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Prognostic Factors for Overall Survival and Risk Stratification of Prostate Cancer Patients with Biochemical Failure

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

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PROGNOSTIC FACTORS FOR OVERALL SURVIVAL AND RISK STRATIFICATION OF PROSTATE CANCER PATIENTS WITH BIOCHEMICAL FAILURE

Thesis format: Monograph

by

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Graduate Program in Epidemiology & Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
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Abstract

Purpose: This study aims to determine prognostic factors for overall survival (OS) in prostate cancer patients after biochemical failure (BF), and identify a risk stratification system to predict OS for prostate cancer patients with BF.

Methods: Univariable and multivariable Cox proportional hazards regression analyses, and recursive partitioning analysis (RPA) were conducted using data from 1246 patients who experienced BF in the Genitourinary Radiation Oncologists of Canada (GUROC) Prostate Cancer Risk Stratification (ProCaRS) database. Two thirds of patients were randomized into a Training cohort (n=831), and the final third into a Validating cohort (n=415).

Results: Age, baseline PSA, T stage, Gleason score, hormone therapy, radiation therapy, nadir PSA, time to biochemical failure (TTBF) and pre-BF PSADT were significant ($p<0.05$) factors on univariable and multivariable analyses for OS after BF. RPA identified 6 unique patient groups that could be categorized into a 2-class risk group based on TTBF, pre-BF PSADT, Gleason score, and age. Comparing high risk to low risk groups, hazard ratios in the Training and Validating cohorts were 3.87 (95% CI: 2.64-5.68; $p<0.01$) and 2.05 (95% CI: 1.22-3.45; $p<0.01$), respectively.

Conclusions: The 2-class post-treatment risk stratification system allows for the identification of high risk and low risk patients in terms of OS after BF to help guide patient selection for future clinical trials and clinical treatment decision-making.

Keywords

Biochemical Failure, Prostate Cancer, Risk Stratification, Recursive Partitioning Analysis

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List of Abbreviations

3D-CRT	Three Dimensional Conformal Radiation Therapy
ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
ASTRO	American Society for Radiation Oncology
BCCA	British Columbia Cancer Agency
BF	Biochemical Failure
BPH	Benign Prostatic Hyperplasia
BT	Brachytherapy
CT	Computerized Tomography
DRE	Digital Rectal Exam
EBRT	External Beam Radiation Therapy
GUROC	Genitourinary Radiation Oncologists of Canada
Gy	Gray (unit)
HDR-BT	High-Dose-Rate Brachytherapy
HRQOL	Health Related Quality of Life
HSREB	Health Sciences Research Ethics Board
IGRT	Image-Guided Radiation Therapy
IMRT	Intensity-Modulated Radiation Therapy

IQR	Interquartile Range
LDR-BT	Low-Dose-Rate Brachytherapy
LHRH	Luteinizing Hormone-Releasing Hormone
MFS	Metastasis Free Survival
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NIH	National Institutes of Health
NOS	Not Otherwise Specified
OS	Overall Survival
PCSS	Prostate Cancer Specific Survival
PFS	Progression Free Survival
PLCO	Prostate, Lung, Colorectal, and Ovarian
PMH	Princess Margaret Hospital
ProCaRS	Prostate Cancer Risk Stratification
PSA	Prostate Specific Antigen
PSADT	Prostate Specific Antigen Doubling Time
RP	Radical Prostatectomy
RPA	Recursive Partitioning Analysis

RT	Radiotherapy
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results
TNM	Tumour Nodes Metastasis
TRUS	Transrectal Ultrasound
TTBF	Time to Biochemical Failure
UICC	Union for International Cancer Control

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Chapter 1 : Introduction

1.1 Prostate Cancer

Prostate cancer is the third leading cause of death from cancer in men in Canada. It is also a significant burden affecting approximately 24,000 persons in 2015 alone. This represents 24% of all new cancer cases among Canadian men in 2015 ("Prostate Cancer Statistics - Canadian Cancer Society" 2015). There has been a reported increase in the incidence of prostate cancer since 1980. Currently there are 99 new cases of prostate cancer for every 100,000 Canadian men estimated in 2015. The rise from the 1980s was due to the increased use of prostate specific antigen (PSA) testing for screening, identifying both new cases and cases of slow growing cancer that were previously undiagnosed (Klotz 2012). Prostate cancer incidence in Canada had a sharp rise since its introduction in 1988 and peaked twice: once in 1993 (with PSA introduction), then in 2001. The second peak in prostate cancer incidence in 2001 may be due to the increase in public awareness of prostate cancer since the disclosure of the federal health minister's diagnosis in that year (Kachuri et al. 2013).

The Canadian Cancer Society estimated that 4,100 men will die from prostate cancer in Canada in 2015 (thus 17 deaths for every 100,000 Canadian men). This indicates that prostate cancer deaths comprise 10% of all cancer deaths in men for the year 2015 ("Prostate Cancer Statistics - Canadian Cancer Society" 2015). According to a report by the Public Health Agency of Canada, the cause-specific mortality rate for prostate cancer has declined since 1995. The report also outlines that the widespread use of screening methods have helped in the decreasing mortality and increasing survival trends in Canada. This may also be due to increased patient awareness of prostate cancer leading to earlier diagnosis, when disease is at an early stage at the beginning of treatment. Improvement in survival trends may also be due to the availability of different combination therapies for prostate cancer during the PSA era (Kupelian et al. 2003). A similar trend was found in the United States by the Surveillance, Epidemiology, and End Results (SEER) Program (Hankey et al. 1999). In the majority of prostate cancer cases, tumours are slow growing and can be treated successfully (Gomella et al. 2011). The

Canadian Cancer Society calculates that the 5 year survival rate for prostate cancer is approximately 96%.

Risk Factors

Risk factors for the development of prostate cancer that have been established in the medical literature include increasing age, race, and family history of prostate cancer. There are numerous risk factors that have been examined in the etiology of the disease such as obesity, or smoking; however studies pertaining to these factors are still inconclusive. The majority of prostate cancer cases are diagnosed in men greater than 65 years of age and are relatively rare among men less than 50 years of age (Crawford 2003; McDavid et al. 2004). The incidence of prostate cancer varies between different ethnic groups and countries. The lower rates are among those in Asia, and the highest rates are among those in North America, Europe and certain parts of Africa. It has been suggested that these differences are a result of genetic susceptibility, unknown risk factors, or an artifact from differences in health care and differences in methods utilized in cancer registration (Grönberg 2003). Men who have immediate family members with prostate cancer have been reported to be 2.4 times likely to be also diagnosed with prostate cancer compared to those with relatives that do not have prostate cancer (Neal et al. 2000). Several case-control studies have investigated whether there was an association between high dietary fat intake and prostate cancer. Some studies suggest a significant relationship between this exposure and outcomes such as death or advanced stage of prostate cancer (Fradet et al. 2009). Smoking had not been found to be a risk factor for prostate cancer. However in several cohort studies, smoking at the time of diagnosis increased the risk of prostate cancer-specific death (Gong et al. 2007).

Screening and Diagnosis

Cells in the prostate that have lost normal control of their growth and division lead to prostate cancer. These uncontrolled cells have varying rates of growth and also have the ability to move to other parts of the body. Initial screening tools commonly used for prostate cancer detection include the Digital Rectal Exam (DRE) and the Prostate Specific Antigen (PSA) test.

PSA is a serum marker used in the screening of prostate cancer. It is a protein produced by the prostate gland and is mainly secreted into seminal fluid, but may also be found in the blood, especially among those with prostatic disease (Stenman et al. 1999). PSA is organ specific, but not tumour specific in the prostate (Abdel-Wahab and Silva 2008). While PSA tests have been used to screen for prostate cancer, there has been great concern about the ability for the test to distinguish between individuals with prostate cancer and patients with an enlarged prostate, otherwise known as benign prostatic hyperplasia (BPH) or other benign pathologies. Prostate cancer may still be present among men who are considered to have normal PSA levels (Nam et al. 2007). Cancers detected through screening tests may be relatively slow growing, and therefore are expected to have a good prognosis (Hankey et al. 1999). While screening can capture clinically significant cancers where mortality can be reduced with treatment, a major drawback is the over-diagnosis of prostate cancer among men with clinically insignificant cancers. In fact, a study conducted on over-diagnosis in PSA screening estimated that 23%-42% of cancer cases detected through screening may not have been diagnosed had individuals not been screened (Draisma et al. 2009). These men undergo greater harm through diagnostic workup, treatment and their related side effects when their prostate cancer was not aggressive enough to have initially required treatment. Depending on the treatment administered, patients may experience urinary, bowel, sexual or other health issues. This not only affects patient quality of life, but also can produce extra costs to the healthcare system (Korfage et al. 2005; Corcoran et al. 2010).

The benefits of population based prostate cancer screening remain questioned within the medical community. The two largest prospective randomized control trials on this topic have led to differing results (Wolf et al. 2010). A U.S. study from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial found that after 10 years of follow-up, there was no reduction in prostate cancer-specific mortality from PSA screening (Andriole et al. 2009). Similarly in an extended follow-up report at 13 years after the PLCO Cancer Screening Trial, there was no evidence of a reduction in prostate cancer mortality (Andriole et al. 2012). A European randomized control trial report demonstrated that there is a 20% reduction in prostate cancer mortality after 9 years of follow-up, and after a follow-up period of 11 years (Schröder et al. 2009; Schröder et al.

2012). Differences between the two studies that require consideration include dissimilar choices in PSA cutoff points, prescreening issues and compliance in screening arms (Wolf et al. 2010).

An updated Cochrane review on prostate cancer screening included both these studies and three other randomized control trials in the literature. The investigators found that screening was associated with an increase in the number of men who were diagnosed with cancer. It was also reported that among the individuals in the screened group, the proportion of individuals with localized prostate cancer was greater, while the proportion of individuals with advanced prostate cancer was greater in the control group. Despite these findings, prostate cancer-specific mortality was not significantly reduced among those screened (Ilic et al. 2013).

Refinements in PSA testing (PSA velocity, free total PSA, age and prostate volume corrected thresholds) and other biomarkers (such as PCA-3) as well as nomograms have been proposed to improve screening performance, but are currently unproven and are not part of standard care (Crawford et al. 2012).

Beyond screening, PSA tests may also be used to monitor a patient who has already been diagnosed with prostate cancer, in other words through surveillance. It may also be used to detect the recurrence of prostate cancer, which may be experienced by approximately 35% of men within 10 years of curative treatment (Pound et al. 1999; Bruce et al. 2012).

The DRE is a physical test administered by a healthcare professional where the prostate gland is felt through the rectum. This test is to investigate the presence of an enlarged prostate gland or any other abnormality. While prostate tumours may be felt through the DRE, small localized tumours may be better detected through the combined use of both PSA and DRE. Even though the combination of PSA and DRE has a low sensitivity and specificity of trusted accuracy in detecting cancer, utilization of both tests allows for gathering more information and increasing the accuracy of early detection methods.

Most prostate cancers are found through case finding at an individual level. In early stages of prostate cancer, there are generally no symptoms. If there are, they are quite

similar to the symptoms of BPH. Some potential symptoms at presentation include dysuria, polyuria, or having a feeling that the bladder has not completely emptied. Other symptoms associated with later stages of prostate cancer include bone pain, weight loss or pain in the pelvic area. Other men may seek out PSA testing because of a family history or other concerns about their individual risk of prostate cancer. Whether prostate cancer is suspected from PSA or the occurrence of symptoms, diagnosis can only be made with a biopsy (Mason and Moffat 2010).

A transrectal ultrasound (TRUS) allows for an image of the prostate to be displayed. A TRUS probe, inserted into the rectum, uses ultrasonic waves to give an image of increased nodularity. Most commonly the cancer cannot be directly visualized and the ultrasound is used to guide needles to systematically sample regions of the gland to take biopsy samples. Biopsies are administered when an abnormal mass is found during a DRE or when a patient has a high PSA level (Gomella et al. 2011). Prostate biopsies of 8-12 tissue samples are taken to determine whether abnormal findings are due to cancer or due to other benign causes. These samples are examined by a pathologist to confirm the diagnosis of cancer and to assign a tumour grade. Grading is assigned based on the similarity or differences between normal and cancer cells at a microscopic level.

Grading and Staging

The Gleason grading system for prostate cancer measures cancer aggressiveness (Thompson et al. 2007). A higher Gleason grade indicates that the aggressive cancer is more likely to spread. The Gleason score is calculated by the sum of the primary and secondary pattern, each given a score between 1 and 5, then added to give a final score between 2 and 10. The primary grade is for the most common tumour pattern while the secondary grade is for the second most common tumour pattern. This grading system has been noted to be directly correlated with mortality rates, to be a predictor of time to recurrence after surgery, and of response to therapy (King 2000).

Small tumours confined within the prostate gland may be treated more successfully when compared to larger tumours within the prostate gland, or tumours that have spread beyond the prostate gland (Thompson et al. 2007). Thus it is important to be able to

classify and measure the extent and severity of prostate cancer for treatment planning and for assessing prognosis. Cancer cell metastases normally begin with local invasion, where prostate cancer cells invade nearby tissue. These cells are able to move outside the capsule of the prostate, resulting in progression of the cancer. Metastasis occurs when cancer cells have spread and have grown in a secondary location, damaging normal cells in these new areas. Lymph node and bone metastases are common sites of spread in prostate cancer (Mason and Moffat 2010).

The classification most commonly used to describe the size and spread of a tumour is the tumour, node and metastasis (TNM) staging system which was first introduced in 1992 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (Cheng et al. 2012). Table 1 shows the latest TNM revision made in 2010. It should also be noted that along with TNM staging, PSA level and Gleason score can be used to further classify tumours into four stages as shown in Table 2.

Table 1: 2010 AJCC Prostate Cancer Staging

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (for example, because of elevated PSA)
T2	Tumour confined within prostate
T2a	Tumour involves one-half of one lobe or less
T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional Lymph Nodes (N)	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Table 2: 2010 AJCC Anatomic Stage/ Prognostic Groups

Group	T	N	M	PSA(ng/mL)	Gleason Score
I	T1a-c	N0	M0	<10	≤6
	T2a	N0	M0	<10	≤6
	T1-2a	N0	M0	Unknown	Unknown
IIA	T1a-c	N0	M0	<20	7
	T1a-c	N0	M0	≥10 and <20	≤6
	T2a	N0	M0	≥10 and <20	≤6
	T2a	N0	M0	<20	7
	T2b	N0	M0	<20	≤7
	T2b	N0	M0	Unknown	Unknown
IIB	T2c	N0	M0	Any	Any
	T1-2	N0	M0	≥20	Any
	T1-2	N0	M0	Any	≥8
III	T3a-b	N0	M0	Any	Any
IV	T4	N0	M0	Any	Any
	Any	N1	M0	Any	Any
	Any	Any	M1	Any	Any

Risk Stratification

Patients are often classified into prognostic groups according to different factors known to affect prostate cancer outcomes. It is important for patient counseling and treatment decision-making (Mohler et al. 2010). Pretreatment risk stratification also plays an important role in the selection and stratification of patients for clinical trials and retrospective clinical research. There are a number of methods to present classification models including nomograms, look-up tables, and regression tree analyses. A simple and generalizable risk-group stratification model that has been widely used and accepted is by D'Amico et al 1998. This system uses three clinical factors and stratifies patients into three groups based on their risk of biochemical failure after radical prostatectomy or radiotherapy (D'Amico et al. 1998). Due to PSA screening, most men are diagnosed with non-palpable and clinically localized disease, when they would have been diagnosed 10 years later by DRE. Since the proportion of patients with localized tumours has greatly increased, the risk of disease progression after radical prostatectomy has decreased greatly. Thus there is concern for older prognostic models, such as that of D'Amico, and their need to be reevaluated and updated to take into consideration the trends in stage migration (Hernandez et al. 2007; Han et al. 2001).

In general, risk groups often include TNM stage, Gleason score, and PSA levels. From these variables, patients may be grouped into low risk, intermediate risk and high risk categories. Some organizations may use clinical variables to identify additional risk groups such as very-low risk, low-intermediate risk, high-intermediate risk, and very high risk. A number of risk stratification systems for patients exist from different institutions or organizations including the Genitourinary Radiation Oncologists of Canada (GUROC) and the National Comprehensive Cancer Network (NCCN) (Rodrigues et al. 2014; Mohler et al. 2010).

Prostate Cancer Treatments

A number of factors are considered in treatment selection for prostate cancer patients. Overall health status and life expectancy should be taken into account as well as type of prostate cancer, PSA level, stage and grade of cancer, metastasis and patient preference.

Potential life expectancy is also an important factor in the treatment decision for a patient. That is, if a patient is expected to have a long life expectancy, prostate cancer may be a cause of morbidity and mortality, and would therefore benefit from undergoing treatment. For a patient with a shorter life expectancy, the likelihood that a patient will die of prostate cancer is reduced due to competing hazards (Thompson et al. 2007; "Treatment of Prostate Cancer - Canadian Cancer Society" 2015). Actuarial tables and risk calculators are available to provide estimates of life expectancy based on patient age and comorbidities (NCCN, MSKCC) ("Prostate Cancer" 2015; Mohler et al. 2010).

Patients with what is considered low-risk prostate cancer may be managed by active surveillance, although some still may opt for treatment. Patients with intermediate and high-risk or aggressive localized disease have a number of different treatment options including radical prostatectomy or radiotherapy (Locke et al. 2015). These three treatments are the primary management options for initial therapy for patients with clinically localized disease, although other modalities of treatment including high intensity ultrasound and cryotherapy have also been investigated (Mohler et al. 2010).

Watchful Waiting

Watchful waiting is sometimes known as deferred treatment or symptom-guided treatment. It encompasses the active decision in the delaying of therapy until the tumour progresses clinically either with or without symptoms. Upon the decision to start treatment, various options include hormone therapy, surgery or radiotherapy. The development of systemic symptoms usually is associated with metastatic disease. Thus, these patients will normally undergo palliative therapy to aid patient quality of life until the end of life. Watchful waiting thus results in the potential under-treatment of those with more aggressive disease and some men with potentially curable cancer may have their life harmed due to prostate cancer related mortality (Adolfsson 2008; Klotz 2006).

Deferred treatment is a potential option for older patients with less aggressive tumours, for those with limited life-expectancy, and also for those who experience recurrence after curative therapies (Aus et al. 2005). The rationale behind watchful waiting is similar to that of active surveillance where prostate cancer is generally slow to progress, and reduce

overtreatment, especially among older men with competing risks of non-cancer mortality (Adolfsson 2008).

Active Surveillance

Active surveillance involves postponing immediate treatment, but requires PSA tests at regular intervals to monitor potential disease progression. The exact schedule for active surveillance differs between centers, but generally includes periodic TRUS guided prostate biopsy. Curative treatment is initiated at predefined points that indicate progression (Adolfsson 2008). This option of surveillance may be suitable for patients for varying reasons. Firstly, a patient's cancer may not progress quickly to cause morbidity or mortality. Active surveillance would therefore reduce the risk of overtreatment (Klotz et al. 2010). Studies on active surveillance alone have varying guidelines in the selection of patients where some belong to low-risk groups and others also include patients with intermediate risk (Dall'Era et al. 2008). There is some concern that surveillance may minimize the time frame that would be optimal for curative treatment, but among carefully selected patients that may be at very low risk, active surveillance still provides a safe alternative to immediate treatment (Tosoian et al. 2011). It still allows the option for curative therapy when a patient is reclassified to be at higher risk. Should a patient decide to initiate other forms of treatment, there are side effects to be considered which may affect the patient's quality of life. Currently, the data on the health related quality of life (HRQOL) of patients who undergo active surveillance compared to curative therapy offer different conclusions. Some studies indicate that men undergoing active surveillance have similar HRQOL to those undergoing active treatments, while other studies indicate that men under active surveillance have worse HRQOL (Daubenmier et al. 2006).

The incorporation of evaluating repeat biopsies or even higher Gleason scores has been suggested for offering curative treatment (Morash et al. 2014). Proposed criteria for men on active surveillance include short PSADT or increased cancer volume or grade progression on repeat biopsy, or patient preference. There is no specified PSADT period for use, as it may be less effective in predicting prostate cancer death at the individual

level (Adolfsson 2008). Due to the differences in guidelines, study estimates on treatment outcomes are difficult to compare.

Radiotherapy (RT)

Radiotherapy is a treatment option for men whose disease seems potentially curable. This form of treatment utilizes high-energy X-rays to kill cancer cells. The basis of radiotherapy stems from the lack of ability for cancer cells to repair damage created by X-rays. Normal cells on the other hand when damaged have better ability for cellular repair. It is the differential between the antitumour effect and normal tissue effects of radiotherapy that leads to the potential of cure with acceptable side effects. Radiotherapy includes external beam radiation therapy (EBRT) or brachytherapy (BT) or a combination of both. Treating with these two methods often leads to high cure rates (Bruce et al. 2012). Even though most prostate cancers are at an early stage when diagnosed, some studies encourage early treatment for patients with longer life expectancy, especially since the natural course of disease leads to progression and metastasis (Johansson et al. 2004).

EBRT

In EBRT, X-rays are directed from a machine, known as a linear accelerator, onto the pelvis to target the prostate gland. As a common form of radiotherapy, EBRT offers the advantage of being able to be given to patients as an outpatient treatment. Most patients are able to tolerate the treatment without major side effects. This treatment is customized for each patient to ensure that the radiation is given in its highest dose to the prostate gland, and lowest dose to the surrounding tissues such as the bladder and rectum. CTs or MRI scans provide information on the prostate and surrounding tissues that are required in the planning stage for EBRT. While the treatment takes a few minutes, the administration of the treatment takes longer and must be repeated on a daily basis (Mason and Moffat 2010). Schedules vary from as short as one week to as long as 8 weeks. Common schedules are between 7 and 8 weeks of treatment.

In the early 1990s when 2 dimensional planning was utilized, total doses were limited from 66 to 70 Gy because of limited ability to deliver treatment precisely (Mohler et al. 2010). Given new radiotherapy technology from new planning software and the use of CTs, known as 3D-conformal radiation therapy (3D-CRT), treatment can be better customized to the position and shape of a patient's prostate gland. Not only does conformal radiotherapy allow dose escalating radiation reducing side effects, but it also provides a means of better tumour control (Locke et al. 2015; Kuban et al. 2008). Intensity-modulated radiotherapy (IMRT) is another development of conformal radiotherapy, offering the ability to target a concave treatment area to spare the rectum and also allowing good tumour control among patients with localized disease (Zelefsky et al. 2006). Image-guided radiotherapy (IGRT) is also available in which radiation machines have image scanners to allow for minor adjustments and correction in the position of radiation beams. Such precision guided therapies have stimulated interest in shorter, high dose per fraction radiotherapy schedules between 1 to 4 weeks of treatment.

Acute side effects and long-term side effects may exist with radiotherapy. Acute side effects such as inflammation of the urethra, bladder and rectum will cause discomfort from passing urine as well as diarrhea. These acute side effects may arise after 2 weeks of treatment and continue to worsen during the course of the treatment. The side effects may still be managed through various methods such as diet and medication. Long term side effects are uncommon, but has been reported to affect 1%-5% of radiotherapy patients (Mason and Moffat 2010).

Brachytherapy

BT is an important treatment option primarily for low and intermediate risk patients. There is also an evolving role of BT in high risk disease. BT involves the delivery of radiation internally using radioactive seeds. Sometimes radioactive seeds may be implanted permanently, as the seeds gradually lose their radioactivity over time. This method would be less likely to affect the rectum and nerves near the prostate since the seeds emit low-energy, short range radiation. Treatment with BT alone is a common option among patients with early, localized prostate cancer (Mohler et al. 2010). This

method of radiotherapy may be unable to irradiate cancer cells that have extended beyond the prostate capsule (Mason and Moffat 2010) .

Low dose rate BT (LDR-BT) can be conveniently administered in one day as a one-time procedure with the help of TRUS to guide the placement of irradiated seeds (Morton and Hoskin 2013). This treatment method reportedly has excellent outcomes and low morbidity among patients with low risk prostate cancer. When compared to RP or EBRT, LDR-BT performs well with long-term survival and lower toxicity. LDR-BT is also associated with lower complication rates. LDR-BT may be used as a monotherapy or along with EBRT as a boost for early detected prostate cancer (Skowronek 2013).

An alternative is the use of temporary high dose rate BT (HDR-BT) where implanted catheters are used to introduce a radioactive iridium source into the prostate gland. This may require multiple treatments. An advantage however is that it allows more control over dose escalation that is not available with LDR-BT (Skowronek 2013).

Both HDR-BT and LDR-BT may be used with or without EBRT and hormone therapy. HDR-BT with EBRT is a common method of therapy for patients with intermediate and high-risk prostate cancer. HDR-BT has been recommended to be used in combination with EBRT since EBRT requires a dose escalation above 70-76 Gy to optimize cancer control and also because HDR-BT is able to spare adjacent tissues from risk of exposure. Several randomized controlled trials of HDR-BT also observed a 10-15% decrease in the risk of biochemical failure, but also increased rectal toxicity. Outcomes on other clinically meaningful endpoints are uncertain (Morton 2014; Michalski et al. 2013). In general, combining BT in treatment for dose escalation has less toxicity compared to increasing EBRT doses alone (Morton and Hoskin 2013).

Surgery

RP is a surgical treatment offered to patients with localized disease to control cancer. RP encompasses the removal of the prostate gland, seminal vesicles and part of the urethra. Depending on the extra characteristics of the tumour and patient sexual function, RP may or may not be nerve-sparing. RP is a method of treatment that potentially removes all

cancer cells and may be recommended when the cancer has not spread outside the prostate (patients with T1 or T2 tumours). Surgical removal of the prostate may be used in combination with other treatments such as radiotherapy (Thompson et al. 2007).

Since the prostate is removed, it is expected that the recurrence of cancer is low among patients with localized disease. If the prostate gland is removed, a small amount of prostate tissue may remain and produce low levels of PSA. It has been reported that 35% of men that are given this method of treatment will have a detectable level of prostate-specific antigen in their serum within 10 years of the surgical treatment (McLeod 2005).

Perioperative morbidity must be taken into consideration when considering RP. Because of this, RP has been primarily recommended for patients who have life expectancies greater than 10 years (Mohler et al. 2010).

Hormone Therapy

Prostate cancer cells require the hormone testosterone for their growth. If a tumour is deprived of testosterone, cancer cells can die from apoptosis. Hormone therapy, also known as androgen deprivation therapy (ADT), helps to control tumour growth, but is unable to completely eliminate it. ADT may be used in various stages of prostatic disease. It may be used by itself in the treatment of localized advance cancer or with metastatic disease, or with radiotherapy as an adjuvant treatment (Mason and Moffat 2010). The use of neoadjuvant (prior to main treatment using RP or radiation therapy) or adjuvant (after RP or radiotherapy) hormone therapy differs from its use as a primary treatment (Thompson et al. 2007).

Luteinizing hormone-releasing hormone (LHRH) agonists or bilateral orchiectomy are both effective for treating prostate cancer. If testosterone cannot be suppressed to levels less than 50 ng/mL with the medical or surgical castration, additional changes in hormone treatment using estrogens, anti-androgens, or steroids may be considered. Adverse events from the use of ADT include, but are not limited to, osteoporosis, insulin resistance, increased risk for cardiovascular disease and diabetes, and loss of secondary sex characteristics (Mohler et al. 2010).

1.2 Biochemical Failure

Follow-up assessments after treatment for prostate cancer are important for identifying and treating any side effects, and also detecting recurrence of prostate cancer. These visits usually include PSA blood tests and DRE. Patients treated by EBRT should have slow declining or stable PSA levels following completion of treatment. However it is important to realize that there are instances when there is one or two sequential rises in PSA levels, followed by a fall without treatment to lower PSA levels, known as PSA bounce. This benign phenomenon has been reported to occur primarily after BT, but also after other treatments including EBRT and three-dimensional conformal radiation therapy (Sengoz et al. 2003; Crook et al. 2007). The implications of PSA bounces are uncertain. Some studies have reported improved survival among those who experience the bounce, while other studies did not find this association (Hinnen et al. 2012; Stock et al. 2003). In general, 30-40% of successfully treated men through BT experience a PSA bounce within 12-18 months after treatment. However there are differences in frequency of PSA bounce reported in literature due to varying definitions of PSA bounce (Caloglu and Ciezki 2009). Currently there is no definition that is able to differentiate between rising PSA levels caused by the recurrence of prostate cancer from a benign PSA bounce.

In other instances of rising PSA levels, biochemical failure is suspected. Defining biochemical failure among patients treated with RP is simpler compared to patients treated with radiation therapy, since the main producer of PSA (the prostate) has been removed. After RP, PSA levels are expected to be undetectable within 6 weeks (Cookson et al. 2007). In a study comparing several definitions of biochemical failure after RP, a PSA value of 0.4 ng/mL followed by another increase was the strongest indicator of the development of distant metastasis (Stephenson et al. 2006).

Prior to January 2005, a definition of biochemical failure after external beam radiotherapy (EBRT) as defined by the initial ASTRO consensus was “three consecutive rises of PSA levels after a PSA nadir” (Roach et al. 2006). The date of biochemical failure in this definition was determined as the date halfway between the nadir date and the first PSA rise or any rise in PSA level significant enough to commence therapy. A

Consensus Conference sponsored by the American Society for Therapeutic Radiology and Oncology (ASTRO) and the Radiation Therapy Oncology Group (RTOG), brought forward concerns of needing a revised definition for biochemical failure. The previous definition was not based on clinical progression or survival and biochemical failure did not necessarily mean patients were experiencing clinical failure (Nielsen 2007). It performed poorly for patients who underwent hormonal therapy, as a false failure could be triggered by small PSA rises after hormone withdrawal. Given the issues with the previous definition of biochemical failure, it was recommended that the ASTRO definition be revised to "a rise by 2ng/mL or more above the nadir PSA after EBRT with or without HT" (Roach et al. 2006). An example of meeting this definition is illustrated in Figure 1 and is now referred to as the Phoenix definition of biochemical failure. Even if a patient meets the definition of having experienced biochemical failure, there is no requirement for immediate treatment (McLeod 2005).

Biochemical failure is experienced by approximately 35% of prostate cancer patients within 10 years of receiving treatment. Among patients who have undergone radical prostatectomy, the 10 year actuarial biochemical progression-free survival (PFS) was reported to be 68%. Patients who were given radiotherapy were found to have a 10 year actuarial biochemical PFS between 50-70%. Among the 35% of patients who have biochemical recurrence, a third developed evidence of metastatic disease within 8 years from when their PSA was elevated (Bruce et al. 2012).

The clinical course of patients with biochemical failure is variable. Some patients quickly experience progression to metastasis, while other patients do not. A study comparing overall survival among men with and without biochemical failure over at 10 year period, found that overall survival was similar for patients after RP. In this study, biochemical failure was defined as a serum PSA of 0.2 ng/mL or greater. Among those with biochemical failure, the 10 year overall survival rate was 88%, among those without biochemical failure, the 10 year overall survival rate was 93% (Jhaveri et al. 1999, Pound et al. 1999).

Treatment options for patients with biochemical failure may include watchful waiting, salvage BT, salvage RP and ADT. Salvage RP may be an option in selected patients after EBRT or BT provided that there is no metastasis (Mohler et al. 2010). However, salvage RP is not usually recommended due to associated surgical risks including urinary and sexual dysfunction. BT after biochemical failure may be considered for treatment, but the optimal dose of radiation still requires study. The early use of ADT compared to the late use of ADT is still debated, but has been reported to be considered the standard of care (Bruce et al. 2012). Factors that influence the timing of initiating ADT include PSA doubling time (PSADT), patient anxiety and the expected side effects of hormone therapy. Biochemical failure with elevating PSA levels cause anxiety among patients and its management is varied and still debated.

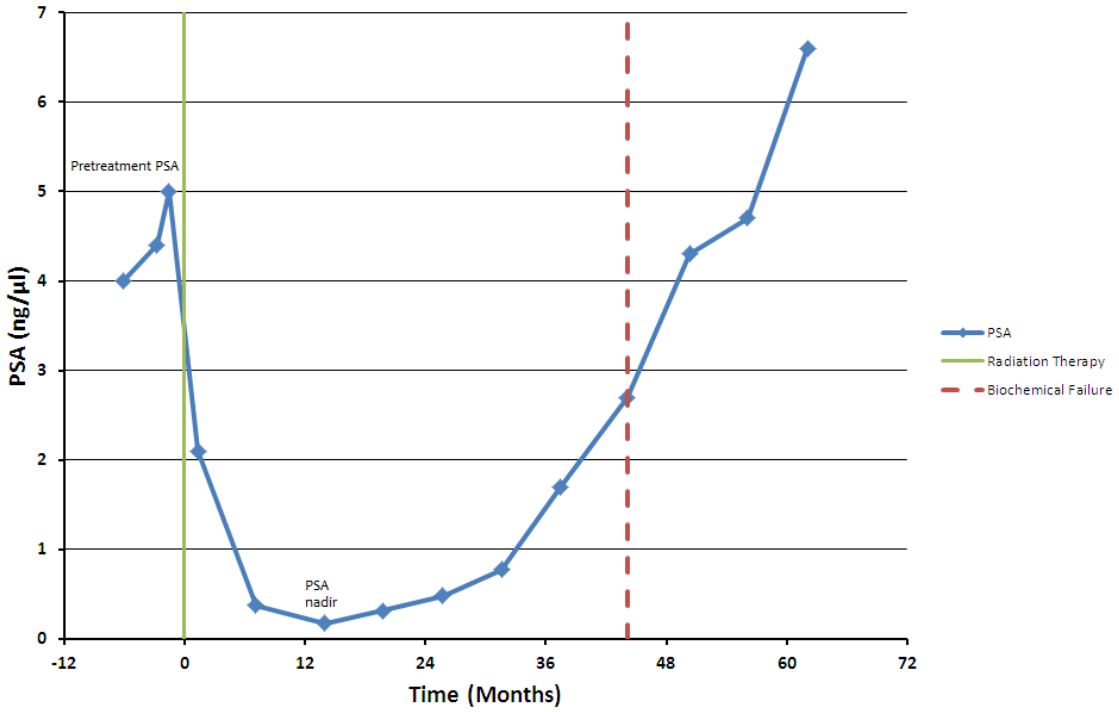

Figure 1: Example of PSA Follow-Up Profile Depicting Biochemical Failure

PSA: Prostate Specific Antigen

1.3 Prostate Cancer Endpoints

Within clinical trials, clinical endpoints refer to important patient–related outcomes being measured. Clinically meaningful endpoints refer to endpoints that directly measure how a patient feels or functions, or how long they survive. These endpoints can be either objective, for example, when looking into survival or a clinical event; or subjective, for example, using a score or rating for symptoms or health related quality of life (De Gruttola et al. 2001).

Endpoints commonly studied for prostate cancer include Overall Survival (OS), Prostate Cancer-Specific Survival (PCSS), and Metastasis-Free Survival (MFS). OS considers deaths from any causes as events. PCSS is estimated by considering only deaths due to prostate cancer and often considers all other causes censored. MFS considers the period until metastasis is detected as an event. These endpoints often require long follow-up periods, therefore surrogate endpoints are often sought out as it not only reduces the duration of clinical trials, but also costs (Fleming and DeMets 1996).

The National Institutes of Health (NIH) has defined surrogate endpoints as biomarkers intended to substitute for a clinical endpoint (Aronson 2005). Biomarkers can be objectively measured and assessed as an indicator of normal biologic processes. They are used because they are faster and easier to study. Because prostate cancer is generally slow growing, using a direct endpoint is often not practical when analyzing effects due to low event rates and long time-to-events post treatment.

Surrogate endpoints can be laboratory measures or a physical sign in a patient that can be used as a substitute for a clinically meaningful endpoint. These markers may help in patient selection for clinical trials and management of disease (Armstrong and Febbo 2009). Ideally, a surrogate endpoint should be within the pathway in which disease occurs, or one where intervention can alter the progression of disease to provide meaningful benefit. Sometimes biomarkers may just be correlated with disease and are not directly related to survival or how a patient feels. Therefore while all surrogate endpoints are biomarkers, not all biomarkers can be considered good surrogate endpoints (Aronson 2005).

The natural history of prostate cancer in men with biochemical failure varies greatly. While biochemical failure has a slight association with metastases, it is not a suitable surrogate endpoint for progression or prostate cancer specific mortality (Simmons et al. 2007). The current definition of biochemical failure is poorly correlated with clinical outcomes such as overall survival, prostate cancer specific survival and metastasis free survival. Therefore better models using clinical outcomes based on other factors than biochemical failure alone are required. Considerations for other definitions of an appropriate surrogate endpoint for prostate cancer are required for clinical trials and for treatment selection after biochemical failure.

1.4 Recursive Partitioning Analysis

Recursive partitioning analysis (RPA) is a type of prediction model that is utilized to create distinct prognostic groups. This method of building decision trees is useful as it divides patients into groups based on their survival, i.e. time at risk (Park et al. 2009; Al-Nachawati et al. 2010). RPA may also divide patient groups by the proportion of experiencing binary outcomes. RPA has been used in a number of different settings such as brain metastases and glioblastomas, to develop useful prognostic models (Scott et al. 2012; Gaspar et al. 1997). Models developed were able to divide patients into subgroups that could be easily used for patient care and clinical trials.

In RPA, the first variable that is found which best splits the data into two homogenous groups based on a specific threshold or cut-point, makes the primary node. For survival outcomes, the split corresponds to calculated hazard ratios. Within each subgroup, the next best split is applied to each group. The division into groups is guided by a principle known as "impurity reduction", where daughter nodes of a tree share more similarities than parent nodes (Strobl et al. 2009). The splits in the decision tree are known as "leaves", where no other split is possible, as is depicted in Figure 2. Leaves are also known as terminal nodes (Gaspar et al. 1997). In the identification of prognostic factors, RPA makes fewer modeling assumptions than proportional hazards. If observations have missing values in a variable being evaluated, it is first ignored for calculating the impurity reduction. The same observations are later included in calculations for impurity reductions in other splits. This method thus does not result in heavy data loss as it would if missing values were completely ignored.

Splitting of nodes in RPA continues until all leaf nodes are pure, or until a pre-specified number of observations in a node is reached, or a node cannot be split given a minimum threshold in measuring impurity (Strobl et al. 2009). A concern for over-fitting exists with prediction modelling. In RPA, a solution to this problem is to "prune" the decision trees. This process removes any splits in the tree that do not add to the prediction accuracy of the model. In practice, this typically translates into requiring a minimum number of 20 observations in a node to enable further splitting, and trimming of downstream branches determined to be of less importance or of insufficient sample size

for further analysis (Pavlopoulos et al. 2004). Additionally for clinical application purposes, RPA generated cut-points may be further modified and rounded to represent more clinically meaningful values.

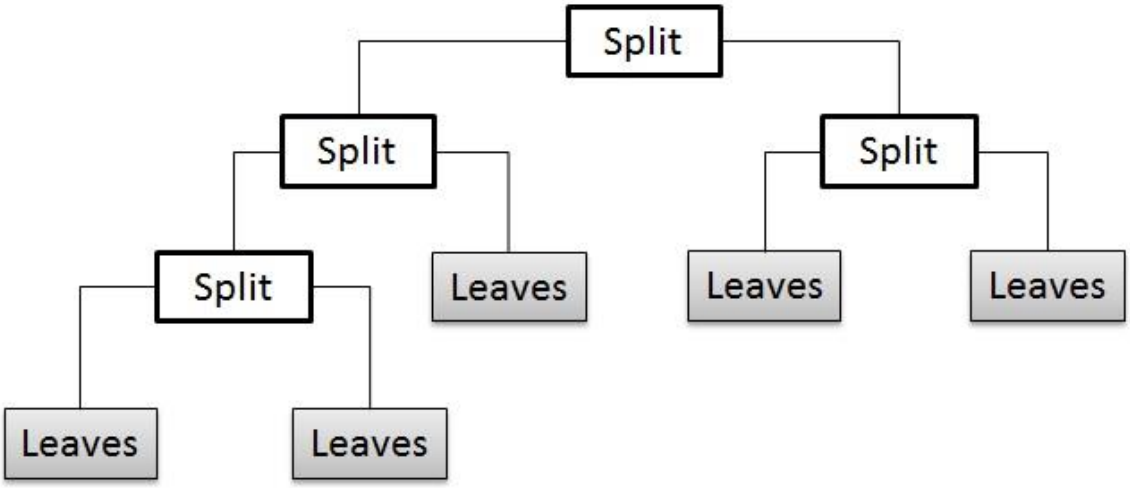

Figure 2: Decision Tree from Recursive Partitioning Analysis

Chapter 2 : Literature Review

The literature review was conducted through PubMed using the search strategy: ((biochemical*[ti] OR PSA[ti] OR prostate specific antigen[ti]) AND (failure*[ti] OR recurren*[ti] OR relapse*[ti])) based on Nguyen *et al.* who identified 19 studies from 1980 to 2013, which examined prognostic factors among patients with BF after RT or RP for MFS, PCSS and OS (Nguyen et al. 2015). An additional 3 studies were identified from 2013-2015, of which all 3 had RT as primary treatments prior to BF. Predictive variables are those significantly associated (α=0.05) with an outcome variable, and may subsequently be used to predict values for the outcomes. Variables that were found to be independently predictive were significantly associated in the presence of other variables.

2.1 Prognostic Factors for MFS among patients with BF

In a review of the literature on prognostic factors among men who experience biochemical failure after RP or RT, it was found that PSADT, Gleason score and time to biochemical failure (TTBF) were more consistently found to be prognostic of MFS. Representative studies are discussed below.

PSADT has been analyzed using various cut points or as a continuous variable. A number of studies have found PSADT as predictive of MFS in both univariable and multivariable analyses. In a retrospective study analyzing 450 men treated with RP who never received adjuvant or salvage therapy before metastatic disease development, Antonarakis *et al.* examined PSADT as in the following categories <3.0, 3.0-8.9, 9.0-14.9 and ≥15.0 months and Gleason score as ≤ 7, 7 and 8-10 (Antonarakis et al. 2012). An earlier study conducted by the same group found Gleason score, T stage, TTBF, PSADT and age as predictive of MFS in univariable analysis, but upon multivariable analysis only PSADT (categorized as ≥9, 3-8.9 and <3 months) was independently predictive of MFS (Antonarakis et al. 2011). A study of PSA kinetics on MFS found that changes in PSADT and in log PSA slope were independent predictors in multivariable analysis (Antonarakis et al. 2012).

A study analyzing the natural history of BF after RP with adjuvant radiotherapy found that on multivariable analysis, increasing Gleason score and PSADT of less than 6 months were significantly associated with systemic progression. The authors defined systemic progression as having a demonstrable metastasis on radionuclide bone scan or computerized tomography (CT) scan, or on biopsies outside the prostatic bed. PSADT was categorized at 6 month intervals. Advanced T stage was found to be associated with the risk of systemic progression, but was not statistically significant. TTBF was also a factor analyzed in this study. However it did not predict systemic progression or PCSS (Boorjian et al. 2012). This finding is very similar to that of Roberts et al; where multivariable analysis indicated PSADT as a significant factor for predicting systemic progression. Univariable analysis identified PSADT and Gleason score as independent predictors (Roberts et al. 2001). Although TTBF was not found to be an independent predictor for MFS and PCSS, it was identified as such in another study by Buyyounouski et al. This group also found that Gleason scores of 7 to 10, PSA nadir $\geq$ 2ng/mL, and decreasing radiation dose were independently predictive of MFS (Buyyounouski et al. 2008).

TTBF has been identified as an important factor after RT to identify patients at high risk for death and metastasis (Buyyounouski et al. 2008). Multivariable analysis conducted among 213 patients treated with LDR-BT also indicated PSADT and TTBF as significant predictors of MFS (Stock et al. 2008). These factors were also found to be significant in a different group of 264 patients undergoing BT±EBRT (Ko et al. 2014).

These significant factors may be useful when discussing adjuvant therapies for patients who have experienced BF. A shorter TTBF has been thought to represent an increased likelihood of metastasis. TTBF greater than 3 years after RP may be likely an indication of local recurrence. As a strong predictor of metastasis, PSADT has been discussed to represent aggressiveness of the original tumour, while TTBF provides information on residual disease following RP (Roberts et al. 2001).

Table 3 summarizes these results.

Table 3: Summary of Prognostic Factors for Metastatic Free Survival after Biochemical Failure

Author, Year	n	Treatment	BF definition	Gleason Score	T stage	TTBF	PSADT	Age	Year of RP	Race	Surgical margin status	Seminal vesicle invasion	Pretreatment PSA	Use of ADT after BF	Duration of ADT	Salvage RT	PSA velocity	Change in PSA slope	PSA nadir	DNA ploidy	BED
Antonarakis et al 2011	190	RP	PSA ≥0.2 ng/ml	U	x	U	U M	x		x	x		x								
Antonarakis et al 2012	450	RP	PSA ≥0.2 ng/ml	U M	x	U	U M	x		U	x		x								
Antonarakis et al 2012	146	RP or RT	PSA ≥0.2 ng/ml	U	x		U M	U						U			U	U M			
Boorjian et al 2011	2426	RP	PSA ≥0.4 ng/ml	M	M	U	M	x	x					x		x					
Boorjian et al 2012	134	RP	PSA ≥0.4 ng/ml	M	x	x	M				x										
Buyounouski et al 2008	211	RT	Nadir + 0.2ng/ml	U M	U M	U M	U M						M						U M		
Roberts et al 2001	879	RP	PSA ≥0.4 ng/ml	U	x	x	U M						x							x	
Stock et al 2008	213	RT	Nadir + 0.2ng/ml	U	x	U M	U M						x								U
Ko et al 2014	264	RT	Nadir +	x	x	M	M	x					x	x							x

			0.2ng/ml																		
Shilkrut et al 2013	175	RT	Nadir + 0.2ng/ml	M	x	M		x					x	M	x						

Where x indicates that a variable was investigated, U indicates a factor was significant upon univariable analysis, M indicates a factor was significant upon multivariable analysis

2.2 Prognostic Factors for PCSS among patients with BF

PSADT, Gleason score and TTBF have been identified most consistently as predictors of PCSS in both univariable and multivariable analyses. Although age has been examined in many univariable and multivariable models, it has been reported to be significant in only one study (Boorjian et al. 2011). Similarly T stage has also been studied, however it has not been found to be statistically significant in a number of studies or does not add value as a pretreatment variable to predict PCSS in the use of risk groups (D'Amico et al. 2003). Other factors that have occasionally been found to be prognostic of PCSS include PSA nadir, and pretreatment PSA values of >20ng/mL. Representative studies are discussed below and are summarized on Table 4.

In a study of 211 men who experienced BF after RT, TTBF was found to be an independent predictor of PCSS (Buyyounouski et al. 2008). In a more recent study of 1722 men with BF after RT by Buyyounouski et al, univariable analysis found Gleason score and TTBF were the most discriminatory prognostic factors for PCSS. Specifically TTBF <18 months was most able to identify patients at risk for death from prostate cancer. Initial PSA and radiotherapy dose were not found to be predictive of PCSS (Buyyounouski et al. 2012). These findings suggest TTBF and PSADT may be useful as surrogate endpoints for PCSS in men with BF. Others found a cut-point of TTBF <2 years or PSADT <12 years was a predictor of death from prostate cancer within 6 months of experiencing BF among radiotherapy patients (Denham et al. 2008).

Different from other studies, a research group analyzing predictors of PCSS among 160 men with BF after EBRT found that Gleason Score and pretreatment PSA >20ng/mL were significant predictors upon multivariable analysis (D'Amico et al. 2003). T stage was analyzed within this cohort but was not statistically significant. In a multivariable analysis of 465 patients experiencing BF after EBRT, Gleason score were also found to be significant predictors of PCSS, as well as PSADT and earlier intervention (Kim-Sing et al. 2004).

Patient pretreatment (initial) PSA (iPSA) was found in one study to be a good predictor of biochemical recurrence-free survival after RP or RT, but not as a prognostic factor for PCSS after BF. Gleason score and T Stage were found to be independently associated with PCSS, but age was not predictive. PSADT was found to be correlated with PCSS, while TTBF was found to be a prognostic factor (Denham et al. 2009)

Prognostic factors among patients experiencing BF after RP vary slightly from patients experiencing BF after RT. Early TTBF was found to be statistically associated with an increased risk of prostate cancer death in 3 studies using multivariable analysis of 379 RP patients, 264 and 175 RT patients (Freedland et al. 2006; Ko et al. 2014; Shilkrut et al. 2013). A larger study of 2426 patients with BF after RP, TTBF was not associated with PCSS, nor with systemic progression. Instead patient age, Gleason score, T stage and PSADT were predictive of PCSS (Boorjian et al. 2011).

Table 4: Summary of Prognostic Factors for Prostate Cancer Specific Survival after Biochemical Failure

Author, Year	n	Treatment	BF definition	Gleason Score	T stage	TTBF	PSADT	Age	Time of intervention	Surgical margin status	Seminal vesicle invasion	Pretreatment PSA	Use of ADT after BF	Duration of ADT	Salvage RT	Radiation dose	PSA nadir	BED
Boorjian et al 2011	2426	RP	PSA ≥0.4 ng/ml	M	M	U	M	M	x				x		x			
Buyyounouski et al 2008	211	RT	Nadir + 0.2ng/ml	U	x	U M	U					x				x	U	
Buyyounouski et al 2012	1722	RT	Nadir + 0.2ng/ml	U	x	U M	x									x	x	
D'Amico et al 2003	160	RT	3 consecutive rises	M	x							M						
Denham et al 2008	436	RT	Nadir + 0.2ng/ml	x	x	M	M	x				x						
Denham et al 2009	454	RT	Nadir + 0.2ng/ml	U	U	M	x	x				M						
Freedland et al 2006	379	RP	PSA ≥0.2 ng/ml	x	x	U M	x	x		x		x						
Kim-Sing et al 2004	544	RT	Vancouver Criteria	U M	U		U M		U M			U	U					
Ko et al 2014	264	RT	Nadir + 0.2ng/ml	x	x	M	x	x				x	x					x
Shilkrut et al 2013	175	RT	Nadir + 0.2ng/ml	M	x	M		x				x	x	x				

Where x indicates that a variable was investigated, U indicates a factor was significant upon univariable analysis, M indicates a factor was significant upon multivariable analysis

2.3 Prognostic Factors for OS among patients with BF

A summary of prognostic factors by study for OS can be found in Table 5. TTBF and PSADT were commonly reported to be significant predictors of OS, where OS was defined as the interval of time from BF to death from any cause. Age was found to be predictive of OS in a few studies upon multivariable analysis. However, it was found to be a weak predictor of OS in one study of 436 men with BF after RT, and was not significant in a study of 154 RT patients with BF after examining for age, pretreatment PSA, TTBF, PSA nadir, Gleason score, T stage and rise in PSA (Denham et al. 2009). In fact, none of the examined variables were found to be predictive of OS (Sandler et al. 2000).

In a univariable analysis of variables, Gleason score, T stage, TTBT, PSADT and age were predictive of OS, but after multivariable analysis, only PSADT when categorized as ≥9, 3-8.9 and <3 months was found to be predictive of OS (Antonarakis et al. 2011). Another study by D'Amico et al., found that PSADT <6 months and age were associated with shorter OS in multivariable analysis (D'Amico et al. 2006). PSADT of <3 months was found to be of greatest risk of OS among patients, although the majority of patients in the cohort studied by Freedland et al., had intermediate PSADTs between 3 and 8.9 months (Freedland et al. 2007). These studies indicate that in general, shorter PSADT are significantly associated with OS.

Freedland et al., also found that earlier TTBF, age and Gleason scores ≥8 were associated with OS. TTBF cut points varied between studies that found it to be a significant factor. One study dichotomized TTBF at 18 months, while another at 2 years (Buyyounouski et al. 2008; Hachiya et al. 2006). Some factors that were significant in other studies include PSA velocity and pretreatment PSA (Wo et al. 2009; Denham et al. 2009).

Table 5: Summary of Prognostic Factors for Overall Survival after Biochemical Failure

Author, Year	n	Treatment	BF definition	Gleason Score	T stage	TTBF	PSADT	age	race	Surgical margin	Pretreatment PSA	PSA nadir	Time to nadir	Comorbidity score	PSA velocity	Use of ADT after BF	BED
Antonarakis et al 2011	346	RP	PSA ≥0.2 ng/ml	U	U	U	U M	U	x	x	x						
Buyyounouski et al 2012	1722	RT	Nadir + 0.2ng/ml	x	x	M	M					M					
D'Amico et al 2006	81	RT	2 consecutive rises of at least 0.2ng/mL after PSA level >1.0ng/mL	x	x		M	M			x						
Freedland et al 2007	379	RP	PSA ≥0.4 ng/ml	M	x	M	M	M	x		x						
Hachiya et al 2006	155	RP	2 consecutive rises ≥0.4ng/mL	U M	U						U M						
Sandler et al 2000	154	RT	3 consecutive rises	x	x	x		x			x	x	x				
Wo et al 2009	89	RT	2 consecutive rises ≥0.2ng/mL after nadir	x	x	x		x						M	M		
Ko et al 2014	264	RT	Nadir + 0.2ng/ml	x	x	M	x	x			x					x	x
Kim et al 2013	108	RT	Nadir + 0.2ng/ml	M	x	M		M			x			M	M	x	

Where x indicates that a variable was investigated, U indicates a factor was significant upon univariable analysis, M indicates a factor was significant upon multivariable analysis

2.4 Objectives

While a number of factors have been indicated in previous studies as prognostic for OS, PCSS and MFS, within the studies there were differences not only in variables examined, but also BF definitions and sample sizes. The studies found had sample sizes between 81 and 2426 patients treated with either RP or RT. The patient population also varied in terms of their treatment for BF. Some patients included in studies had received adjuvant therapy, while others had not. There is much controversy surrounding the timing in administration of salvage therapy for patients experiencing BF, thus it is important to develop a model of clinical outcomes at the time of BF.

Currently no risk stratification system has been made to identify patients at high risk or low risk of death after BF. The use of risk stratification systems would play an important role in patient selection in clinical trials and decision-making to determine the best treatments for patients of differing risks of having clinically significant endpoints after BF.

There are two main objectives of the current study:

1) To identify prognostic factors of overall survival after BF within the GUROC ProCaRS database

2) To build a risk stratification system that would allow the identification of low and high risk groups of patients with BF

Chapter 3 : Method

3.1 GUROC ProCaRS Database

The Genitourinary Radiation Oncologists of Canada (GUROC) Prostate Cancer Risk Stratification (ProCaRS) database consists of 7974 patients. Patient data were compiled from 7 databases at 4 institutions including 3771 patients from the British Columbia Cancer Agency (BCCA), 1752 patients from Princess Margaret Hospital (PMH), 2257 patients from L'Hotel Dieu de Québec and 194 from McGill University Health Centre (Rodrigues et al. 2014). For this study the GUROC ProCaRS database was used to determine predictors of overall survival after biochemical failure. These factors were also used to identify a low risk and high risk group among men experiencing biochemical failure. The GUROC ProCaRS database was commissioned by GUROC and solely encompasses information on patients treated with radiotherapy.

Ethics approval for the study was obtained from the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) and can be found in Appendix I.

Of the 7974 patients in the database, 1246 (15.6%) were identified who met the Phoenix definition of biochemical failure (2.0ng/mL above nadir PSA). Patients who were given salvage hormone therapy prior to reaching biochemical failure were excluded from this analysis. These patients were excluded because the initiation of their treatment for biochemical failure was dependent on other clinical factors as opposed to a specific PSA value. Two thirds of the 1246 patients were randomly grouped into a training set (n=831), and the final third was grouped into a validation set (n=415) for both univariable and multivariable Cox proportional hazards regression analyses, and recursive partitioning analysis.

3.2 Statistical Analyses

Descriptive analyses on patient clinical characteristics, treatment characteristics, and patient outcome and biochemical data were conducted. These statistics were reported as mean and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests (or Fisher's exact test as appropriate) for categorical data and two-sample t-tests for continuous data were conducted to assess for differences in characteristics between Training and Validating groups. Categorical variables included T stage, total Gleason score, positive cores greater or equal to 50%, bilateral biopsy status, radiation treatment type, year of initiation of radiotherapy, EBRT dose > 70Gy, hormone therapy, causes of death and biochemical failure ≤5 years from date of radiotherapy. Continuous variables include age, baseline PSA, EBRT dose and fractionation, LDR and HDR doses, duration of adjuvant hormone therapy, nadir PSA, TTBF, PSADT, time to nadir and time from BF to death. PSADT was also assessed as a categorical variable defined as 0-6 months, 6-12 months and greater than 12 months.

Univariable Cox proportional hazards regression analyses were conducted to determine factors that were individually associated with overall survival among patients who experienced BF. Multivariable Cox proportional hazards regression analyses were conducted using backward elimination procedures, sequentially removing factors until all remaining covariates had p-values < 0.05, to identify significant predictors of overall survival after BF among patients in Training set. Final predictors identified from multivariable analyses and from the literature review were included in RPA using data in the Training dataset to identify a high risk and low risk group for overall survival after BF. Variables such as age, PSADT, TTBF were kept as continuous variables as the RPA would choose the values to stratify factors according to the impurity reduction principle. A minimum number of 20 observations in a node before further splitting was specified (Pavlopoulos et al. 2004). Downstream branches of less importance or of insufficient sample size were trimmed manually.

From preliminary risk groups identified by RPA, overall survival was estimated from Kaplan-Meier survival curves. Log-Rank tests were utilized to determine if the risk

groups were statistically different from each other and between Training and Validating groups. Based on overall survival estimates from Kaplan-Meier survival plots, high risk and low risk groups were identified. Hazard ratios comparing high risk to low risk were reported with associated p-value and C-indices with 95% confidence intervals (CI).

Log-minus-log survival plots were used to graphically assess for any violation of the proportional hazards assumption. Further diagnostic testing through Kolmogorov tests were also conducted. Any violation in the proportional hazards assumption identified using either method required that risk groups be assessed as a time-dependent covariate (Vittinghoff et al. 2012). Cox proportional hazards regression incorporating a time-dependent covariate with risk group (i.e. riskgroup*log(survival)) was utilized to determine if risk group remained a significant predictor of overall survival over time.

All descriptive, univariable and multivariable Cox proportional hazards regression analyses were conducted using SAS version 9.4 software (SAS institute, Cary NC). Recursive partitioning analysis was conducted using the R language environment for statistical computing version 3.1.3 (open source, www.r-project.org) and the "rpart" package. Two-sided statistical testing at the 0.05 level of significance was used for all analyses.

3.3 Variables

A number of factors were used in analyses including age, clinical data on the tumour (stage, total Gleason score), treatment (EBRT versus other, hormone therapy), and biochemical data (pretreatment PSADT, pre-biochemical failure PSADT, TTBF, nadir PSA, months to nadir PSA). A detailed variable list of the GUROC ProCaRS database may be found in Appendix II. Overall survival was defined as survival after BF.

PSADT Calculations

One of the factors found in the literature to be correlated with overall survival in prostate cancer patients who have experienced biochemical failure is PSA doubling time (PSADT). Three versions of PSADT were calculated each based on two PSA values with corresponding times:

1) Pretreatment PSADT ("Pre-RT PSADT"), which is based on the last 2 PSA values (PSA1 and PSA2) before radiotherapy was administered

2) Pre-BF PSADT ("PSADT Nadir-Last"), calculated using the nadir PSA (PSA3) and first PSA value before BF (PSA5), and finally

3) Pre-BF PSADT ("PSADT Last-2") based on the last 2 PSA values prior to BF (PSA4 and PSA5)

PSADT was calculated by the natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time between PSA measurement for each patient (Pound et al. 1999; Patel et al. 1997).

Using Figure 3 for guidance on PSADT calculations:

$$1)\ Pre-RTPSADT = \frac{Log\ 2}{\frac{Log\ (PSA2) - Log(PSA1)}{(Time2 - Time1)}}$$

$$2)\ PSADT\ Nadir-Last = \frac{Log\ 2}{\frac{Log\ (PSA5) - Log(PSA3)}{(Time5 - Time3)}}$$

$$3)\ PSADT\ Last-2=\frac{Log\ 2}{\frac{Log\ (PSA5)-Log(PSA4)}{(Time5-Time4)}}$$

Each PSADT calculation was evaluated using separate multivariable models. In some cases PSADT could not be calculated either due to insufficient data or due to undefined values (i.e. no change in PSA values). Figure 4 provides an example of a PSA follow-up profile of a patient with pretreatment PSADT that provides a negative value. Additional PSADT variables were obtained by excluding PSADT with negative and missing values.

PSADT was kept as a continuous variable in univariable, multivariable, and RPA to determine the optimal PSADT cutoff level. Hazard ratios for PSADT were reported at 3 month intervals along with 95% CI. Additionally, PSADT was categorized into PSADT less than 6 months, between 6-12 months, and 12 months and greater, for univariable and multivariable analysis.

Radiation Treatment

While the GUROC ProCaRS database provides 5 categories of radiation treatments (HDR-BT only, HDR-BT+EBRT, LDR-BT only, LDR-BT+ EBRT, and finally EBRT only), treatments were recategorized into 2 overall categories: EBRT only versus Other. Apart from EBRT only, the number of patients who have BF and were treated with BT were quite low, as is demonstrated in Table 7.

Total Gleason Score

Gleason score was initially comprised of 9 individual categories (2-10), however for univariable and multivariable analyses this was modelled as 4 categories. Gleason score values of 6 and 7 remained unchanged, but those between 2 and 5 and those between 8 and 10 formed the remaining 2 categories.

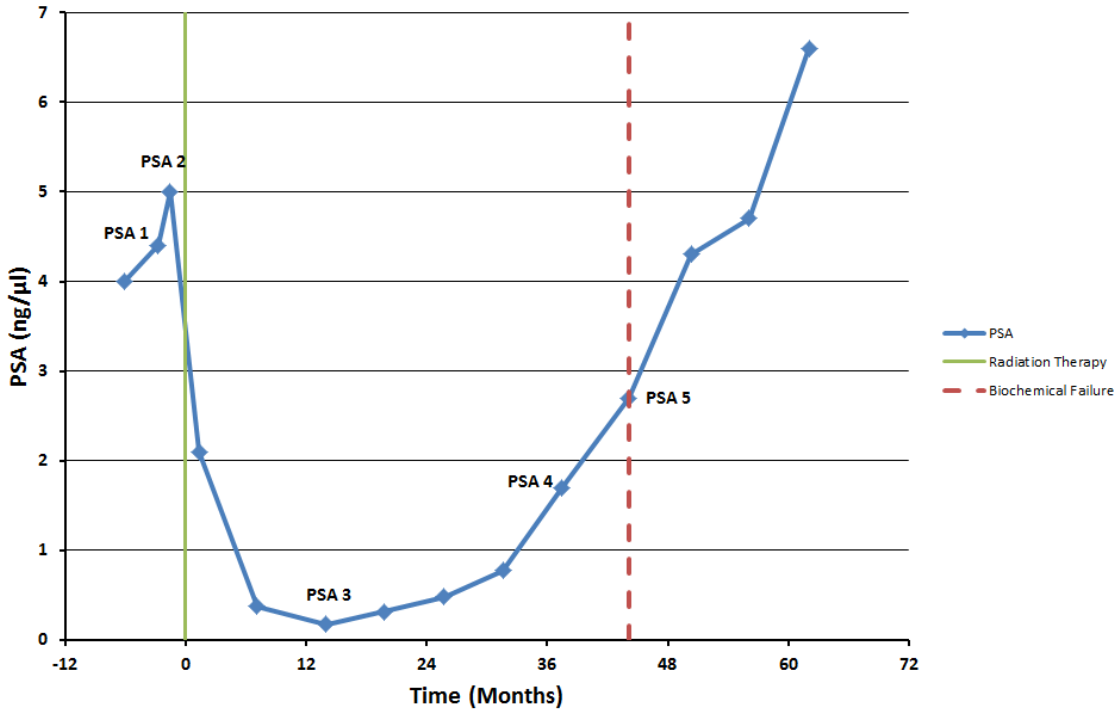

Figure 3: PSA values for calculating PSADT

$$1)\ Pre-RTPSADT = \frac{Log\ 2}{\frac{Log\ (PSA2) - Log(PSA1)}{(Time2 - Time1)}}$$

$$= \frac{Log\ 2}{\frac{Log\ (5.00) - Log(4.40)}{(-1.58 - (-2.76))}}$$

$$= \frac{0.693}{\frac{1.61 - 1.48}{1.18}}$$

$$= \frac{0.693}{\frac{0.13}{1.18}}$$

$$= \frac{0.693}{0.11}$$

$$= 6.30$$

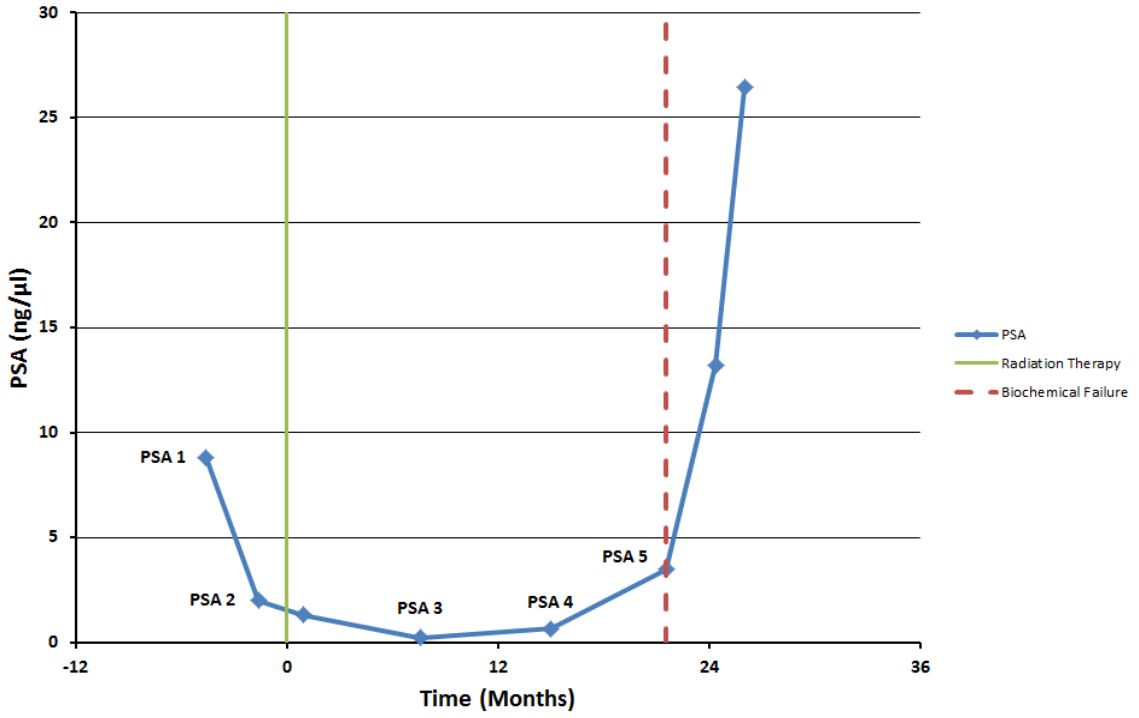

Figure 4: Example of PSA Follow-Up Profile Depicting Negative Pre-treatment PSADT

Chapter 4 : Results

4.1 Descriptive Analysis

Various descriptive statistics for all patients, with and without BF are presented in Tables 6 to 8. Among the 1246 patients with BF included in analysis, there were 486 deaths overall. Of these deaths, 255 (52.27%) were deaths due to prostate cancer, while deaths from other causes or not otherwise specified were comprised of 197 (40.53%) and 34 (7.00%), respectively. In contrast, of patients without BF, there were 744 deaths overall of which only 18 (2.42%) were deaths due to prostate cancer. 83.87% of deaths were due to other causes within these patients.

The mean age of patients with BF was 68.90 ± 7.17 years. The mean time after RT to BF was 48.14 ± 30.79 months, and the mean time from BF to death was 52.39 ± 38.35 months. Median baseline PSA for patients with BF was 10.00 ng/mL (IQR= 6.67- 17.00). Of those that did not have BF, median baseline PSA was 6.40 ng/mL (IQR= 4.70- 8.90). 13.78% of BF patients had a Gleason score between 8 to 10, whereas 3.29% of patients without BF had a Gleason score between 8 to 10. In addition, a greater proportion of patients who had PSA recurrence had T3 and T4 tumours (23.13% and 2.12%, respectively), when compared to patients without BF (5.43% and 0.36%, respectively).

According to D'Amico risk stratification, 18.55% of BF patients were of low risk, while 51.79% of patients without BF were low risk. A greater proportion of BF patients were of high risk when compared to patients without BF (43.63% and 12.74%, respectively).

Table 6: Patient Clinical Characteristics

Characteristic	**n**	**All Patients (N=7974)**	**Patients with Biochemical Failure (N=1246)**	**Patients without Biochemical Failure (N=6728)**
Age- mean± SD (min to max)	7970	67±7 (34 to 88)	69±7 (43 to 88)	66±7 (34 to 86)
Baseline PSA (ng/mL)- median (IQR: Q1, Q3)	7844	6.80 (4.90, 9.70)	10.00 (6.67, 17.00)	6.40 (4.70, 8.90)
Centre- n(%)	7974			
BCCA Registry		3771 (47.29)	858 (68.86)	2913 (43.30)
Laval		2257 (28.30)	115 (9.23)	2142 (31.84)
McGill		194 (2.43)	13 (1.04)	181 (2.69)
PMH		1752 (21.97)	260 (20.87)	2913 (43.30)
T stage- n(%)	7860			
1		3553 (45.20)	297 (24.19)	3256 (49.22)
2		3613 (45.97)	621 (50.57)	2986 (45.14)
3		644 (8.19)	284 (23.13)	354 (5.35)
4		50 (0.64)	26 (2.12)	19 (0.29)
Gleason Score- n(%)	7839			
2		17 (0.22)	3 (0.25)	14 (0.21)
3		39 (0.50)	9 (0.74)	30 (0.45)
4		252 (3.21)	43 (3.52)	209 (3.16)
5		577 (7.36)	151 (12.38)	426 (6.44)
6		4267 (54.43)	381 (31.23)	3886 (58.71)
7		2301 (29.35)	465 (38.11)	1836 (27.74)
8		229 (2.92)	100 (8.20)	129 (1.95)
9		151 (1.93)	64 (5.25)	87 (1.31)
10		6 (0.08)	4 (0.33)	2 (0.03)
Positive Cores greater or equal to 50%- n(%)	4475	1686 (37.68)	n=780 430 (55.13)	n=3695 1256 (33.99)
Bilateral Biopsy Status- n(%)	2999			
N/A		30 (1.00)	1 (0.14)	29 (1.27)
Negative		1725 (57.52)	351 (48.82)	1374 (60.26)
Positive		1243 (41.45)	367 (51.04)	876 (38.42)
Unknown		1 (0.03)	0 (0.00)	1 (0.04)

Table 7: Patient Treatment Characteristics

Characteristic	n	All Patients (n=7974)	Patients with Biochemical Failure (n=1246)	Patients without Biochemical Failure (n=6728)
Radiation Type- n(%)	7974			
Brachy(HDR)+EBRT		711(8.92)	36(2.89)	675 (10.03)
Brachy(LDR)+EBRT		52(0.65)	7(0.56)	45 (0.67)
Brachy(HDR) only		26(0.33)	0(0.00)	26 (0.39)
Brachy(LDR) only		4508(56.53)	228(18.30)	4280 (63.61)
EBRT only		2677(33.57)	975(78.25)	1702 (25.30)
RT Start Year- n(%)	7973			
1994 to 1999		1953 (24.50)	727 (58.35)	1226 (18.23)
2000 to 2002		1973 (24.75)	276 (22.15)	1697 (25.23)
2003 to 2005		2238 (28.07)	155 (12.44)	2083 (30.96)
2006 to 2010		1809 (22.69)	88 (7.06)	1721 (25.58)
EBRT- n(%)	7974	3440 (43.14)	1018 (81.70)	2422 (36.00)
EBRT: Dose > 70 Gy- n(%)	3440	719 (20.90)	197 (19.35)	522 (21.55)
EBRT: Dose (Gy)- mean± SD (min to max)	3439	63.32±11.78 (19.00 to 79.80)	66.73±7.70 (40.00 to 79.80)	61.89±12.86 (19.00 to 79.80)
EBRT: Number of Fractions- mean± SD (min to max)	2838	33.17±6.35 (10.00 to 42.00)	33.38±5.66 (20.00 to 42.00)	33.05±6.69 (10.00 to 42.00)
EBRT: Dose per Fraction (cGy)- mean± SD (min to max)	2838	208±29 (179 to 300)	205±24 (179 to 300)	210±32 (180 to 300)
EBRT: Biologic Equivalent Dose (Gy)- mean± SD (min to max)	2838	137.50±13.56 (37.05 to 165.00)	135.92±10.38 (85.50 to 165.00)	138.35±14.92 (37.05 to 165.00)
LDR- n(%)	7974	4560 (57.19)	235 (18.86)	4325 (64.28)
LDR: Dose (Gy)- mean± SD (min to max)	4560	153.88±13.20 (89.00 to 217.00)	154.35±13.12 (104.00 to 193.00)	153.85±13.21 (89.00 to 217.00)
HDR- n(%)	7974	737 (9.24)	36 (2.89)	701 (10.42)
HDR: Dose- mean± SD (min to max)	727	17.04±3.97 (10.00 to 38.00)	16.51±4.49 (10.00 to 20.00)	17.06±3.94 (10.00 to 38.00)

Brachytherapy- n(%)	7974	5297 (66.43)	271 (21.75)	5026 (74.70)
Hormone Therapy- n(%)	7974	2999 (37.61)	551 (44.22)	2448 (36.39)
Adjuvant Hormone Therapy Duration- mean± SD (min to max)	2660	10.45±14.37 (0.10 to 143.74)	15.04±21.00 (0.23 to 142.82)	9.31±11.91 (0.10 to 143.74)
D'Amico- n(%) Low Intermediate High	7850	 3653 (46.54) 2814 (35.85) 1383 (17.62)	 230 (18.55) 469 (37.82) 541 (43.63)	 3423 (51.79) 2345 (35.48) 842 (12.74)

Table 8: Patient Outcome and Biochemical Characteristics

Characteristic	n	All Patients (n=7974)	Patients with Biochemical Failure (n=1246)	Patients without Biochemical Failure (n=6728)
Nadir PSA (ng/mL)- mean± SD (min to max)	7706	0.67±4.08 (0.00 to 291.90)	1.64±9.41 (0.00 to 291.90)	0.45±0.64 (0.00 to 9.15)
Time to Nadir (months)- mean± SD (min to max)	7706	13.09±12.29 (0.00 to 132.27)	13.56±10.24 (0.00 to 105.13)	12.99±12.69 (0.00 to 132.27)
Clinical/Pathology confirmed Local Relapse- n(%)	7974	381 (4.78)	319 (25.60)	62 (0.92)
Dead- n(%)	7974	1230 (15.43)	486 (39.00)	744 (11.06)
Cause of Death-n(%) NOS Other Of Disease	1230	 136 (11.06) 821 (66.75) 273 (22.20)	 34 (7.00) 197 (40.53) 255 (52.47)	 102 (13.71) 624 (83.87) 18 (2.42)
Death 5 yr- n(%)	7974	453 (5.68)	131 (10.51)	322 (4.79)
Prostate Cancer Death ≤5 years-n(%)	7974	106 (1.33)	94 (7.54)	12 (0.18)
TTBF- mean± SD (min to max)	1246	--	48.14±30.79 (1.45 to 185.07)	--
Time from BF to Death- mean± SD (min to max)	1246	--	52.39±38.35 (0.00 to 161.91)	--
PreRT PSADT- mean± SD (min to max)	532	--	5.57±91.15 (-218.15 to 1862.62)	--
PreRT PSADT No Neg- mean± SD (min to max)	189	--	37.75±143.97 (0.02 to 1862.62)	--
PreBF Nadir and Last PSADT- mean± SD (min to max)	1036	--	20.51±86.03 (-1118.51 to 1751.45)	--
PreBF Nadir and Last PSADT No Neg- mean± SD (min to max)	1001	--	25.92±73.52 (0.08 to 1751.45)	--
PreBF Last2 PSADT- mean± SD (min to max)	1120	--	7.51±55.19 (-820.16 to 383.88)	--
PreBF Last2 PSADT No	945	--	18.20±29.87	--

Neg- mean± SD (min to max)			(0.08 to 383.88)	

Descriptive statistics by Training and Validating group for clinical characteristics of patients within the GUROC ProCaRS database with BF are provided in Table 9. Table 10 describes patient treatment characteristics for each group (Training and Validating), while Table 11 provides descriptive statistics on patient outcomes for each group (Training and Validating).

Chi-square tests and two-sample t-tests for categorical and continuous variables found that the Training and Validating groups were not significantly different in patient characteristics, treatment characteristics, patient outcome and biochemical data. All p-values were found to be greater than 0.05. No significant difference in overall survival was observed comparing Training and Validating sets based on Kaplan-Meier estimates as shown in Figure 5 (Log-Rank: $p=0.34$).

Table 9: Clinical Characteristics of Patients with Biochemical Failure by Group

Characteristic	**n**	**Training (n=831)**	**Validating (n=415)**	**Total**
Age- mean± SD (min to max)	1246	69±7 (45 to 88)	69±7 (43 to 84)	1245
Baseline PSA (ng/mL)- median (IQR: Q1, Q3)	1246	10.40 (6.78, 17.80)	9.50 (6.40, 16.00)	1234
Centre- n(%)	1246			
BCCA Registry		564 (67.87)	294 (70.84)	858
Laval		82 (9.87)	33 (7.95)	115
McGill		8 (0.96)	5 (1.20)	13
PMH		177 (21.30)	83 (20.00)	260
Tstage- n(%)	1228			
1		196 (23.90)	101 (24.75)	297
2		423 (51.59)	198 (48.53)	621
3		185 (22.56)	99 (24.26)	284
4		16 (1.95)	10 (2.45)	26
Gleason Score-n(%)	1220			
2		1 (0.12)	2 (0.50)	3
3		6 (0.73)	3 (0.75)	9
4		29 (3.55)	14 (3.48)	43
5		97 (11.86)	54 (13.43)	151
6		253 (30.93)	128 (31.84)	381
7		322 (39.36)	143 (35.57)	465
8		68 (8.31)	32 (7.96)	100
9		40 (4.89)	24 (5.97)	64
10		2 (0.24)	2 (0.50)	4
Positive Cores greater or equal to 50%- n(%)	780	293 (56.89)	137 (51.70)	430
Bilateral Biopsy Status- n(%)	719			
N/A		1 (0.21)	0 (0.00)	1
Negative		233 (48.64)	118 (49.17)	351
Positive		245 (51.15)	122 (50.83)	367

Table 10: Treatment Characteristics of Patients with Biochemical Failure by Group

Characteristic	n	Training (n=831)	Validating (n=415)	Total
Radiation Type-n(%)	1246			
Brachy(HDR)+EBRT		25 (3.01)	11 (2.65)	36
Brachy(LDR)+EBRT		6 (0.72)	1 (0.24)	7
Brachy(HDR) only		--	--	--
Brachy(LDR) only		150 (18.05)	78 (18.80)	228
EBRT only		650 (78.22)	325 (78.31)	975
RT Start Year- n(%)	1246			
1994 to 1999		479 (57.64)	248 (59.76)	727
2000 to 2002		184 (22.14)	92 (22.17)	276
2003 to 2005		108 (13.00)	47 (11.33)	155
2006 to 2010		60 (7.22)	28 (6.75)	88
EBRT- n(%)	1246	681 (81.95)	337 (81.20)	1018
EBRT Dose >70 Gy-n(%)	1018	135 (19.82)	62 (18.40)	197
EBRT Dose (Gy)-mean± SD (min to max)	1246	6673±790 (4000 to 7980)	6673±729 (4000 to 7980)	1018
EBRT Fractions- mean± SD (min to max)	1246	33.44±5.71 (20.00 to 42.00)	33.26±5.57 (20.00 to 42.00)	992
EBRT Dose per Fraction (cGy) - mean± SD (min to max)	1246	205±24 (179 to 300)	206±25 (180 to 300)	992
EBRT Biologic Equivalent Dose (Gy) - mean± SD (min to max)	1246	136.04±10.61 (85.50 to 165.00)	135.67±9.93 (85.50 to 155.61)	992
LDR- n(%)	1246	156 (18.77)	79 (19.04)	235
LDR Dose (Gy)- mean± SD (min to max)	1246	154.35±14.09 (104.00 to 193.00)	154.37±11.04 (136.00 to 183.00)	235
HDR- n(%)	1246	25 (3.01)	11 (2.65)	36
HDR Dose- mean± SD (min to max)	1246	1742±418 (1000 to 2000)	1455±472 (1000 to 2000)	35
Brachytherapy- n(%)	1246	181 (21.78)	90 (21.69)	271
Hormone Therapy-n(%)	1246	384 (46.21)	167 (40.24)	551
Adjuvant Hormone Therapy Duration-mean± SD (min to	1246	13.55±17.46 (0.23 to 100.96)	18.45±27.22 (0.23 to 142.82)	531

max)				
D'Amico	1240			
Low		144 (17.39)	86 (20.87)	230
Intermediate		321 (38.77)	148 (35.92)	469
High		363 (43.84)	178 (43.20)	541

Table 11: Outcome and Biochemical Characteristics of Patients with Biochemical Failure by Group

Characteristic	n	Training (n=831)	Validating (n=415)
Nadir PSA (ng/mL) - mean± SD (min to max)	1246	1.45±5.14 (0.00 to 130.00)	2.02±14.57 (0.01 to 291.90)
Time to Nadir (months) - mean± SD (min to max)	1246	13.25±9.99 (0.00 to 105.13)	14.17±10.70 (0.00 to 99.78)
Clinical/Pathology confirmed Local Relapse- n(%)	319	217 (26.11)	102 (24.58)
Dead- n(%)	486	314 (37.79)	172 (41.45)
Cause of Death-n(%) NOS Other Of Disease	486	 17 (5.41) 131 (41.72) 166 (52.87)	 17 (9.88) 66 (38.37) 89 (51.74)
Death 5 yr- n(%)	131	79 (9.51)	52 (12.53)
Time from Biochemical Failure to Death- mean± SD (min to max)	1246	52.71±37.72 (0.00 to 156.88)	51.76±39.62 (0.00 to 161.91)
TTBF- mean± SD (min to max)	1246	47.86±30.25 (1.45 to 185.07)	48.69±31.87 (4.60 to 153.33)
CRS (Prostate Cancer Death)- n(%)	255	166 (19.98)	89 (21.45)
Biochemical Failure ≤5 years- n(%)	862	580 (69.80)	282 (67.95)
PreRT PSADT- mean± SD (min to max)	T:354 V: 178	7.39±109.06 (-218.15 to 1862.62)	1.96±34.43 (-95.64 to 194.38)
PreRT PSADT No Neg- mean± SD (min to max)	T: 134 V: 55	41.61±168.41 (0.02 to 1862.62)	28.34±46.67 (0.89 to 194.38)
PreBF Nadir and Last PSADT- mean± SD (min to max)	T: 693 V:343	22.09±96.02 (-1118.51 to 1751.45)	17.31±61.05 (-398.79 to 451.10)
PreBF Nadir and Last PSADT No Neg- mean± SD (min to max)	T: 672 V: 329	26.48±84.63 (0.08 to 1751.45)	24.77±42.72 (1.02 to 451.10)
PreBF Last2 PSADT- mean± SD (min to max)	T: 745 V: 375	7.51±56.10 (-820.16 to 383.88)	7.52±53.40 (-648.63 to 334.75)
PreBF Last2 PSADT No Neg- mean± SD (min to max)	T: 633 V: 312	18.00±29.09 (0.08 to 383.88)	18.60±31.46 (0.55 to 334.75)

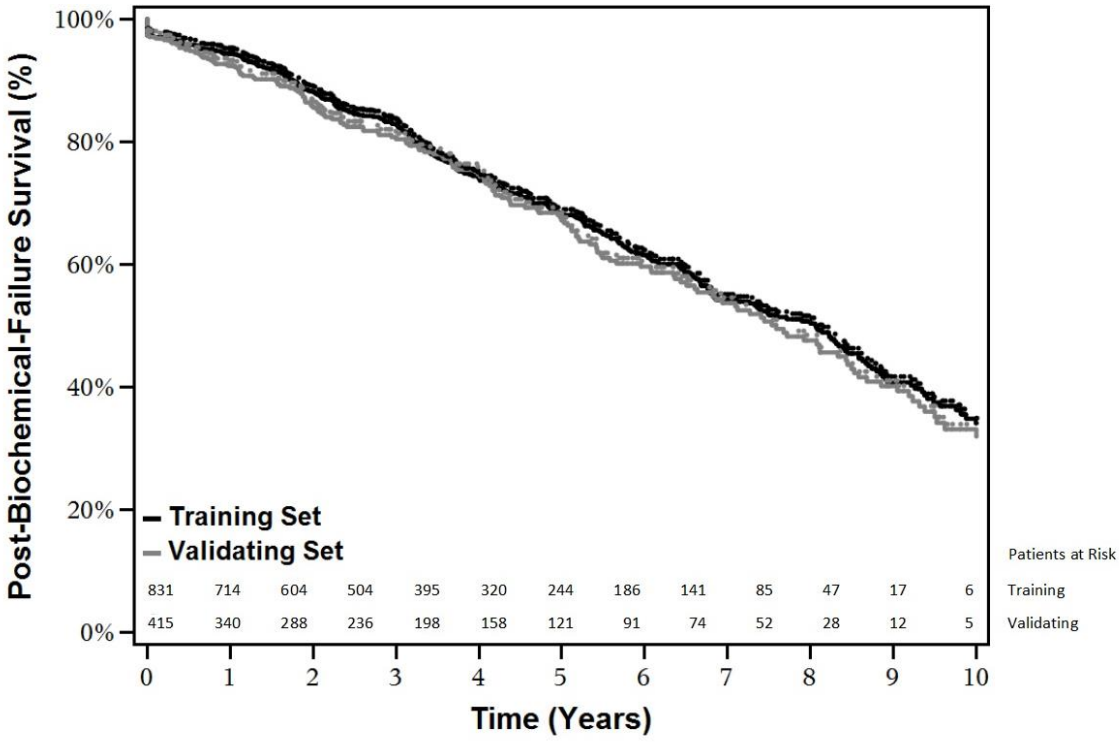

Figure 5: Post-Biochemical Failure Survival and Patients at Risk in Training and Validating Dataset (Log-Rank: p=0.34).

4.2 Univariable and Multivariable Analyses

Table 12 provides the results of univariable and multivariable analysis on the Training set (N=831). Variables included in analysis were age, baseline PSA, T stage, total Gleason score, hormone therapy, radiation treatment, nadir PSA, time to nadir, PSADT and TTBF. PSADT was assessed as a continuous and categorical variable in Table 12 and 13 respectively.

Upon univariable analysis a number of factors including age, T stage, higher Gleason scores, hormone therapy, radiation treatment, and nadir PSA were found to be independent predictors for overall survival.

The first multivariable model with Pre-RT PSADT analyzing OS after BF produced age, baseline PSA, T stage, hormone therapy, nadir PSA, and TTBF as significant predictors. The second model with PSADT Nadir-Last, identified similar factors except for nadir PSA which was excluded. Radiation treatment and Gleason score were additionally found as significant predictors for OS within this model. The final model (PSADT Last-2) found that all variables included in the model, except for PSADT Last-2 and time to nadir, were significant predictors of OS.

Multivariable analyses using PSADT as a categorical variable offered similar results to the models using PSADT as a continuous variable, however pre-BF PSADT (Nadir-Last, and Last-2), were found to be significant predictors of OS after BF.

Table 12: Univariable and Multivariable Regression Models for Overall Survival among Patients with Biochemical Failure with PSADT as a Continuous Variable

	Training Cohort (n=831)							
	Univariable		Multivariable 1 (Pre-RT PSADT)		Multivariable 2 (PSADT Nadir-Last)		Multivariable 3 (PSADT Last2)	
Independent Variables	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age per 1 year increase	1.03 (1.01, 1.04)	<0.01	1.06 (1.01, 1.10)	0.01	1.03 (1.01, 1.06)	0.01	1.03 (1.002, 1.05)	0.03
Baseline PSA per 1 ng/mL increase	1.00 (1.00, 1.01)	0.28	0.98 (0.96, 0.995)	0.02	0.99 (0.98, 1.00)	0.04	0.99 (0.98, 0.999)	0.03
T stage								
2 vs. 1	1.41 (0.98, 2.04)	0.07	1.59 (0.60, 4.18)	0.35	1.24 (0.82, 1.89)	0.30	1.33 (0.86, 2.05)	0.20
3 vs. 1	2.34 (1.61, 3.41)	<0.01	2.42 (0.89, 6.59)	0.08	1.65 (1.05, 2.59)	0.03	1.82 (1.15, 2.90)	0.01
4 vs. 1	3.81 (2.02, 7.19)	<0.01	9.60 (1.90, 48.42)	<0.01	3.30 (1.30, 8.38)	0.01	3.08 (1.28, 7.43)	0.01
Total Gleason Score								
6 vs. 2 to 5	0.99 (0.68, 1.44)	0.97			1.07 (0.70, 1.64)	0.74	1.06 (0.68, 1.65)	0.81
7 vs. 2 to 5	1.41 (1.02, 1.96)	0.04	--	--	1.19 (0.80, 1.75)	0.39	1.15 (0.77, 1.70)	0.50
8- 10 vs. 2 to 5	2.52 (1.75, 3.62)	<0.01			1.87 (1.19, 2.95)	<0.01	1.97 (1.26, 3.10)	<0.01
Hormone Therapy Yes vs. No	1.46 (1.16, 1.82)	<0.01	2.02 (1.14, 3.60)	0.02	1.46 (1.09, 1.97)	0.01	1.48 (1.09, 2.00)	0.01
Radiation Treatment EBRT only vs. other	0.23 (0.13, 0.42)	<0.01	--	--	0.44 (0.23, 0.84)	0.01	0.38 (0.19, 0.74)	<0.01
Nadir PSA per 1 ng/mL increase	1.03 (1.01, 1.04)	<0.01	1.07 (1.02, 1.12)	<0.01	--	--	1.03 (1.02, 1.05)	<0.01
Time to Nadir per month increase	1.01 (1.00, 1.02)	0.07	--	--	--	--	--	--
PreRT PSADT per 3 month increase	0.99 (0.97, 1.01)	0.21	--	--	--	--	--	--

NoNeg								
PreBF Nadir-Last PSADT per 3 month increase NoNeg	0.996 (0.99, 1.01)	0.44	--	--	--	--	--	--
PreBF Last2 PSADT per 3 month increase NoNeg	1.002 (0.99, 1.02)	0.79	--	--	--	--	--	--
TTBF per month increase	1.00 (1.00, 1.01)	0.07	1.02 (1.01, 1.03)	<0.01	1.01 (1.003, 1.02)	<0.01	1.01 (1.004, 1.02)	<0.01

Table 13: Univariable and Multivariable Regression Models for Overall Survival among Patients with Biochemical Failure with PSADT as a Categorical Variable

	Training Cohort (n=831)							
	Univariable		Multivariable 1 (Pre-RT PSADT)		Multivariable 2 (PSADT Nadir-Last)		Multivariable 3 (PSADT Last2)	
Independent Variables	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age per 1 year increase	1.03 (1.01, 1.04)	<0.01	1.06 (1.01, 1.10)	0.01	1.03 (1.01, 1.06)	0.01	1.03 (1.003, 1.05)	0.03
Baseline PSA per 1 ng/mL increase	1.00 (1.00, 1.01)	0.28	0.98 (0.96, 0.995)	0.02	0.99 (0.98, 0.998)	0.02	0.98 (0.97, 0.995)	<0.01
T stage								
2 vs. 1	1.41 (0.98, 2.04)	0.07	1.59 (0.60, 4.18)	0.35	1.23 (0.81, 1.86)	0.33	1.36 (0.88, 2.10)	0.17
3 vs. 1	2.34 (1.61, 3.41)	<0.01	2.42 (0.89, 6.59)	0.08	1.69 (1.08, 2.64)	0.02	1.73 (1.08, 2.76)	0.02
4 vs. 1	3.81 (2.02, 7.19)	<0.01	9.60 (1.90, 48.42)	<0.01	3.57 (1.38, 9.23)	<0.01	2.97 (1.21, 7.27)	0.02
Total Gleason Score								
6 vs. 2 to 5	0.99 (0.68, 1.44)	0.97					1.09 (0.70, 1.70)	0.71
7 vs. 2 to 5	1.41 (1.02, 1.96)	0.04	--	--	--	--	1.13 (0.76, 1.69)	0.55
8- 10 vs. 2 to 5	2.52 (1.75, 3.62)	<0.01					1.86 (1.18, 2.94)	<0.01
Hormone Therapy Yes vs. No	1.46 (1.16, 1.82)	<0.01	2.02 (1.14, 3.60)	0.02	--	--	1.41 (1.04, 1.92)	0.03
Radiation Treatment EBRT only vs. other	0.23 (0.13, 0.42)	<0.01	--	--	0.35 (0.18, 0.66)	<0.01	0.27 (0.13, 0.55)	<0.01
Nadir PSA per 1 ng/mL increase	1.03 (1.01, 1.04)	<0.01	1.07 (1.02, 1.12)	<0.01	--	--	1.03 (1.02, 1.04)	<0.01
Time to Nadir per month increase	1.01 (1.00, 1.02)	0.07	--	--	--	--	--	--
Pre-RT PSADT NoNeg 6-12 months vs. 0-6 months	0.71 (0.38, 1.33)	0.28	--	--	--	--	--	--

12+ months vs. 0-6 months	0.69 (0.40, 1.21)	0.19						
PreBF Nadir-Last PSADT NoNeg								
6-12 months vs. 0-6 months	0.82 (0.56, 1.19)	0.29	--	--	0.63 (0.42, 0.94)	0.02	--	--
12+ months vs. 0-6 months	0.73 (0.52, 1.01)	0.06			0.39 (0.26, 0.59)	<0.01		
PreBF Last2 PSADT NoNeg								
6-12 months vs. 0-6 months	0.60 (0.43, 0.85)	<0.01	--	--	--	--	0.43 (0.29, 0.63)	<0.01
12+ months vs. 0-6 months	0.76 (0.56, 1.04)	0.08					0.48 (0.32, 0.70)	<0.01
TTBF per month increase	1.00 (1.00, 1.01)	0.07	1.02 (1.01, 1.03)	<0.01	1.01 (1.01, 1.02)	<0.01	1.01 (1.01, 1.02)	<0.01

4.3 Recursive Partitioning Analysis

A recursive decision tree of patients using the Training set was created to provide a post-BF risk stratification model. The main outcome for model building was 5 year overall survival after BF. Both pre-treatment and post-treatment factors were included in the predictive model and were identified from multivariable analyses and from literature review. Pre-treatment factors included age, baseline PSA, T stage and total Gleason score. Post-treatment factors included nadir PSA, time to nadir, TTBF, PSADT Nadir-Last, and PSADT Last-2.

The preliminary RPA model provided a tree with 7 terminal nodes as depicted in Figure 6. TTBF $\geq$ 6.5 versus < 6.5 years was selected as the primary node. Secondary splits incorporated both PSADT definitions: Pre-BF PSADT Last-2 at approximately 5 months and Pre-BF PSADT Nadir-Last at 1 year. Third level predictors in the RPA were Gleason score (2-7 versus 8-10) and age at approximately 65 years. Downstream branches from Pre-BF PSADT Nadir-Last were trimmed as they were of smaller sample size and did not provide added value.

From preliminary RPA, a 6-class risk group system was identified based on TTBF, Pre-BF PSADT Nadir-Last and Pre-BF PSADT Last-2, Gleason score and age (Table 14). Survival at 5 years from the 6 risk groups were then estimated from Kaplan-Meier survival curves from the Training Cohort (Figure 7). While each risk group was comprised of differing prognostic factors and splits, Kaplan-Meier survival curves indicated that the 6 risk group categories could be replaced with a 2-class risk system to identify patients as either high risk or low risk for premature death. Specifically risk group 1 and 3 would make up patients at low risk, and risk groups 2, 4, 5 and 6 make up a high risk category (Figure 8). While risk group 6 indicated a single group at greater risk than the other risk groups, it was placed into the high risk category due to its small sample size. Figure 8 also presents the frequency of patients within the Training and Validating cohorts. Kaplan-Meier survival curves for the Validating Cohort can be seen in Figure 9.

Table 14: 6-Class Risk Group

Risk Group	
1	TTBF < 6.5 years + Pre-BF PSADT Last-2 ≥ 5 months + Gleason score = 2-7
2	TTBF < 6.5 years + Pre-BF PSADT Last-2 ≥ 5 months + Gleason score = 8-10
3	TTBF < 6.5 years + Pre-BF PSADT Last-2 < 5 months +Age < 65 years
4	TTBF < 6.5 years + Pre-BF PSADT Last-2 <5 months + Age ≥ 65 years
5	TTBF ≥ 6.5 years + Pre-BF PSADT Nadir-Last ≥ 1 year
6	TTBF ≥ 6.5 years + Pre-BF PSADT Nadir-Last < 1 year

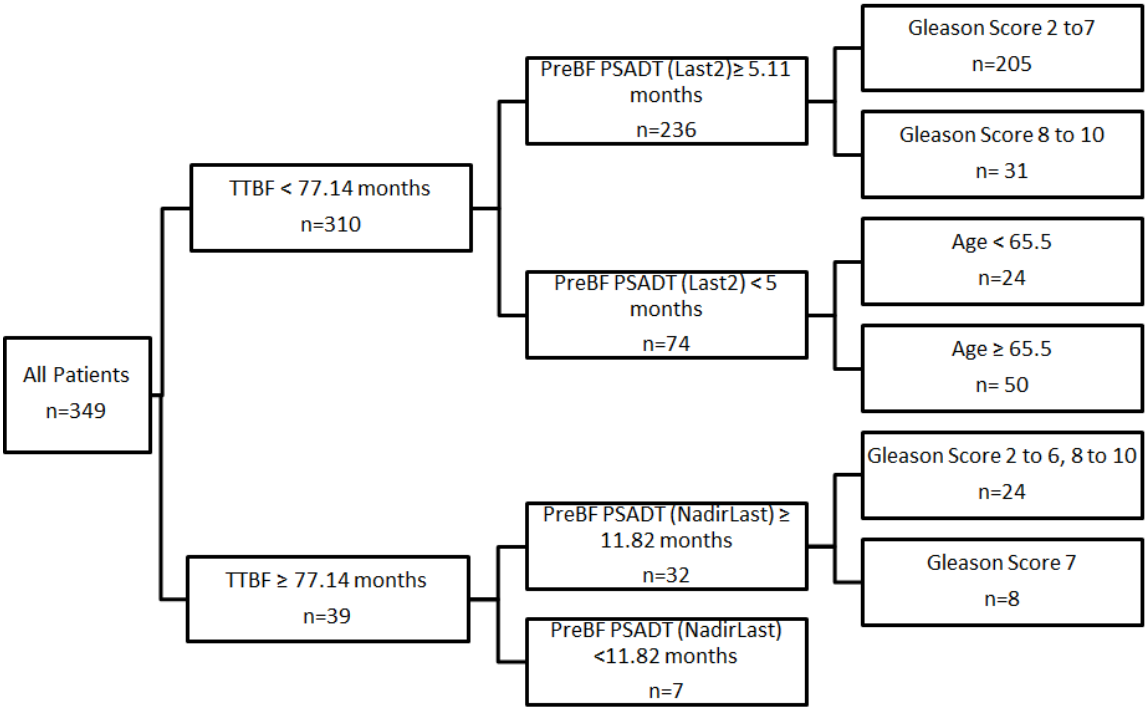

Figure 6: Preliminary RPA Tree

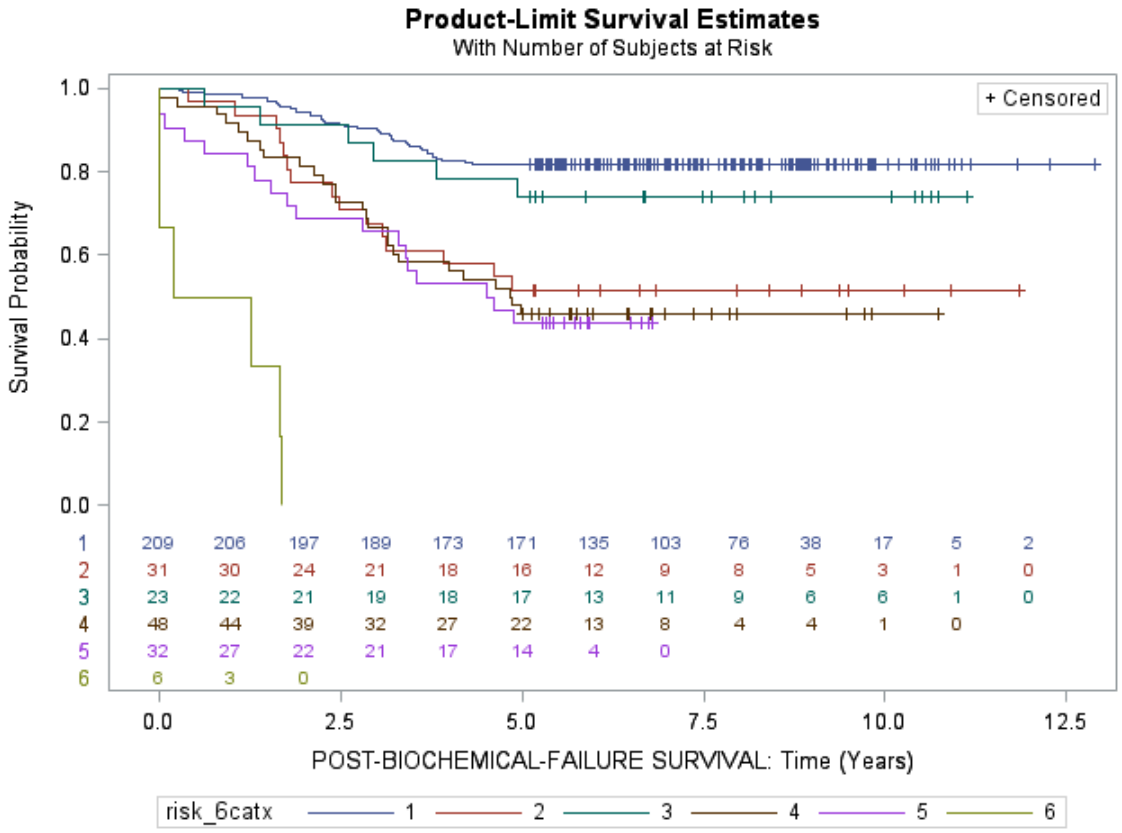

Figure 7: **Kaplan-Meier survival curves of 6 Risk Group categories in Training Cohort (Log-Rank: p<0.01).**

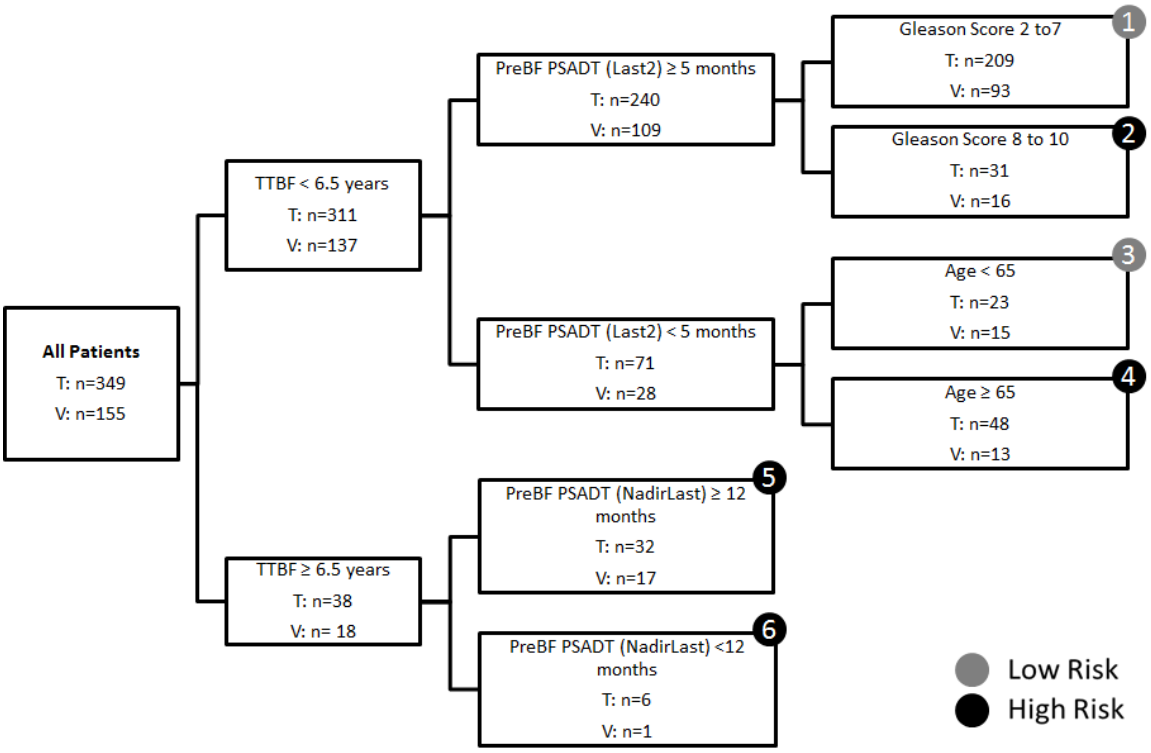

Figure 8: Low and High Risk Groups from RPA after Trimming

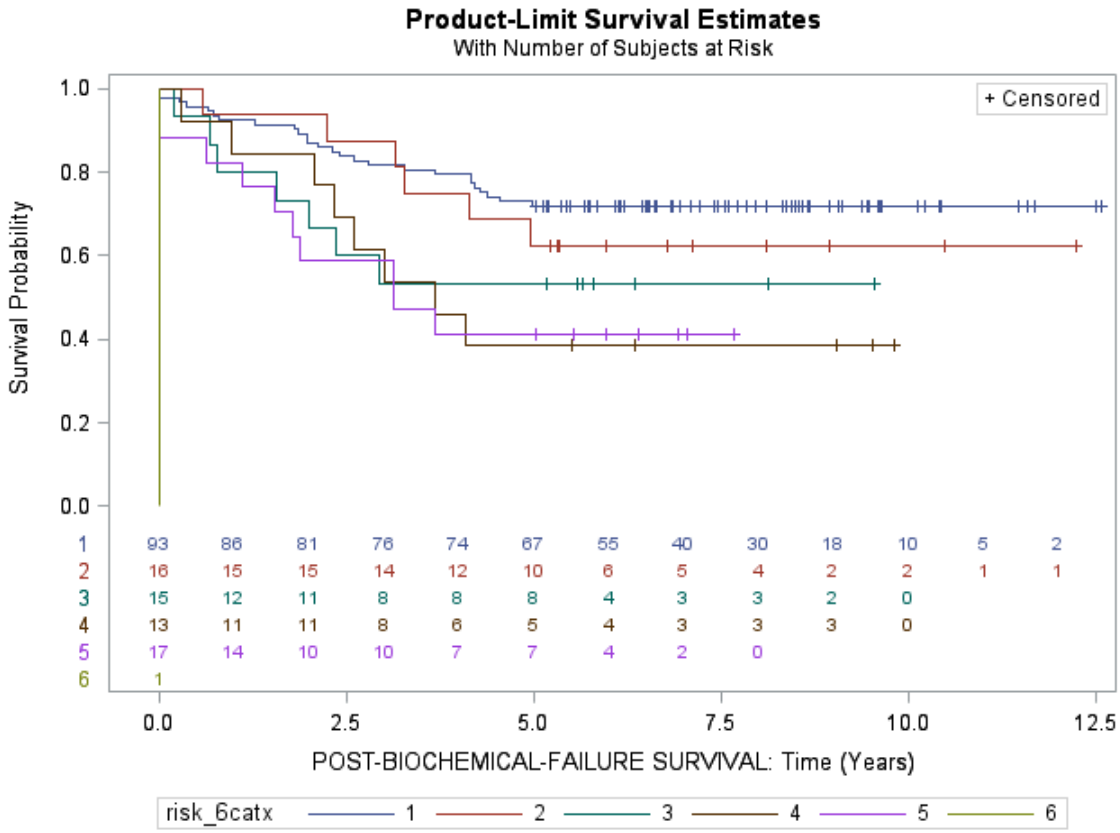

Figure 9: Kaplan-Meier survival curves of 6 Risk Group categories in Validating Cohort (Log-Rank: p<0.01).

Results from the Training cohort demonstrated good differentiation between risk groups (Log-Rank: $p<0.01$) as shown in Figure 10. Figure 11 depicts corresponding results for the Validating cohort. Differences in each risk group between Training and Validating groups were also analyzed using the Log-Rank test (Figure 12 and 13). Patients defined as low risk in both Training and Validating groups were found to be significantly different in terms of OS (Log-Rank: $p=0.01$). This difference may be due small sample size. 81.03% and 69.44% of patients were censored in the Training and Validating cohorts respectively. In contrast, patients defined as high risk in both the Training and Validating cohorts were not significantly different from each other (Log-Rank: $p=0.83$). Approximately 45.12% of the patients were censored in both groups. Figures 14 to 19 compare survival within each 6-class Risk Group between Training and Validating cohorts, and were not significantly different from each other.

Based on Kaplan-Meier estimates for OS, high risk and low risk prognostic groups may be identified. Hazard ratios for high risk versus low risk for 5-year OS are reported in Table 15 with associated p-values, C-indices, and 95% confidence intervals (CI) for both Training and Validating Cohorts. The hazard ratios for 5-year OS for the Training cohort was 3.87 (95% CI: 2.64-5.68; $p<0.01$) and for the Validating cohort was 2.05 (95% CI: 1.22-3.45; $p<0.01$). Table 16 presents similar data for 6-class risk groups. As model development was based on the Training dataset, this would explain for differences in hazard ratios between the Training and Validating set. Both 2-class risk groups and 6-class risk groups still demonstrate the ability to identify groups of higher risk compared to lower risk.

Table 17 presents all patients in both Training and Validating datasets in their respective risk groups created after RPA to determine if they were comparable given centre contributions.

Median survival after BF among low risk patients were 6.91 years and 6.27 years in Training and Validating cohorts respectively. High risk patients had a median survival of 4.62 and 4.13 years after BF in Training and Validating cohorts.

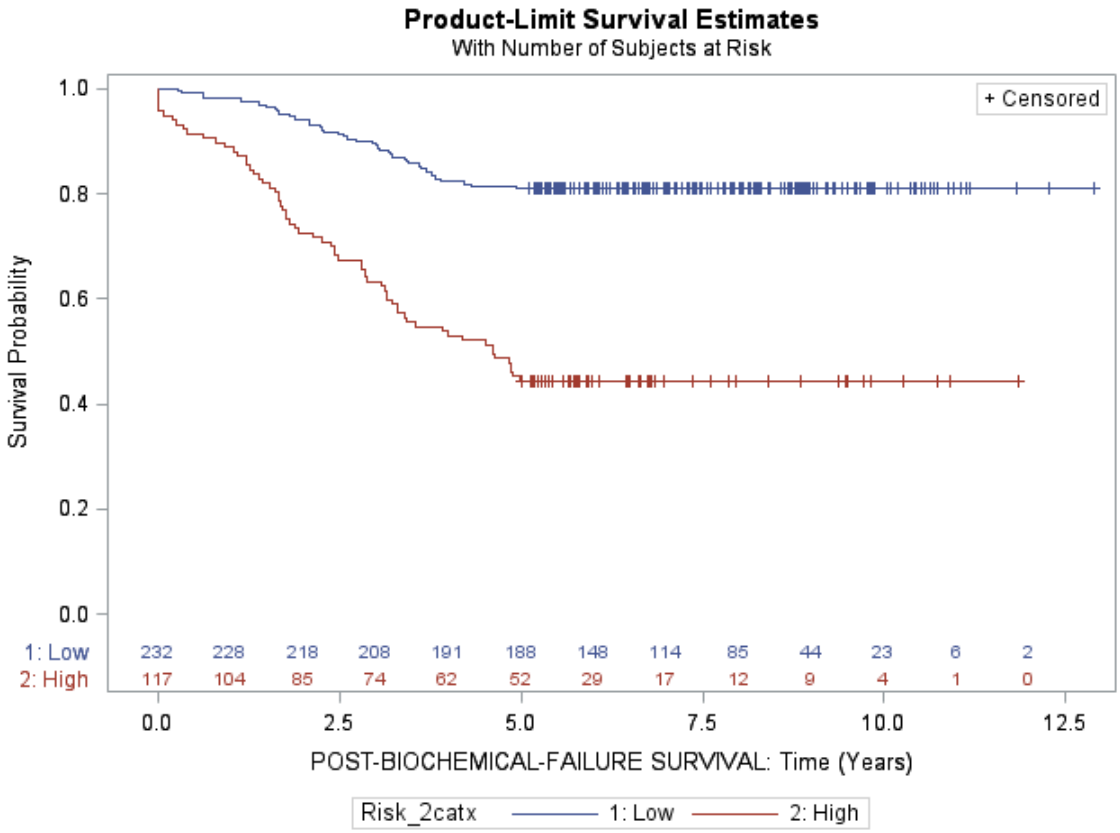

Figure 10: **Kaplan-Meier Plot of 2 Risk Group Categories from Training Cohort (Log-Rank: p <0.01).**

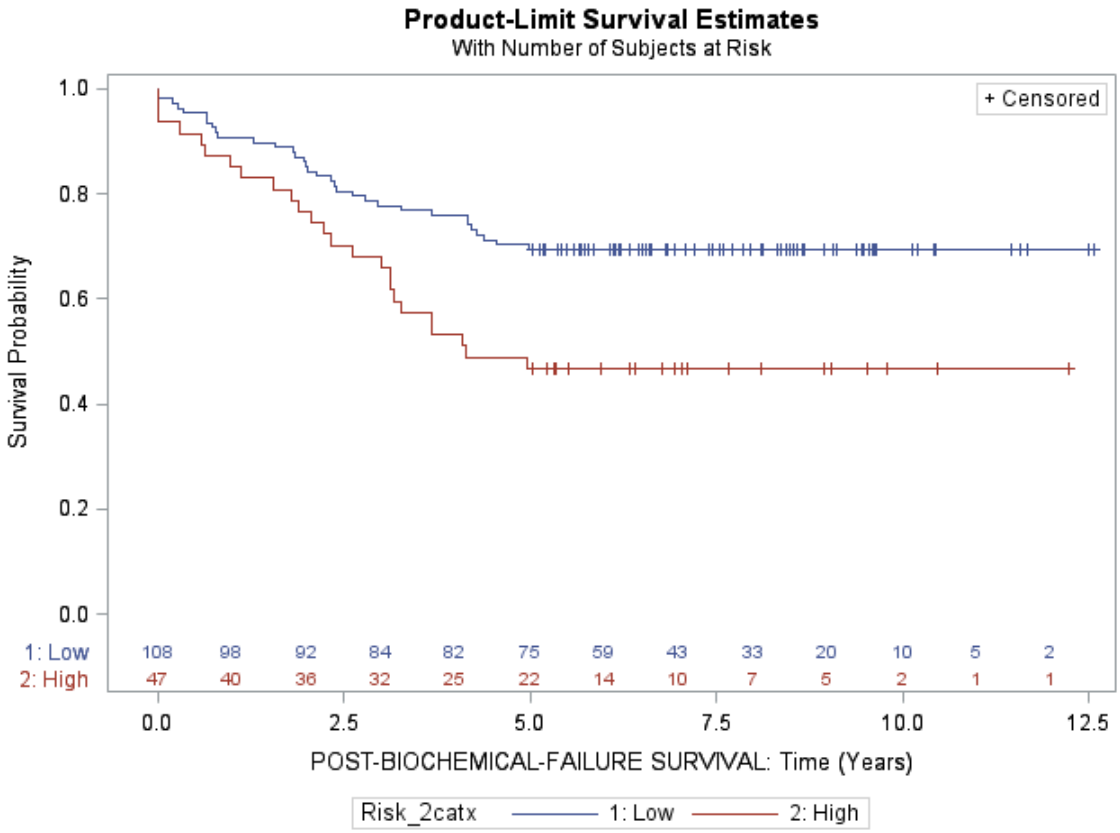

Figure 11: **Kaplan-Meier Plot of 2 Risk Group Categories from Validating Cohort (Log-Rank: p<0.01).**

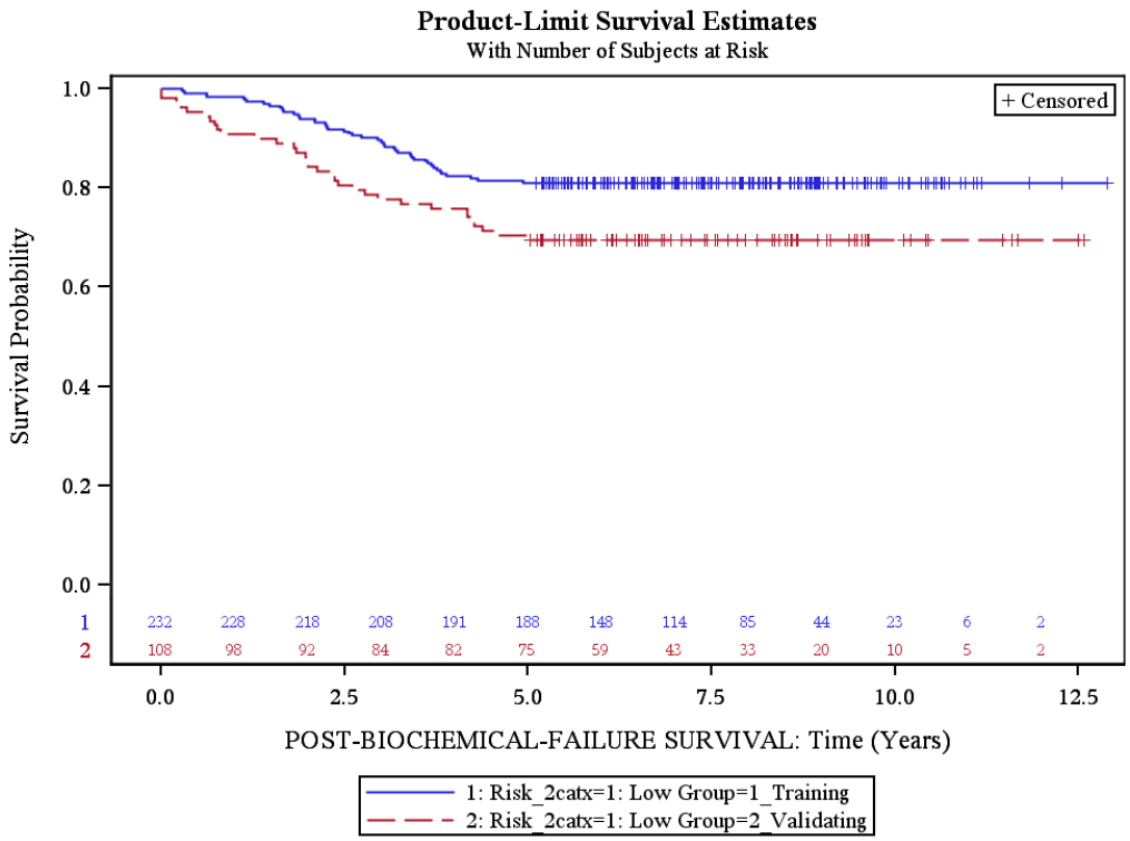

Figure 12: **Kaplan-Meier Plot of Low Risk Group for Training and Validating Cohorts (Log-rank: p=0.01).**

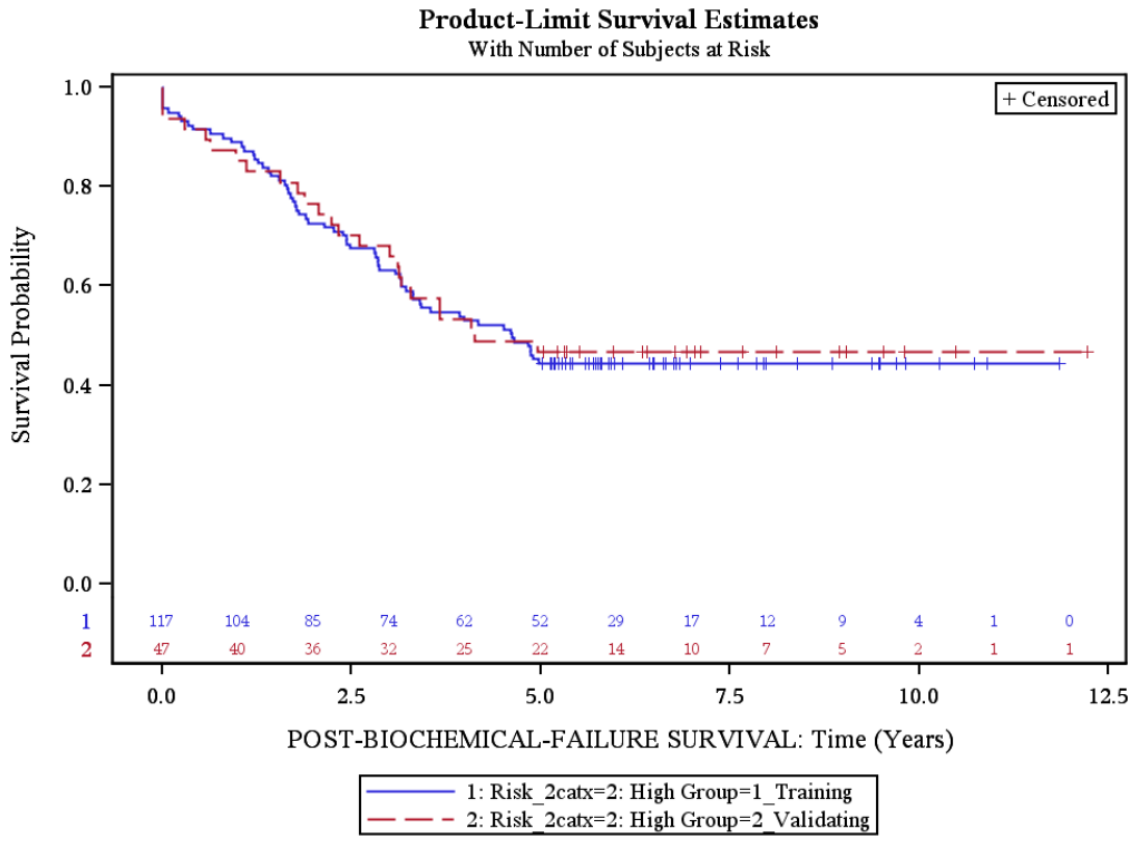

Figure 13: **Kaplan-Meier Plot for High Risk Group for Training and Validating Cohorts (Log-Rank: p=0.83).**

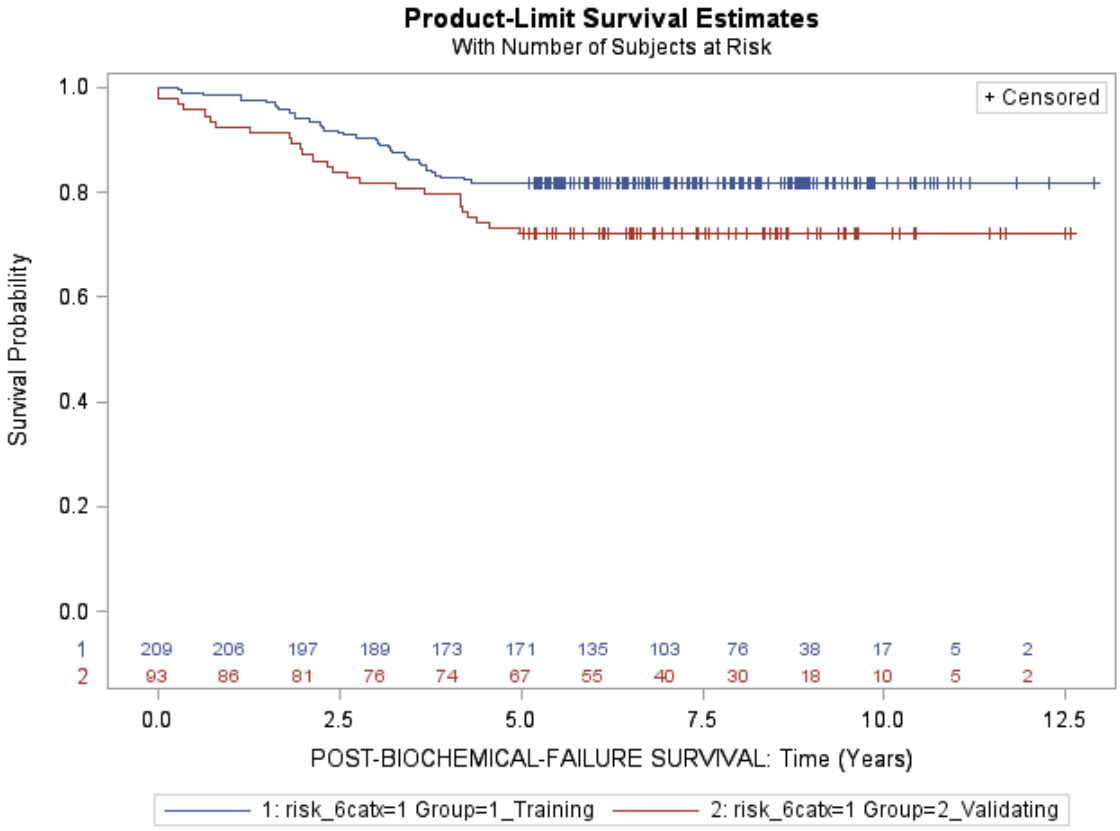

Figure 14: **Kaplan-Meier Plot for Risk Group 1 for Training and Validating Cohorts (Log-Rank: p=0.05).**

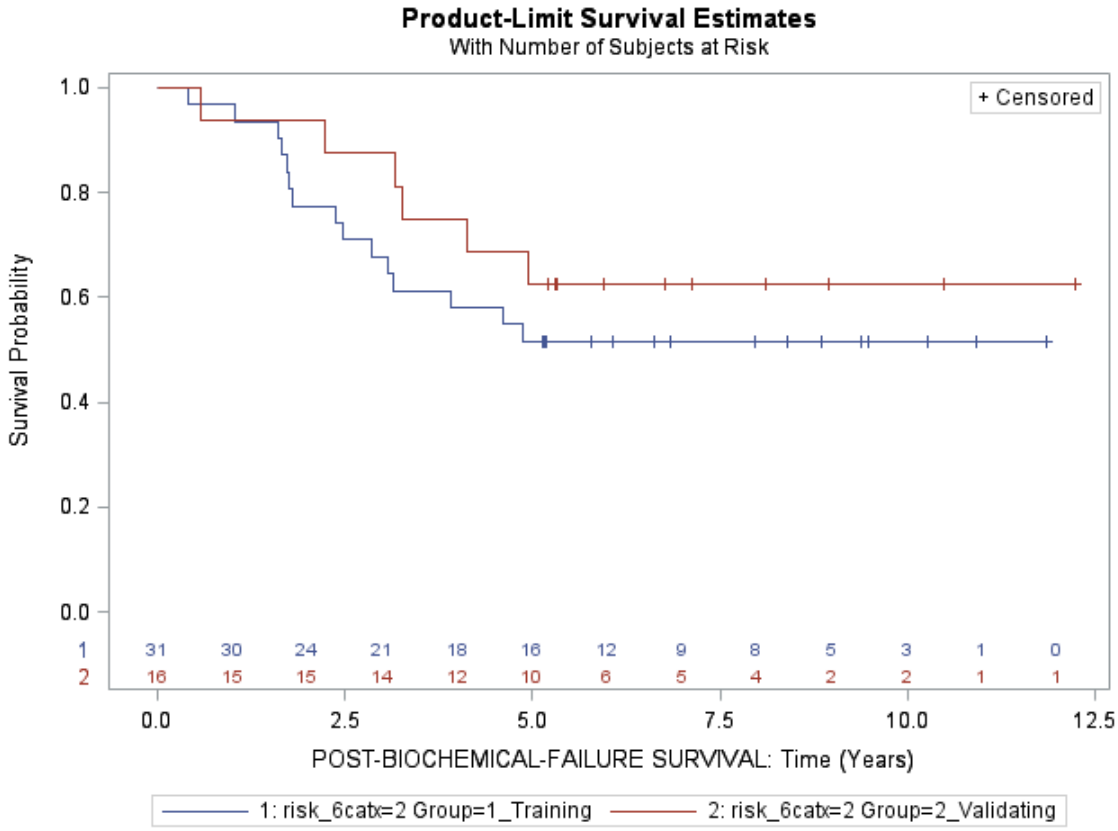

Figure 15: **Kaplan-Meier Plot for Risk Group 2 for Training and Validating Cohorts (Log-Rank: p=0.38).**

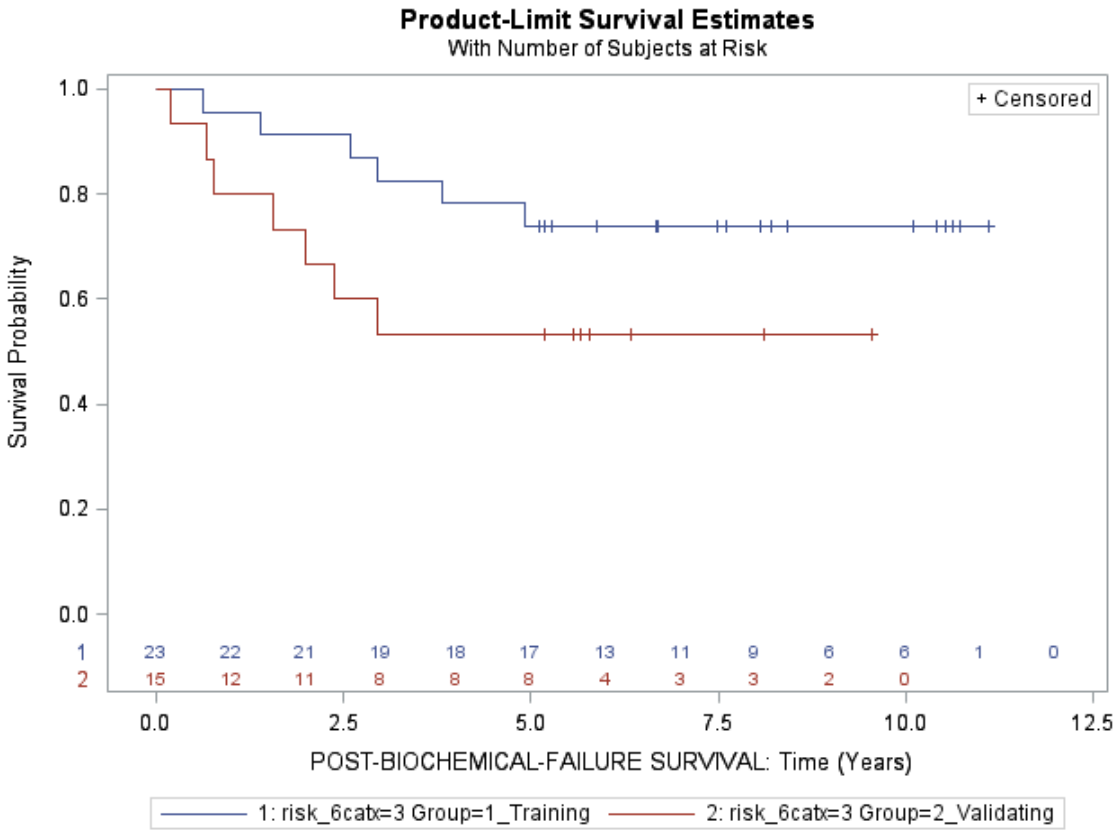

Figure 16: **Kaplan-Meier Plot for Risk Group 3 for Training and Validating Cohorts (Log-Rank: p=0.13).**

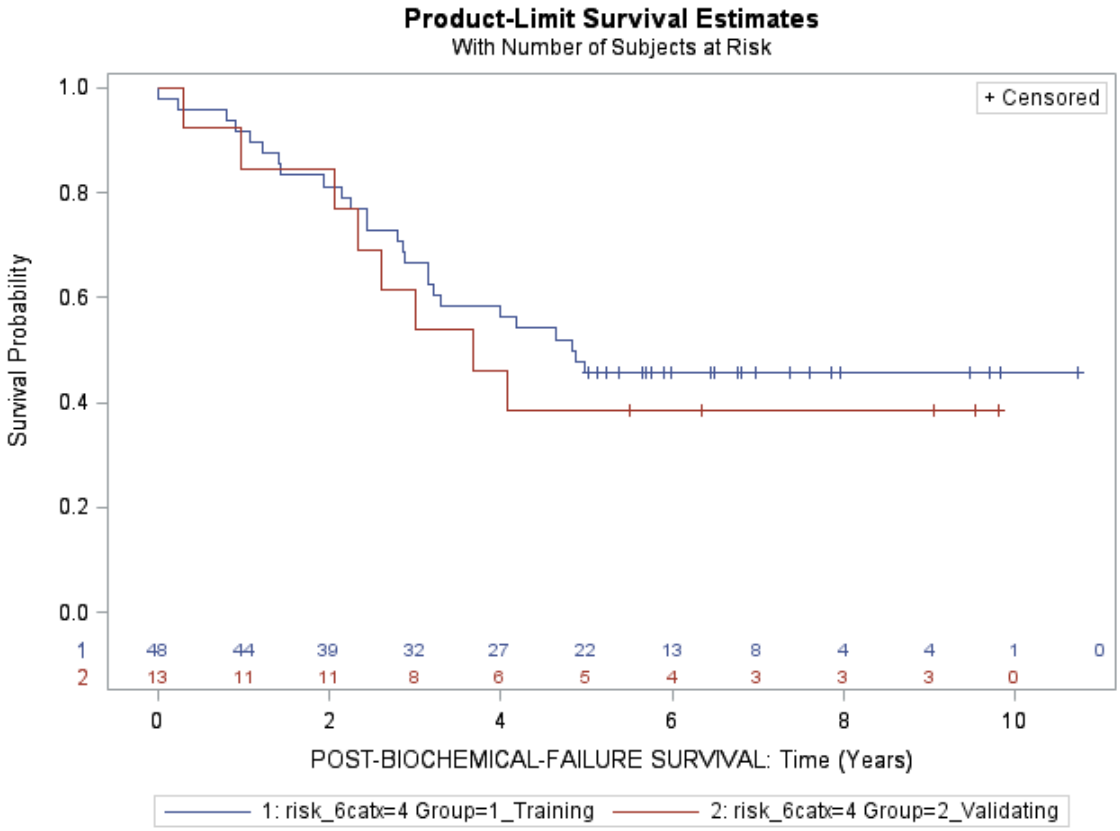

Figure 17: **Kaplan-Meier Plot for Risk Group 4 for Training and Validating Cohorts (Log-Rank: p=0.57).**

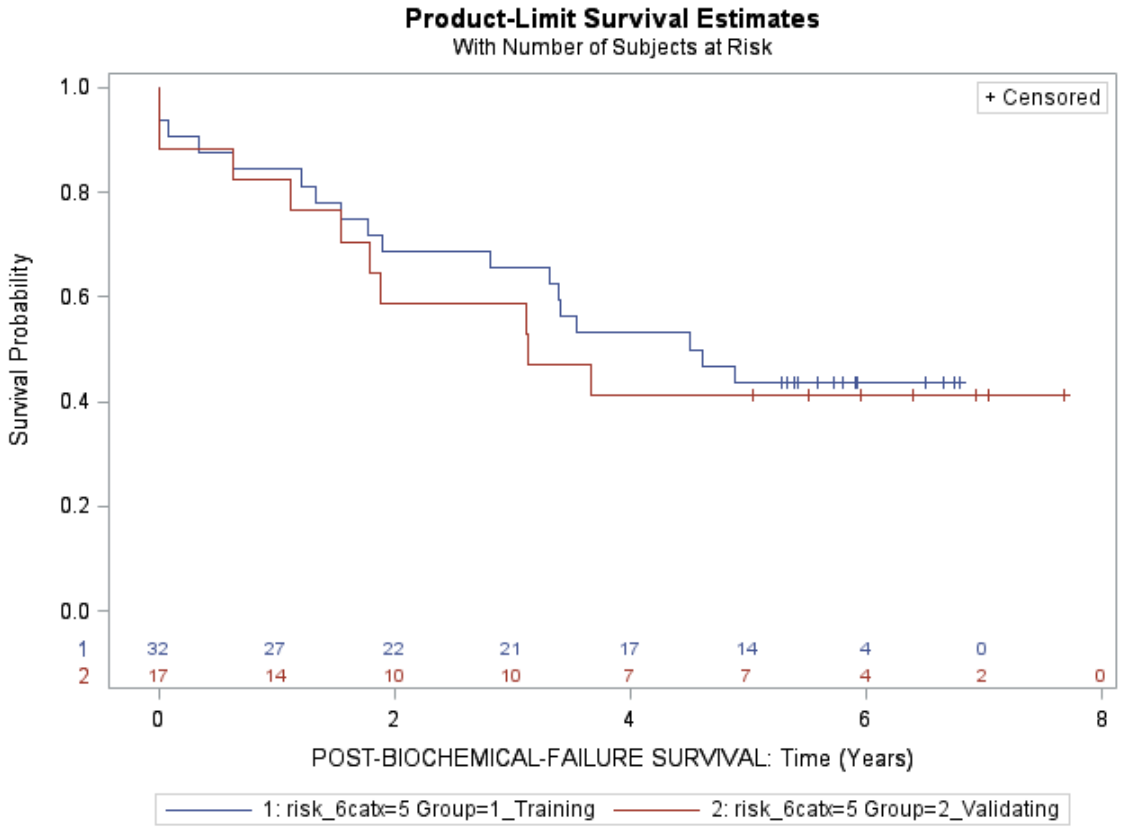

Figure 18: **Kaplan-Meier Plot for Risk Group 5 for Training and Validating Cohorts (Log-Rank: p=0.71).**

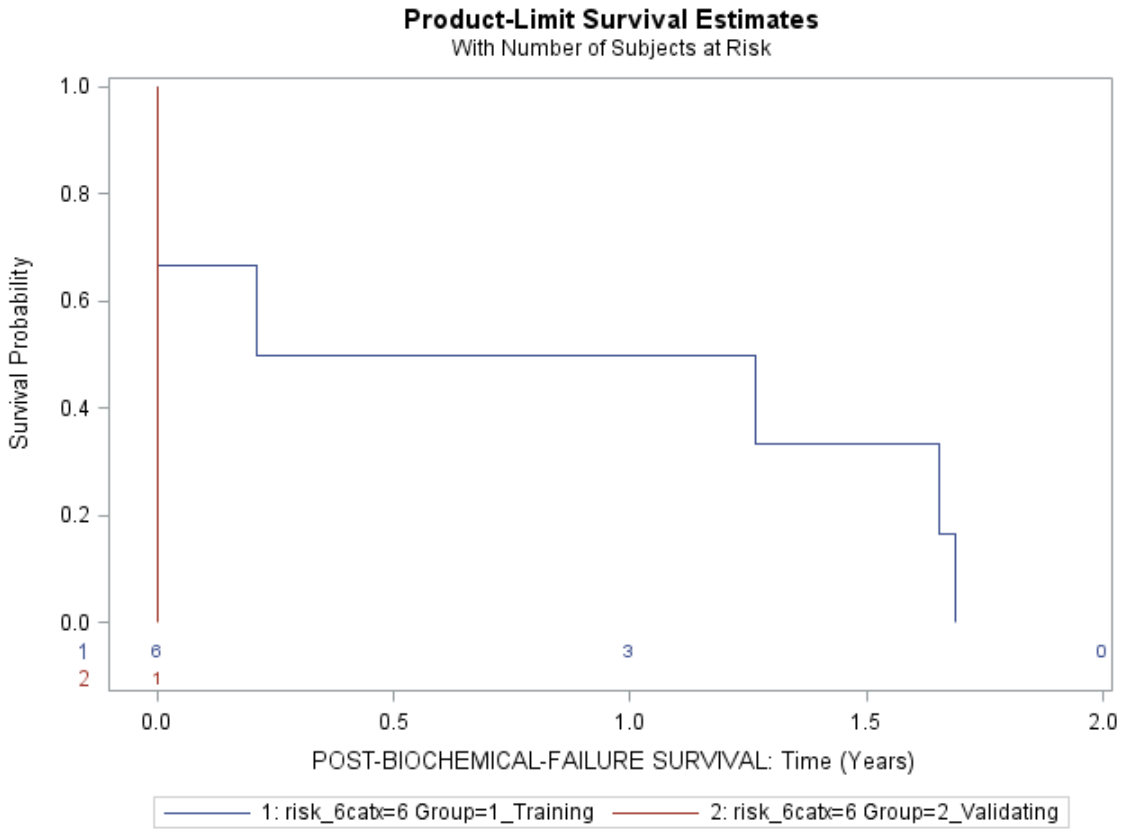

Figure 19: **Kaplan-Meier Plot for Risk Group 6 for Training and Validating Cohorts (Log-Rank: p=0.25).**

Table 15: Hazard Ratio and associated 95% CI, p-value and c-index for Training and Validating Cohorts in 2-Class Risk Group

	Hazard Ratio: High Risk vs. Low Risk	95% CI	p-value	c-index
Training	3.87	2.64 to 5.68	<0.01	0.69
Validating	2.05	1.22 to 3.45	<0.01	0.60

Table 16: Hazard Ratio and associated 95% CI, p-value and c-index for Training and Validating Cohorts in 6-Class Risk Group

Risk Group	Training				Validating			
	Hazard Ratio	95% CI	p-value	c-index	Hazard Ratio	95% CI	p-value	c-index
2 vs. 1	3.30	1.82- 6.01	<0.01	0.71	1.34	0.55-3.26	0.52	0.64
3 vs. 1	1.49	0.63- 3.53	0.36		2.11	0.91-4.86	0.08	
4 vs. 1	3.77	2.29- 6.21	<0.01		2.76	1.25-6.11	0.01	
5 vs. 1	4.19	2.39- 7.35	<0.01		2.94	1.42- 6.11	<0.01	
6 vs. 1	41.07	16.31- 103.40	<0.01		57.98	6.34- 531.51	<0.01	

Table 17 All Patients in Low and High Risk Category Groups by Centre

Centre	**Low**- n(%)	**High**- n(%)
British Columbia Cancer Agency	190 (81.90)	100 (85.47)
L'Hotel Dieu de Québec	12 (6.03)	6 (5.13)
McGill University Health Centre	0 (0.00)	0 (0.00)
Princess Margaret Hospital	28 (12.07)	11 (9.40)

4.4 Evaluation of the Proportional Hazards Assumption

Proportional hazards assumptions were first assessed graphically using log-minus-log survival plots for the 2 risk categories identified through RPA (Figure 20). Log-minus-log survival plots for the 6-class risk groups are also depicted in Figure 21. Figures 22 to 26 compares each risk group to Risk Group 1. Cross-over and lack of parallelism between the 2 categories was observed indicating possible violation of the proportional hazards assumption. Further assessment using the Kolmogrov test offered a less subjective evaluation of the proportional hazards assumption.

The Kolmogrov test was assessed for all patients in Figure 27 for the 2-class Risk Group, and 29 to 34 for the 6-class Risk Group. This test was found to be significant ($p<0.05$) further suggesting a violation of proportional hazards assumptions. In the 6-class Risk Groups, using Risk Group 1 as the reference, Risk Group 3 is the only assessment indicating a potential violation of the proportional hazards assumption ($p=0.04$).

Given the violation of proportional hazards, the 2 and 6-class risk group categories were assessed as time-dependent covariates to determine if the groups remained a significant predictor of survival for any time during the follow-up period. Results from the corresponding Cox proportional hazards regression model are shown in Table 18, indicating a likelihood ratio of $p=0.02$. Although the 2-class risk group was shown to violate the proportional hazards assumption, when assessed as a time-varying covariate, it continues to be a significant predictor of survival. Similarly, the corresponding regression model for the 6-class risk group produced a likelihood ratio of $p<0.01$, indicating the 6-class risk group was also a significant predictor of survival when assessed as a time-dependent covariate (Table 19).

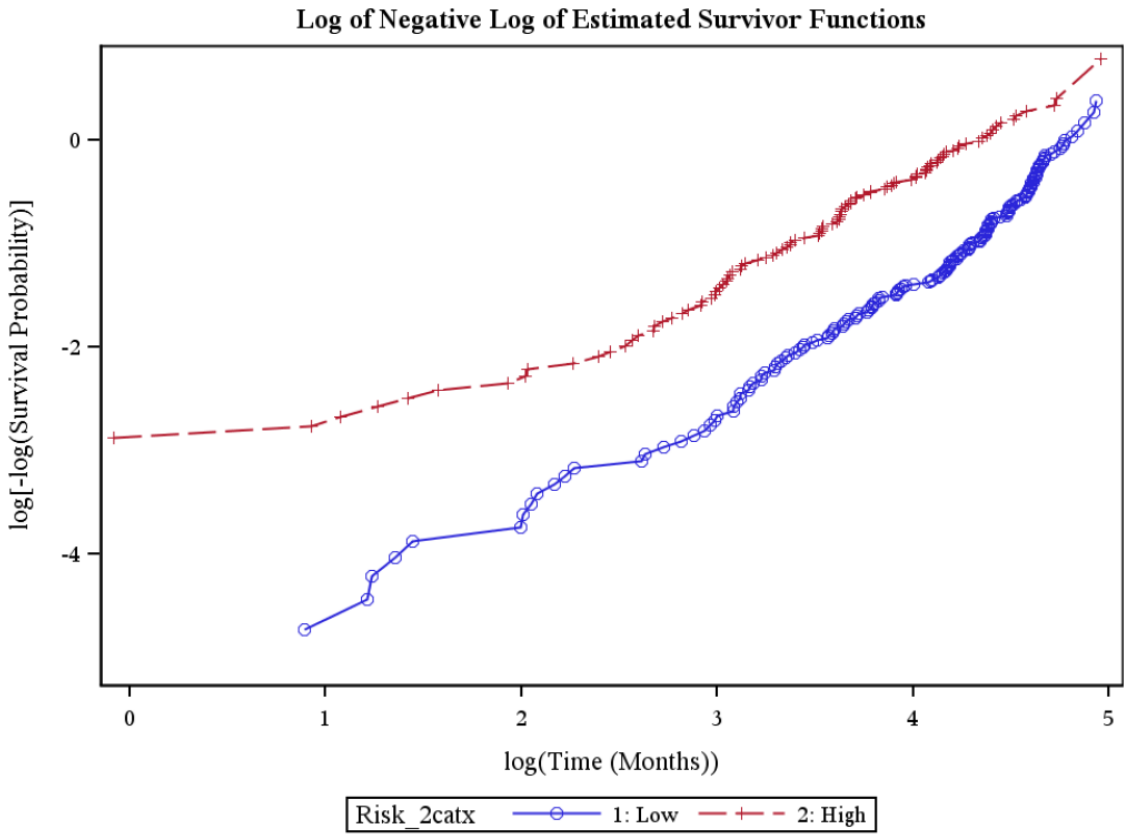

Figure 20: Log-Minus-Log Survival Plots for All Patients within High and Low Risk Categories Identified through RPA

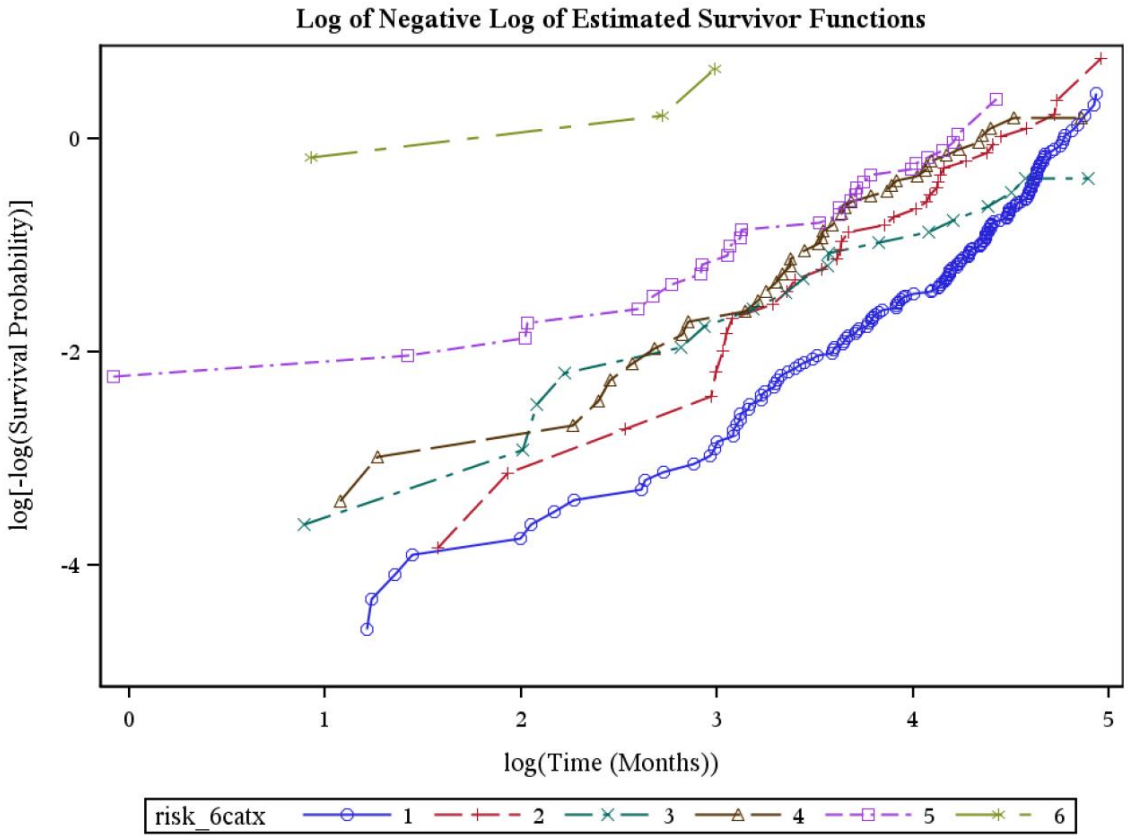

Figure 21: Log-Minus-Log Survival Plots for All Patients within 6-Class Risk Groups Identified through RPA

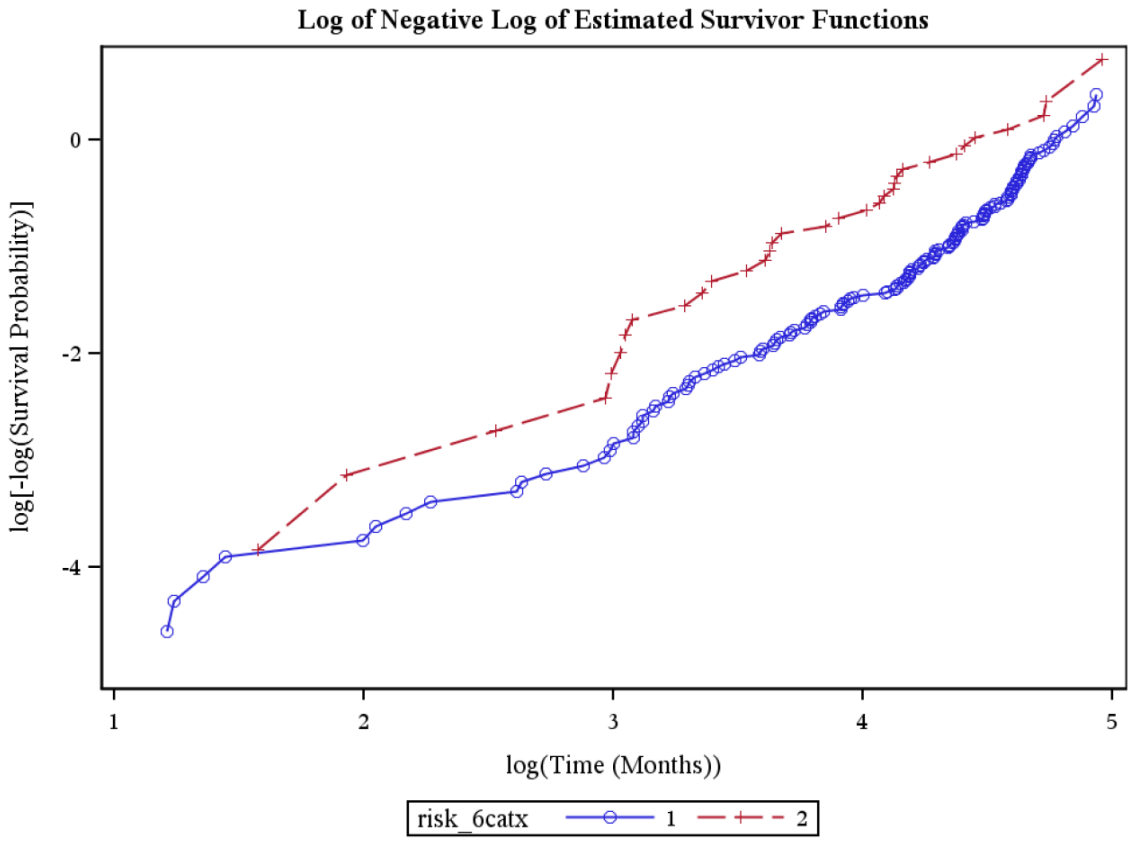

Figure 22: Log-Minus-Log Survival Plots for All Patients within Risk Group 1 and Risk Group 2

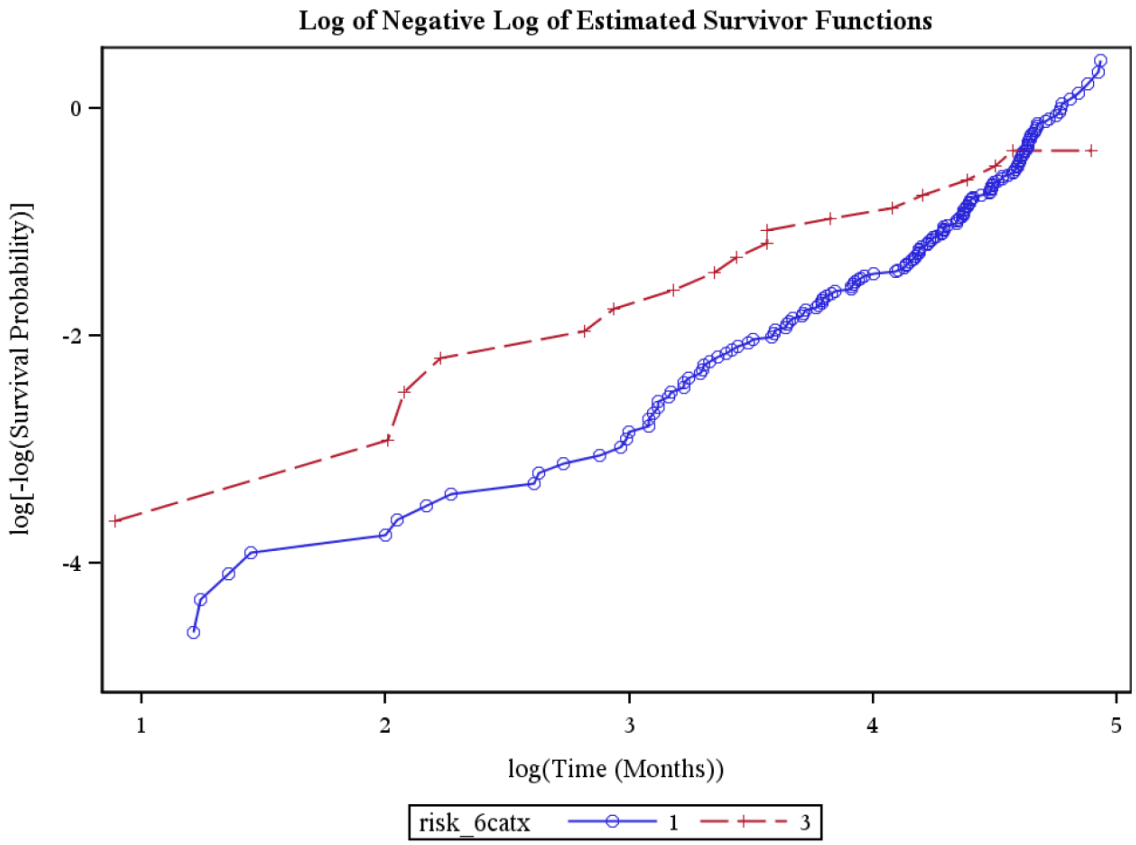

Figure 23: Log-Minus-Log Survival Plots for All Patients within Risk Group 1 and Risk Group 3

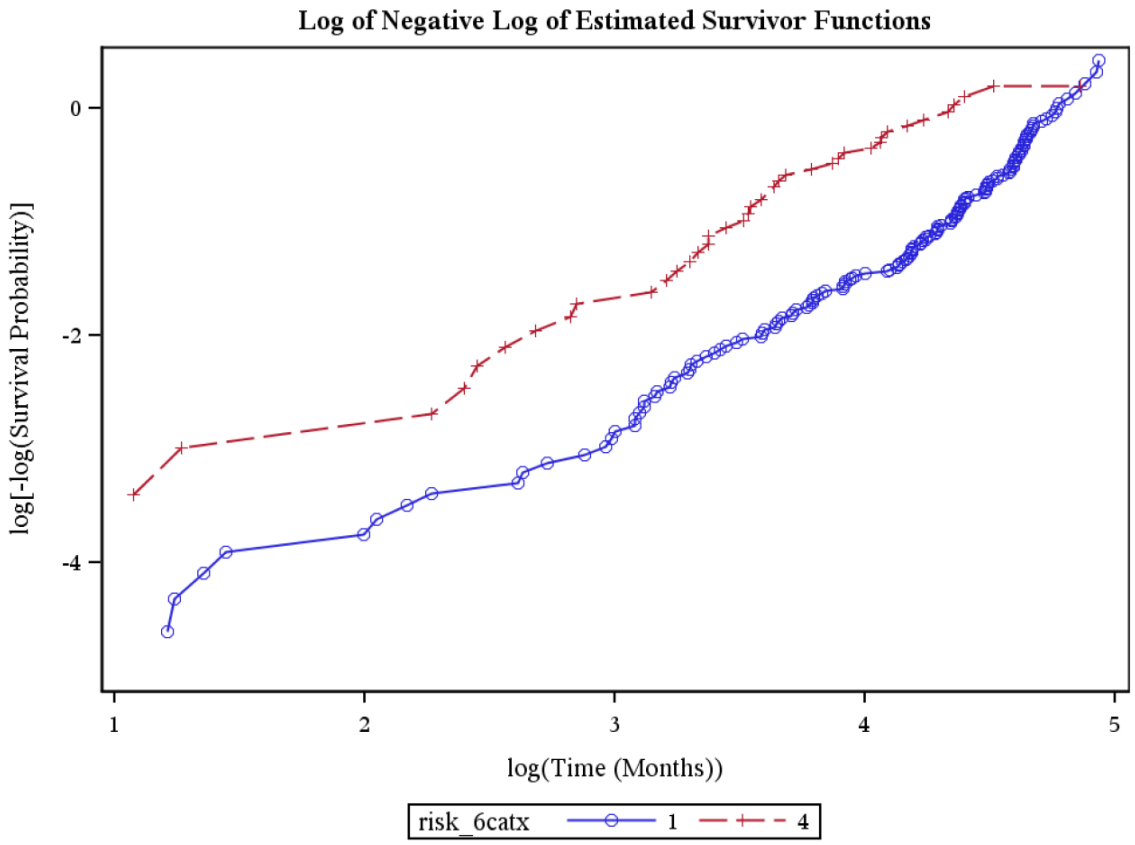

Figure 24: Log-Minus-Log Survival Plots for All Patients within Risk Group 1 and Risk Group 4

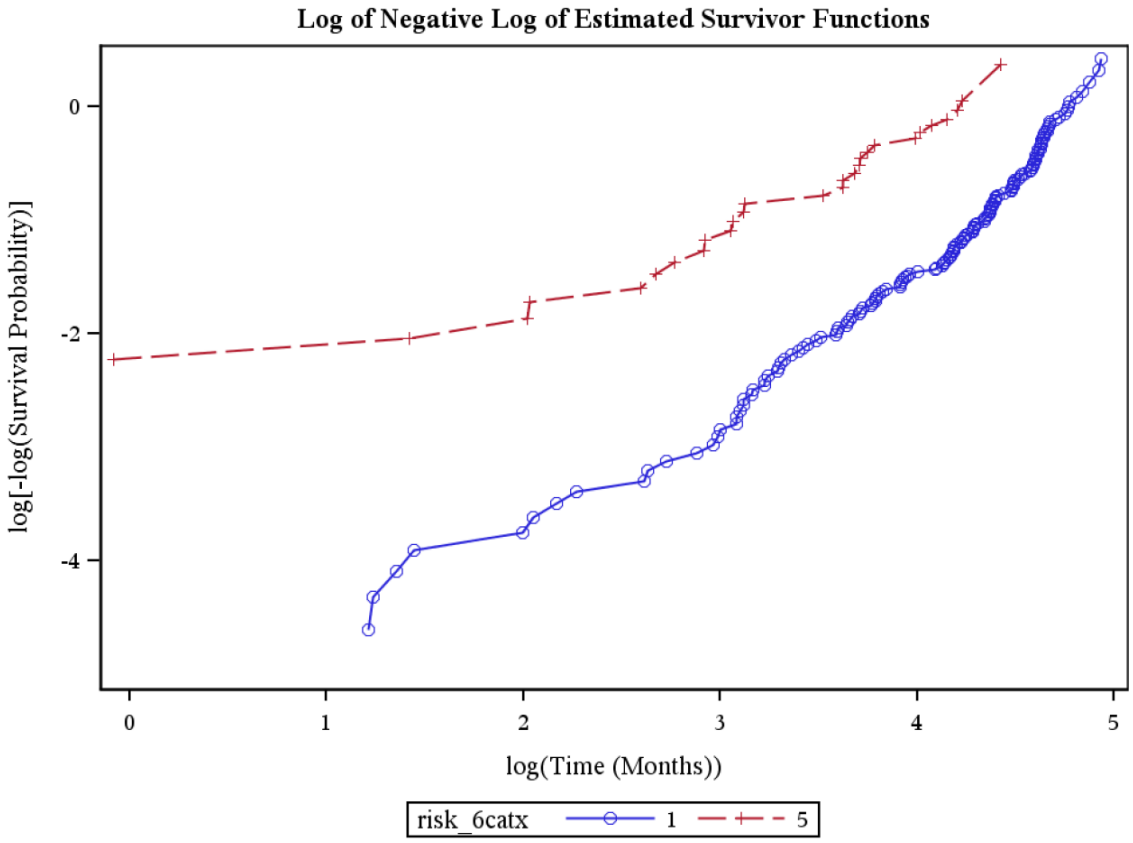

Figure 25: Log-Minus-Log Survival Plots for All Patients within Risk Group 1 and Risk Group 5

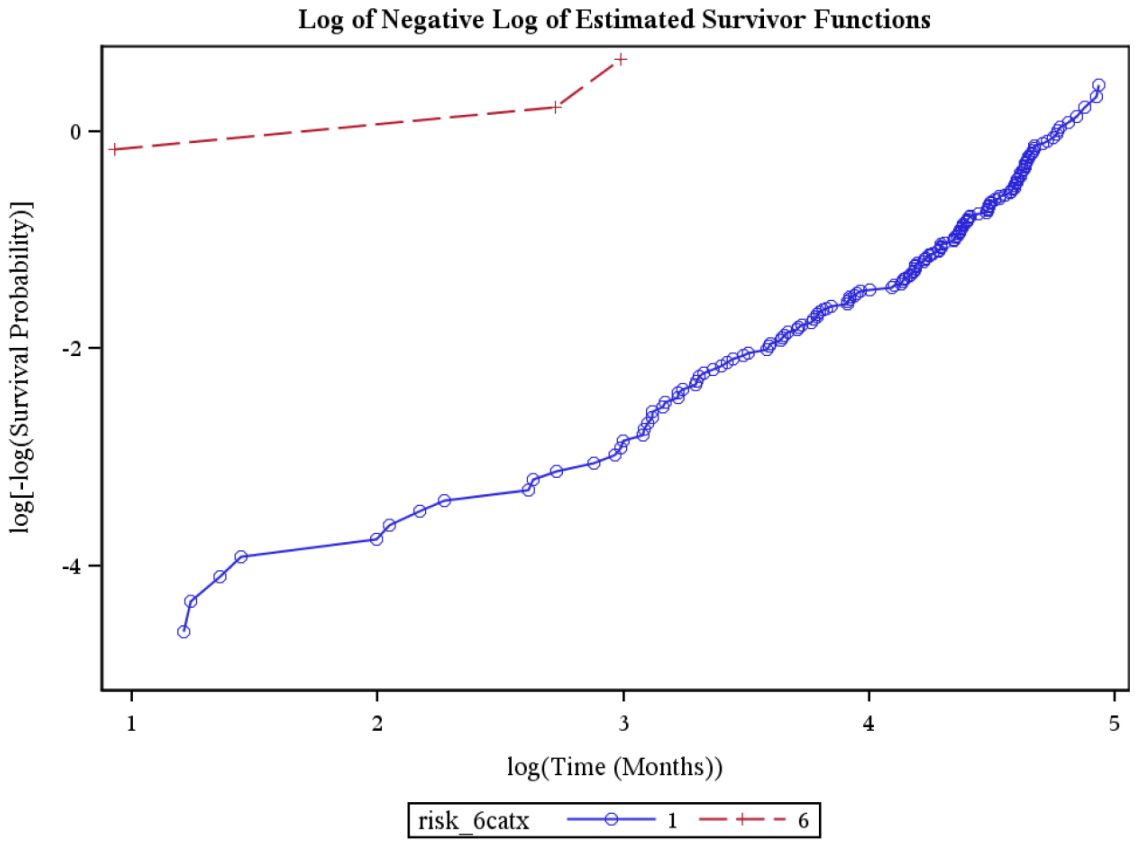

Figure 26: Log-Minus-Log Survival Plots for All Patients within Risk Group 1 and Risk Group 6

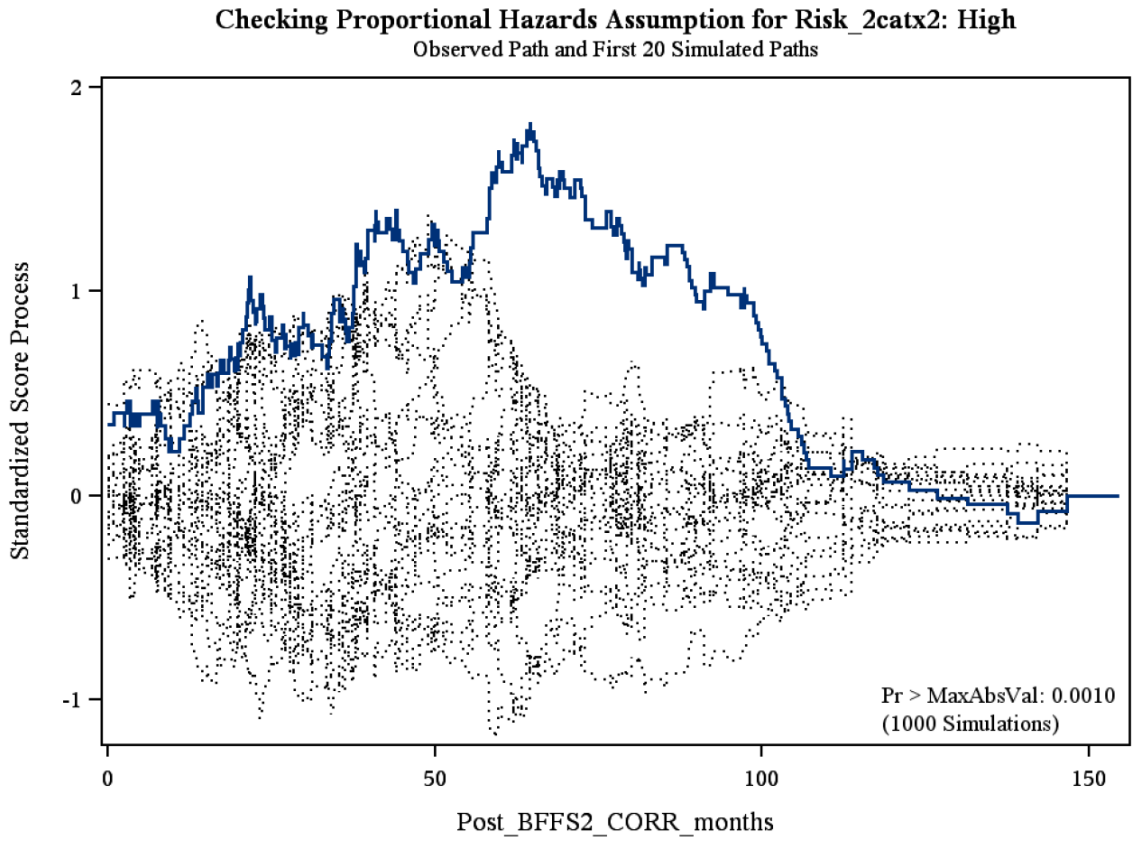

Figure 27: Supremum (Kolmogorov Test) for All Patients in 2-Class Risk Groups

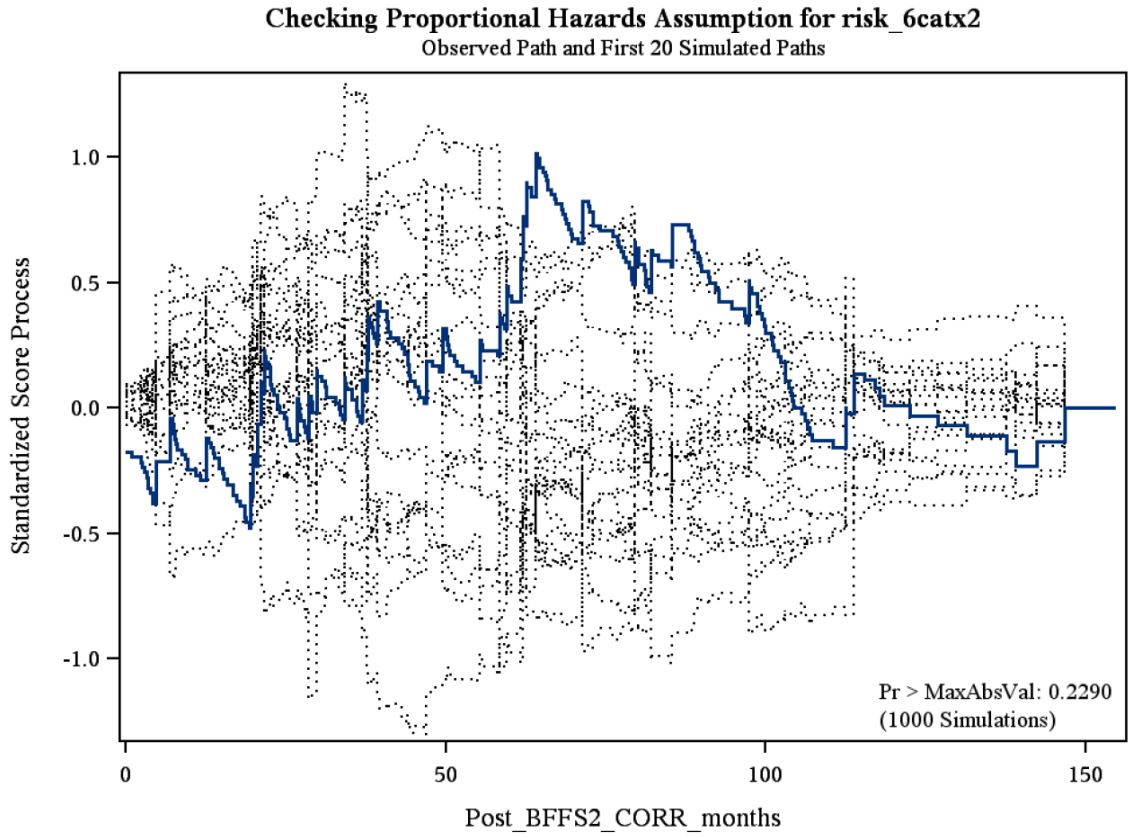

Figure 28: Supremum (Kolmogorov Test) for All Patients in Risk Group 2 compared to Risk Group 1 in 6-Class Risk Group

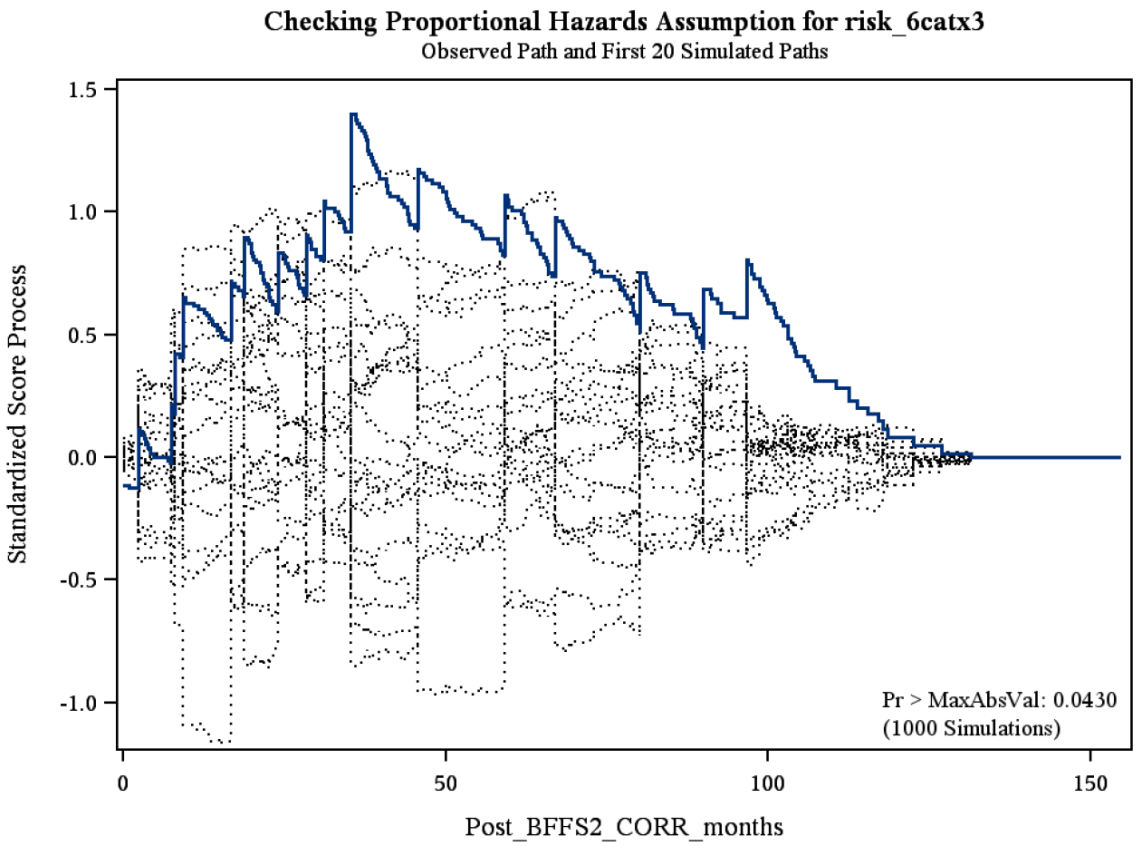

Figure 29: Supremum (Kolmogorov Test) for All Patients in Risk Group 3 compared to Risk Group 1 in 6-Class Risk Group

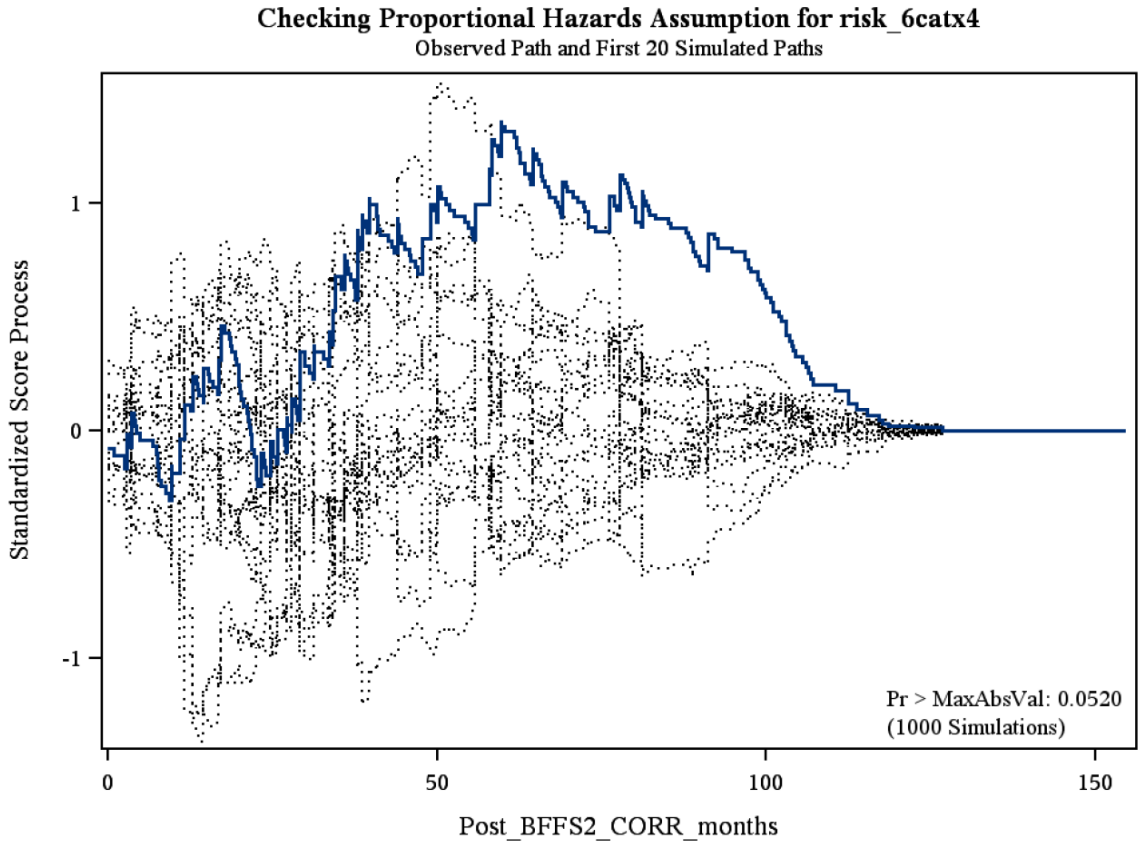

Figure 30: Supremum (Kolmogorov Test) for All Patients in Risk Group 4 compared to Risk Group 1 in 6-Class Risk Group

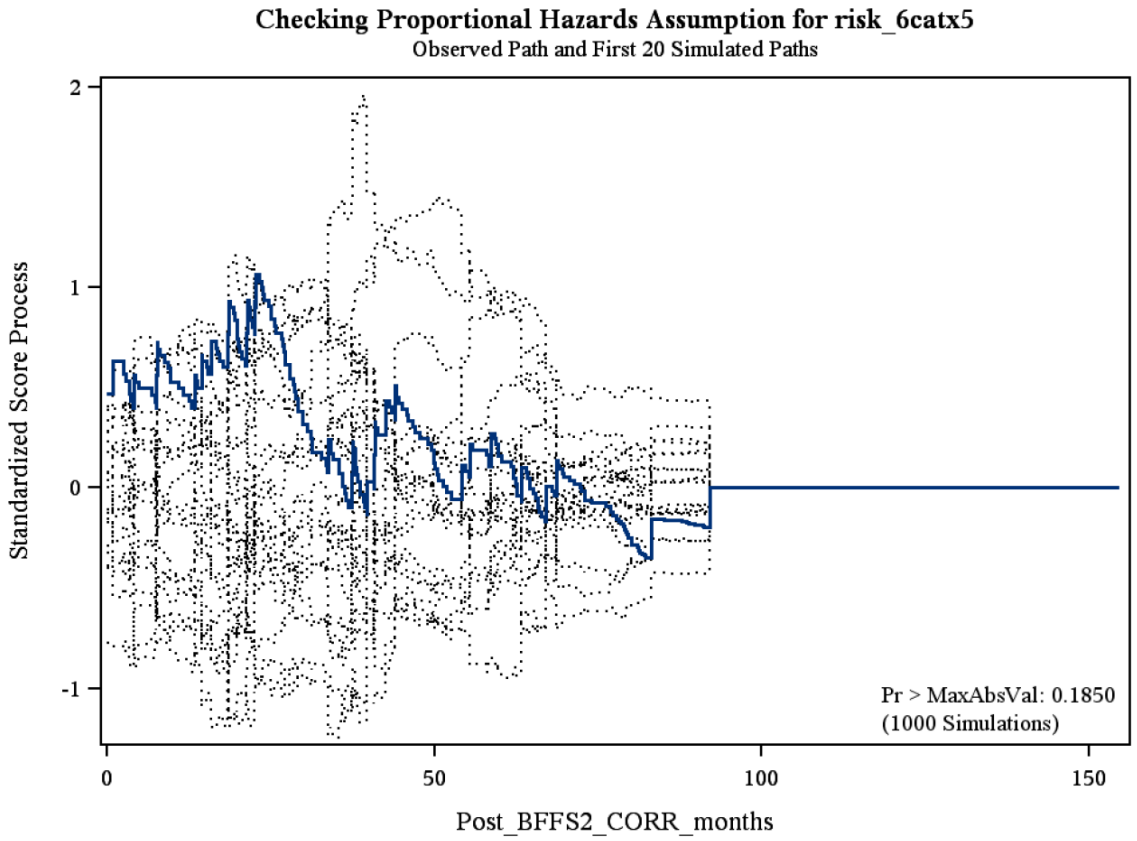

Figure 31: Supremum (Kolmogorov Test) for All Patients in Risk Group 5 compared to Risk Group 1 in 6-Class Risk Group

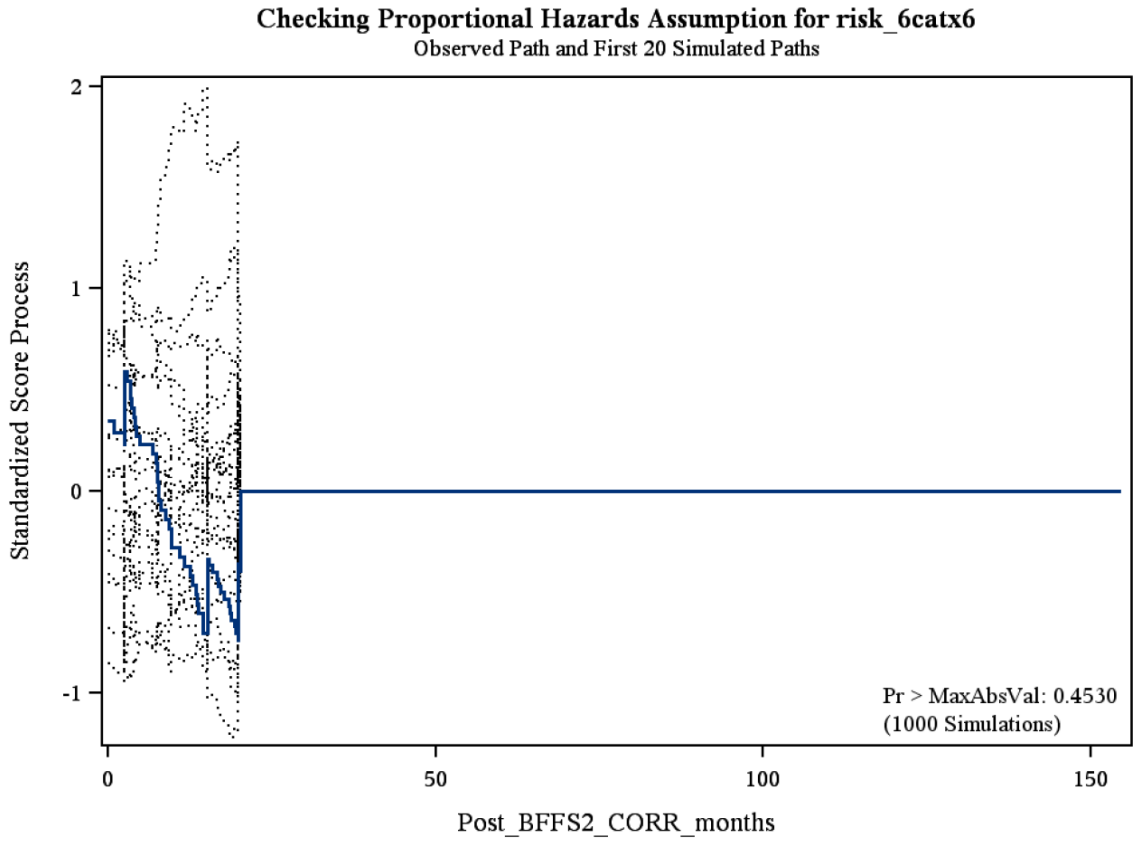

Figure 32: Supremum (Kolmogorov Test) for All Patients in Risk Group 6 compared to Risk Group 1 in 6-Class Risk Group

Table 18: 2-Class Risk Group as Time Varying Covariate

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	7.2996	2	0.0260
Score	7.9767	2	0.0185
Wald	7.6187	2	0.0222

Table 19: 6-Class Risk Group as Time Varying Covariate

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	71.4309	6	<.0001
Score	155.8073	6	<.0001
Wald	84.4405	6	<.0001

Chapter 5 : Discussion

5.1 Limitations

Much heterogeneity exists in PSADT definitions in the medical literature, which impairs the ability to make direct comparisons from univariable and multivariable analyses. Apart from how PSADT is calculated, it should be noted that not all patients will have positive values for PSADT. A proportion of patients will have PSADT values that are either negative, indicative of declining PSA over time in some instances, or undefined due to missing data or no change in PSA between time points. Depending on the definition(s) used, the proportion of patients unavailable for PSADT testing may vary within patient populations. PSADT also requires that patients have longer and regular follow-up data in order to have enough PSA measurements to allow for its calculation. For instance, the examination of Pre-RT PSADT required at least two PSA measurements available prior to start of radiotherapy, which was only available in a minority of patients.

Final RPA classified patients using 2 definitions of pre-BF PSADT. While it would be preferable to have a classification identifying PSADT using one definition, the two PSADT calculations measure differently. Pre-BF PSADT calculated using the last 2 PSA values before BF (Last-2) gives an indication of the immediate kinetics prior to BF while pre-BF PSADT calculated using nadir PSA and the last PSA value prior to BF (Nadir-Last), provide information on long-term PSA kinetics. This analysis demonstrated that both definitions are beneficial to predicting 5-year overall survival after biochemical failure.

Random split-sample methods, where 2/3 of the original data are used to develop the model and 1/3 is used for validation, decreases statistical power for model development (Hendriksen et al. 2013). Although this method is not preferred, the GUROC ProCaRS database offers a large data set for evaluating and developing a model. In addition, this approach has been widely adopted within the (radiation) oncology literature for observational studies, particularly for the examination of survival outcomes, which allows for both graphical and quantitative comparisons (Lambin et al. 2013).

The division into Training and Validating cohorts allowed for the assessment of internal validity of the prediction model. Moderate or acceptable discriminatory ability of a model does not guarantee that it will perform similarly in a different group of patients. Therefore methods of external validation are necessary perhaps in different institutes or clinical settings.

5.2 Post-Treatment Risk Stratification

Using data from a large database of RT patients, univariable and multivariable Cox proportional hazards regression analyses found a number of prognostic factors for OS after BF. Many of the factors in our study are similar to those found in literature with studies of smaller sample sizes. A summary of these variables may be found in Table 20. TTBF and PSADT were more consistently found in literature to be predictive of OS upon multivariable analysis. Other studies in literature found age to be a weak predictor or not significant among many other factors as well. This study, however, found that age, baseline PSA, higher T stage (T3 and T4 versus T1), higher Gleason score (8-10 versus 2-5), hormone therapy, radiation therapy, nadir PSA, TTBF and shorter pre-BF PSADT (when categorized as <6, 6-12, and >12 month intervals) as significant ($p<0.05$) factors upon univariable and multivariable analyses based on the Training cohort.

The benefit of using RPA and keeping variables as continuous is that cut-points will be based on optimal discrimination between groups, instead of categorization which creates information loss and may be potentially arbitrary and subjective. The choice of threshold of categorization is usually determined by data used for developing models and therefore makes the model unstable and less generalizable in its applications to other individuals (Hendriksen et al. 2013). Numerous cut-points for TTBF and PSADT in multivariable analyses have been observed in studies of varying sample sizes. PSADT has also been calculated in a number of different ways (Daskivich et al. 2006).

The identification of a high risk group of patients with BF is of great importance in clinical research for prostate cancer. Prior to our study, there was no risk stratification for patients with BF for OS following date of BF, although one study has examined PCSS. This previous risk stratification predicting PCSS after BF was conducted using data from 485 patients with BF in a clinical trial of 802 patients with locally advanced prostate cancer in Australia and New Zealand. This group used only PSADT and TTBF to explore its predictive accuracy (Steigler et al. 2012).

Our study identified 6 unique patient groups based on TTBF, pre-BF PSADT (calculated with nadir and last, and last 2 PSA values), Gleason score, and age. Of these 6 groups, it

was found that 2 groups could be collapsed into a low risk group, and 4 groups could be combined as a high risk group based on their survival profiles. Hazard ratios from both Training and Validating cohorts confirmed that the high risk group identified patients who were at greater risk for death compared to patients identified as low risk. A study analyzing overall survival after BF among 154 patients demonstrated a median survival of 5.9 years after BF (Sandler et al. 2000). Using 2-class risk groups, low and high risk median survival could be determined. Median survival after BF among low risk patients were 6.91 years and 6.27 years in Training and Validating cohorts respectively. High risk patients had a median survival of 4.62 and 4.13 years after BF in Training and Validating sets.

The c-index is commonly used to assess the predictive ability of statistical models. A c-index of 0.5 implies that a model has no predictive ability, while a c-index of 1 implies perfect predictive ability. The 6-class risk stratification model gave rise to c-indices of 0.71 and 0.64 Training and Validating cohorts. The 2-class model gave rise to c-indices of 0.69 and 0.60 respectively. These values describe a modest to acceptable predictive ability, when c-statistics are considered to have acceptable discrimination when between 0.7 and 0.8 (Antonarakis et al. 2012). While collecting more variables for model development may have helped with predictive ability, the ProCaRS database consists of retrospectively collected data.

Overall, the 2-class post-treatment risk stratification system, which has been internally validated, allows for the identification of a high risk and low risk of patients with BF after RT which will play an important role in guiding patient selection for future clinical trials and treatment decisions.

Table 20: Summary of Prognostic Factors of Overall Survival after Biochemical Failure among Patients with Radiotherapy as Primary Treatment

Author, Year	n	Treatment	BF definition	Gleason Score	T stage	TTBF	PSADT	age	Pretreatment PSA	PSA nadir	Time to nadir	Comorbidity score	PSA velocity	Use of ADT after BF	BED
Wang, 2015	831	RT	Nadir + 0.2ng/ml	U M	U M	M	U M	U M	M	U M	x			U M	
Buyyounouski et al 2012	1722	RT	Nadir + 0.2ng/ml	x	x	M	M			M					
Ko et al 2014	264	RT	Nadir + 0.2ng/ml	x	x	M	x	x	x					x	x
Kim et al 2013	108	RT	Nadir + 0.2ng/ml	M	x	M		M	x			M	M	x	
Sandler et al 2000	154	RT	3 consecutive rises	x	x	x		x	x	x	x				
Wo et al 2009	89	RT	2 consecutive rises ≥0.2ng/mL after nadir	x	x	x		x				M	M		
D'Amico et al 2006	81	RT	2 consecutive rises of at least 0.2ng/mL after PSA level >1.0ng/mL	x	x		M	M	x						

Where x indicates that a variable was investigated, U indicates a factor was significant upon univariable analysis, M indicates a factor was significant upon multivariable analysis

5.3 Future Directions

Due to the small number of patients recorded with metastasis and death from prostate cancer in the GUROC ProCaRS database, this study focused analyses on OS following BF. Future studies focusing on post-treatment risk stratification for PCSS and MFS may provide useful classifications and comparisons for patients with BF after RT.

While this study was internally validated, there exists the need to determine whether the prediction model performs well with other patients in different institutes. External validation provides information from the new population that differs from the population used for the development of the model. If the model performs well, then it indicates that it may be used in both populations. If not, further considerations can be made in updating the model, or assessing if the model is still able to contribute to predicting outcomes for patients adequately (Hendriksen et al. 2013; Collins et al. 2015).

Given the results from univariable and multivariable analyses and RPA in identifying important prognostic factors for OS and a high risk group, the next steps would be to build a nomogram for prostate cancer patients with BF after RT and compare to proposed RPA risk groups. Nomograms are often used in cancer prognosis, as they are able to provide a single estimate of the probability of a specific outcome. They can also be readily available in the clinical setting to aid in physician-patient interactions. Since nomograms are able to give individualized predictions, they can be used to identify and stratify patients for participation in clinical trials as well (Iasonos et al. 2008).

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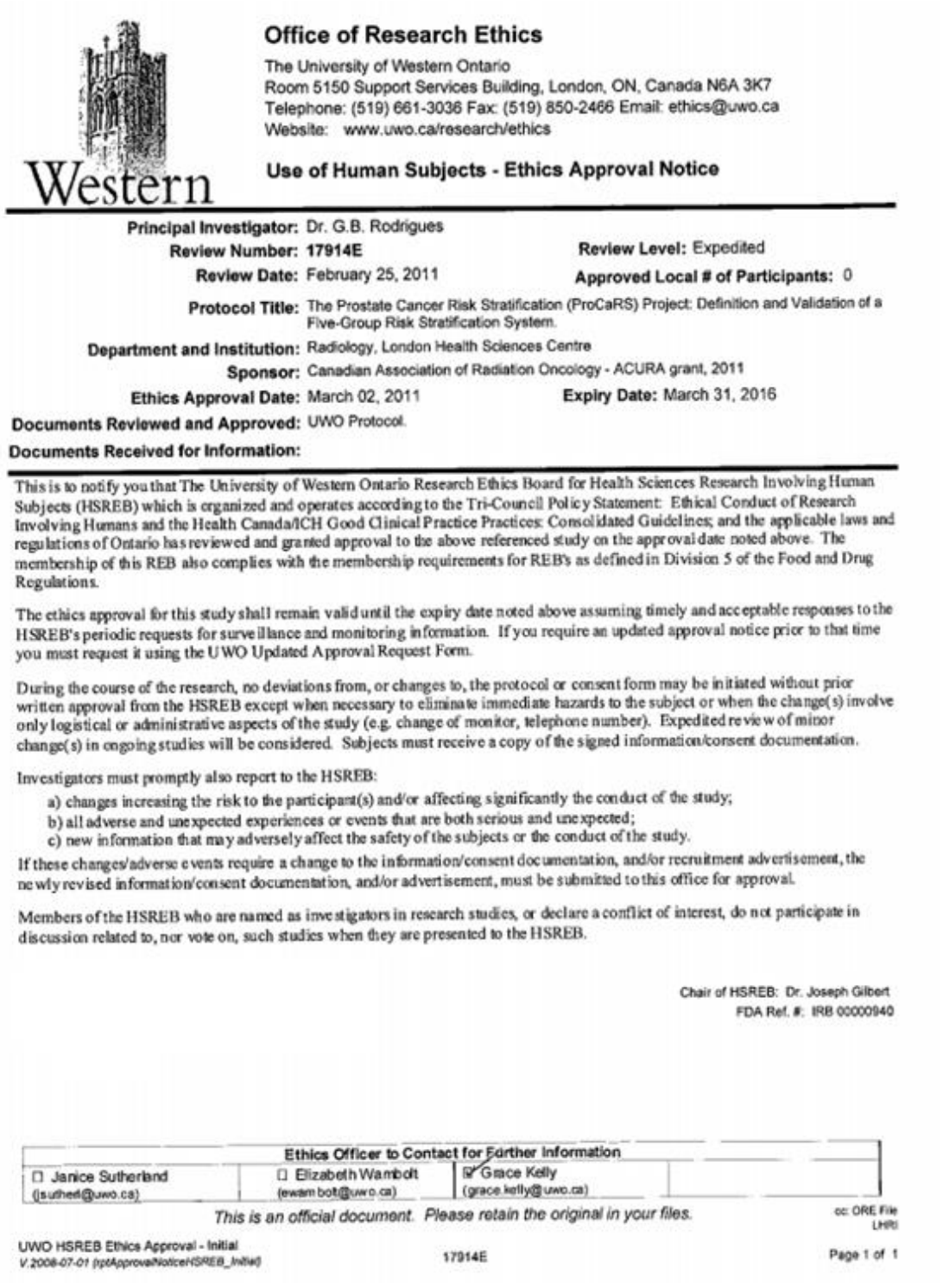
Appendices

Appendix I: Ethics Approval



Western

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. G.B. Rodrigues
Review Number: 17914E **Review Level:** Expedited
Review Date: February 25, 2011 **Approved Local # of Participants:** 0
Protocol Title: The Prostate Cancer Risk Stratification (ProCaRS) Project: Definition and Validation of a Five-Group Risk Stratification System.
Department and Institution: Radiology, London Health Sciences Centre
Sponsor: Canadian Association of Radiation Oncology - ACURA grant, 2011
Ethics Approval Date: March 02, 2011 **Expiry Date:** March 31, 2016
Documents Reviewed and Approved: UWO Protocol.
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland (jsuther@uwo.ca)	☐ Elizabeth Wambolt (ewambolt@uwo.ca)	☑ Grace Kelly (grace.kelly@uwo.ca)	

This is an official document. Please retain the original in your files.

cc: ORE File
LHRI

UWO HSREB Ethics Approval - Initial
V.2008-07-01 (rptApprovalNoticeHSREB_Initial)

17914E

Page 1 of 1

Appendix II: Variable List

GUROC ProCaRS Database (N=7,974): Variable List		
#	**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]
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)
15	Tstage_CORR_4catx	T-Stage (excluding Sub-Type): n = 7860 (frequency missing = 114)
19	GleasonPattern_CORR	Gleason Pattern: 1+1, 1+2…5+4, 5+5
21	GleasonMajor_CORR	Gleason Major: Re-derived based on FIRST number in Gleason Pattern **CORRECTED**
23	GleasonMinor_CORR	Gleason Minor: Re-derived based on SECOND number in Gleason Pattern **CORRECTED**
25	GleasonTotal_CORR	Total Gleason Score: Re-derived based on corrected Gleason Major and Minor **CORRECTED**
26	GleasonTotal_CORR_4cat	Total Gleason Score (4 categories): (1) 2-5, (2) 6, (3) 7, (4) 8-10
34	PosCores_ge50pct	Biopsy Cores: Postive Cores: (1) ≥ 50 % , (0) < 50%
36	Bilat_Biopsy_Status_CORR	Bilateral Biopsy Status: No, Yes, Unknown, N/A
37	Hormones	Hormones: (1) Yes, (0) No
38	HormStart	Hormones: Start Date
39	HormEnd	Hormones: End Date
40	AdjHT_months	Adjuvant Hormone Therapy (Months): ZEROs coded as MISSING
41	AdjHT_monthsx	Adjuvant Hormone Therapy (Months): ZEROs kept as ZEROs (for modelling) except if HormEnd Missing [Nomogram Manuscript]
42	AdjHT_months_OLD	Adjuvant Hormone Therapy (Months): ZEROs kept as ZEROs (for modelling)
45	RTStart_Year_4cat	RT Start Year (4 categories): (1) 1994-1999, (2) 2000-2002, (3) 2003-2005, (4) 2006-2010

GUROC ProCaRS Database (N=7,974): Variable List—Page 2/3		
#	**Variable**	**Description**
48	EBRT	EBRT: (1) Yes, (0) No
49	EBRT_Dose	EBRT Dose (cGy)
50	EBRT_Dose_GT70	EBRT Dose: (1) > 70 Gy, (0) ≤ 70 Gy
52	EBRT_Fractions	EBRT: Number of Fractions
53	EBRT_FractionDose	EBRT: Dose per Fraction (cGy)
54	EBRT_BED_Gy	EBRT Biologic Equivalent Dose (Gy)
55	LDR	LDR: Low Dose Rate Brachytherapy
56	LDR_Dose	
57	LDR_Fractions	
58	HDR	HDR: High Dose Rate Brachytherapy
59	HDR_Dose	
60	HDR_Fractions	
61	Brachy	Brachytherapy: (1) Yes, (0) No
62	Radiation_Type	Radiation Type: Brachy + EBRT, Brachy only, EBRT only
63	Radiation_Type_5cat	Radiation Type (5 categories): Brachy(LDR) only, Brachy(HDR) only, EBRT only, Brachy(LDR) + EBRT, Brachy(HDR) + EBRT
64	LocalRelapse	Clin/Path confirmed Local Relapse
66	PostRTHormStart	Salvage Hormone Therapy Start Date
67	Dead	Dead: (1) Dead, (0) Alive
68	Dead_5yr	Dead (≤ 5 years): (1) Dead, (0) Alive
71	Survival_months	Survival in MONTHS
78	CauseofDeath_CORRx	Denominator = 7974
87	Amico	AMICO Classification: Low, Intermediate, High
109	CRS	Prostate Cancer Death (aka Cancer-Related/Specific Survival): (1) Yes, (0) No (Equivalent to "CRStatus")
110	CRS_5yr	Prostate Cancer Death (≤ 5 years): (1) Yes, (0) No
112	CRS_months	Cancer-Related/Specific Survival in MONTHS
130	BFFS2	Biochemical Failure (aka Biochemical-Failure-Free Survival): (1) Yes, (0) No (Equivalent to "PhBFFS2Stat" - ASTRO II Phoenix Definition)
132	BFFS2_months	Biochemical-Failure-Free Survival in MONTHS

GUROC ProCaRS Database (N=7,974): Variable List—Page 3/3		
#	**Variable**	**Description**
134	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).
135	BFFS2_CORR_months	Biochemical-Failure-Free Survival CORRECTED in MONTHS
137	BFFS2_5yr	Biochemical Failure CORRECTED (≤ 5 years): (1) Yes, (0) No
138	BFFS2_months_5yr	Biochemical-Failure-Free Survival CORRECTED in MONTHS (corresponds with "BFFS2_5yr")
139	Nadir_PSA	Nadir PSA (ng/mL)
140	Nadir_Months	Time-to-Nadir in MONTHS
141	Post_BFFS2_CORR_months	Time (months) from Biochemical Failure CORRECTED (BFFS2_CORR) to Death / Last Follow-up [Outcomes Manuscript / Tara's Post BF Analysis]

Appendix III: R Code and Output

```
> # RPA Model 3.6: 5-Year Survival: All Factors (Survival Function):
>
> RPA36_5Yr_Both_Surv <- rpart (Surv (Post_BFFS2_CORR_Years, Dead_5Year) ~ Age + BasePSA
+ factor(Tstage_CORR_4catx) + factor(GleasonTotal_CORR_4cat) + factor(Hormones) +
factor(Radiation_Type_2cat) + factor(procars_5cat) + Nadir_PSA + Nadir_Months +
BFFS2_CORR_months + PSA_DT_PreBF_NadirLast_NoNeg + PSA_DT_PreBF_Last2_NoNeg, maxdepth=3,
na.action=na.omit, data=Training_N831)
>
> print(RPA36_5Yr_Both_Surv)
n=349 (482 observations deleted due to missingness)

node), split, n, deviance, yval
      * denotes terminal node

 1) root 349 440.16240 1.0000000
   2) BFFS2_CORR_months< 77.14168 310 343.63300 0.8376554
     4) PSA_DT_PreBF_Last2_NoNeg>=5.113436 236 226.07600 0.6230686
       8) factor(GleasonTotal_CORR_4cat)=1_2to5,2_6,3_7 205 171.47460 0.4888697 *
       9) factor(GleasonTotal_CORR_4cat)=4_8to10 31  40.70061 1.6572990 *
     5) PSA_DT_PreBF_Last2_NoNeg< 5.113436 74  99.59061 1.6197440
      10) Age< 65.5 24  25.67778 0.7836384 *
      11) Age>=65.5 50  67.06904 2.0989240 *
   3) BFFS2_CORR_months>=77.14168 39  72.95443 2.7292900
     6) PSA_DT_PreBF_NadirLast_NoNeg>=11.82306 32  53.39676 2.0802530
      12) factor(GleasonTotal_CORR_4cat)=1_2to5,2_6,4_8to10 24  26.84216 1.4566410 *
      13) factor(GleasonTotal_CORR_4cat)=3_7 8  19.29453 4.2208080 *
     7) PSA_DT_PreBF_NadirLast_NoNeg< 11.82306 7  10.72648 5.7438950 *
> summary(RPA36_5Yr_Both_Surv)
Call:
rpart(formula = Surv(Post_BFFS2_CORR_Years, Dead_5Year) ~ Age +
    BasePSA + factor(Tstage_CORR_4catx) + factor(GleasonTotal_CORR_4cat) +
    factor(Hormones) + factor(Radiation_Type_2cat) + factor(procars_5cat) +
    Nadir_PSA + Nadir_Months + BFFS2_CORR_months + PSA_DT_PreBF_NadirLast_NoNeg +
    PSA_DT_PreBF_Last2_NoNeg, data = Training_N831, na.action = na.omit,
    maxdepth = 3)
  n=349 (482 observations deleted due to missingness)

          CP nsplit rel error    xerror       xstd
1 0.05355981      0 1.0000000 1.0057660 0.04972013
2 0.04081761      1 0.9464402 1.0187924 0.05374824
3 0.03158086      2 0.9056226 1.0072310 0.05512709
4 0.02006348      3 0.8740417 0.9850322 0.05769114
5 0.01649406      4 0.8539782 0.9954432 0.06072058
6 0.01554835      5 0.8374842 1.0005402 0.06128865
7 0.01000000      6 0.8219358 1.0046644 0.06187529

Variable importance
             BFFS2_CORR_months   PSA_DT_PreBF_NadirLast_NoNeg
                            24                             19
      PSA_DT_PreBF_Last2_NoNeg factor(GleasonTotal_CORR_4cat)
                            18                             18
                     Nadir_PSA                            Age
                             7                              5
     factor(Tstage_CORR_4catx)                   Nadir_Months
```

```
                              4                              3
   factor(Radiation_Type_2cat)                       BasePSA
                              1                              1

Node number 1: 349 observations,    complexity param=0.05355981
  events=109,  estimated rate=1 , mean deviance=1.26121
  left son=2 (310 obs) right son=3 (39 obs)
  Primary splits:
      BFFS2_CORR_months              < 77.14168 to the left,  improve=23.70076, (0
missing)
      Nadir_PSA                      < 0.735    to the right, improve=16.24569, (0
missing)
      factor(GleasonTotal_CORR_4cat) splits as  LLLR,         improve=15.67358, (0
missing)
      PSA_DT_PreBF_Last2_NoNeg       < 5.113436 to the right, improve=14.05951, (0
missing)
      factor(Tstage_CORR_4catx)      splits as  LLRR,         improve=10.72834, (0
missing)
  Surrogate splits:
      Nadir_Months             < 29.30595 to the left,  agree=0.897, adj=0.077, (0 split)
      PSA_DT_PreBF_Last2_NoNeg < 85.52677 to the left,  agree=0.894, adj=0.051, (0 split)

Node number 2: 310 observations,    complexity param=0.04081761
  events=84,  estimated rate=0.8376554 , mean deviance=1.108493
  left son=4 (236 obs) right son=5 (74 obs)
  Primary splits:
      PSA_DT_PreBF_Last2_NoNeg       < 5.113436 to the right, improve=17.98006, (0
missing)
      PSA_DT_PreBF_NadirLast_NoNeg   < 6.814712 to the right, improve=15.69468, (0
missing)
      factor(GleasonTotal_CORR_4cat) splits as  LLLR,         improve=14.96850, (0
missing)
      Nadir_PSA                      < 0.975    to the right, improve=12.69945, (0
missing)
      factor(procars_5cat)           splits as  LRLRR,        improve=11.67494, (0
missing)
  Surrogate splits:
      PSA_DT_PreBF_NadirLast_NoNeg < 5.194712 to the right, agree=0.897, adj=0.568, (0
split)
      BFFS2_CORR_months            < 18.51335 to the right, agree=0.813, adj=0.216, (0
split)
      Nadir_PSA                    < 0.065    to the right, agree=0.790, adj=0.122, (0
split)
      factor(Radiation_Type_2cat)  splits as  LR,           agree=0.784, adj=0.095, (0
split)
      Nadir_Months                 < 2.036961 to the right, agree=0.777, adj=0.068, (0
split)

Node number 3: 39 observations,    complexity param=0.02006348
  events=25,  estimated rate=2.72929 , mean deviance=1.870626
  left son=6 (32 obs) right son=7 (7 obs)
  Primary splits:
      PSA_DT_PreBF_NadirLast_NoNeg   < 11.82306 to the right, improve=15.137290, (0
missing)
      factor(GleasonTotal_CORR_4cat) splits as  LLRR,         improve=12.785170, (0
missing)
```

```
      Nadir_PSA                      < 0.235    to the right, improve=11.396040, (0
missing)
      PSA_DT_PreBF_Last2_NoNeg       < 10.69603 to the right, improve=11.259570, (0
missing)
      BasePSA                        < 9.8      to the left,  improve= 9.624019, (0
missing)
  Surrogate splits:
      Nadir_PSA                  < 0.035    to the right, agree=0.897, adj=0.429, (0
split)
      factor(Tstage_CORR_4catx) splits as  RLLR,         agree=0.872, adj=0.286, (0
split)
      BFFS2_CORR_months          < 81.87269 to the right, agree=0.846, adj=0.143, (0
split)
      PSA_DT_PreBF_Last2_NoNeg   < 5.117525 to the right, agree=0.846, adj=0.143, (0
split)

Node number 4: 236 observations,    complexity param=0.03158086
  events=49,  estimated rate=0.6230686 , mean deviance=0.957949
  left son=8 (205 obs) right son=9 (31 obs)
  Primary splits:
      factor(GleasonTotal_CORR_4cat) splits as  LLLR,         improve=13.935100, (0
missing)
      Nadir_PSA                      < 1.305    to the right, improve=10.158680, (0
missing)
      factor(procars_5cat)           splits as  LRLRR,        improve= 8.836434, (0
missing)
      BFFS2_CORR_months              < 37.19097 to the left,  improve= 8.808492, (0
missing)
      factor(Tstage_CORR_4catx)      splits as  LLRR,         improve= 8.219032, (0
missing)
  Surrogate splits:
      factor(Tstage_CORR_4catx) splits as  LLLR,         agree=0.873, adj=0.032, (0
split)
      Nadir_PSA                  < 7.65     to the left,  agree=0.873, adj=0.032, (0
split)

Node number 5: 74 observations,    complexity param=0.01554835
  events=35,  estimated rate=1.619744 , mean deviance=1.345819
  left son=10 (24 obs) right son=11 (50 obs)
  Primary splits:
      Age                          < 65.5     to the left,  improve=6.883038, (0 missing)
      factor(Radiation_Type_2cat) splits as  RL,           improve=6.180697, (0 missing)
      BasePSA                      < 20.95    to the right, improve=4.838822, (0 missing)
      Nadir_Months                 < 1.445585 to the left,  improve=3.954354, (0 missing)
      factor(Tstage_CORR_4catx)    splits as  LRRR,         improve=3.922247, (0 missing)
  Surrogate splits:
      BasePSA                       < 4.05     to the left,  agree=0.730, adj=0.167, (0
split)
      Nadir_Months                  < 1.445585 to the left,  agree=0.689, adj=0.042, (0
split)
      PSA_DT_PreBF_NadirLast_NoNeg < 14.78638 to the right, agree=0.689, adj=0.042, (0
split)

Node number 6: 32 observations,    complexity param=0.01649406
  events=18,  estimated rate=2.080253 , mean deviance=1.668649
  left son=12 (24 obs) right son=13 (8 obs)
  Primary splits:
```

```
      factor(GleasonTotal_CORR_4cat) splits as  LLRL,         improve=9.400000, (0
missing)
      Age                            < 67       to the left,  improve=5.823388, (0
missing)
      BasePSA                        < 11.4     to the left,  improve=4.409422, (0
missing)
      BFFS2_CORR_months              < 96.9692  to the left,  improve=2.909912, (0
missing)
      factor(Hormones)               splits as  LR,           improve=2.608843, (0
missing)
  Surrogate splits:
      BFFS2_CORR_months        < 82.9076  to the right, agree=0.812, adj=0.250, (0 split)
      PSA_DT_PreBF_Last2_NoNeg < 7.477049 to the right, agree=0.812, adj=0.250, (0 split)
      Nadir_Months             < 5.190965 to the right, agree=0.781, adj=0.125, (0 split)

Node number 7: 7 observations
  events=7,  estimated rate=5.743895 , mean deviance=1.532354

Node number 8: 205 observations
  events=34,  estimated rate=0.4888697 , mean deviance=0.8364617

Node number 9: 31 observations
  events=15,  estimated rate=1.657299 , mean deviance=1.312923

Node number 10: 24 observations
  events=6,  estimated rate=0.7836384 , mean deviance=1.069907

Node number 11: 50 observations
  events=29,  estimated rate=2.098924 , mean deviance=1.341381

Node number 12: 24 observations
  events=11,  estimated rate=1.456641 , mean deviance=1.118423

Node number 13: 8 observations
  events=7,  estimated rate=4.220808 , mean deviance=2.411816
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Curriculum Vitae

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Post-secondary Education and Degrees:	University of Western Ontario London, Ontario, Canada 2013-2015 M.Sc. Queen's University Kingston, Ontario, Canada 2009-2013 B.Sc.H.
Honours and Awards:	Western Graduate Research Scholarship University of Western Ontario 2013-2015 Dean's Honour List Queen's University 2011-2013 Excellence Scholarship Queen's University 2009
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