HDR)_and_EBRT" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_HDRvsEBRT_INT;
class Radiation_Type_Num (param=ref ref="1");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_Num RT5cat_Log_BFFS2/rl;
RT5cat_Log_BFFS2=Radiation_Type_Num*LOG(BFFS2_CORR_months);
run;


ods graphics off;
```

OS Comparison Low-risk LDR vs EBRT PS Matched Cohort:

```
ods graphics on;
libname thesis 'P:\Graham\Thesis';
```

```
Title "Low Risk: LDR vs EBRT (Propensity Score Match)";


proc lifetest data=Thesis.Final_LDRvsEBRT_LOW_PS outsurv=S_LOW_LDRvsEBRT_PS maxtime=120
notable
plots=(survival(atrisk=0 to 120 by 24));
time Survival_Months*Dead(0);
label Survival_Months = 'Time (Months)';
strata Radiation_Type_5cat / group=pair;
run;

/*Creating Kaplan Meier Curves*/
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "LDR" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.survival_lr;
plot SURVIVAL*Survival_Months = Radiation_Type_5cat /
vaxis=axis1 haxis=axis2 legend=legend1;
format survival percent12.;
run;

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum
Test*/
proc phreg data=Thesis.Final_LDRvsEBRT_LOW_PS covs(aggregate);
  class Radiation_Type_5cat (param=ref ref="EBRT_only");
  model Survival_Months*Dead(0) = Radiation_Type_5cat /rl;
  id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT ressch=Radiation_Type_5cat;
run;

/*Log of Negative Log of Estimated Survival Visual Test*/
proc lifetest data=Thesis.Final_LDRvsEBRT_LOW_PS notable maxtime=120
  plots=(lls);
  time Survival_Months*Dead(0);
  strata Radiation_Type_5cat;
  label Survival_Months = 'Time (Months)';
  survival out=out;
run;

/*Schoenfeld Residual Plot*/
proc sgplot data=outRT;
loess x=Survival_Months y=Radiation_Type_5cat2;
```

```
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT;
var Radiation_Type_5cat2;
with Survival_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for OS Using Extended Cox PH Model*/
data TDC_LDRvsEBRT_low;
  set Thesis.Final_LDRvsEBRT_LOW_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(LDR)_only" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_LDRvsEBRT_low;
class Radiation_Type_Num (param=ref ref="1");
model Survival_months*Dead(0) = Radiation_Type_Num RT5cat_Log_Surv/rl;
RT5cat_Log_Surv=Radiation_Type_Num*LOG(Survival_months);
run;
data thesis.S_LOW_LDRvsEBRT_PS;
set S_LOW_LDRvsEBRT_PS;
run;
```

BFFS Comparison Low-risk LDR vs EBRT PS Matched Cohort:

```
proc lifetest data=Thesis.Final_LDRvsEBRT_LOW_PS  notable outsurv=BFFS_LOW_LDRvsEBRT_PS
maxtime=120
  plots=(survival(atrisk=0 to 120 by 24));
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat / group=pair;
  label BFFS2_CORR_months = 'Time (Months)';
run;

/*Creating Kaplan Meier Curves*/
goptions cback=white;
symbol1 line=1 color=black width=2 i=stepj;
symbol2 line=4 color=black width=2 i=stepj;
axis1 label=(angle=90 'Survival (%)'
font="Swiss/bold")
order=(0 to 1 by 0.2)
major=(height=3) minor=none color=black;
axis2 label=('Time (Months)'
font="Swiss/bold")
order=(0 to 120 by 24)
major=(height=3) minor=none color=black;
legend1 label=none mode=protect position=(bottom left inside)
offset=(-8 -4) across=1
value=(tick=1 justify=L "LDR" font="Swiss/bold"
tick=2 justify=L "EBRT" font="Swiss/bold");
ods pdf startpage=now;
proc gplot data=thesis.bff_lr;
plot SURVIVAL*bffs2_CORR_Months = Radiation_Type_5cat /
vaxis=axis1 haxis=axis2 legend=legend1;
```

```
format survival percent12.;
run;

/*Cox PH Regression of Treatment Type Stratified by Matched Pair with Kolmogorov-Supremum Test*/
proc phreg data=Thesis.Final_LDRvsEBRT_LOW_PS covs(aggregate);
class Radiation_Type_5cat (param=ref ref="EBRT_only");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_5cat /rl;
id pair;
assess proportionalhazards / resample seed=1004;
output out=outRT2 ressch=Radiation_Type_5cat;
run;
/*Log of Negative Log of Estimated Survival Visual Test*/
proc lifetest data=Thesis.Final_LDRvsEBRT_LOW_PS notable maxtime=120
  plots=(lls);
  time BFFS2_CORR_months*BFFS2_CORR(0);
  strata Radiation_Type_5cat;
  label BFFS2_CORR_months = 'Time (Months)';
  survival out=out2;
run;

/*Schoenfeld Residual Plot*/
proc sgplot data=outRT2;
loess x=BFFS2_CORR_Months y=Radiation_Type_5cat2;
title 'Schoenfeld residuals plot for Radiation_5cat';
run;

/*Schoenfeld Global Test*/
proc corr data=outRT2;
var Radiation_Type_5cat2;
with BFFS2_CORR_Months;
run;

/*Test for Radiation Type as Time Dependent Covariate for bFFS Using Extended Cox PH Model */
data TDC_LDRvsEBRT_low;
  set Thesis.Final_LDRvsEBRT_LOW_PS;
If Radiation_Type_5cat = "EBRT_only" then Radiation_Type_Num = 1;
If Radiation_Type_5cat = "Brachy(LDR)_only" then Radiation_Type_Num = 2;
run;
proc phreg data=TDC_LDRvsEBRT_low;
class Radiation_Type_Num (param=ref ref="1");
model BFFS2_CORR_months*BFFS2_CORR(0) = Radiation_Type_Num RT5cat_Log_BFFS2/rl;
RT5cat_Log_BFFS2=Radiation_Type_Num*LOG(BFFS2_CORR_months);
run;

data thesis.BFFS_LOW_LDRvsEBRT_PS;
set BFFS_LOW_LDRvsEBRT_PS;
run;
```

Appendix XII

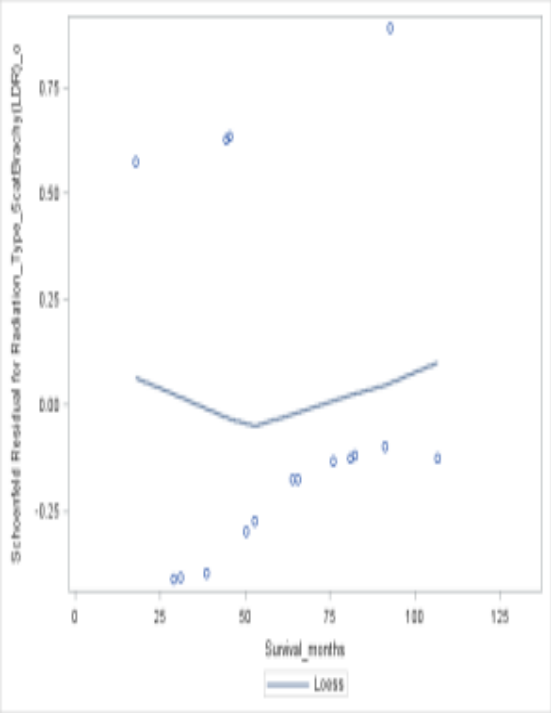
Results of Global and Visual Tests for Proportional Hazards Assumption and Testing of Extended Cox Models Using Time Dependent Covariates

Results of PH Assumption Tests and Test for Treatment as Time Dependent Covariate Using Log(Survival Time in Months) in Intermediate-Risk LDR vs EBRT Comparison:

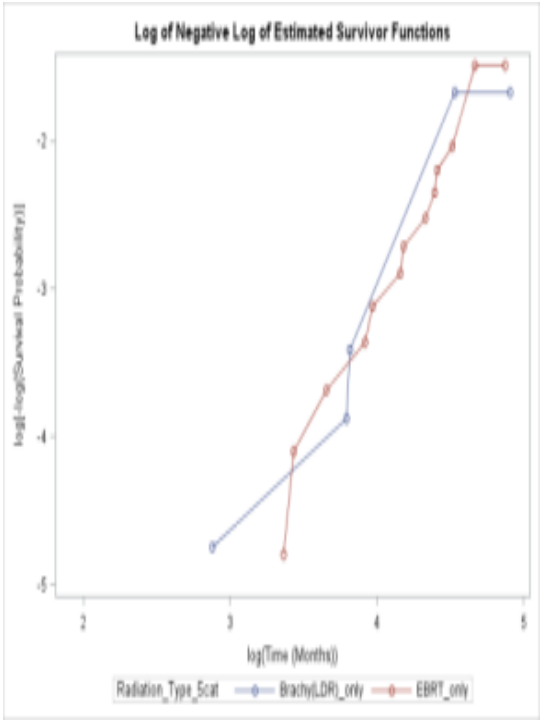
Overall Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



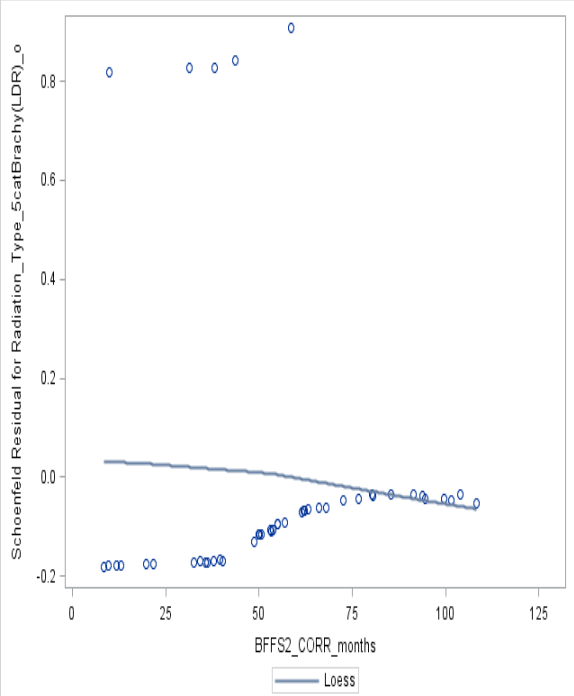
Global Tests:

Proportional Hazard Assumption Global Test Used	p-value
Schoenfeld Test	0.8958
Suprmum-Kolmogorov Test	0.8030
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.9075
Reported p-value (from Adjusted Cox PH, with no TDC)	0.6867

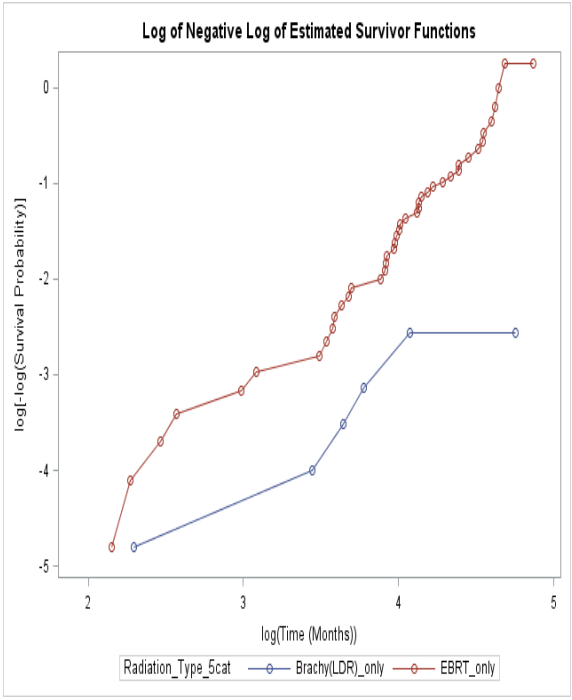
Biochemical Failure Free Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



Global Tests:

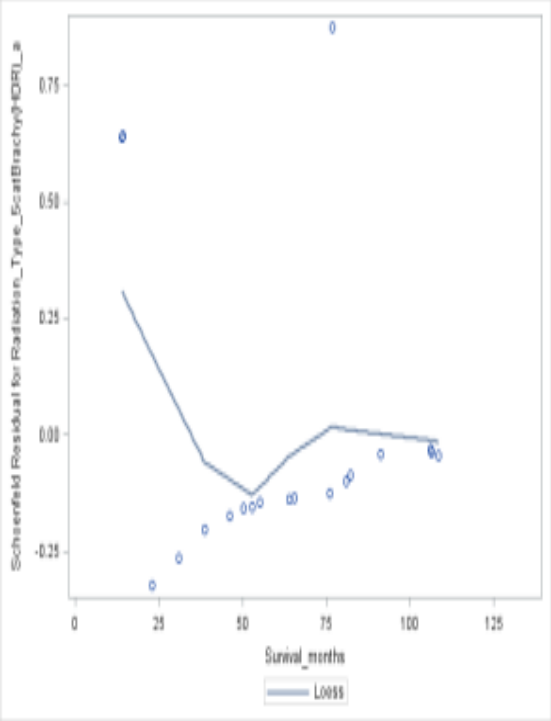
Proportional Hazard Assumption Test Used	p-value
Schoenfeld Test	0.5993
Suprmum-Kolmogorov Test	0.7160
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.6944
Reported p-value (from Adjusted Cox PH, with no TDC)	0.0012

Results of PH Assumption Tests and Test for Treatment as Time Dependent Covariate Using Log(Survival Time in Months) in Intermediate-Risk HDR+EBRT vs EBRT Comparison:

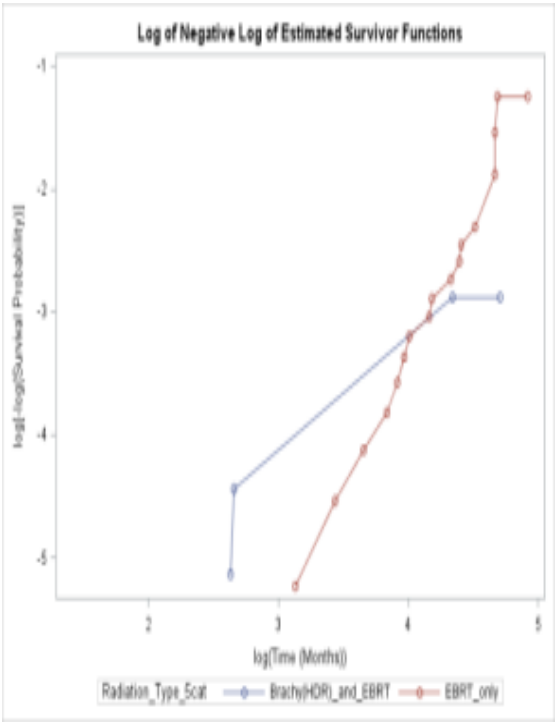
Overall Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



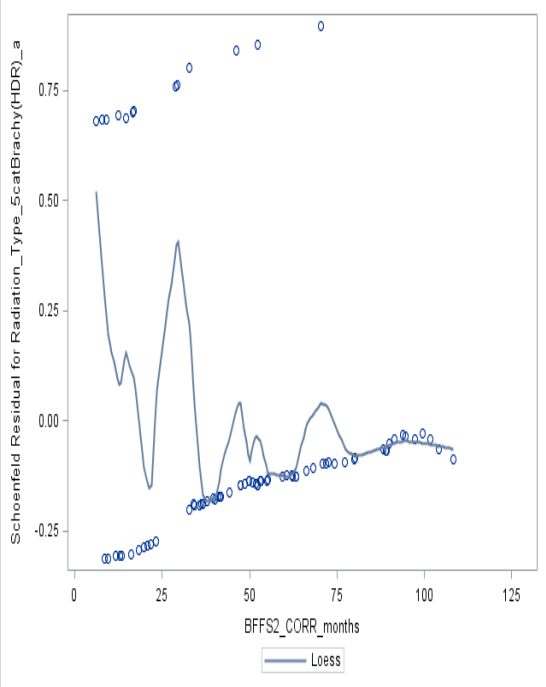
Global Tests:

Proportional Hazard Assumption Test Used	p-value
Schoenfeld Test	0.5176
Suprmum-Kolmogorov Test	0.2020
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.2714
Reported p-value (from Adjusted Cox PH, with no TDC)	0.4696

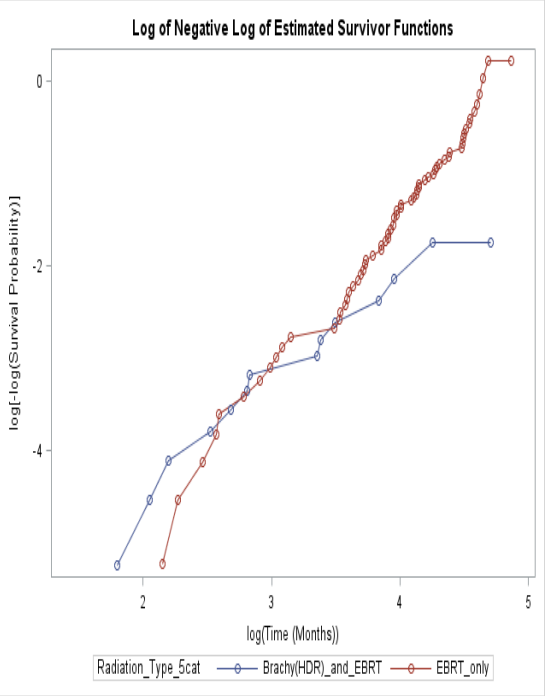
Biochemical Failure Free Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



Global Tests:

Proportional Hazard Assumption Test Used	p-value
Schoenfeld Test	0.1184
Suprmum-Kolmogorov Test	0.0840
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.0654
*Reported p-value (from Extended Cox PH, with TDC, using Likelihood Ratio Tests with 2 degrees of freedom)	0.0066
Reported p-value (from Adjusted Cox PH, with no TDC, from Sensitivity Analysis)	0.0185

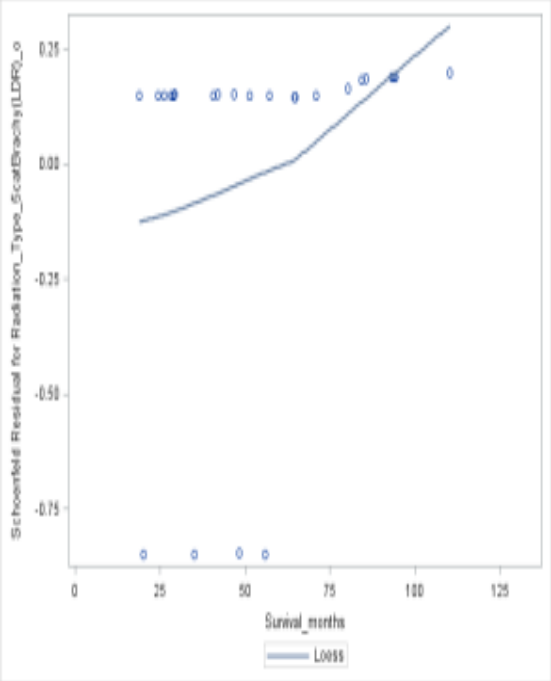
*p-value reported in study for this comparison

Results of PH Assumption Tests and Test for Treatment as Time Dependent Covariate Using Log(Survival Time in Months) in Low-Risk LDR vs EBRT Comparison:

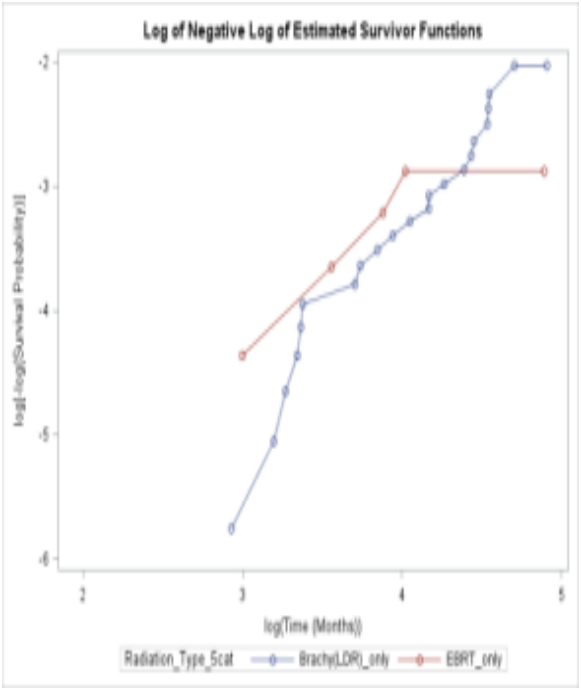
Overall Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



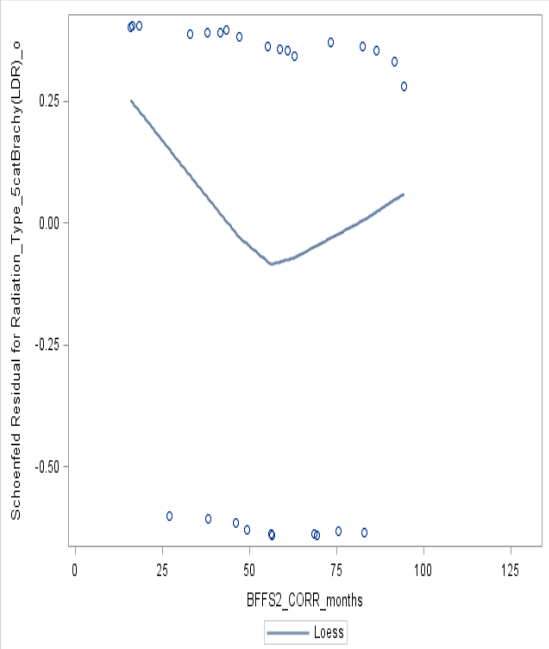
Global Tests:

Proportional Hazard Assumption Test Used	p-value
Schoenfeld Test	0.1471
Suprmum-Kolmogorov Test	0.1350
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.2004
Reported p-value (from Adjusted Cox PH, with no TDC)	0.4999

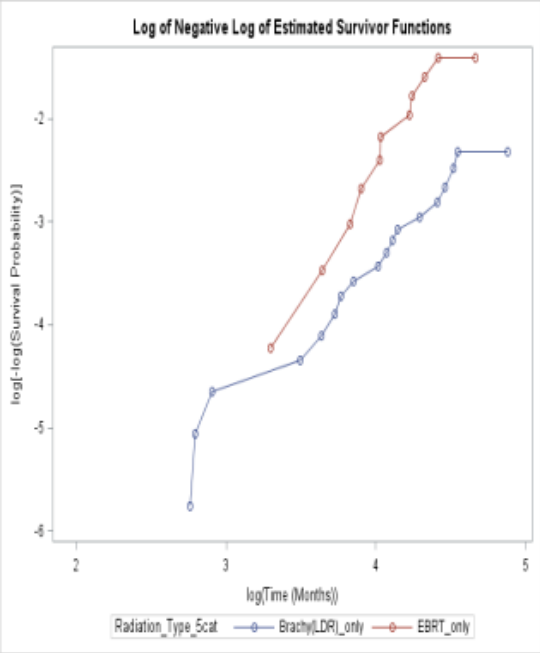
Biochemical Failure Free Survival:

Visual Tests:

Schoenfeld Plot:



Log(-Log) Survival Plot:



Global Tests:

Proportional Hazard Assumption Test Used	p-value
Schoenfeld Test	0.5897
Suprmum-Kolmogorov Test	0.6380
Test Using Extended Cox PH Regression Including Treatment as TDC using Scale of Log(Survival Months)	0.3594
Reported p-value (from Adjusted Cox PH, with no TDC)	0.0041

Appendix XIII

SAS Code Used for Power Calculations

Intermediate-risk LDR vs EBRT Power Calculation:

```
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.86 0.81)
refsurvival = "control"
hazardratio = 0.1 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
ntotal = 254
power = .;
run;
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.86 0.75)
refsurvival = "control"
hazardratio = 0.1 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
ntotal = 254
power = .;
run;
```

Intermediate-risk HDR+EBRT vs EBRT Power Calculation:

```
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.86 0.81)
refsurvival = "control"
hazardratio = 0.1 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
ntotal = 388
power = .;
run;
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.86 0.75)
refsurvival = "control"
hazardratio = 0.1 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
ntotal = 388
power = .;
run;
```

Low-risk LDR vs EBRT Power Calculation:

```
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.95 0.89)
refsurvival = "control"
hazardratio = 0.2 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
groupweights = (1 4)
```

```
ntotal = 400
power = .;
run;
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.95 0.75)
refsurvival = "control"
hazardratio = 0.2 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
groupweights = (1 4)
ntotal = 400
power = .;
run;
proc power;
twosamplesurvival test=logrank
curve("control") = (1 2) : (0.84 0.75)
refsurvival = "control"
hazardratio = 0.2 to 0.95 by 0.05
accrualtime = 1
followuptime = 1
groupweights = (1 4)
ntotal = 400
power = .;
run;
```

Curriculum Vitae

Graham Douglas Smith MRT(T), BMSc (Hons), BSc

EDUCATION

Post-Graduate Training and Qualifications:

Sept 2012 - present: Master's of Science
Department of Epidemiology and Biostatistics
University of Western Ontario (UWO)
London, ON

Sept 2008 - Jan 2012: Radiation Therapist – M.R.T. (T)
Medical Radiation Technologist Training in Radiation Therapy
Michener Institute of Applied Health Sciences
Toronto, ON

Sept 2008 - Jan 2012: Joint Radiation Therapy Degree and Bachelor of Science
University of Toronto/Michener Institute of Applied Health Sciences
Toronto, ON

Radiation Therapy Clinical Training:

Sept 2011 - Dec 2011: Radiation Therapy Clinical Practicum
Kingston General Hospital
Kingston, ON

Sept 2010 - Apr 2011: Radiation Therapy Clinical Practicum
Odette Cancer Centre
Sunnybrook Hospital
Toronto, ON

Undergraduate Training:

Sept 2003 - Apr 2008: Honours Bachelor of Medical Sciences
University of Western Ontario (UWO)
London, ON

PUBLICATIONS:

Peer-Reviewed Online Journals:

Smith G, Rodrigues G. Comparative Review of Consensus-Based Clinical Target Volume Definitions For Prostate Radiotherapy. 2013. Cureus 5(7): e128. doi:10.7759/cureus.128

Abstracts:

A. Ravi, **G. Smith**, J. Lee, R. Tirona. An Evaluation of the Geometric and Dosimetric Accuracy of using Automatic Deformable Registration to Improve the Efficiency in Adaptive Radiation Therapy Treatment Planning for Head and Neck Cancer Patients. 2011. Int J Rad Onc Biol Phys 81(2) Supp. pp. S838-S839.

ADDITIONAL RESEARCH EXPERIENCE:

Projects:

May 2013 - present: MSc Thesis
Thesis Title: "Propensity score matched pair analysis comparing brachytherapy radiation treatment techniques to external beam radiation for low and intermediate risk prostate cancer patients"
Department of Epidemiology and Biostatistics
Supervisor: Dr. George Rodrigues
University of Western Ontario (UWO)
London, ON

Jan 2012 - Apr 2013: Voluntary Research Assistant
Assistant to Dr. George Rodrigues
London Regional Cancer Program
London Health Sciences Centre
London, ON

Sep 2010 - Apr 2011: Radiation Therapy Clinical Practicum Research Project
Odette Cancer Centre
Sunnybrook Hospital
Toronto, ON

Oral and Poster Presentations:

Mar 2014: Poster Presentation
Poster Title: "Overall survival and biochemical failure-free survival comparison of brachytherapy treatment options versus external beam radiation therapy for both low and

intermediate-risk prostate cancer: A propensity-score matched analysis."
London Health Research Day
London, ON

Oct 2011: Poster Presentation
Poster Title: "An Evaluation of the Geometric and Dosimetric Accuracy of using Automatic Deformable Registration to Improve the Efficiency in Adaptive Radiation Therapy Treatment Planning for Head and Neck Cancer Patients. "
American Society for Radiation Oncology (ASTRO) 53rd Annual Meeting
Miami Beach, FL

Apr 2011: Oral Presentation at Sunnybrook Hospital Medical Physics Rounds
Title of Talk: "Can deformable registration improve efficiency in adaptive radiation therapy treatment planning for head and neck cancer patients?"
Department of Medical Physics and Radiation Therapy
Odette Cancer Centre
Sunnybrook Hospital
Toronto ON

Mar 2011: Podium Presentation
Title of Talk: "Can deformable registration improve efficiency in adaptive radiation therapy treatment planning for head and neck cancer patients?"
RTi3 Radiation Therapy Conference
Toronto, ON

Awards:

Nov 2013 Nominated for Carol Buck Graduate Scholarship Award (2013)

Mar 2011: Best student submitted abstract and best podium speaker
RTi3 Radiation Therapy Conference
Toronto, ON