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A COST-EFFECTIVENESS FRAMEWORK TO EVALUATE A PREDICTIVE COMPANION DIAGNOSTICS OF SELECTING MEN WITH HIGH RISK LOCALIZED PROSTATE CANCER FOR NEOADJUVANT OR ADJUVANT CHEMOTHERAPY IN THE U.S.

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ABSTRACT OF THE DISSERTATION

A COST-EFFECTIVENESS FRAMEWORK TO EVALUATE A PREDICTIVE COMPANION DIAGNOSTICS OF SELECTING MEN WITH HIGH RISK LOCALIZED PROSTATE CANCER FOR NEOADJUVANT OR ADJUVANT CHEMOTHERAPY IN THE U.S.

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Patients with high-risk localized prostate cancer (HRLPC) are difficult to manage. They are at high risk of recurrence, metastasis, or even early death. The standard of care (SOC) has been the same for many years. Chemotherapy is being actively tested in clinical trials for HRLPC patients. Since chemotherapy is associated with cytotoxicity, a treatment strategy with companion diagnostics (CDX) is needed to choose chemo respondents. The objective of this study is to build a cost-effectiveness framework to analyze the economic value of CDX to select HRLPC patients for chemotherapy.

An area under the curve cost-effectiveness model, which considers three treatment strategies, i.e., treating all patients with SOC, treating all patients with chemo, or selectively treating with chemotherapy with assistance of a CDX (personalized medicine), was constructed. Data inputs were drawn primarily from a database analysis based on the Surveillance Epidemiology and End Results (SEER)-Medicare Database in conjunction with secondary data based on literature reviews. Overall, 24,094 HRLPC patients receiving active treatments between 1990 and 2011 were identified. Metastasis-free survival, overall survival, and cost patterns were analyzed for the

entire cohort as well as subgroups. Cost-effectiveness measures including incremental cost-effectiveness ratios were calculated. Both one-way sensitivity analysis and probabilistic sensitivity analysis were conducted to understand the effect of data inputs on cost-effectiveness results.

If a generic chemotherapy provided meaningful clinical benefits and was administrated for only 6-month treatment, and if the companion diagnostics test was given for free, it was cost-effective to treat HRLPC patients using both strategies, including treating all with chemotherapy and personalized medicine versus SOC. The personalized treatment strategy was the most cost-effective choice. The result was highly sensitive to treatment duration, effectiveness, treatment costs, as well as assumptions of CDX (prevalence, sensitivity, and specificity). A diagnostic manufacturer could charge a reasonable price for the companion diagnostics test consistent with current pricing practice.

This study provides an analytical tool to understand the economic value of an effective treatment and its companion diagnostics. Various simulations indicated that personalized treatment strategy is always preferred. The model can be extended to analyze the value of CDX in broader cancer diseases settings.

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DEDICATION

This thesis is dedicated to my beloved wife Yanhong Huang and daughter Fiona He.

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LIST OF ABBREVIATIONS

3D-CRT	Three-dimensional conformal radiotherapy
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike information criterion
AICc	AIC with a correction for finite sample sizes
ALK	Anaplastic lymphoma kinase
AML	Acute myeloid leukemia
AS	Androgen suppression
ASCO	American Society of Clinical Oncology
AST	Androgen suppression therapy
AUA	America Urological Association
AUC	Area under the curve
b.i.d.	twice a day
BFS	Biochemical free survival
BIC	Bayesian information criterion
BMD	Bone marrow density
BT	Brachytherapy
CAB	Combined androgen blockade
CALGB	Cancer and Leukemia Group B
CAPRA	Cancer of the Prostate Risk Assessment
CDX	Companion diagnostics
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptance curve
CHAARTED	Chemo Hormone therapy versus Androgen Ablation Randomized Trial
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CPT	Current procedural terminology
CRC	Colorectal cancer
CRPC	Castrate-resistant prostate cancer
CRT	Conformal radiotherapy
CTC	Circulating tumor cell
DALY	Disability-Adjusted Life Year
DES	Diethylstilbestrol
df (Q)	Degree of freedom of Q
DNA	Deoxyribonucleic acid
EAU	European Association of Urology
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor

EMP	Estramustine phosphate
EVPI	Expected value of perfect information
FDA	U.S. Food and Drug Administration
FISH	Fluorescence in situ hybridization
FN	False negative
FP	False positive
G-CSF	Granulocyte colony-stimulating factor
GDP	Gross domestic product
GI	Gastrointestinal
GL	Gleason score
GU	Genitourinary
Gy	Gray
HCPCS	Healthcare common procedure coding
HER-2	Human epidermal growth factor receptor -2
HR	Hazard ratio
HRLPC	High risk localized prostate cancer
HRQOL	Health related quality of life
HTA	Health technology assessment
I^2	Statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemical
IMRT	Intensity-modulated radiation therapy
IQR	Interquartile range
IV	Intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
LHRHa	Luteinizing hormone-releasing hormone agonists
LY	Life year
mCRPC	Metastatic castration resistant prostate cancer
MeSH	Medical subject headings
MFS	Metastasis free survival
MTD	Maximum tolerated dose
NB	Net monetary benefit
NCCN	The National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National health service
NICE	National institute for health and clinical excellence
NMA	No measurable amount
NSAA	Non-steroid anti-androgen
NSCLC	Non-small cell lung cancer

OS	Overall survival
P	Prevalence
PCR	Polymerase chain reaction
PFS	Progression free survival
PIVOT	Prostate Cancer Intervention versus Observation Trial
PO	Oral administration
PORT	Prostate Patient Outcome Research Team
PPV	Positive predictive value
PSA	Prostate-specific antigen
PT	Proton beam therapy
QALY	Quality adjusted life year
RCT	Randomized clinical trial
RFS	Recurrence/relapse free survival
RGQ	Rotor-Gene Q software
RNA	Ribonucleic acid
RP	Radical prostatectomy
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
S	Sensitivity
SBRT	Stereotactic body radiation therapy
Sp	Specificity
SPCG	the Scandinavian Prostate Cancer Group
SD	Sexual dysfunction
SE	Standard error
SEER	Surveillance epidemiology and end results
SEK	Swedish Krona
SOC	Standard of care
SWOG	Southwest Oncology Group
TEC	Paclitaxel estramustine phosphate carboplatin
t.i.d.	Three time a day
TN	True negative
TNM	TNM classification of malignant tumors
TP	True positive
VBA	Visual basic for application
WTP	Willingness to pay
WW	Watchful waiting
τ^2	Between-studies variance

Chapter 1. Introduction

1.1 High risk localized prostate cancer (HRLPC)

Prostate cancer is a common malignancy in U.S. men. The National Cancer Institute (2015a) estimated that 233,000 men were diagnosed with and 29,480 men died of prostate cancer in 2014. One out of 6 men will be diagnosed with prostate cancer during their lifetime (National Cancer Institute [NCI], 2015a). Around 2.6 million men are currently living with prostate cancer (NCI, 2015b). The causes remain poorly understood. Established risk factors are age, race/ethnicity, and family history (Pienta & Esper, 1993). Other risk factors, such as prostatitis, sexually transmitted infection, vasectomy, obesity, and smoking have been evaluated but their roles remain inconclusive (American Cancer Society, 2015).

TNM Classification of Malignant Tumors (TNM) has been used to classify the severity of prostate cancer (NCCN [National Comprehensive Cancer Network], 2014). T1 tumors are too small to be seen or felt during examination (NCCN, 2014). T2 tumors can be felt but are still inside prostate gland (NCCN, 2014). In stage T3, tumors break through the capsule of the prostate gland. Most stage T3 tumors are operable (Ward et al. 2005). T4 tumors spread to nearby organs (NCCN, 2014). N indicates the amount of spread to neighboring lymph nodes (NCCN, 2014).N0 means no positive regional nodes whereas N1 means metastasis in regional nodes (NCCN, 2014). M stands for distant metastasis (NCCN, 2014). If a tumor does not spread to distant organs, patient is in M0. Otherwise, he is in M1 (NCCN, 2014). The definition of high-risk localized prostate cancer varies, but most definitions used TNM staging in combination with other clinical parameters, e.g., Gleason score and prostate-specific antigen (PSA). Gleason score is a histopathological grading system with score between 2 and 10 indicating the likelihood that

tumor spreads, e.g., Gleason score 8-10 means that tumor is poorly differentiated or undifferentiated (NCCN, 2014). Prostate-Specific Antigen (PSA) is protein produced by prostate cancer (NCI, 2015b).The National Institute for Health and Care Excellence (NICE, 2008b) categorized localized prostate cancer patients into three risk groups based on the above-stated three clinical values. It defined high risk localized prostate cancer (HRLPC) as PSA greater than 20 ng/ml, Gleason score greater than 7, or clinical stage of no less than T2c based on D'Amico et al. (1998) and in line with the guideline of the American Urological Association (AUA) (Thompson et al. 2007) as well as the guideline of the European Association of Urology (EAU) (Heidenreich et al. 2014). In the National Comprehensive Cancer Network (NCCN, 2014) guideline, HRLPC is divided into two categories: clinically localized (T3a or Gleason score greater than 7 or PSA >20ng/ml) or locally advanced (T3b to T4). Compared to D'Amico et al. (1998), this definition is more stringent because staging does not include T2c. The classification of the Cancer of the Prostate Risk Assessment (CAPRA) (Cooperberg et al. 2006) incorporated additional risk factors into risk assessment, e.g., age, percent positive biopsy cores along with PSA, staging, and Gleason scores. The total score ranged between 0 and 10. Those with total score greater than 5 were defined as high risk (Cooperberg et al. 2006). Other definitions exist, e.g., Radiation Therapy Oncology Group (RTOG) (Patel et al. 2005; Rosenthal et al. 2009) defined patients with the following criteria as high risk: PSA 20-100ng/ml and Gleason score greater than or equal to 7 or stage greater than or equal to T2, PSA less than 100ng/ml, and Gleason score between 8 and 10. In summary, most definitions converged to a high PSA value (e.g., 20 ng/ml and above), a high Gleason score (e.g., between 8 and 10), or advance stage (T2b and above). Different definitions of HRLPC are summarized in Table 1.1. No consensus has yet been reached on a standard definition of HRLPC.

The prevalence and incidence of HRLPC in the US are not well understood probably due to various definitions. Copperberg, Broering & Carroll (2010) estimated that high-risk disease accounted for 15% of all prostate cancer diagnoses based on the definition of D'Amico et al. (1998). If using the criteria of CAPRA (Cooperberg et al. 2006), the rate is 10.7%. Future studies on a fair estimation of prevalence and incidence of HRLPC are warranted.

The prospect of survival varies according to the ways in which the data were reported. Lu-Yao et al. (2009) reported the ten-year prostate cancer-specific mortality of 25.6% for men with poorly-differentiated tumors based on SEER-Medicare Linked Database who were diagnosed with stage T1/T2 prostate cancer after age 65 between 1992 and 2000 in the US. A few long term RCTs (Wilt et al. 2012; Bill-Axelson et al. 2014) showed that the median survival of similar groups of patients was about 12 years. Although HRLPC is a heterogeneous group with some people may be at risk of early death (Marciscano et al. 2012), averagely life expectancy of this group is relatively long (Wilt et al. 2012; Bill-Axelson et al. 2014).

1.2 Current treatment approaches for high risk localize prostate cancer

Patients in this group are difficult to manage. Some diseases are at high risk of progression or fatal while others can be managed well by treating primary tumor (Marciscano et al. 2012). Unlike castration resistant prostate cancer, HRLPC patients are hormone sensitive. NICE (2008b) suggested two options. First, androgen withdrawal via luteinizing hormone-releasing hormone agonists (LHRHa) or bilateral orchiectomy gets rid of the supply of endogenous hormone (NICE 2008b). Second, anti-androgen reduces the effect of the endogenous hormone (NICE 2008b). For systemic treatment, NICE (2008b) recommended administering neoadjuvant and concurrent LHRHa for 3 to 6 months in men receiving radiotherapy for local advanced prostate cancer. For radiotherapy, NICE (2008b) recommended pelvic radiotherapy for those with a greater than 15%

risk of pelvic lymph node involvement as well as for those receiving neoadjuvant hormone therapy and radiotherapy. The EAU guideline (Heidenreich et al. 2014) indicates that surgery, radiotherapy alone, and radiotherapy combined with adjuvant hormone therapy were effective for clinical stage T3a. For Gleason score between 8 and 10, it is suggested that patients with high-grade tumor still have a good prognosis after surgery (Heidenreich et al. 2014). For patients with PSA > 20 ng/ml, radical prostatectomy (RP) is the first step (Heidenreich et al. 2014). For very high risk patients with cT3b to T4, N0, or any T and N1 carcinoma, optimal treatment should include multimodal treatment (Heidenreich et al. 2014). EAU suggests of following strategies: radiotherapy for patients with T3 with greater than 5-10 years of life expectancy or symptomatic patients (T3-4, PSA>50 ng/mL, PSA doubling time less than 1 year) and combination therapy of adjuvant hormone therapy combined with external beam radiation (Heidenreich et al. 2014). NCCN (2012) guideline recommended multimodal treatment when single agent resulted in poor treatment response and high failure rates. Initial therapy could be chosen from the following: 1) radioactive therapy, including three-dimensional conformal radiotherapy (3D-CRT) / intensity-modulated radiation therapy (IMRT) with daily image guided radiotherapy with long-term neoadjuvant or concomitant or adjuvant androgen deprivation therapy (ADT) for 2 to 3 years; 2) radiotherapy (3D-CRT / IMRT) combined with brachytherapy (BT) with or without short-term neoadjuvant or concomitant or adjuvant ADT for 4 to 6 month; and 3) RP plus pelvic lymph node dissection. For locally advanced patients, initial therapy was similar as above, with the third option augmented with ADT in selected patients (NCCN, 2014). The AUA (Thompson et al. 2007) guideline prefers active treatment to watchful waiting, which includes RP or a combination treatment, such as radiotherapy with ADT. It is suggested (Thompson et al. 2007) that high risk localized prostate cancer patients should look into active treatment options, such as RP or ADT based on high quality randomized clinical trials (RCT).

In summary, most treatment guidelines suggest monotherapy, such as surgery, radiation, or adjuvant ADT, or multimodal treatment, including surgery followed by radiotherapy, and adjuvant hormone therapy. However, the clinical community (Marciscano et al. 2012) believes that unmet needs are still prevalent for some patients who are at high risk of death. The existing treatments are not sufficient for those patients. They may benefit from more forward-looking strategies that combine systematic treatment with local treatment.

1.3 New interventions emerges as potential solution for HRLPC

Recently, chemotherapy (FDA [U.S. Food and Drug Administration] 1996; Pean et al. 2012) has been established as the standard of care (SOC) for metastatic castration resistant prostate cancer (mCRPC). Mitoxantrone achieved palliative response (FDA, 2010) while docetaxel and cabazitaxel achieved prolonged patient survival in previous studies (FDA 1996; Pean et al. 2012). Docetaxel also showed an excellent biochemical response rate and objective radiographic response in mCRPC (FDA 1996). Clinical practice of chemotherapy focuses mainly on symptomatic patients with metastases or visceral metastasis.

The landmark Chemo Hormone therapy versus Androgen Ablation Randomized Trial (CHAARTED) reported that docetaxel added at the start of ADT prolonged overall survival (OS) of patients with metastatic hormone naïve prostate cancer at American Society of Clinical Oncology (ASCO) 2014 (Sweeney et al. 2014). Docetaxel plus ADT improved the median survival of ADT alone from 44 months to 57.6 months (Sweeney et al. 2014). The hazard ratio (HR) of OS for docetaxel plus ADT was 0.61 (95% confidence interval (CI): 0.47-0.80) versus ADT alone (Sweeney et al. 2014). Docetaxel is effective for patients with metastatic prostate cancer not only after ADT (FDA 1996), but also at the start of the hormone therapy (Sweeney et

al. 2014). The success of docetaxel in metastatic prostate cancer inspired researchers to keep exploring chemotherapy in earlier cancer stage.

Based on the mechanism of action, chemotherapy can be more active at the beginning of androgen resistance because the burden of androgen independent cells is still low (Marciscano et al. 2012). Micro metastatic disease can undergo cytotoxic treatment earlier (Marciscano et al. 2012).Chemotherapy such as docetaxel might have a synergistic effect with radiotherapy by radio-sensitizing tumor cells at primary sites while tackling micro metastatic diseases (Marciscano et al. 2012). In other hormone related cancers, e.g., breast cancer, the benefit of early, high-risk use of chemotherapy has been proven (Ravdin et al. 1995; Valeria et al 2001). It is possible that chemotherapy potentially may play an important role in preventing relapse and delaying disease progression for HRLPC patients. The downside of chemotherapy is adverse events (AE), particularly, cytotoxicity. Treatment associated AEs, such as neutropenia, febrile neutropenia, or thrombocytopenia (FDA 1996; Pean et al. 2012), compromise patient's health related quality of life (HRQOL), resulting in additional disease burden. Not every patient tolerates chemotherapy well and some may not respond or even develop early resistance.

Because HRLPC patients have relatively long life expectancy compared to metastatic prostate cancer (Lu-Yao et al. 2009; Bill-Axelson et al. 2014; Wilt et al. 2012), it is difficult to conduct clinical trials focused on overall survival because of long-term follow-up, cross-over, and other factors. Nevertheless, emerging clinical evidences suggest that chemotherapy might improve health outcomes in HRLPC patients. In a phase III study that compared ADT plus docetaxel and estramustine (ADT+DE) with ADT in high risk localized prostate cancer, Fazazi et al. (2014) reported a clinically meaningful but not statistically significant trend favoring ADT+DE versus ADT with HR=0.79 (95% CI: 0.55-1.13). Neoadjuvant chemotherapy combined with hormone

therapy and radiotherapy also showed potential benefits (Hirano et al. 2010). A few phase III trials sponsored by the government and academic research institutes are currently investigating the clinical benefit of chemotherapy for HRLPC with the hope that chemotherapy can eradicate the residual tumor cells after local therapy (Patel et al. 2005; Clinicaltrials.gov 2015b). Primary endpoints include OS, biochemical free survival (BFS), recurrence/relapse free survival (RFS), or progression free survival (PFS).

1.4 Personalized medicine for HRLPC patients

For low risk localized prostate cancer patients, watchful waiting / active surveillance might be sufficient. It may not work for some high risk patients because disease progresses rapidly. Chemotherapy might be a solution for some patients, but not for all. Companion diagnostics (CDX) is important to screen those who might benefit from such aggressive intervention. Currently CDX have become the norm for identifying the effective therapy in oncology. A predictive CDX can be defined as a test, which predicts the chance of response. Both NICE (2012a) and FDA (2014a) defined CDX as device/test developed to select patients who would benefit from particular treatments. In a broader sense, CDX may also include information beyond tests (Omics in personalised medicine, 2010), e.g., a nomogram including other patient specific information.

Biomarkers of prostate cancer can be categorized by biomaterials, i.e., blood or plasma, tissue, urine, or semen. Prostate tissue has the richest source of potential prostate cancer biomarkers. Tests based on tissue are usually expensive and invasive. For example, prostate needle biopsy is conducted to look for overexpression of Alpha-methylacyl-CoA racemase (AMACR) (Jiang et al. 2013), a gene that contributes to prostate cancer risk. Blood or plasma is less expensive and less invasive. Test of blood or plasma included circulating tumor cells (CTC), micro RNA (mina), and

PSA (Velonas et al. 2013). Blood or plasma have better concentration of molecules compared to urine or semen, but they are relative complicate. Tests based on urine or semen are non-invasive, providing large volume of biomaterials. However, urine or semen tests have low concentration of molecules with substantial variation among patients (Velonas et al. 2013).

Biomarkers can also be classified based on their association with treatment. Prognostic markers are independent of the treatment and are useful in assessing the risk of disease recurrence. Predictive markers, on the other hand, are usually based on a single trait or signature of traits that classifies patients on the basis of their response to certain interventions. Other types of biomarkers such as predisposition biomarkers, diagnostic biomarkers and monitoring biomarkers can also be distinguished (Jain, 2010). In this study, CDX is referred to as predictive biomarker because it is used to direct treatment decision.

PSA is one of the most intensively researched prostate cancer biomarkers. While it provides good information about the aggressiveness of the tumor or treatment response, it does not have a good predictability because of high false positive rate (Stenman et al. 2005). Prognostic value of PSA is also limited (Stenman et al. 2005). The refined PSA test was investigated including different molecular PSA forms and rate of PSA increases. For instance, Hanninen, Venner, and North (2009) found that rapid rate of PSA decline, measured as a shorter PSA half-life, might be an indicator of longer OS of patients with prostate cancer. CTC count is a biomarker recently approved by FDA (2013a) to monitor the performance of mCRPC patients. Found in the peripheral blood of patients with various metastatic carcinomas, CTC cells were estimated to account for one cell in a billion nucleated cells (FDA, 2013a). Pal et al. (2014) showed that CTC was detectable in HRLPC patients. Further studies are needed to understand the value of CTC in the treatment of HRLPC patients.

The development of prognostic and predictive biomarkers of prostate cancer is progressing fast. Gene fusions, mRNA, miRNAs, immunology, as well as cancer specific micro particles have been extensively examined to identify a responsive subgroup for drug treatment (Velonas et al. 2013). One example is Prostate Px®, a test developed to improve the accuracy of prostate cancer recurrence (Zubek et al. 2009). Based on biopsy sample, it uses predictive equation combining biopsy Gleason scores, PSA levels, and biopsy findings to find suitable patients for salvage treatment (Zubek et al. 2009).

Nomograms were developed to identify high-risk patients and to screen patients for certain treatment based on initial patient characteristics. Kattan, Eastham, Stapleton, Wheeler, and Scardino (1998) developed an externally validated nomogram to predict the five year probability of disease free survival after RP. The nomogram was based on clinical stage, primary and secondary Gleason score, PSA levels immediately before prostate biopsy and prostatic capsular invasion, surgical margin status, seminal vesicle invasion, and lymph node status. Kattan nomogram redefined the risk profile of many high-risk patients. As predictive biomarker based on tests might be expensive for screening the entire population, nomograms can be combined with biomarkers to target a patient group for screening and thus save costs.

Currently, the linkage between the above mentioned biomarkers / nomograms and response to chemotherapy has not yet been established for HRLPC. Both pharmaceutical and diagnostics manufacturers have incentives to investigate companion diagnostics for better clinical outcomes in treating prostate cancer, since FDA has approved a new school of medicines for mCRPC, i.e., cabazitaxel, sipuleucel-T, abiraterone acetate, enzalutamide and radium-223 chloride.

1.5 The need of economic evaluation for personalized medicine

With emerging evidences, chemotherapy might prove to be feasible as a neoadjuvant or adjuvant treatment of HRLPC. Considering the risk associated with chemotherapy, it is necessary to have a CDX to identify patients that would benefit most from the procedure. A few treatment strategies with both chemo agents and CDX can be implemented for HRLPC patients. Although exceptions apply, the CDX and the drug treatment should be assessed simultaneously (FDA, 2013b) from the perspective of regulatory as well as health technology evaluation. Payers want to know whether the value of such treatment strategy is worth the money. They assess not only clinical benefits of drugs and companion diagnostics test, but also the economic aspects, e.g., budget effect and cost-effectiveness. Both pharmaceutical and diagnostics manufacturers need to understand the financial viability of developing each technology from a global perspective. Drug developers want the most accurate test available to the greatest number of physicians at the lowest cost in the shortest turnaround time. Their interests are to maximize the value of drugs. In contrast, diagnostic tests developers want the best drugs so that they can maximize the values of their tests along with the commercial value of their products. The following framework addresses some questions stakeholders might have.

- Is it cost-effective to treat all HRLPC patients with neoadjuvant or adjuvant chemotherapy if the treatment is clinically effective?
- Does the result change if selecting patients chosen by companion diagnostics and treating them with chemotherapy?
- What are the key drivers of the conclusions?

To do this, an effectiveness and safety profile has to be demarcated for the chemotherapy and its CDX test for HRLPC patients. Major tasks include assessing the clinical benefit and risk of chemotherapy for neoadjuvant or adjuvant HRLPC to infer longitudinal direct medical costs and

to compute patient's utility values based on the literature reviews. Chapter 2 reviews information on neoadjuvant and adjuvant chemo trials in the high risk localized prostate cancer, RCTs of the metastatic prostate cancer, and related cost and utility studies as well as information on companion diagnostics in the late stage cancer diseases. Synthesized evidences will be leveraged for model development. Chapter 3 analyzes the survival outcomes based on a cohort identified from the SEER-Medicare Linked Database. Chapter 4 describes how to estimate costs using the same data source. Chapter 5 addresses a few technical issues with cost-effectiveness modeling for CDX. Chapter 6 shows whether treating all patients with chemotherapy or selecting patients for chemotherapy by a CDX is a cost-effective choice compared to standard of care under certain clinical and economic assumptions. The economic value of a companion diagnostics device is discussed at the end of the chapter.

With a modeling framework, this study examines whether it makes economic sense to treat a high-risk patient with chemotherapy and whether a CDX provides best value for the money. Evaluation during the development phase can direct decision-making of manufacturers regarding the development and commercialization. During the launch phase, it guides payers and patients to make rational choice.

Table 1.1 Summary of definition of high risk localized prostate cancer (HRLPC)

Institute	**Definition** [a]
NCCN (2014)	High risk localized: PSA>20 ng/ml or GL 8–10 or stage T3a; Local advanced: Stage T3b to T4
D'Amico et al. (1998) EAU (Heidenreich et al. 2014) NICE (2008b) AUA (Thompson et al. 2007)	PSA>20 ng/ml or GL 8–10 or Stage ≥T2c
CAPRA (Cooperberg et al. 2006)	Total score ≥6, where score comprises of age, PSA, staging, GL, percent positive biopsy core etc. Total score range 0-10
RTOG (Patel et al. 2005, Rosenthal et al. 2009)	Any T stage, PSA 20-100 ng/ml, GL≥7 or stage≥T2, PSA<100ng/mL, GL 8-10

Abbreviation: NCCN=The National Comprehensive Cancer Network, NICE=National Institute for Health and Clinical Excellence; AUA=American Urological Association; EAU=European Association of Urology; CAPRA=Cancer of the Prostate Risk Assessment; RTOG=Radiation Therapy Oncology Group; PSA=prostate-specific antigen; GL=Gleason score

[a] Definitions converged to a high PSA value (e.g., ≥20 ng/ml), a high Gleason score (8-10) or advanced stage (≥T2b).

Chapter 2. Systematic reviews of clinical effectiveness of HRLPC and cost-effectiveness

An economic model needs clinical inputs of treatment effectiveness, safety, tolerability, patient HRQOL data, and medical resource utilization patterns. Without simulating a clinical trial, the best approach is to gather information from the literature along with medical history records, e.g., cancer registry, commercial databases, or patient medical records that include both electronic records and patient charts. A set of literature reviews was conducted to inform health economics modeling. The first objective was to extract clinical data on efficacy, safety, and tolerability of HRLPC and metastatic prostate cancer to guide assumptions on the clinical profile of chemotherapy. The second objective was to summarize modeling methodology in localized prostate cancer to identify useful data for model inputs. The third objective was to find evidences of companion diagnostics in oncology to make justifiable assumptions to profile the companion diagnostics device for chemotherapy in HRLPC.

2.1 Systematic Review of clinical effectiveness in HRLPC

A systematic literature review of clinical studies on chemotherapy for HRLPC was conducted. Overall, 162 articles were retrieved with the following Medical Subject Headings (MESH) terms: *(high risk AND prostate cancer) AND (mitoxantrone or doxorubicin, cinblastine or paclitaxel or docetaxel or estramustine or etoposide or carboplatin or vinorelbine or cabazitaxel)* from PubMed database. Figure 2.1 indicates that 114 papers were excluded because they were clinical reviews or were focused on wrong diseases (e.g., mCRPC). Because “localized” was not a keyword, other high-risk prostate cancers, including metastasis, were retrieved. Thus, 48 studies were included in this review. In addition, three ASCO abstracts and one press release were added to reflect the status of ongoing trials.

Table 2.1 summarizes the key features of each neoadjuvant and adjuvant study. Besides patient sample sizes and inclusion criteria, country, chemotherapy treatment regimen, and clinical outcomes were also included. Inclusion criteria were mostly based on TNM clinical stage, Gleason score, PSA, or sometimes life expectancy. Neoadjuvant treatments were either phase I or II, small and single arm studies focusing on safety and tolerability. Phase III studies were rare. Most common outcome measures were BFS or PFS. In contrast, phase III trials in adjuvant chemotherapies were more common. Many large studies are still ongoing as of February 28, 2015.

2.1.1Findings in neoadjuvant chemotherapy

For neoadjuvant chemotherapy, docetaxel was one of the most frequently tested agents. Nine single docetaxel studies were identified (Chen et al. 2012; Chi et al. 2008; Drecier et al. 2004; Febbo et al. 2005; Magi-Galluzzi et al. 2007; Mathew et al. 2009; Oh et al. 2001; Ross et al. 2012; Vuky et al. 2009). Not every study reported efficacy outcome. Some studies reported changes in RFS (Chi et al. 2008), PSA level reduction (Dreicer et al. 2004; Oh et al. 2001; Ross et al. 2012) or reduction in tumor (Febbo et al.2005). However, all studies mentioned above showed safety and tolerability. The treatment duration was usually no more than 6 months. Because efficacy was not evident, Magi-Galluzzi et al. (2007) concluded that single chemotherapy was not enough to manage HRLPC. Multimodal treatment approach targeting multiple molecular targets is necessary to eradicate the malignant cells in HRLPC (Magi-Galluzzi et al. 2007).

Other single chemo agents were also considered in neoadjuvant HRLPC. Hirano et al. (2010) assessed the safety and efficacy of a treatment regimen of neoadjuvant conventional ADT plus estramustine phosphate (EMP) combined with 3D-CRT or neoadjuvant LHRHa alone for patients

with intermediate- to high-risk prostate cancer in Japan. Although it was a small sample (N=39) phase II study, statistically significant biochemical recurrence free survival for EMP versus LHRHa arm was observed. The treatment duration of neoadjuvant LHRHa plus EMP was 6 months (Hirano et al. 2010). Koie et al. (2012) tested the safety and efficacy of neoadjuvant low-dose EMP and LHRHa in 142 HRLPC patients. The treatment duration of EMP was 6 months. About 4.9% patients achieved no residual prostate cancer (pT0) and 87% patients had negative surgical margins (Koie et al. 2012). With a median 34.9 months of follow-up, 84.3% patients achieved PSA progression-free survival (Koie et al. 2012). No safety issues were found. Besides EMP, paclitaxel (Shepard et al. 2009; Hussain et al. 2012) was also tested in this population. Treatment durations were no more than 8 weeks. Grade 3/4 cytotoxic adverse events were reported in one study (Shepard et al. 2009).

Concomitant chemotherapy regimen was also popular in neoadjuvant chemotherapy. EMP was combined with other microtubule inhibitor, including vinorelbine, vinblastine, paclitaxel, or docetaxel for HRLPC. Several studies (Beer et al. 2004; Carles et al. 2010; Clark et al. 2001; Friedman et al. 2008; Garzotto et al. 2010; Khil et al. 1997; O'Brien et al. 2010; Ryan et al. 2004; Zelefsky et al. 2000) investigated the above-mentioned combination with treatment durations of less than 6 months. Those regimens were well tolerated but the efficacy was not proven. Since EMP and docetaxel showed good response in mCRPC (Hussain et al. 2003), EMP and docetaxel combination was also studied in some studies (Kim et al. 2011; Ko et al. 2002; Narita et al. 2012; Prayer-Galetti et al. 2007; Sella et al. 2008). In those studies, EMP and docetaxel combination was shown to be safe without proven efficacy. The treatment cycles were also short (less than or equal to 6 months). Cancer and Leukemia Group B (CALGB) 90203 (Eastham et al. 2003) was so far the largest phase III trial, with 700 patients, to investigate the clinical benefit of neoadjuvant EMP (280 mg t.i.d. days 1-5) plus docetaxel (70 mg/m^2 on day 2 per 3 weeks cycle)

for HRLPC patients defined as T1 to T3a, N_X and M0. Patients were randomized to either 6 cycles of chemotherapy or surgical intervention (Eastham et al. 2003). Clinical endpoints included DFS, OS, and safety measures. No results were reported as of February 28, 2015. Triple and quadruple chemo regimens were also explored since each chemo agent demonstrated unique properties, including anti-gonadotropic effects and anti-tumor effect. Konety et al. (2004) investigated paclitaxel, carboplatin, and EMP. Cancer and Leukemia group B 99811 study treated patients with paclitaxel, EMP, and carboplatin for 16 weeks (Kelly et al. 2008). Twenty-seven of 34 patients completed the study, only one patient was found with grade 3 AE (Kelly et al. 2008). The triple neoadjuvant chemo regimen was feasible and tolerable. Pettaway et al. (2000) studied KAVE (ketoconazole, doxorubicin, vinblastine, and EMP). Their findings are similar to those reported in Kelly et al. (2008).

In summary, neoadjuvant chemotherapy for HRLPC was safe with short treatment durations. Because most studies were single arm trials, reduction in PSA level and percentage of progression free survival were reported for clinical improvement. Clinical efficacy was not strong largely because of small sample size, short follow up, and single arm design. Future large head-to-head studies, like CALGB 90203 (Eastham et al. 2003), are needed. A surrogate endpoint, such as biochemical recurrence survival and progression free survival instead of overall survival, is more feasible.

2.1.2 Findings in adjuvant chemotherapy

The rationale of adjuvant chemotherapy was to eradicate the remaining small tumor cell with local therapy, i.e., hormone therapy, radiation, or surgery. More phase III studies were identified for adjuvant chemotherapy. Besides PFS and BFS, overall survival and prostate related mortality were also included as endpoints because phase III design is capable of demonstrating at least a

trend in change. Like in neoadjuvant setting, docetaxel was the most commonly tested agent in adjuvant setting. Kibel et al. (2007) followed 77 patients who were treated with 6 cycles of docetaxel given 4 to 12 weeks after RP. The actual median PFS was longer than the predicted value based on the Kattan nomogram (Kattan et al. 1997). No tolerability concern was reported. It is worthy to note that Kattan nomogram was used as a historical control in this study. Other small studies (Bolla et al. 2010; Dibase et al. 2011; Perrotti et al. 2008) demonstrated that adjuvant docetaxel was feasible and safe. A few phase III studies are still ongoing. Veterans Affairs Cooperative Studies Program study 553 (Montgomery et al. 2008) randomized 636 men with high risk (T3-T4, GL>=7 and pre-operation PSA>20 or 50% 5-year progression) into either SOC or docetaxel on day 1 of a cycle, with each cycle lasting 3 weeks and combined with prednisone. SOC arm included surveillance with addition of ADT at the time of biochemical relapse. The primary endpoint is PFS and targeted completion year is 2016. No results have been reported yet. The Scandinavian Prostate Cancer Group trial 13 (Kellokumpu-Lehtinen et al. 2012) randomized HRLPC patients to receive either 6 cycles of docetaxel or no docetaxel after RT. Starting in 2006, this trial is ongoing, with final analysis planned in 2017.

Other single chemo agents were also considered. The national prostate project was the first trial to demonstrate the clinical benefit and safety of adjuvant EMP (Schmidt et al. 1996). Patients were assigned to three arms, i.e., EMP, cyclophosphamide, and observation, for 2 years. At 10-year follow up, EMP arm showed improved PFS for patients receiving definitive irradiation. Such benefit was particularly evident for patients with extensive nodal involvement (Schmidt et al. 1996). Wang et al. (2000) reported an adjuvant mitoxantrone in local advanced prostate cancer and metastatic patients. The intervention arm included 4 courses of mitoxantrone at 3 weekly intervals plus flutamide 250 mg versus flutamide 250 mg only (Wang et al. 2000). The beneficial trend of overall response rates (55% vs 39%, p=0.3) and PSA responses (82% vs 64%, p=0.11)

were reported (Wang et al. 2000). In non-metastasis group, median OS (80 vs 36 month, p=0.04) was statistically significant (Wang et al. 2000). However, consistent with other mitoxantrone studies (Berry et al. 2002; Kantoff et al. 1999; Tannock et al. 1996), in mCRPC, mitoxantrone did not show any survival benefit in metastatic patients. The Southwest Oncology Group (SWOG) S9921 study was a large Phase III study comparing Combined Androgen Blockade (CAB) to CAB plus 6 cycles of mitoxantrone (12 mg/m^2) (Dorff et al. 2011). Primary endpoint was OS. It was closed prematurely in 2007 due to three cases of acute myeloid leukemia (AML). In a single arm study, Cetnar et al. (2008) looked at adjuvant paclitaxel and EMP in HRLPC. The treatment included 4 cycles of paclitaxel 90mg/m^2 weekly. Overall, 17 patients completed the treatment Cetnar et al. (2008). There was no treatment related death. Grade 3 or 4 AEs were uncommon. Ploussard et al. (2010) randomized 47 men with adjuvant ADT with or without paclitaxel after RP. Preliminary PSA outcome was encouraging. This adjuvant study did not show HRQOL degradation, as measured by EORTC QLQ-C30 questionnaires (Ploussard et al. 2010).

Combination chemotherapies were also explored. Bagley et al. (2002) examined 25 HRLPC patients treated with vinblastine, doxorubicin, and mitomycin for 6 cycles concomitantly with radiation and ADT. Ten years of follow up indicated that chemotherapy was well tolerated Bagley et al. (2002). No efficacy result is available. The GETUG-12 trial (Fizazi et al. 2014) was a Phase III RCT comparing two treatments. Treatment arm included goserelin of 10.8 mg given once per 3 months for 3 years, 4 cycles of docetaxel 70 mg/m^2 given once per 3 weeks, and EMP of 10 mg/kg/day given on days 1-5 (ADT+DE) whereas comparator arm included 10.8 mg (ADT) of goserelin given once per 3 months for 3 years. With a median follow-up of 7.6 years, the HR of PFS for ADT+DE arm versus ADT arm was 0.75 (p=0.06) (Fizazi et al. 2014). In patients whose Gleason scores were less than 8, HR of PFS was 0.55 (95%CI 0.36-0.84) (Fizazi et al. 2014). No long-term toxicity is reported. The South Sweden Prostate Cancer Study Group

(Lundgren et al. 1995) randomized 285 men to either 80 mg polyuestradiol 3 times daily or 280 mg EMP two times daily. The comparison was immediate estrogen or EMP versus deferred endocrine treatment in non-metastatic prostate cancer. Treatment duration was not disclosed (Lundgren et al.1995). After 15 years of follow up, the early EMP was significantly better compared to the deferred treatment in prostate related mortality, though no difference emerged in overall survival (Lundgren et al.1995). RTOG 9902 was a phase III trial with 397 HRLPC patients comparing adjuvant chemotherapy with paclitaxel, EMP, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy to long-term androgen suppression plus radiotherapy (Rosenthal et al.2009; Sandler et al. 2010). This trial failed to reach its accrual goal because of toxicity. A summary report showed no difference for OS and BFS between two treatment arms at 5-year follow-up (Rosenthal et al.2009). Many factors could contribute to the failure. Sample size reduction due to premature termination of the study was thought to be the key. TAX 3501 (Eisenberger et al.2012) followed a 2 (immediate versus deferred ADT) by 2 (6 cycles of 75mg/m^2 docetaxel given one per 3 weeks versus no chemo) factorial design following RP. Although the study aimed to recruit 2,000 patients, it was terminated after 228 patients enrolled. No further information was available. RTOG 0521 study (Patel et al. 2005) was a Phase III study comparing androgen suppression (8 weeks LHRHa plus oral anti-androgen followed by RT) with androgen suppression plus docetaxel (6-cycle docetaxel on the 1st day for 12 days of each cycle). Primary endpoint was OS. Secondary endpoint included DFS (Patel et al. 2005). The target completion year is 2016. While the result of RTOG 0521 is yet to be reported, a single arm study (N=74), RTOG 0621(Hurwitz et al. 2014) was reported by the same institute. The docetaxel regimen included 6 cycles of 75 mg/m^2 docetaxel administered once every 3 weeks. The results of a 3-year follow-up of this study (NRG oncology, 2014 Sep 12) presented at the American Society for Radiation Oncology 56th Annual Meeting in 2014 showed

that the addition of systemic androgen suppression therapy (AST) and docetaxel improved the patients' freedom from disease progression by more than 20% compared to historical control.

In summary, current neoadjuvant and adjuvant chemotherapy in HRLPC suggested potential improvement, as measured by surrogate endpoints, such as progression free survival (Fizazi et al. 2014), disease free survival (Dibiase et al. 2011), or prostate cancer related mortality (Bagley et al.2002; Lundgren et al. 1995). A few trials studied OS (Prayer-Galetti et al. 2007; Schmidt et al. 1996; Wang et al.2000; Lundgren et al.1995). Generally, chemotherapy was well tolerated. One mitoxantrone trial ended earlier because of three cases of AML (Dorff et al. 2011).Treatment durations were mostly short, e.g., generally less or equal to 6 months. In one study (Schmidt et al. 1996) treating patients with EMP was up to 2 years. Because of relatively long life expectancy, it is difficult to demonstrate overall survival for this patient group. Although no large adjuvant or neoadjuvant chemotherapy trial has resulted in statistically significant OS, the results reflected by surrogates of adjuvant chemotherapy studies look promising.

2.2 Strategic review of Phase III chemotherapy in metastatic prostate cancer

In contrast to HRLPC, the clinical effectiveness of chemo agents in metastatic prostate cancer was proven through large phase III trials. A literature search was conducted to identify studies that included mitoxantrone, docetaxel, and cabazitaxel for metastatic prostate cancer. Studies comparing those drugs with agents not FDA approved were not in scope of the review.

Only docetaxel and cabazitaxel achieved both clinically meaningful and statistically significant overall survival benefit for mCRPC. Tannock et al. (2004) showed that the HR of docetaxel administered once every 3 weeks was 0.76 compared to mitoxantrone. Fossa et al. (2007) reported the overall survival HR of 0.54 of patients treated with docetaxel weekly compared to

placebo with the background treatment of prednisone. De Bono et al. (2010) demonstrated the OS benefit of cabazitaxel versus mitoxantrone with HR of OS of 0.70. Besides mCRPC, Sweeney et al. (2014) reported the results of CHAARTED study. Median overall survival of 75mg/m^2 of docetaxel given together with ADT every 3 weeks for maximum 6 cycles versus ADT only was 57.6 months versus 44.0 months, respectively, reflecting a net gain of 13.6 month (Sweeney et al. 2014).The treatment duration was only up to 6 cycles, with each cycle lasting 3 weeks (Sweeney et al. 2014). CHAARTED study also demonstrated that docetaxel was well tolerated in the ADT naïve metastatic prostate cancer patients. In contrast, mitoxantrone (Berry et al. 2002; Kantoff et al.1999; Tannock et al.1996) did not show statistically significant OS improvement compared to corticosteroids.

A summary of completed chemotherapy, including mitoxantrone, docetaxel, and cabazitaxel, in metastatic prostate cancer is shown in Table 2.2. Since mitoxantrone did not achieve statistical significance, and it was treated as palliative treatment, only docetaxel and cabazitaxel studies were selected for a meta-analysis for a pooled efficacy. The meta-analysis was conducted using the Comprehensive Meta-analysis tool (Biostat, USA) available at: http://www.meta-analysis.com /index.php. With both fixed and random models, the treatment effect was 0.711 (Figure 2.2) for chemo treated mCRPC. A low I^2 indicated that the heterogeneity of the studies was mild. Excluding cabazitaxel, the treatment effects of random model and fixed model were 0.7 and 0.725, respectively. Including the Sweeney et al. 2014 study into the meta-analysis, the treatment effect was 0.691(Figure 2.3).

2.3 Systematic review of cost-effectiveness analysis of localized prostate cancer

A literature search was conducted to identify studies that conducted cost-effectiveness analysis of localized prostate cancer in the Cochrane library, MEDLINE / PubMed and the Tufts CEA

Registry (Tufts Medical Center 2007-2013). The Mesh term was "*cost-effectiveness and localized prostate cancer".* The term "prostate cancer" was searched in the Tufts CEA registry. By excluding clinical reviews, economic reviews, clinical studies, cost studies, and cost-effectiveness studies conducted for other diseases, 26 studies evaluated cost-effectiveness for localized prostate cancer were found.

The Prostate Patient Outcome Research Team (PORT) modeled the effect of initial therapy for localized prostate cancer. Fleming et al. (1993) compared three different intervention strategies, RP, EBRT, and watchful waiting (WW) by constructing a Markov model with 3 progressive disease stages (1. no evidence of metastatic disease; 2. hormonally controlled metastatic disease; 3. refractory metastatic disease) and 2 absorption states (1. death from prostate cancer and 2. non-prostate cancer related death). They concluded that WW was always a reasonable choice whereas RP and EBRT might be beneficial for selected patients (Fleming et al. 1993). Beck et al. (1994) analyzed the PORT model. With updated transition probabilities, RP was cost-effective, indicating that the PORT model was sensitive to underlying transition probabilities (Beck et al. 1994). The changing transition probability reflected technology advancement. Kattan et al. (1997) estimated the benefit for RP versus WW using the same model. In a subgroup analysis, healthier patients (younger than 70 years old with low to moderate comorbidities) benefitted from RP whereas men older than 70 years and with high co-morbidities benefitted more from WW (Kattan et al. 1997). Based on the same model, Hummel et al. (2003) conducted a comprehensive systematic review of cost-effectiveness of new and emerging early prostate cancer treatment. They compared 3D-CRT to traditional radiotherapy and BT to radiotherapy and adapted the PORT model to the UK setting. 3D-CRT was cost-effective compared with traditional radiotherapy (Hummel et al. 2003). BT might be cost-effective but have high uncertainty. Lyth et al. (2012) adapted the PORT model to the Swedish setting and modified the model structure.

The states of hormonally controlled metastasis and refractory metastasis were replaced by symptomatic and refractory disease, respectively. Conclusions depended on age, Gleason score, and PSA values. RP was cost-effective when patients' age was less than 70 or equal to 75, Gleason was 7-9 (regardless of PSA), or Gleason was 5-6 (with PSA >20) (Lyth et al. 2012). For 75 years old patients with low Gleason and PSA score, RP was not cost-effective (Lyth et al. 2012).

Although the PORT model is probably the most cited model for localized prostate cancer, other cost-effectiveness models were also developed. For example, Bayoumi et al. (2000) constructed a model evaluating 6 androgen suppression strategies: diethylstilbestrol (DES), orchiectomy, a non-steroid anti-androgen (NSAA), an LHRHa, and combinations of an NSAA with and an LHRHa or orchiectomy. Orchiectomy was likely to be the most cost-effective option (Bayoumi et al. 2000) Parthan et al. (2012) developed a decision tree model to analyze the economic value of stereotactic body radiation therapy (SBRT) versus IMRT and proton radiation therapy (PT) for localized prostate cancer. Nine transition states included death, no toxicity, gastrointestinal (GI) only, genitourinary (GU) only, sexual dysfunction (SD) only, GI and GU, GI and SD, GU and SD, GI and GU and SD (Parthan et al. 2012). Simulated patient was a 65 year old man with localized prostate cancer eligible for external radiation therapies but not eligible for surgery. This study focused on treatment related AEs assuming equal efficacy. They reported that SBRT was a more cost-effective strategy compared to IMRT and PT (Parthan et al. 2012). Study of Cooperberg et al. (2013) was claimed to be the most comprehensive cost-effectiveness analysis for localized prostate cancer because it considered treatment sequence. The following treatment options were analyzed: open RP, laparoscopic-assisted RP, robot-assisted RP, 3D-CRT, IMRT, BT and BT + EBRT. Surgery was more cost effective compared to RT and was associated with higher QALY (Cooperberg et al. 2013).

Two studies analyzed the cost-effectiveness of biomarkers in selecting localized prostate cancer patients for active treatment. Calvert et al. (2003) leveraged with a Markov model to analyze three treatment strategies for 60 year old patients with Gleason score 5~7, namely, 1) watchful waiting or monitoring; 2) treating everyone with radical prostatectomy; 3) select subgroup for radical prostatectomy by using a DNA ploidy as prognostic marker. The Markov disease states included metastasis free, metastasis, prostate cancer related death, and death from other causes, considering the UK National Health Service (NHS) perspective (Calvert et al. 2003). Transition probabilities were obtained from literatures. They assumed 22% of patients were in need of the radical prostatectomy (Calvert et al. 2003). Zubek et al. (2009) analyzed three treatment strategies for prostatectomy patients who were at risk of bio-chemical recurrence by using a decision tree model. They compared the Kattan postoperative nomogram (Kattan et al. 1997) and the Prostate Px® test, which included additional morphometric and immunofluorescence features for risk prediction, selecting patients for secondary (adjuvant/salvage) treatment versus SOC (Zubek et al. 2009). Similar to the PORT model (Fleming et al.1993), five disease states ('Local Recurrence', 'Metastatic Disease', 'Metastatic Disease Hormone Refractory', and 'Dead') were included. They concluded that the Prostate Px® test was a more cost-effective strategy compared to SOC (Fleming et al.1993).

Table 2.3 summarized all 26 studies on the localized prostate cancer. In conclusion, studies used either Markov transition probability model or decision tree model. In most cases, the model involved a few disease progression stages and one to two absorption stages (death). All studies focused on established clinical inventions, as chemotherapy was not yet the scope of localized prostate cancer. Two studied considered CDX strategy. One study (Calvert et al. 2003) focused on selecting patients for radical prostatectomy and the other study (Zubek et al. 2009) selected patients for adjuvant radiation treatment. Both studies considered sensitivity and specificity of the

tests. One used Markov transition probability model (Calvert et al. 2003) and the other used decision tree model (Zubek et al. 2009).

Many studies reported treatment costs, event costs (e.g., surgery), state costs (biochemical recurrence), and utility values at different stage. Table 2.4 lists the key costs data reported. All costs were standardized according to the 2013 consumer price index of medical care. Information presented in Table 2.4 reviews the benchmark studies conducted based on the SEER-Medicare Linked Database described in Chapter 4. Those studies came utilized various estimations for cost. For instance, Copperberg et al.'s (2003) end of life estimate was $16,000 more than that of Bayoumi et al. (2000). Due to different data sources and study methods, the results varied. Roehrborn et al. (2009) reported total costs for stage 3 and stage 4 prostate cancer patients as $22,030 and 25,521, respectively. Based on SEER-Medicare, they assessed only the first-year data without adjusting for inflation. In addition, the 30 days costs of Cabazitaxel was also included based on Q1group (2015) in this study.

Utility values were typically calculated on a scale from 0 to 1, with a deceased state assigned a value of 0 and 1 representing a state of perfect health. One key assumption was that an additional QALY had the same value regardless to patient profile. Utility was additive, i.e., if patients received active treatment and that treatment was associated with utility change (either decrement or increment), their utility values would change correspondingly. If the disease status changed, the corresponding utility would change too. For example, utility is set to 0 if the patient dies. Chen et al. (2008) found that patients with localized prostate cancer after localized treatment reported high health states. The mean utility of patients was 0.80. Patients with good sexual function rated their health utility as high as 0.85. Patients with poor urinary incontinence were associated with a health utility of 0.67. Hayes et al. (2010) set the heath utility of biochemical

recurrence at 0.68 based on Stewart et al. (2005) and other unpublished Stewart studies. Fryback et al. (2003) reported utility of 0.84 for no recurrence localized prostate cancer. Cooperberg et al. (2013) came up with higher baseline utility based on an expert panel. For patients with remission, the utility was 0.94. It became 0.84 when biochemical recurrence was treated with hormone and 0.78 when treated without hormone. Other studies also looked at localized prostate cancer. Table 2.5 summarized the utility studies for localized and metastatic prostate cancer.

2.4 Review of companion diagnostics approved by FDA for oncology medicines

Table 2.6 summarized FDA approved/cleared companion devices for oncology drugs as of February 28, 2015. Costs of CDx and its associated drug, as well as sensitivity, specificity, rate of expression were included if information is available. Five types of cancer were included, i.e., breast cancer, colorectal cancer, non-small lung cancer (NSCLC), gastrointestinal stromal tumors (GISTs) and melanoma. A companion diagnostics device for prostate cancer is not available. Those CDXs predict tumor response to tyrosine-kinase inhibitors. So far we don't have a CDX for either immune-oncology drugs or chemotherapy. Targeted gene expression varied from 25% (Mark et al. 1999) to 95% (Abbott Molecular Inc. 2011). Available reported sensitivity and specificity range as 85% (Choti & Johnston) to 100% (Cappellini, Cohen, & Eleftherio 2008) and 92% (Cappellini, Cohen, & Eleftherio 2008) to 100% (Abbott Molecular Inc. 2011) respectively. For instance, the cost of Therascreen KRAS RGQ PCR Kit is $196.99 (CMS, 2014b). It detected 97% KRAS mutations (Qiagen, 2012). KRAS mutation expressed 40% in CRC patients (Qiagen, 2012). The monthly cost of cetuximab was $10,000 (Rapaport, 2009 Jun 29). The costs of CDX were generally a fraction of drug monthly costs if the drug was still under pattern protection. Within CDX, Fluorescence in situ hybridization (FISH) test is generally more expensive, more time consuming and more accurate than immunohistochemistry (IHC) (Pollack, 2006Sep 28).

Table 2.1) Summary of neoadjuvant and adjuvant chemotherapy in men with high risk localized prostate cancer (HRLPC)

Author	Patients	Chemotherapy Regimen [a]	Clinical Outcome [b]	Country	Inclusion Criteria [c]
Oh et al. (2001)	15	Docetaxel weekly for 4 weeks	67% achieved PSA > 50% decline	US	Age range 43-63, median 54, cT3, PSA > 20 ng/ml, GL ≥ 8
Drecier et al. (2004)	29	Docetaxel 40 mg/m^2/week. iv for 30 minutes, for 6 weeks	24% achieved PSA > 50% decline	US	Age range 49-71, median 61, T2b-T3, PSA >15 ng/ml, GL ≥ 8
Febbo et al. (2005)	19	Weekly docetaxel followed by RP for 6 months	No pathologic complete response	US	Age range 43-63, median 54, PSA>20ng/ml, GL 8-10
Magi-Galluzzi et al. (2007)	28	Docetaxel at a dose of 40 mg/m^2 /week, for 6 weeks	At median follow up 49.5 month, 57% had biochemical failure	US	Age range 49-72, median 62, ≥T2b, PSA=15 ng/ml, GL≥8
Chi et al. (2008)	72	Docetaxel (35 mg/m^2 iv) for 3 cycles, with each cycle of 6 consecutive weeks for treatment followed by a 2-week rest	Well tolerated	CA	Age range 46-78, median 59, T3, GL >7, PSA>20ng/ml
Vuky et al. (2009)	31	Docetaxel and Gefitinib for 2 months before RP. Docetaxel was given weekly for 3weeks with 1 week off for 2 cycles, with 1 cycle of 4 weeks	No pathologic complete response	US	Age range 46-74, median 60, T2b-T3, PSA 20 ng/ml, GL ≥ 8
Mathew et al. (2009)	39	Docetaxel 30 mg/m^2 iv weekly over 1 hour on days 1, 8, 15 and 22 of every 6 weeks cycle with 600 mg oral imatinib daily for 3 cycles	53% were free from progression at a median follow up of 39 months	US	Age range 44-71, median 57, cT2+, PSA>20ng/ml, GL 8-10; or cT2b, PSA>10ng/ml, GL=7
Chen et al. (2012)	18	Docetaxel + IMRT + ADT, docetaxel was given by iv over 1 hour weekly for 8 weeks	2-year BFS was 94%	US	Age range 45-77, median 62, T3, GL 8-10, PSA >20ng/ml
Ross et al. (2012)	42	Docetaxel 70 mg/m^2 every 3 weeks for 6 cycles and Bevacizumab 15 mg/m^2 every 3 weeks for 5 cycles	12 patients achieved a 50% reduction and 9 patients achieved a >50% post treatment decline in PSA	US	Age range 40-66, median 55, cT3, PSA>20 ng/mL or PSA velocity >2 ng/mL/y, GL 8-10; GL= 7 & T3; cT2, PSA >10, ≥50% biopsy cores involved / Gleason score 7
Hirano et al. (2010)	39	EMP vs. LHRH, EMP daily at 560 mg in 2 divided doses for 6 months	4-year BFS 61% vs. 49%	JP	Age range 61-86, median 72, ≥ T3, PSA ≥ 20 ng/ml, GL 8-10

Koie et al. (2012)	142	EMP 280mg/day vs. Placebo added on to LHRHa (Leuprolide 11.25mg or Goserelin acetate 10.8mg every 3 months) for 6 months before RP.	At a median follow-up period of 34.9 months, PSA-free survival was 84.3%. No serious adverse events were reported	JP	Mean age 67.4, IQR(65,72), Risk defined by the D'Amico stratification system
Shepard et al. (2009)	19	2 cycles of 150 mg/m^2 Nab-paclitaxel weekly for 3 weeks during each 4-week cycle, followed by RP with bilateral lymphadenectomy.	PSA decreased in 18 patients, well tolerated	US	Age range 51–72, median 64 cT2b-T4, GL>7, PSA≥15 ng/ml
Hussain et al. (2012)	59	ADT, pelvic RP and weekly Paclitaxel (40, 50, or 60 mg/m^2/week for 6 weeks)	5 and 7 year OS rates were 83% and 67%, no differences in OS between 3 treatments	US	Age range 46-79, median 60, 1. cT2b-4N0N+ M0; 2. GL>7; 3. PSA 10-20ng/ml, GL 7+; 4. PSA 20-150 ng/ml
Khil et al. (1997)	65	EMP + Vinblastine × 7 weeks prior to radiotherapy. EMP 450 m^2 daily in 3 divided dose and a weekly iv dose of Vinblastine, given concurrently during the 7week course of RT	5-yr BFS: T2, 49%; T3, 38%; T4, 17%	US	T2-4, GL 4-10, locally advanced
Zelefsky et al. (2000) Ryan et al. (2004)	27	EMP + Vinblastine × 16 weeks prior and concomitant	Well tolerated	US	GL ≥ 8 & PSA >10 ng/ml; GL7 & PSA > 20 ng/ml; T3 & PSA > 20 ng/ml; T4N0M0; TxN1M0
Beer et al. (2004)	22	4 cycles of docetaxel 35 mg/m^2 and increasing doses of Mitoxantrone starting at 2 mg/m^2 repeated weekly for 3 weeks of a 4-week cycle before prostatectomy	Median PSA decline of 41%	US	Age range 52–74, median 63, cT2c, cT3a, PSA ≥ 15 ng/ml, GL ≥ 4 +3
Friedman et al. (2008)	15	3-6 cycles of docetaxel (36 mg/m^2 iv on days 1, 8, and 15) and Capecitabine (1250 mg/m^2/day orally divided twice a day, on days 5–18) every 4 weeks	40% experienced a ≥ 50% decline in PSA	US	Age range, 40–71 median 58, >T2, PSA≥15 ng/ml, GL≥8, ECOG ≤1
Carles et al. (2010)	50	EMP daily and Vinorelbine 3 cycles, in combination with 3D-CRT, EMP for totally 9 weeks	PFS at 5year was 72%	SP	Age range 35-76. Median 67, Tx, PSA 26, GL≥8

Garzotto et al. (2010), O'Brien et al. (2010)	57	Weekly docetaxel 35mg/m^2 and escalating Mitoxantrone to 4mg/m^2 prior to prostatectomy. Patients were treated with 16 weeks of chemotherapy	Relapse free survival at 2 years and 5 years was 65.5% and 49.8% years respectively	US	Age median 63 (range 49–74). 10- year life expectancy T2c/T3a Or PSA≥15 ng/ml, or GL ≥4+3, ECOG≤1
Clark et al. (2001)	18	EMP 10 mg/kg/day and Etoposide 50 mg/m^2/day orally in divided doses on days 1 through 21 for 3 cycles (4 weeks a cycle)	All patients achieved an undetectable PSA level	US	Age range 50-69, median 58, cT2b-c or T3 with PSA ≥ 15 ng/ml or GL ≥ 8
Hussain et al. (2003)	21	Chemotherapy of docetaxel (70 mg/m^2) on day 1 and EMP (280 mg t.i.d.) on days 1 to 3 every 3 weeks for 3-6 cycles	The 5- and 7-year OS rates were 83% and 67% respectively	US	Age range 46 to 79, median 60, ≥ cT2b, PSA ≥ 15 ng/ml, GL > 8
Ko et al. (2002)	12	4 cycles of EMP 280mg PO t.i.d. × 5 days of each cycle and docetaxel 70mg/m^2 iv q3w	Well tolerated	US	cT3, PSA ≥ 20 ng/ml, GL 8-10
Prayer_galetti et al. (2007)	22	LHRHa, EMP and docetaxel, 3-week cycles EMP (600 mg/m^2 daily from day 1–21) and docetaxel (70 mg/m^2 on day 1), total 4 cycles	42% disease progress free at median follow up of 53 months	IT	Age range 55–73, median 63, T3-4, PSA>ng/ml, GL 8-10
Sella et al. (2008)	22	Docetaxel 70 mg/m^2 on day 2 and EMP 280 mg orally t.i.d. on days 1 to 5 consecutive q3w for 4 cycles	Median PFS 30 months	IL	Age range 49 to 70, median 61, T2c-T4, PSA>=20ng/ml, GL>7
Kim et al. (2011)	24	Docetaxel 36mg/m^2 weekly and EMP 140 mg orally t.i.d. for 3 consecutive days q4w for 3 cycles	2 year PFS 45%, 21 of 22 achieve PSA reduction >25%. No CR	US	Age range 46–71, median 62, T3, PSA>10ng/ml, GL>7
Narita et al. (2012)	18	Docetaxel 30 mg/m^2 weekly along with oral 560 mg EMP b.i.d. for 6 consecutive weeks	14 were disease free without PSA recurrence.	JP	Age range 57-69, median 67 T3, preoperative PSA ≥15 ng/ml, and/or GL>9
Eastham et al. (2003)	700	RP vs. (280 mg orally t.i.d., days 1 to 5) and docetaxel (70 mg/m^2 iv on day 2 of each cycle before RP 6 cycles (3 weeks a cycle)	Well tolerated	US	T1-T3a, NX, M0, patients with 10 year life expectancy
Konety et al. (2004)	36	4 cycles of Paclitaxel and Carboplatin and EMP	45% remains biochemical recurrence free at a median follow up of 29 months	US	Age range 40-68, median 56.6, cT1-2 with PSA ≥ 20 ng/ml, cT3-4, GL ≥ 8

Kelly et al. (2008)	34	4 cycles (4 weeks a cycle) of continuous weekly Paclitaxel at 80 mg/m^2 iv with EMP at 280 mg orally t.i.d for 5 days a week and Carboplatin on day 1 of every cycle	Median PSA progression-free survival was 12.1 months	US	Age median (range),61 (52-75) T1 to 2, PSA ≥20ng/ml, GL 7-10
Pettaway et al. (2000)	33	3-month combination regimen consisting of two 6-week cycles of a modified weekly regimen of Ketoconazole and Doxorubicin, alternating with Vinblastine and EMP	All patients achieved an undetectable PSA level postoperatively	US	Age range 40-70, median 59, cT1-2, PSA > 10 ng/ml, GL ≥ 8, cT2b-c, GL ≥ 7
Kibel et al. (2007)	77	6 cycles docetaxel following surgery, given 4 to 12 weeks following surgery.	At a median 29.2 months 60.5% progressed. 1- and 2- year PFS was 63.2% and 41.7%, respectively. Median PFS was 15.7 months	US	Age range 43–76, mean 60, cT1a-cTxN1, PSA= 15.1ng/ml, GL 7-10, M0,50%+ risk for recurrence at year 3
Perrotti et al. (2008)	20	IMRT and concurrent weekly docetaxel as a continuous 30 minute infusion for 8 weeks.	At median follow up 11.7 month,85% was biochemical recurrence free	US	Age range 50–78, median 64, ≥T3, GL 8-10; GL= 7 and PSA>10 ng/ml
Bolla et al. (2010)	50	Docetaxel 3 weeks after the completion of 3D-CRT. docetaxel was given for 3 cycles, each cycle for every 3 weeks	5 year DFS 66.72%, 5 year OS 92.15%	FR	Age range 48–76 median 50, T1-T2, GL>7 or PSA>20ng/ml, T3-4 N0 M0, cN1- or pN1- M0
Dibiase et al. (2011)	42	Three cycles of docetaxel (35 mg/m^2 per week, Days 1, 8, and 15 every 4 weeks). All patients received 2 years of androgen deprivation	5- and 7- year from biochemical failure were 89.6% and 86.5%, DFS 76.2% and 70.4% respectively	US	Age range 47–75 median 62.5, PSA>20ng/ml; GL=7 and PSA>10ng/ml; or GL 8-10, or T2b to T3.
Montgomery et al. (2008)	636	Docetaxel 75 mg/m^2 q3w + prednisone 5mg PO b.i.d. for 6 cycles vs. SOC	Well tolerated	US	T2c-T4, PSA>20ng/ml, GL 8-10
Kellokumpu-Lehtinen et al. (2012)	100	6 cycles of docetaxel q3w + hormonal treatment vs. hormonal	Effectiveness not reported. Safety and tolerability was demonstrated	SE	Age mean (SD), docetaxel 65(7), control 66(6), T2, PSA >10,GL 7 (4+3); T2, any PSA,GL 8—10; or any T3 tumors
Schmidt et al. (1996)	184	Cyclophosphamide × 2 years *v* EMP × 2 years	EMP improved RFS. No difference in OS	US	Locally advanced prostate cancer

Wang et al. (2000)	96	Mitoxantrone + LHRHa\ antiandrogen *vs.* LHRHa\ antiandrogen	Median OS :80 months Disease-specific survival (DSS): 36month; Locally advanced OS: 84 months DSS*:* 41 months	UK	Age median and range, Combined therapy70 (55-84) Hormone therapy 74 (56-87) > cT3 localized or metastatic disease
Dorff et al. (2011)	983	CAB to CAB + 6 cycles of mitoxantrone 12 mg/m^2 q3w	Placebo arm 5-yr BFS 92.5% and 5-yr overall survival was 95.9%. Terminated due to AE	US	Age median and range 60.7 (40-82), GL ≥ 8 preoperative PSA >15 ng/ml or both
Cetnar et al. (2008)	17	4 cycles of paclitaxel weekly for 3 weeks, followed by 1 week rest	2-year PSA failure 70%. The median time to PSA failure 19 months	UK	Age range 51–69, median 60, pre prostatectomy PSA 4.1-53.3ng/ml, GL 6-9,
Ploussard et al. (2010)	47	Paclitaxel + ADT, paclitaxel 100 mg/m^2 once a week for 8 weeks	No differences in EORTC QLQ-C30	FR	Age range 49-68, mean 61.4, PSA > 20ng/ml, and/or T3b-T4 and /or N1, GL≥8
Bagley et al. (2002)	25	Vinblastine 3 mg/m^2 on Days 1 and 3, Doxorubicin 40 mg/m^2 on Day 1, and Mitomycin 10/m^2 on Day 1.Treatment was repeated every 3 weeks for a total of 6 cycles, but Mitomycin was given only on treatment cycles 1,3 and 5	At year 10 the cumulative cancer specific survival 81%, for node positive patient the rate of 10years relapse free is 82%	US	Age (median, range), 66 (56–74) T3, N+
Fizazi et al. (2014)	413	ADT+ docetaxel +EMP vs. ADT. docetaxel 70 mg/m^2 q3w , EMP 10 mg/kg/d d1-5, Aspirin 300 mg (or Coumadin) for thrombo prophylaxis x 4 cycles	8-year PFS rate was 62% (55-69) vs. 53% (45-60), HR=.75 (p=0.06). In GL<8 subgroup, the 8-year PFS HR=0.55(.36-.84)]	FR	Age(median, range), 64 (47-77) T3-T4, PSA ≥ 20 ng/ml, pN+, GL (GS) ≥8,
Lundgren et al. (1995)	285	Polyestradiol phosphate plus Ethinylestradiol, EMP vs. deferred therapy	No difference in OS, statistically significant in prostate related mortality	SE	Age distribution was reported T0a to T3NXm0
Rosenthal et al. (2009)	397	AS+RT vs. AS + RT + Paclitaxel, EMP and Etoposide. 4 cycles of chemotherapy. The regimen: (1) oral EMP 250 mg 3 times daily for the first 14 of every 21days, (2) oral Etoposide 50 mg/m2 in divided doses twice daily for the first 14 of every 3 weeks, and (3) Paclitaxel 135 mg/m^2 iv within 1 h on Day 2 of each 21-day cycle	Closed after 4 year due to excess thromboembolic and severe toxicities	US	Age range (42-81) median 66, GL≥7 and PSA between 20 and 100 ng/ml, ≥T2, GL between 8 and 10, PSA<100 ng/ml

Eisenberger et al. (2012)	1996	Immediate vs. deferred ADT x18 months ± 6 cycles of docetaxel q3w in a 2x2 factorial design	Terminated due to poor accrual	US	Undetectable PSA, M0
Patel et al. (2005)	600	AS and 3D-CRT/IMRT vs AS and 3D-CRT/IMRT followed by chemotherapy with docetaxel and prednisone	-	US	Age not reported 1. Any T-stage, PSA ≤ 150, GL≥ 9; 2. ≥ T2, PSA < 20, GL 8; 3. Any T-stage, PSA ≥ 20-150, GL 8 4. any T-stage, PSA ≥ 20-150, GL 7
Hurwitz et al. (2014) , NRG oncology (2015)	74	Post RP, androgen suppression therapy (AST) and docetaxel (6 cycles of docetaxel 75 mg/m^2 q3w)	Freedom from disease progression was improved more than 20 percent compared with historical control	US	Either PSA nadir >0.2 ng/ml and GL ≥7, or PSA nadir ≤0.2 ng/ml with GL ≥8 and stage ≥pT3.

Abbreviations, RTOG=radiation therapy oncology group, t.i.d.=three time a day, b.i.d.=twice a day, Gy= gray, PO=Oral administration, q.= every, d.=day, w.=week, h=hour, RFS=recurrence/relapse free survival, PSA= prostate specific antigen, PFS=progression free survival, BFS=biochemical-free survival, OS=overall survival, GL=Gleason score, RNA= Ribonucleic acid, IQR= interquartile range, RT=Radiation therapy, RP= radical prostatectomy, KAVE=ketoconazole, doxorubicin, vinblastine, and estramustine phosphate, NMA=no measurable amount, EMP=estramustine phosphate, VP-16= etoposide, TEC=paclitaxel, estramustine phosphate, carboplatin, LHRHa= luteinizing hormone–releasing hormone agonist, GI,=gastrointestinal, GU=genitourinary, IMRT=Intensity-modulated radiation therapy ADT=androgen deprivation therapy, iv= intravenous, 3D-CRT = three-dimensional conformal radiotherapy, EBRT=External beam radiation therapy, CAB =combined androgen blockade, AS=Androgen suppression, CALGB =Cancer and Leukemia Group B, JP=Japan, SP=Spain, SE=Sweden, CA=Canada, IT=Italy, FR=France, IL=Israel

[a] The duration of chemotherapy is usually equal to or less than 6 months

[b] Outcomes include OS, BFS, RFS and PFS as well as safety data

[c] Definitions converged to a high PSA value (e.g., ≥20 ng/ml), a high Gleason score (8-10) or advanced stage (≥T2b).

Table 2.2) Completed Phase III chemotherapy studies in metastatic prostate cancer patients

Study	Treatment	Sample Size	HR & 95% CI
Tannock et al. (1996)	Mitoxantrone (12 mg/m^2 iv q3w)+Prednisone versus Prednisone	161	0.8 (0.59, 1.09)
Kantoff et al. (1999)	Mitoxantrone (14 mg/m^2 iv q3w) + Hydrocortisone versus Hydrocortisone	242	1 (0.8,1.3)
Berry et al. (2002)	Mitoxantrone (12 mg/m^2 iv q3w for 6 cycles) + Prednisone versus Prednisone	120	0.92 (0.59, 1.42)
Tannock et al. (2004)	Prednisone +Docetaxel (up to 10 cycles of 1.75 mg/m^2 of docetaxel 1-hour iv on day 1 every 3 weeks or 30 mg/m^2 30-minute iv on days 1, 8, 15, 22, and 29 of a 6-week cycle q3w) versus Prednisone +mitoxantrone (12 mg/m^2 of as a 30-minute infusion on day 1 q3w)	1,006	0.76 (0.62, 0.94)
Fossa et al. (2007)	Docetaxel weekly (6 cycles of 30 mg/m^2 on days 1, 8, 15, 22, and 29 as a 1-hour iv) + prednisone versus prednisone	109	0.54 (0.32, 0.91)
De Bono et al. (2010)	Cabazitaxel(10 cycles of 25 mg/m^2 given iv over 1 hour q3w) + prednisone or mitoxantrone (12 mg/m^2 given iv over 15–30 minutes q3w) +prednisone	755	0.70 (0.59,0.83)
Sweeney et al. (2014)	Docetaxel (75mg/m^2 q3w for maximum 6 cycles) +ADT versus ADT only	790	0.61 (0.47,0.80)

Abbreviations: ADT =Androgen deprivation therapy, CI= Confidence interval, q3w= every 3 week, iv = intravenous

Table 2.3) Systematic Review of cost utility analysis in localized prostate cancer

Study	Patients	Country	Intervention versus comparator	Costs	QALYs	ICER
Fleming et al. (1993)	Localized stage A or B, Age strata, 60, 65, 70 & 75.	USA	RP, EBRT, and watchful waiting	RP and radiation therapy may be beneficial for selected groups, particularly in younger patients with higher grade tumors		
Kattan et al. (1997)	Localized prostate cancer, Age strata 60, 65, 70 & 75.	USA	RP vs. watchful waiting	RP is beneficial for younger men and harmful for older men		
Bayoumi et al. (2000)	Clinically evident, local recurrence of prostate cancer, or stage C. base case simulates one age 65 man	USA	DES	$3,600	4.64	Referent case
			Orchiectomy	$7,000	5.1	$7,500/QALY
			NSAA	$16,100	4.98	Not cost-effective
			NSAA + orchiectomy	$20,700	5.05	
			LHRHa	$27,000	5.08	
			NSAA + LHRHa	$40,300	5.03	
Jager et al. (2000)	Localized	USA	magnetic resonance (MR)	$10,568	12.53	MR cost saving
			RP	$11,669	12.52	
Hummel et al. (2003)	Early localized prostate cancer, model one age 65 man	UK	3D-CRT vs. Traditional Radiotherapy	£162-548	0.56 - 0.09	Between £288 and £5,929 /QALY
			BT vs. RP	£527 to negative	1.08 to negative	Between £490/QALY and not cost-effective
Calvert et al. (2003)	Early localized prostate cancer, model one age 60 man	UK	Observation vs. RP vs. Using a DNA ploidy as prognostic biomarker select patients for RP	Biomarker approach vs. Observation £12,608 /QALY, treating all with RP is dominated by other two treatments		
Moeremans et al. (2004)	Early prostate cancer	Belgium	Bicalutamide +SOC vs. SOC	€27,059 /QALY		
Konski et al. (2005)	Localized	USA	RT	$29,240	5.48	$2,153/QALY
			RT plus total androgen suppression	$31,286	6.43	
Lundkvist et al. (2005)	Localized	UK	Proton vs. SOC	Proton therapy was cost-effective for appropriate risk groups		
Wang et al. (2005)	Localized	USA	RT and 6 month AST vs. RT alone	Cost saving		

Hayes et al. (2010)	Low risk prostate cancer	USA	Initial treatment vs. active surveillance	Active treatment 11.07 QALY, Brachytherapy 10.57 QALY, IMRT 10.23 QALY		
Konski et al. (2006)	70-year-old with intermediate-risk prostate cancer	USA	IMRT vs. CRT	$40,101/QALYs		
Konski et al. (2007)	Localized prostate cancer	USA	Proton vs. SOC	$63,578/QALY for a 70-year-old man and $55,726/QALY for a 60-year-old man.		
Shimizu et al. (2007)	Localized prostate cancer, age strata 60,70,80	Japan	Watchful waiting, curative therapy(CT) and salvage therapy (ST)	Gleason 2-6, Watchful waiting yielded greatest QALE		
				Gleason 7, CT was controversial,		
				Gleason 8, ST was beneficial		
O'Malley et al. (2007)	Localized Prostate cancer	Australia	Laparoscopic remotely assisted RP vs. open surgery	A$2,264 ~24,457 /QALY		
Zubek et al. (2009)	Localized prostate cancer	USA	Prostate Px® test, nomogram, and current practice.	Prostate Px® test, nomogram, and current practice were 8.11, 7.39, and 6.47, respectively. The expected costs were $17,549, $14,162, and $14,105		
Ito et al. (2010)	A hypothetical cohort of men aged 70 years with locally advanced or high-risk localized prostate cancer (T2c to T4N0) starting a 2-year course of ADT after radiation therapy	USA	A BMD test and selective alendronate therapy vs. no test and no alendronate treatment	$178	0.0027	$66,800/QALY
			Universal alendronate therapy without a BMD test vs a BMD test and selective alendronate therapy	$1,501	0.0084	$178,700/QALY
Hohwü et al. (2011)	Localized prostate cancer	Denmark	Robotic-Assisted Laparoscopic Radical Prostatectomy vs. RP	€64,343 /QALY		
Parthan et al. (2012)	Model 65 year old male with localized prostate cancer	USA	IMRT vs. SBRT	$8,195	-0.062	More expensive and less effective
			PT vs. SBRT	$44,539	-0.047	
Hodges et al. (2012)	Localized	USA	IMRT vs. SBRT	IMRT cost saving		
Yong et al. (2012)	Localized	USA	IMRT vs. 3DCRT	$26,768 /QALY		
Sher et al. (2012)	Localized	USA	IMRT vs. R-SBRT, NR-SBRT	IMRT over R-SBRT $285,000/QALY, IMRT over NR-SBRT $591,100/QALY		

Lyth et al. (2012)	Age <75 with PSA ≤50 ng/ml and ≤T2N0M0 well- or moderately differentiated localized prostate	Sweden	RP and watchful waiting for different patient groups	21,026 ~ 858,703 SEK for those aged 65 to 75 years
Cooperberg et al. (2013)	low-, intermediate-, and high-risk, T3a, N0, M0, mean age 65, probability distributions were sampled 250 times and 250 first-order simulations	USA	Open RP, laparoscopic-assisted RP, robot-assisted RP , 3D-CRT,IMRT, BT, and EBRT+BT	Surgery was preferred over RT for lower-risk men, whereas combined EBRT+BT compared favorably for high-risk men
Hatoum et al. (2013)	locally advanced of metastatic prostate cancer	USA	Degarelix vs. leuprolide	$245/QALY
Close et al. (2013)	Localized	UK	Robotic vs. laparoscopic prostatectomy	£18,329/QALY

Abbreviations, PSA=prostate-specific antigen, ICER =incremental cost-effectiveness ratio, DES=diethylstilbestrol, NSAA= non-steroidal anti-androgen, LHRHa= Luteinizing hormone-releasing hormone agonists, 3D-CRT =Three-Dimensional Conformal Radiation Therapy, RP= Radical prostatectomy, AST=androgen suppression therapy, RT =radiation therapy, BMD= Bone Marrow Density, IMRT= Intensity-modulated radiation therapy, SBRT= Stereotactic body radiation therapy , PT= proton beam therapy, BT =Brachytherapy, EBRT=external-beam radiation therapy, SEK=Swedish Krona, QALY=Quality adjusted life year, QALE=quality-adjusted life expectancy, CAB= combined androgen blockade, SOC=standard of care, MR= magnetic resonance

Table 2.4) Systematic review of cost estimated for localized prostate cancer

	Direct Medical costs	Year of costs	Costs of 2013	References
Remission (annual cost)				
With neoadjuvant ADT	$1,481	2009	$1,685	Copperberg et al. (2013)
With adjuvant ADT	$2,267	2009	$2,579	Copperberg et al. (2013)
Local recurrence				
Without salvage therapy	$1,775	2009	$2,019	Copperberg et al. (2013)
ADT (annual)	$1,791	2009	$2,037	Copperberg et al. (2013)
RT (one-time)	$27,586	2009	$31,379	Copperberg et al. (2013)
Surgery (one-time)	$8,547	2009	$9,722	Copperberg et al. (2013)
Metastasis				
Annual management	$2,212	2009	$2,516	Copperberg et al. (2013)
Evaluation (one-time)	$960	2009	$1,092	Copperberg et al. (2013)
Treatment (one-time)	$15,773	2009	$17,942	Copperberg et al. (2013)
Secondary malignancy	$11,465	2009	$13,042	Copperberg et al. (2013)
Prostate cancer death (last year of life)	$40,807	2009	$46,419	Copperberg et al. (2013)
Cost of pre-terminal care	$17,000	1998	$30,036	Bayoumi et al. (2000)
Treatment cost				
SBRT	$20,889	2011	$22,312	Parthan et al. (2012)
IMRT	$28,805	2011	$30,767	Parthan et al. (2012)
PT	$65,250	2011	$69,695	Parthan et al. (2012)
Annual Stage 3 costs	$22,030	- [a]		Roehrborn et al. (2009)
Annual Stage 4 costs	$25,521	-		Roehrborn et al. (2009)
Cost of Cabazitaxel (monthly)		2015	$8,819.8	Q1Medicare.com (2015)

Abbreviations, ADT= androgen suppression therapy, RT= Radiation therapy, IMRT= Intensity-modulated radiation therapy, SBRT =Stereotactic body radiation therapy, PT= proton beam therapy, DES= diethylstilbestrol, NSAA= non-steroidal anti-androgen, LHRHa= Luteinizing hormone-releasing hormone agonists,

[a] year of cost was not reported in paper

Table 2.5) A summary of utilities of patients with prostate cancer

	Localized	Metastatic
Chen et al. (2008)	0.80	
Hayes et al. (2010)	0.68	
Stewart et al. (2005)	0.84	0.67
Fryback et al. (1993)	0.84	
Copperberg et al. (2013)	0.94	0.45
Cowen et al. (1996)	0.72	0.42
Chapman et al. (1998)		
Impersonal	0.78	0.51
Personal	0.78	0.72
Chapman et al. (1999)	0.84	0.66
Krahn et al. (2003)	0.86	0.85
Patient Standard Gamble	0.80	0.75
Health Utilities Index	0.80	0.81
Quality of Well Being rating scale	0.66	0.62
Bennet et al. (1997)		
Physician		0.83
localized prostate cancer		0.53
Metastatic prostate cancer		0.58
Volk et al. (2004)		
Husbands		0.72
Wives		0.86
Couples		0.83
Total Mean	0.80	0.68

Mean utility of localized prostate cancer patients were 0.80. The average utility of metastasis was 0.68

Table 2.6) Recent FDA approved companion diagnostics in oncology (FDA, 2014b)

CDX device	Cost and performance of device	Monthly Drug costs*
Therascreen KRAS RGQ PCR Kit	Test cost $196.99 (CMS, 2014b), KRAS mutation expressing 40%, sensitivity 97%(Qiagen,2012)	Cetuximab ($10,000) (Rapaport 2009 Jun 29) Panitumumab ($8,000) (Pollack 2006, Sep 28)
DAKO EGFR PharmDx	Test cost $40(Buckley & Kakar, 2007), EGFR expressing 72.8-82.1% (Dako)	
SPOT-Light HER2 CISH Kit	CISH costs between FISH and IHC (Ross et al. 2009), very high concordance with FISH. HER 2 gene 25-30% expression (Mark et al.1999)	Trastuzumab ($5,800) (Blair et al. 2012)
HER-2/Neu gene detection system	Test cost $140 (Shah & Chen, 2010), HER 2 gene 25-30% expression(Mark et al.1999), accuracy 95.7% (Press et al. 2002)	
PathVysion HER-2 DNA Probe Kit	Test cost $140 (Shah & Chen, 2010), HER 2 gene 25-30% expression (Mark et al.1999), accuracy 97.4% (Press et al. 2002)	
Bond Oracle HER2 IHC system	Test cost $10 (Shah & Chen ,2010), specificity and sensitivity equivalent to the PathVysion (Carlson, 2011)	
PATHWAY Her2 (clone CB11)	HER 2 gene 25-30% expression (Mark et al.1999), sensitivity 89.7%(Press et al. 2002)	
HER2 CISH PharmDX kit	HER 2 gene 25-30% expression(Mark et al.1999)	
INFORM HER2 Dual ISH DNA Probe Cocktail	Test cost $225, total cost $512 (Carlson, 2011), sensitivity 95.4% and specificity 96% (Shah & Chen, 2010)	
INSITE HER-2/Neu kit	HER 2 gene 25-30% expression (Mark et al.1999)	
HercepTest	Cost $500 (Blair et al.2012), HER-2 expression score 3+ about 10% (Blair et al. 2012), Sensitivity 88.9% & specificity 100% (Press et al. 2002)	Trastuzumab ($5,800) (Blair et al. 2012), Pertuzumab ($5,900) (Carroll 2012 Jun 9)
HER2 FISH PharmDx kit	Cost $70 (Genomeweb.com, 2008 Jul 16), HER-2 expression score 3+ about 10% (Blair et al. 2012)	
THxID BRAF kit	Test cost $178.80 (CMS, 2014b), 50% of melanomas expression (The University of Michigan department of pathology, 2011)	Tramatenib ($9,135)(Chung & Reilly 2015)
Cobas® EGFR Mutation Test	Test cost $329.18(CMS, 2014b), detecting 72.97% case (Wang & Chen, 2013)	Erlotinib (generic)
Vysis ALK Break Apart FISH Probe Kit	Test cost $1,500(Blair et al. 2012), Sensitivity 100% and specificity 100% (Abbott Molecular Inc. 2011), ALK expressing 2-7% (Blair et al. 2012)	Crizotinib ($9,600) (Blair et al. 2012)
c-Kit pharmDX assay to identify CD 117	Test cost $10 (Shah & Chen 2010), 85-95% expressing (Choti & Johnston)	Imatinib ($7,666)(Experts in chronic Myeloid leukemia, 2013)

Cobas 4800 BRAF V600 Mutation Test	Test cost $120–$150(Blair et al. 2012), BRAF V600E mutation ~40% (Blair et al. 2012), Specificity 99.4 (Qu et al. 2013)	Vemurafenib ($4,700) (Blair et al. 2012)
FerriScan R2-MRI Analysis System	Test cost $335 (Honor Health. 2015), Sensitivity of >85% and specificity of >92% (Cappellini et al 2008)	Deferasirox (generic)
BRACanalysis CDx	Test cost $3,340 (Secord et al. 2013), 22% express (Labmedica International staff writers, 2004 Nov5).Sensitivity 99.92% and specificity >99.99% (Myriadpro .2015)	Olaparib ($6,356) (Secord et al. 2013)

Abbreviation, KRAS=Kirsten rat sarcoma viral oncogene homolog, RGQ= Rotor-Gene Q software ,PCR= polymerase chain reaction, EGFR= epidermal growth factor receptor, HER-2= human epidermal growth factor receptor -2, CISH= Chromogenic in situ hybridization, IHC= immunohistochemical, BRAF=v-raf murine sarcoma viral oncogene homolog B1, ALK= Anaplastic lymphoma kinase, FISH= Fluorescence in situ

*Some monthly costs were converted from annual costs

Figure 2.1) Study selection for review of clinical effectiveness

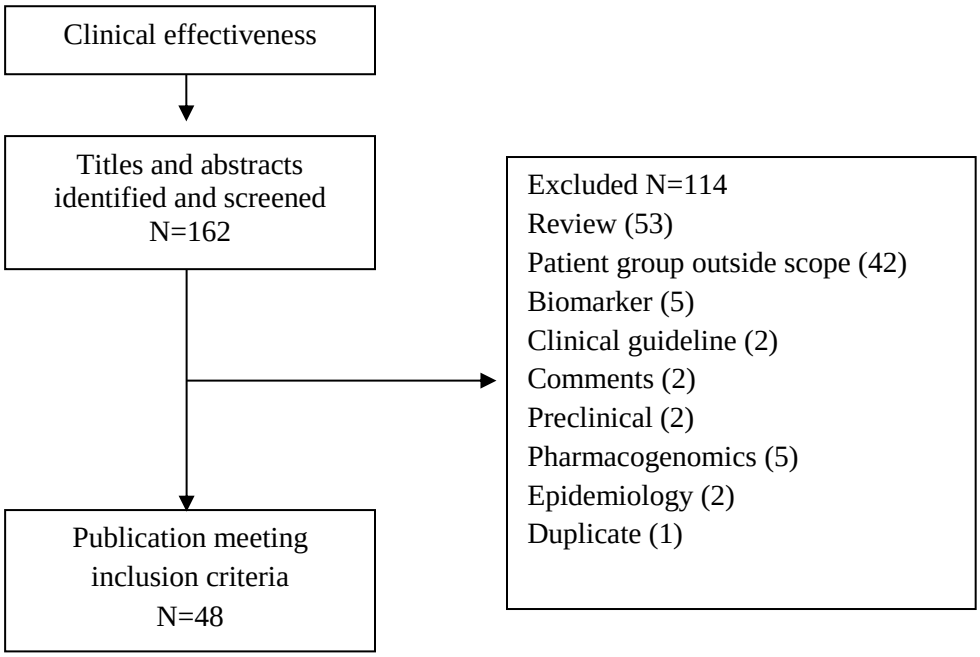
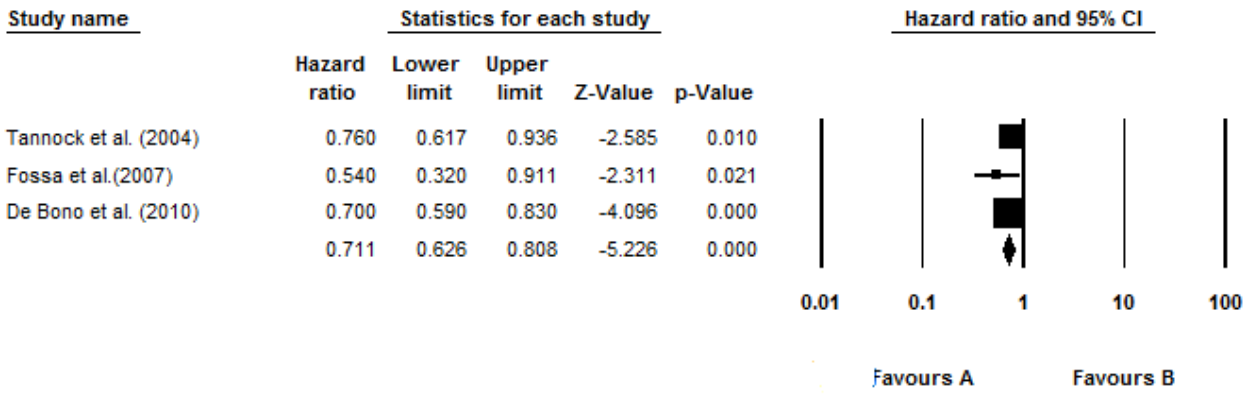


Figure 2.2) Meta-analysis of chemotherapy in mCRPC



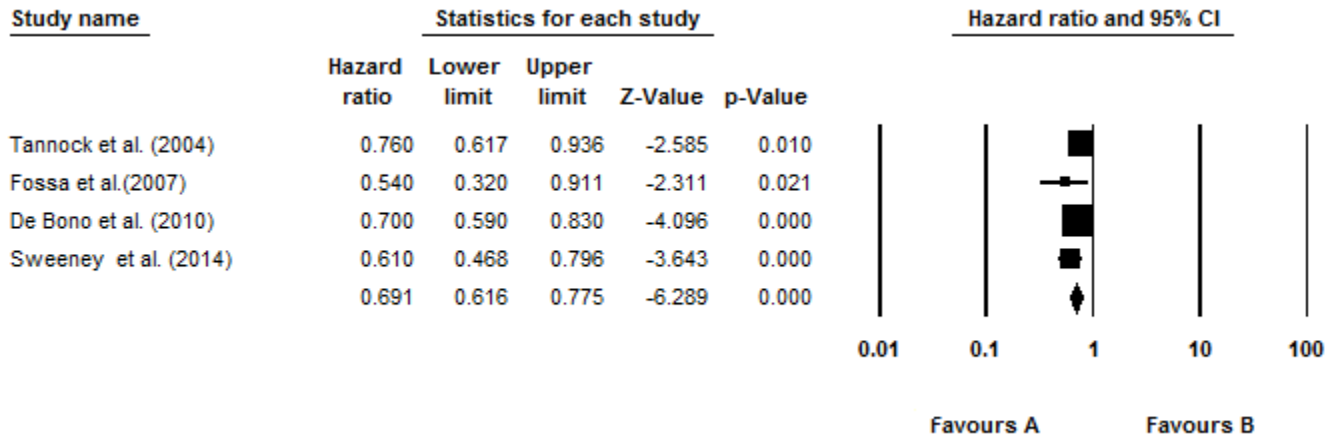
Summary statistics [a]

Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				τ^2		
	Point estimate	Lower limit	Upper limit	Z	P	Q	df (Q)	P	I^2	τ^2	Standard Error	Variance	Tau
Fixed	0.711	0.626	0.808	-5.226	0.000	1.491	2.000	0.475	0.000	0.000	0.016	0.000	0.000
Random	0.711	0.626	0.808	-5.226	0.000								

Abbreviation: Z=Z score, Q=Cochran's Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method, df (Q)= degree of freedom of Q, I^2= statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance $\tau 2$= between-studies variance

[a] Above three studies are the pivotal trials for docetaxel and cabazitaxel to have label in mCRPC. The pooled effectiveness versus comparator is 0.71

Figure 2.3) Meta-analysis of chemotherapy in metastatic prostate cancer



Summary statistics [a]

Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				τ^2		
	Point estimate	Lower limit	Upper limit	Z	P	Q	df (Q)	P	I^2	τ^2	Standard Error	Variance	Tau
Fixed	0.691	0.616	0.775	-6.289	0.00	2.525	3.000	0.471	0.000	0.000	0.013	0.000	0.000
Random	0.691	0.616	0.775	-6.289	0.00								

Note, Z, Z score, Q=Cochran's Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method, df (Q)= degree of freedom of Q, I^2= statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance $\tau 2$= between-studies variance

a Considering the CHAARTED study (Sweeney et al. (2014)), the pooled effectiveness versus comparator is 0.69

Chapter 3. Estimate survival outcomes by using SEER-Medicare Linked Database

3.1 Overview

Although some studies showed a trend of overall survival benefit associated with chemotherapy, overall survival was not proven when treating HRLPC patients with chemotherapy. Clinical effectiveness of a CEA model needs to be based on assumptions. Clinical endpoints (e.g., metastasis-free survival, overall survival) for HRLPC patients from a representative US cancer registry are needed to ensure the model is generalizable to US patients. This is consistent with health technology assessment (HTA) recommendations (Philips et al. 2004; NICE 2008a) of using good-quality non-randomized studies. The objective of this chapter is to describe the clinical outcomes and to analyze how baseline risk factors, such as age at diagnosis, cancer severity, year of diagnosis, and initial treatment modality, predict survival outcomes.

3.2 Methods

3.2.1 Data sources

The Surveillance, Epidemiology, and End Results (SEER) program is a population based tumor registry covering 26% of the U.S. population (Warren et al. 2002). The SEER-Medicare Linked Database provides long-term follow up since cancer diagnosis. With the data on both clinical outcomes and cost, it is a rich source to study risk profiles as well as cost patterns of high-risk localized prostate cancer patients in the U.S.

Lu-Yao et al. (2009) estimated the ten-year prostate cancer-specific mortality and all-cause mortality for localized prostate cancer patients who were diagnosed with stage T1-T2 cancer between 1992 and 2002 by using SEER-Medicare. They reported 10-year all-cause mortality by age and severity (clinical stage and Gleason score). For instance, for age group between 66 and

69 and poorly differentiated staged T2 patients, the median survival was about 7 years following the diagnosis of prostate cancer (Lu-Yao et al. 2009). Different from the study above, this chapter focused only on the high risk localized prostate cancer based on NCCN (2012) criteria (clinically localized with either T3a or Gleason score 8-10 or PSA>20ng/ml, or locally advanced stage higher than T3b) and followed patients since they received prostatectomy, radiotherapy, or hormone therapy.

3.2.2 Patients selection

Patients were eligible for inclusion if they were diagnosed with prostate cancer between January 1991 and December 2011 (N=672,634). At the diagnosis, patients were 65 or older. Those who were younger than 65 (N=128,121) were mostly likely enrolled due to disability. Included patients should have been enrolled in Medicare part A and B to get complete treatment history (Patients who were not Medicare part A and part B, N=197,333). Patients were excluded from the study if they were enrolled in a Medicare Health Maintenance Organization or were eligible for Medicare based on end-stage renal disease (ESRD) or disability (N=38,071); their prostate cancer was identified at autopsy because no follow-up medical care would had been provided (N=5,743); or had other cancer either before or after diagnosis of prostate cancer (N=12,830). Patients who did not undergo an active treatment (N=5,053) in this period were excluded. As the day of the month was not reported in SEER-Medicare Linked Database, month was used as unit of timing. The index month was defined as the earliest month during which patients received at least one of the following, prostatectomy, radiotherapy, or hormone therapy. The rationale was that an active treatment was needed in conjunction with chemotherapy. At index month, patients were still alive. They were qualified as high risk localized prostate cancer (Not HRLPC, N=196,211), and their cancer did not spread (Metastasis at diagnosis, N=41,344). If treated after

metastasis (N=22,653), they were excluded from the cohort. Patients who died within 6 months from index month (N=1,191) were excluded, as those patients might have had serious conditions, since the selected patient group has a relatively long life expectancy (Lu-Yao et al. 2012). Overall, our cohort comprised 24,094 patients. If patients were still alive on December 2011, they were censored out on December 2011.

3.2.3 Outcome assessment

Metastasis-free survival was a composite endpoint. It captured the event of metastasis and death. Metastasis was identified applying two methods. One method used the ICD-9-CM code (CMS 2015, Dolan et al. 2012). Specifically, secondary and unspecified malignant neoplasm of lymph nodes (196), secondary malignant neoplasm of respiratory and digestive systems (197), and secondary malignant neoplasm of other specified sites (198) were used as triggers to identify secondary malignancy (CMS 2015). The other method was chemotherapy because it was the only agent for treating mCRPC before 2011. Healthcare Common Procedure Coding System (HCPCS) code starting with 'J9' was used (Find-a-code. 2015). Both methods were combined to assess the metastasis.

Based on the review of Chapter 2 (Table 2.1), the inclusion criteria of clinical trials in this patient group focused on age, Gleason score, PSA value, and tumor staging. Studies showed that survival differed according to age (Lu-Yao et al. 2009), cancer severity (Lu-Yao et al. 2009), prostatectomy (Wilt et al. 2012), and year of diagnosis (Wilding et al. 2005). A few variables including age, disease severity, year of diagnosis, and treatment modality were selected to predict outcome. For simplicity, those variables were categorized as binary variables. For instance, the severity of cancer was either clinically localized (T3a or Gleason score 8 to 10 or PSA >20 ng/ml) or locally advanced (T3b to T4), which is consistent with the NCCN guideline (2012).

3.2.4 Statistical methods

Kaplan-Meier curves of metastasis-free survival and overall survival were estimated. Cox proportional hazards model was conducted to understand the effect of age group (65-75 or 75+), severity of cancer, diagnosis period, and treatment modality (prostatectomy versus no prostatectomy) on both overall survival and metastasis free survival. The parametric functions of the survival outcomes were also estimated to construct the model. It was done by exploring different parametric function forms for survival outcomes, including exponential, Weibull, log-normal and log-logistic. All analyses in this and next chapter were performed using SAS statistical software, version 9.2 (SAS Institute Inc. 2008).

3.3 Results

3.3.1Patient baseline

Overall, 24,094 patients were included in the study. Patient selection flow was presented at Figure 3.1. As Gleason score was not available in the database before 2004, patient characteristics are reported in Table 3.1 stratified by two periods (prior to 2004 and post to 2004). Average age was 72.8 years at index date. No major differences were found in terms of age, race, region and comorbidities. About 80% of patients were white and near half of the patients were from the west. Most people (about 70%) were without comorbidity. More patients were in clinical stage T0-T2 in the period after 2004, as indicated by Gleason score. Less prostatectomy surgeries were performed for patients who were diagnosed after 2004 compared to those diagnosed prior to 2004.

3.3.2 Survival outcomes

The median survival of the entire cohort was 139 month, about 11.6 years (See Figure 3.2, panel A). The interquartile range (IQR) was (73, 220) months. Nearly 18% of patients survived at least 20 years. Overall survival by two age groups is shown in Figure 3.2 Panel B, i.e., patients aged 65 to 74 and patients older than 74. The median overall survival of the younger group was 169 month, with IQR of (98, 239) months, and the median overall survival of the older group was 91 months, with IQR of (46, 145) months. Younger patients were expected to live longer. In Figure 3.2 panel C, overall survival was stratified by the severity of cancer. The median overall survival of clinical localized group was 142 months, with IQR of (75, 227) months whereas medial overall survival of locally advanced group was 116 months, with IQR of (56, 196) months. The locally advanced group had worse outcome, consistent with the classification of disease severity. Figure 3.2 Panel D reported the overall survival by the period of diagnosis. For patients diagnosed after 2000, the median survival was 144 months, with IQR of (85, not reached) months. For patients who were diagnosed between 1995 and 1999 and those diagnosed before 1995, the median survival was 135 months (IQR= (65, 213) months) and 121 months (IQR= (59,207) months), respectively. Recently diagnosed patients were expected to have better overall survival. Figure 3.2 Panel E shows the overall survival by whether patients had prostatectomy. Patients with prostatectomy showed a more favorable outcome, with median survival of 189 months (IQR= (117, not reached) months) compared to 105 months (IQR= (54,166) months) for those without prostatectomy. All results above were statistically significant ($p<0.05$), as measured by log-rank test (both raw test and Sudak test).

The median metastasis-free survival (MFS) was 78 months, with IQR of (19, 167) months (Figure 3.3). Stratified analysis of MFS was similar to that of overall survival. Instead of discussing each group, a summary of log-rank tests for different strata is presented in Table 3.2. In summary, locally advanced older patients and no prostatectomy treatment were still associated with worse

outcomes, consistent with the pattern of overall survival. Unlike in the case of overall survival, metastasis-free survival stratified by diagnosis period showed no differences between patients diagnosed after 2000 and the patients who were diagnosed between 1995 and 1999.

The results from multivariate proportional hazards model (Table 3.3) were consistent with parametric models. Patients who were either locally advanced, older patients (75 years of age and older), or diagnosed before 2000 had significantly higher risk of mortality, whereas prostatecomy served as a protective factor. For instance, compared to younger patients, patients who were older than 74 had 92.3% higher risk of death. Hence, age was one important risk factor for this patient group. In the metastastic free survival model, locally advanced older patients without prostatectomy treatment had worse outcomes. Diagnosis year was not statistically significant.

3.3.3 Parametric fitting of survival outcomes

The performance of four models (exponential, Weibull, log-normal, and log-logistic distribution) in estimating metastasis-free survival was tested. The Akaike Information Criterion (AIC), AICc (AIC with a correction for finite sample sizes), and Bayesian Information Criterion (BIC) measures that were used to assess how well alternative models described the data were computed for each model (Table 3.4). Based on model selection criteria, the Weibull model was the best for MFS, since the criteria values of AIC, AICc, BIC and log likelihood were the smallest (Table 3.4). Figure 3.4 showed the Kaplan-Meier curve of the observed MFS (irregular dotted line) as well as parametric curves. Both log-normal and log-logistic fitting curves had high tails, indicating that a fair amount of patients enjoyed long life, which is not true. These two curves almost overlaped, staying at the top of the graph towards the tail in Figure 3.4. Log-normal curve and log-logistics curve fitted the observed data well before the month 80, but remained well

above the data points starting from month 120. From month 140, the observed Kaplan-Meier curve was between the fitted curve of Weibull and exponential functions. Exponential curve might predict observations at the tail acurately, but the performance at a beginning of the curve is poor. Following the criteria statistics, Weibull distribution was selected for the cost-effectiveness model. The best model by the selection criteria did not garrantee a perfect fit. Table 3.5 summarized different parametric models to estimate MFS.

Likewise, Weibull, exponential, log-logistics, and log-normal functions were fitted with overall survival. When Weibull, log-logistics, and log-normal distributions were tested, the Hessian matrices were negative, causing computation for OS parametric fitting not converging. Although exponential distribution converged, the fitted curve deviated from the observed Kaplan-Meier curve (Figure 3.5) substantially. Alternative solutions were explored. For example, one solution was to solve the parameters of Weibull distribution by randomly selecting two points on the Kaplan-Meier curve. Two points (37, 0.887) and (238, 0.197) were chosen randomly. A Weibull curve was plotted through these points. Figure 3.5 shows that the fitted curve based on such method performed method compared to the exponential function. Of course, if we had actual invention arm, we could always use the Kaplan-Meier curve or piecewise exponential function instead of one function form. Table 3.6 summarizes different parametric models to estimate OS.

3.4 Discussions

Previous studies compared the overall survival from SEER with electronic medical record and found high level of agreement (Albertsen et al. 2000; Penson et al. 2001), indicating that the overall survival of prostate cancer patients reported by SEER was reliable. The estimation of OS in this study is consistent with a few experimental studies. Bill-Axelson et al. (2014) compared radical prostatectomy versus watchful waiting in early prostate cancer in the Scandinavian

Prostate Cancer Group Study Number 4 (SPCG-4). They reported median year of overall survival of high-risk patients (N=695) was about 12 years. Wilt et al. (2012) found that the median years of overall survival of high risk localized patients were 9 and 11 for the observational arm and radical prostatectomy arm, respectively. Compared to those studies, the median OS of 11.6 years in this study is a reasonable estimate.

Bill-Axelson et al. (2014) also showed that relative risk (RR) of radical prostatectomy versus watchful waiting was 0.71 (95% CI: 0.59 - 0.86) for the whole group, though it was not statistically significant (0.84, 95% CI: 0.61 - 1.19) for high-risk group. Wilt et al. (2012) showed that prostatectomy was associated with about 2 years additional overall survival compared to watchful waiting. Consistent with the above studies, patients who started with radical prostatectomy also showed favorable outcome in this study with even larger differences (7 years, compared to other active treatments). Based on the definition of the variable of treatment modality, the treatment of prostatectomy group might include radiotherapy and hormone therapy. Patients in this group received more careful medical attention compared to the group receiving other treatments. More importantly, selection bias can play an important role as surgery candidate should be fit. Consequently, these patients have better survival outcome. Additional studies should look into the benefit of prostatectomy in this patient group compared to other treatments in SEER-Medicare Linked Database and adjust identifiable confounders. Furthermore, different survival outcomes can be attributable to migration of cancer staging and grade, i.e., the definition of cancer staging or Gleason score over the years. Jani et al. (2007) showed a grade migration from well differentiated to moderately differentiated disease over the study period in SEER.

Usually, studies on SEER-Medicare Linked Database started with the month of diagnosis, e.g., Lu-Yao & Yao 1997, Godley et al. 2003 and Lu-Yao et al. 2012. This study defined the starting

time as the month of the first active treatment. Hence, it excluded the period when patients were diagnosed and followed by watchful waiting. By definition, survival curve does not directly represent the study that starts with the month of the diagnosis, as appears commonly in the literature.

One limitation is that the results of metastastatic free survival were not validated, as it was not routinely reported in observation study (time to metastasis instead) for high risk localised prostate cancer. The speed of reduction of the Kaplan-Meier curve of MFS slowed near the tail. It is possible that ICD 9 codes for metastasis were not correctly captured in earlier period of claims or that staging or PSA value was not precise. Some lower risk patients diagnosed in early years were included in this patient group. Other information bias also exists in defining MFS. There are some concerns about using SEER to identify bone marrow metastasis (Onukwugha et al. 2012). Another limitation is that sample selection criteria was not consistent, as Gleason scores were missing before 2004. Patients included at different periods might not be similar. In addition, as SAS PROC LIFEREG computation did converge; thus, forcing a Weibull distribution to cross two observation points was not optimal, as it ignored most data points. This delimma is an issue only when we have to construct a hypothetical treatment arm. If a head to head study is available, we can use the data at hand to either fit the data using more flexible function forms or use the Kaplan-Meier curve directly.

The main strength of this study was that it was a population based, US specific patient registry data with long term follow up. Since a health economic model from a US payer perspective needs to build its decision based on representative population, this study is more favorable than either Wilt et al. (2012) or Bill-Axelson et al. (2014), even though those published studies might have better assessment of metastasis. Study results of completed or ongoing phase III studies can be

used to inform the model. In addition, the dataset provided enough data to investigate subpopulation. If needed, it is feasible to build all the covariates into the cost-effectiveness model, e.g., we can just assess a subgroup, such as age 75+, or the local advanced patients.

In summary, overall survival of US patients with high-risk localized prostate cancer based on SEER-Medicare Linked Database was consistent with other large studies. The result of metastasis-free survival estimation was one of best that we could obtain based on observational studies. Such information is important for cost-effectiveness model in the following chapters.

Table 3.1) Patient characteristics

N (%)	Diagnosed <=2003	Diagnosed >=2004	All
Sample size	14,790	9,304	24,094
Year of diagnosis, median (IQR)	1998(1993,2001)	2007(2005,2008)	2002(1996,2006)
Follow up median (IQR), months	107(70,142)	48(34,66)	76(44,119)
Age at study index (mean, std)	72.6(5.5)	73.02(6.1)	72.75(5.7)
Race			
African American	1,446(9.8%)	1,110(11.9%)	2,556(10.6%)
White	12,252(82.8%)	7,376(79.3%)	19,628(81.5%)
Other	1,092(7.4%)	818(8.8%)	1,910(7.9%)
Gleason Score			
<8		2,674(28.7%)	2,674(28.7%)
8		3,707(39.8%)	3,707(39.8%)
9		2,436(26.2%)	2,436(26.2%)
10		236(2.5%)	236(2.5%)
Unknown		251(2.7%)	251(2.7%)
Clinical stage			
T0-T2	8,558(57.9%)	7,978(85.8%)	16,536(68.6%)
T3a	2,777(18.8%)	709(7.6%)	3,486(14.5%)
T3b	1,100(7.4%)	361(3.9%)	1,461(6.1%)
T4	415(2.8%)	163(1.8%)	578(2.4%)
Other	1,940(13.1%)	93(1.0%)	2,033(8.4%)
Modality of treatment [a]			
Radiotherapy	6,710(45.4%)	5,109(54.9%)	11,819(49.0%)
Prostatectomy	6,741(45.6%)	3,306(35.5%)	10,047(41.7%)
Hormone therapy	1,339(9.1%)	889(9.6%)	2,228(9.3%)
Vital status at last of follow up (12/31/2011)			
Died	8,372(56.6%)	1,585(17.0%)	9,957(41.3%)
Alive	6,418(43.4%)	7,719(83.0%)	14,137(58.7%)
Charlson comorbidity [b]			
0	10,645(71.5%)	5,929(63.7%)	16,574(68.8%)
1	1,849(12.5%)	1,559(16.8%)	3,408(14.1%)
2+	668 (4.5%)	839 (9.0%)	1,507 (6.3%)
Unknown	1,628(11.5%)	977(10.5%)	2,605(10.8%)
SEER regions			
Northeast	1,930(13.1%)	1951(21.0%)	3,881(16.1%)
North-central	3,363(22.7%)	870(9.4%)	4,233(17.6%)
West	7,388(50.0%)	4276(46.0%)	11,664(48.4%)
South	1,492(10.1%)	1520(16.3%)	3,012(12.5%)
Unknown	617(4.2%)	687(7.4%)	1,304(5.4%)

Abbreviation, IQR= interquartile range

[a] The treatment hierarchy was surgery, radiotherapy and hormone therapy. If a patient had them all, he was classified as surgery.

[b] if patient had no coverage one year prior to his diagnosis, and his prior Charlson index was missing, then his comorbidity was set as unknown.

Table 3.2) Metastasis-free survival by subgroup

Group	N	Median (IQR), months	p-value
Total	24,094	74(18,162)	
By severity [a]			
Clinical Localized	22,055	78(19,167)	<0.0001
Locally advanced	2,039	51(13,119)	
By age group [b]			
Between 65 and 74	16,175	99(23,199)	<0.0001
Above 75	7,919	46(12,105)	
By diagnosis period			
<=1995 (a)	5,870	80(34,156)	
1996-2000 (b)	3,921	69(19,165)	.022 (2001+ versus <=1995)
2001+ (c)	14,303	77(12,174)	0.85 (2001+ versus 1996-2000)
By treatment [c]			
Prostatectomy	10,047	131(44,222)	<0.0001
Radiotherapy or ADT	14,047	49(11,115)	

Abbreviation, ADT=androgen deprivation therapy, IQR= interquartile range
[a] Locally advanced patients have short median of MFS than those of clinical localized
[b] Older patients (age≥75) have short median of MFS than those of age between 65 and 74
[c] Patient started with prostatectomy are associated with favorable MFS

Table 3.3) Multivariate proportional hazard model of Overall Survival (OS) and Metastasis-free Survival (MFS)

	OS				MFS			
	Parameter	SE	P-value	HR	Parameter	SE	P-value	HR
Locally advanced	0.226	0.031	<.0001	1.254	0.315	0.027	<.0001	1.370
Age 75+	0.655	0.022	<.0001	1.923	0.326	0.018	<.0001	1.385
Diagnosed before 2000	0.400	0.024	<.0001	1.492	-0.040	0.018	0.027	0.961
Prostatectomy	-0.820	0.024	<.0001	0.441	-0.692	0.019	<.0001	0.500

Abbreviation, SE=standard error, HR=hazard ratio
Note: patients who were locally advanced, older (≥75), and not being treated with prostatectomy were expected to have worse prognosis

Table 3.4) Goodness of fit of model selection

	Weibull	Log-normal	Log-logistic	Exponential
MFS				
2 log likelihood	76,696[a]	77,404	165,412	167,425
AIC	76,700	77,408	165,416	167,427
AICC	76,700	77,408	165,416	167,427
BIC	76,717	77,424	165,432	167,435
OS				
2 log likelihood	-313,825	-315,279	-313,127	19,914
AIC	-313,821	-315,275	-313,123	19,916
AICC	-313,821	-315,275	-313,123	19,916
BIC	-313,806	-315,261	-313,109	19,923

Abbreviation, AIC= Akaike information criterion AICC= AIC with a correction for finite sample sizes BIC =Bayesian information criterion

[a] Weibull was chosen for MFS as it was associated with lowest 2log likelihood, AIC, AICC and BIC.

Table 3.5) Predictive model of Metastasis-free survival

SAS output	Weibull*	Exponential	Log-normal	Log-logistics
Intercept	4.7188 (0.0119)	4.6463 (0.0082)	4.1068 (0.0150)	4.1635 (0.0140)
Scale	1.4228 (0.0101)	1(0)	2.0743 (0.0128)	1.1864 (0.0083)
Weibull scale	112.0329 (1.3357)	104.2035 (0.8558)		
Weibull shape	0.7028 (0.0050)	1 (0)		

*Final model was chosen

Table 3.6) Predictive model of Overall Survival

SAS output	Weibull manually fit*	Exponential
Intercept		0.0001 (0.01)
Weibull scale	0.000767	1.0001 (0.01)
Weibull shape	1.399615	1 (0)

*Final model was chosen

Figure 3.1) Patients selection flowchart

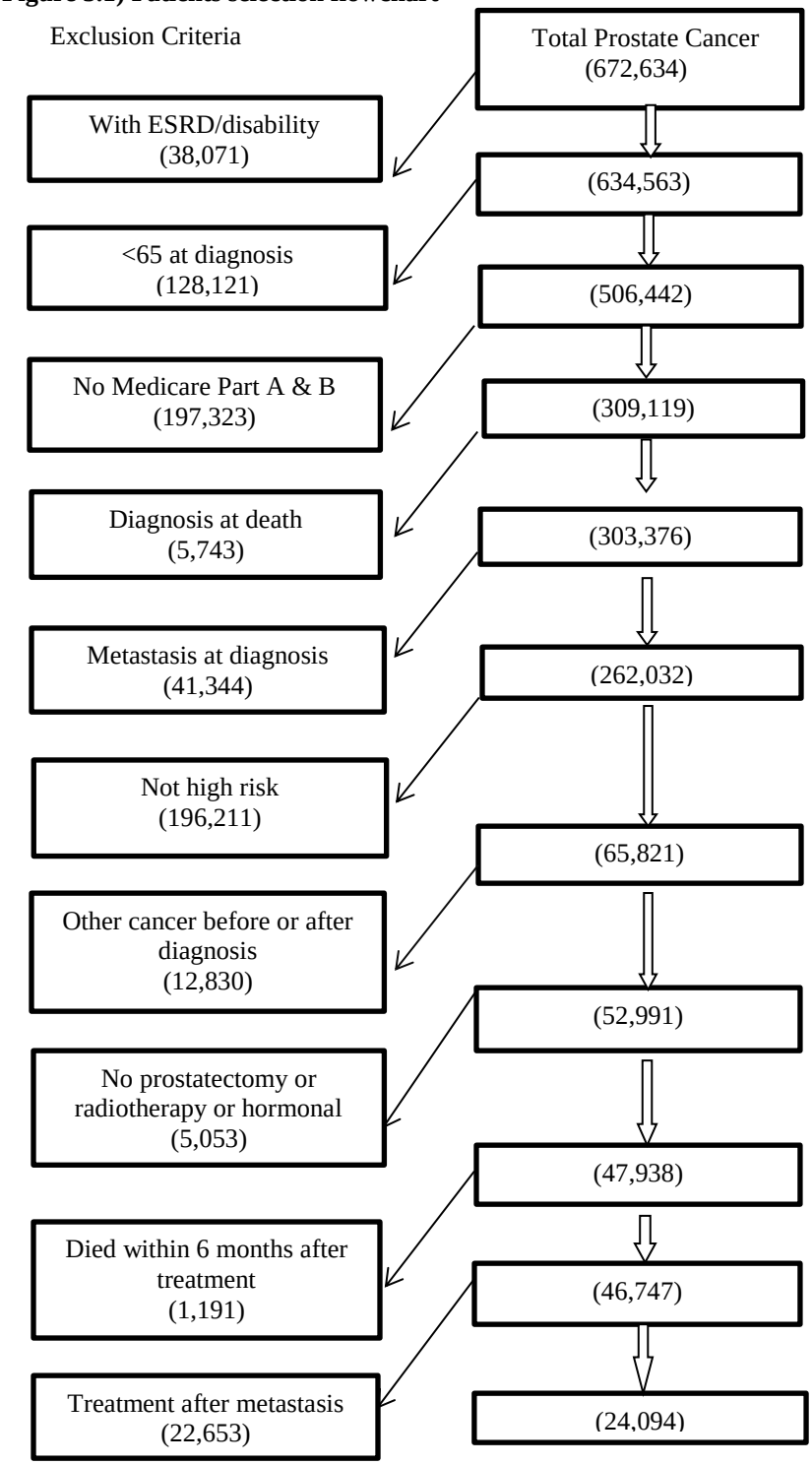
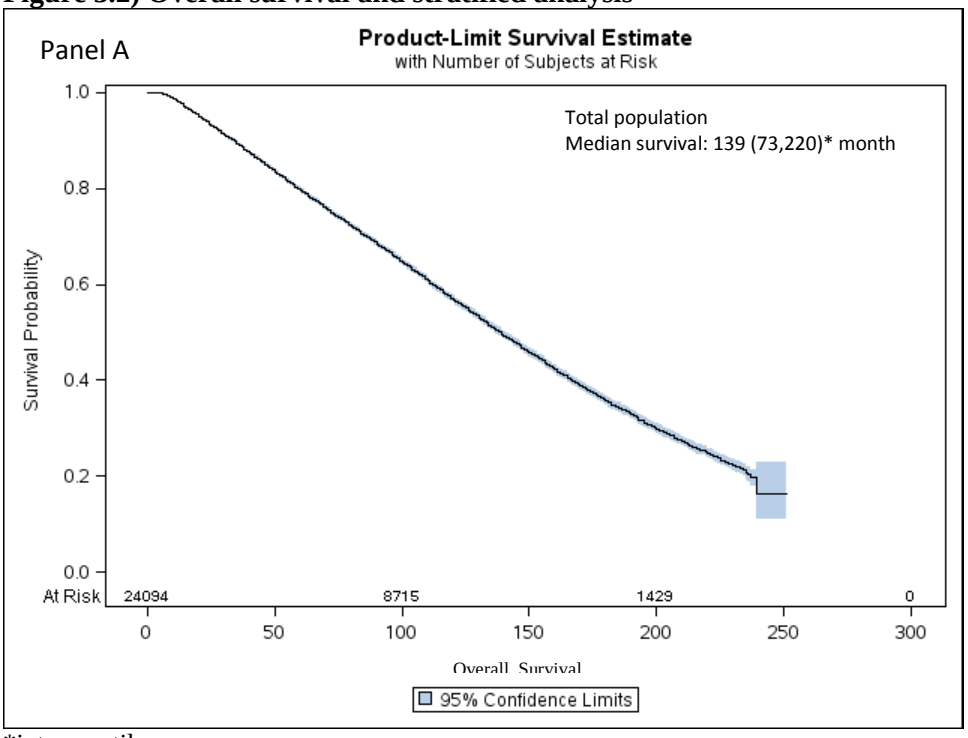
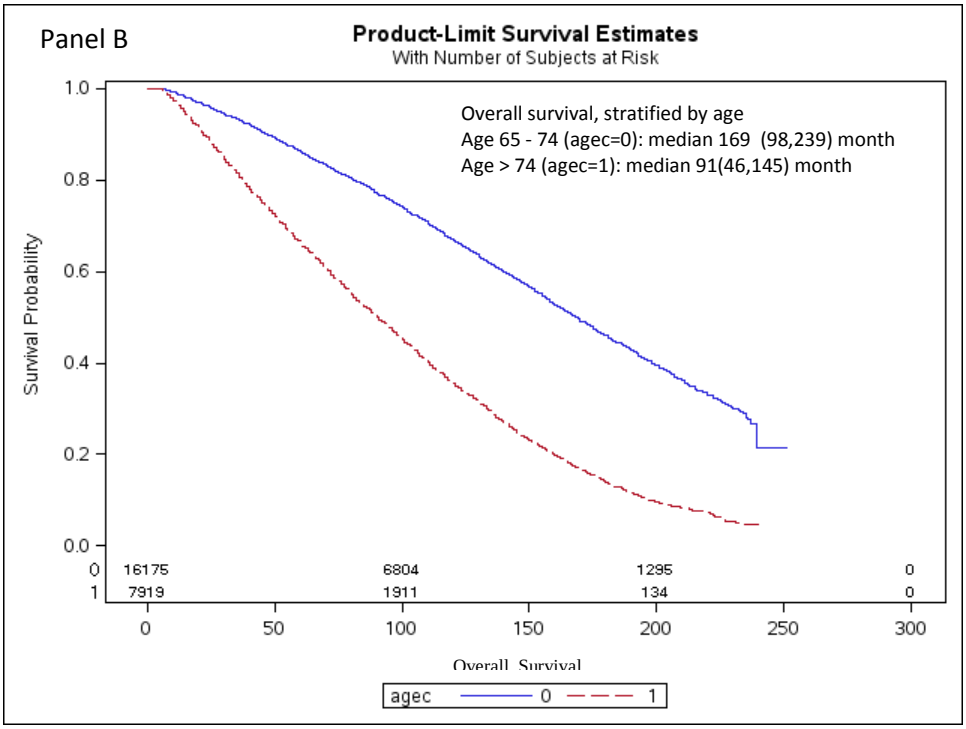


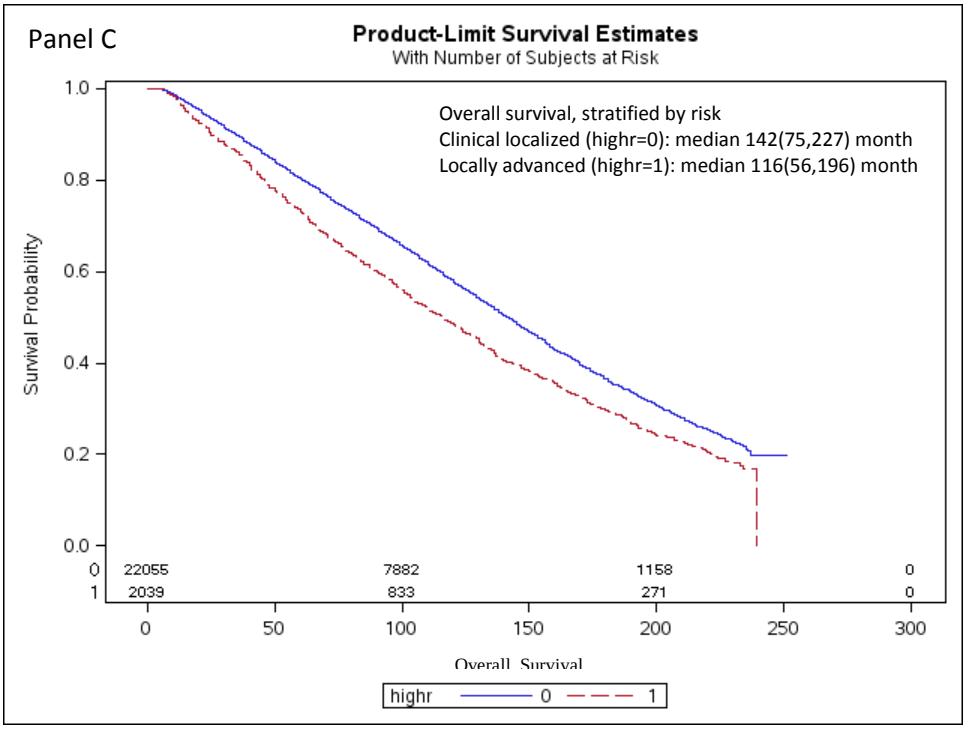
Figure 3.2) Overall survival and stratified analysis



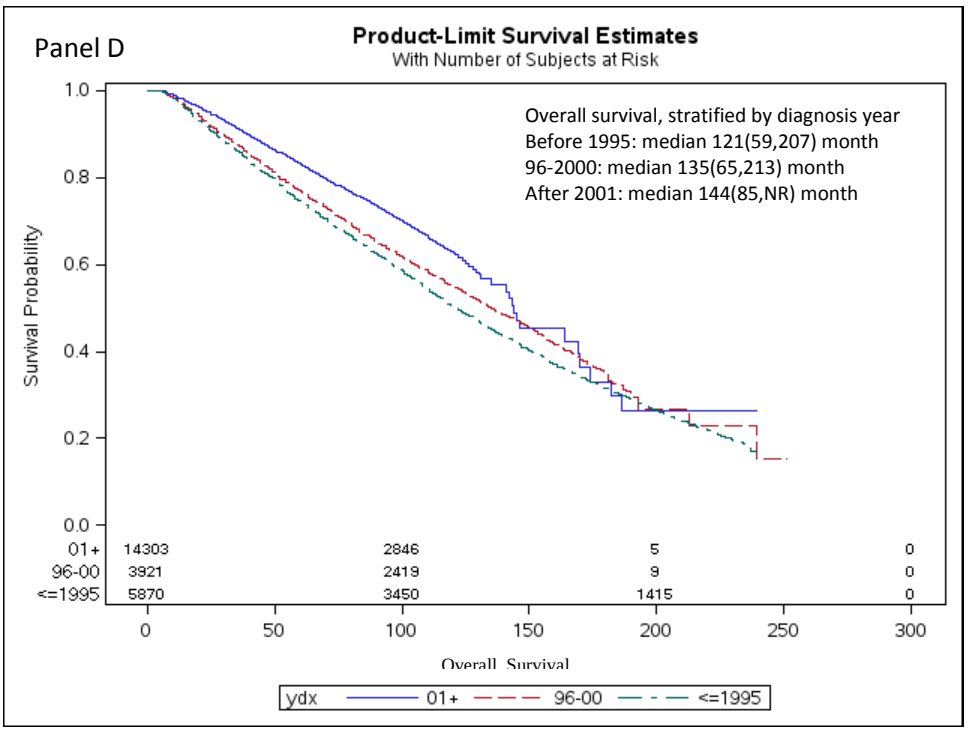
*interquartile range

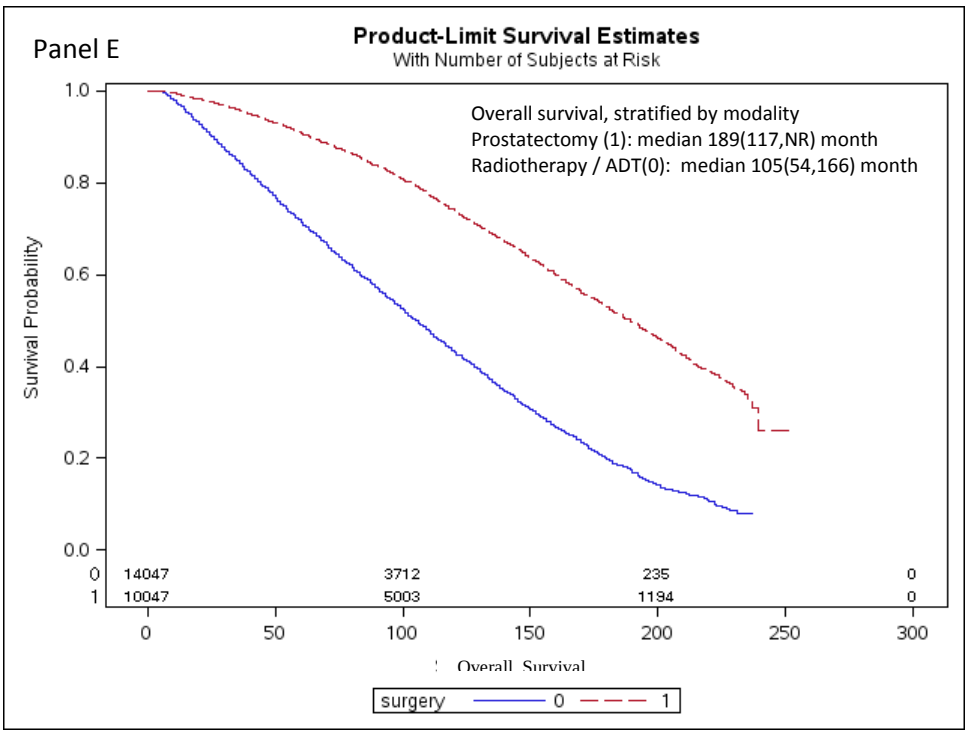


Panel C



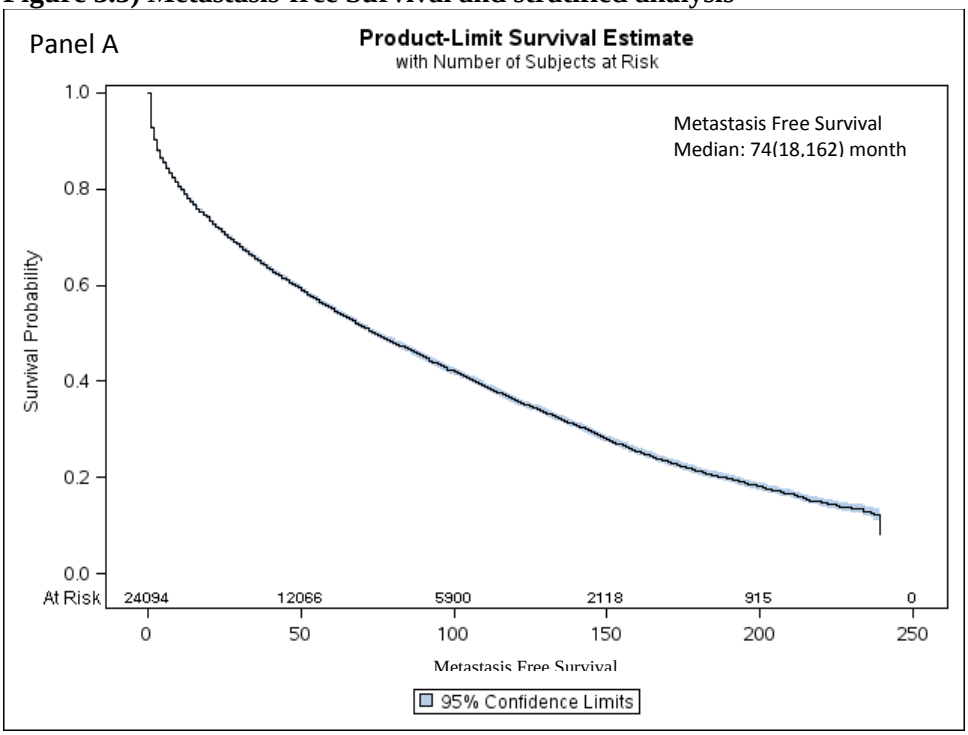
Panel D

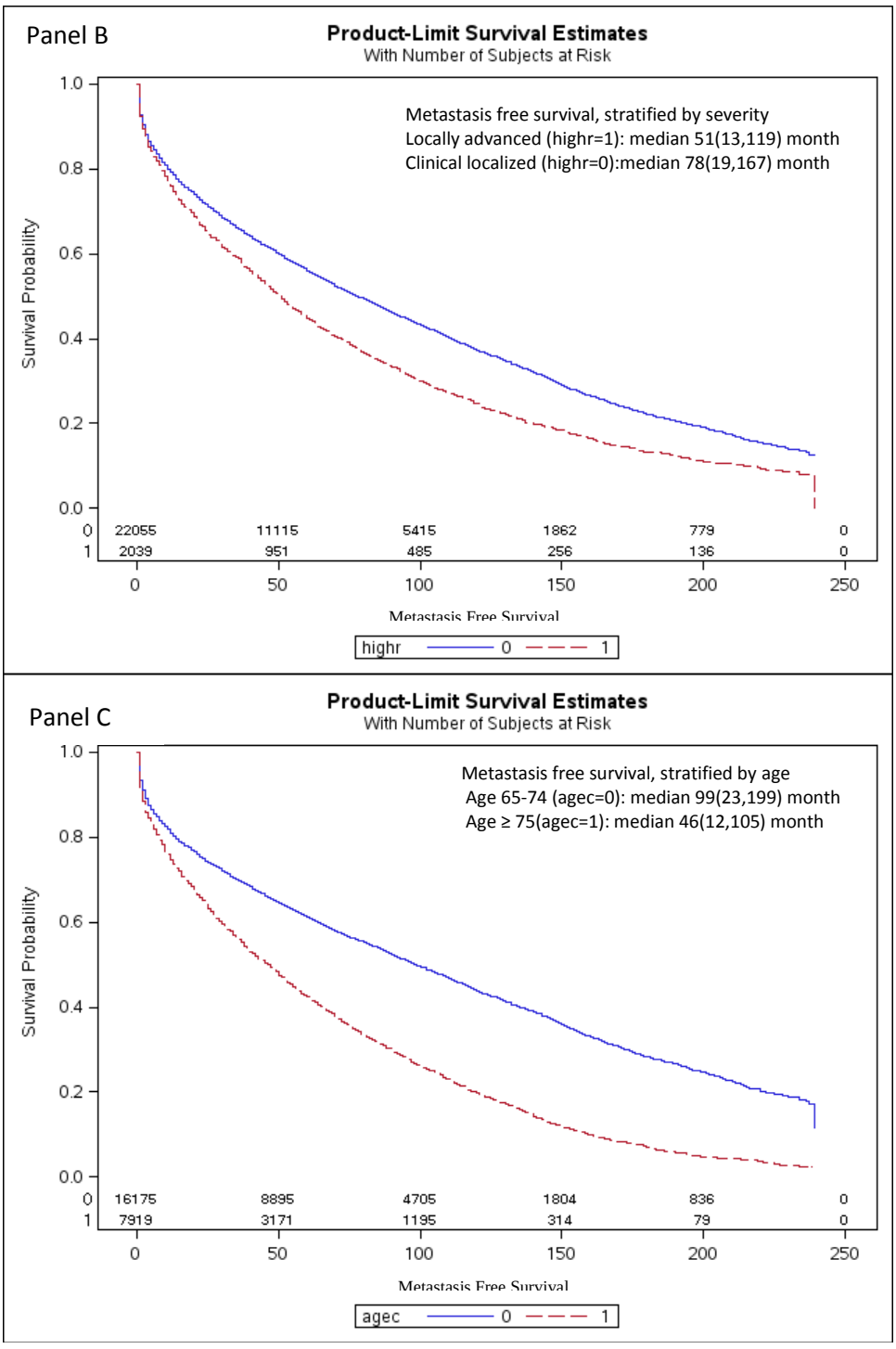


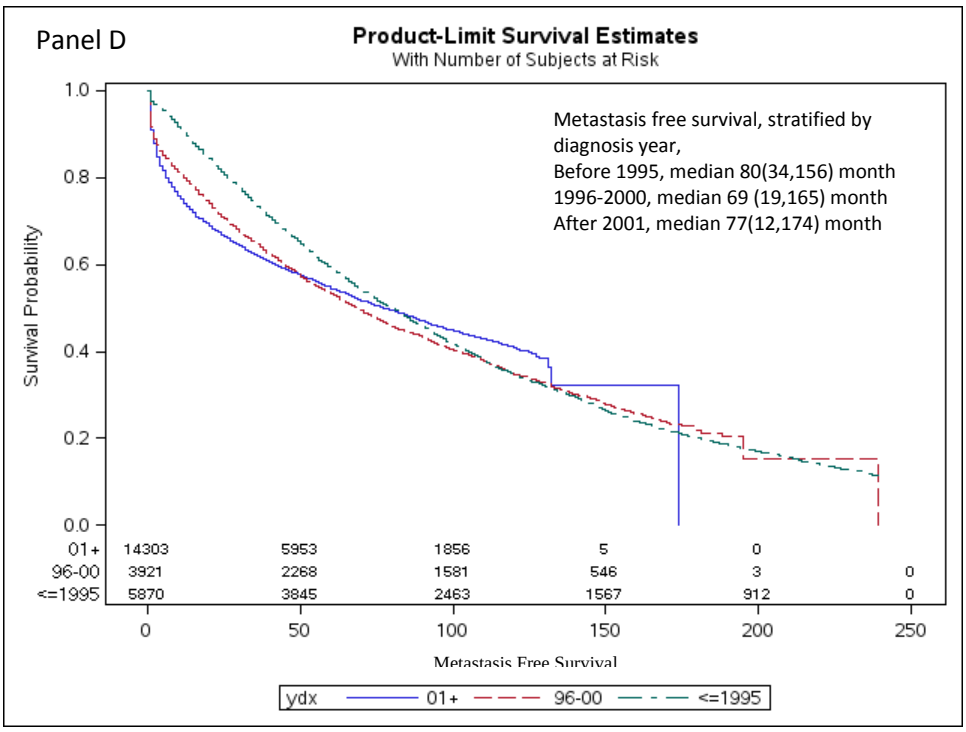


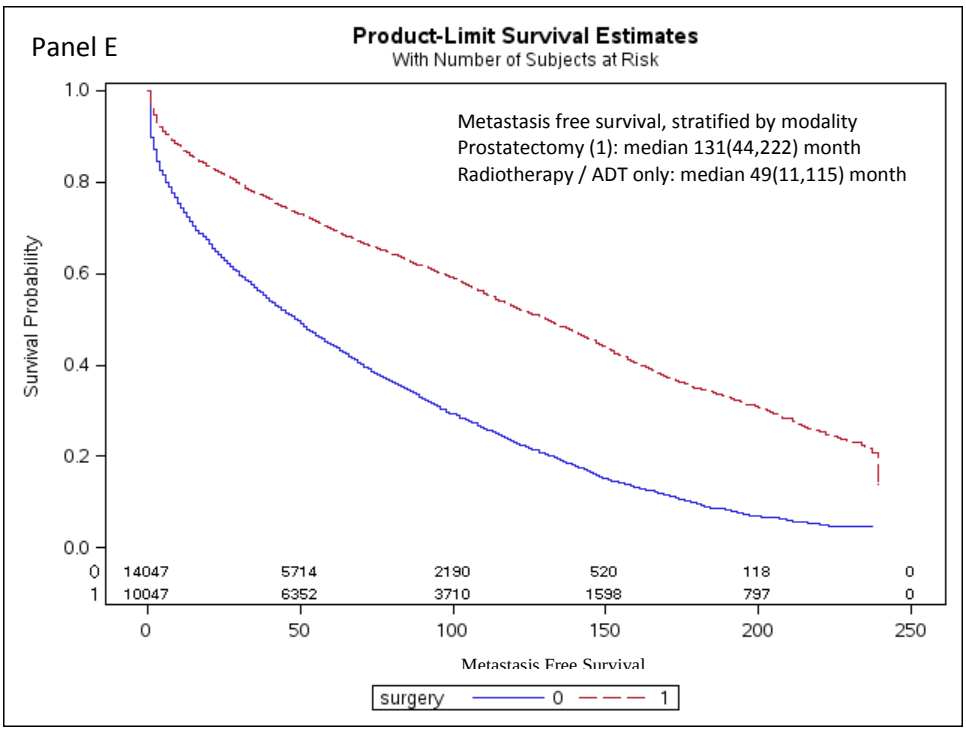
Note: NR= not reached, interquartile ranges were included in brackets

Figure 3.3) Metastasis-free Survival and stratified analysis



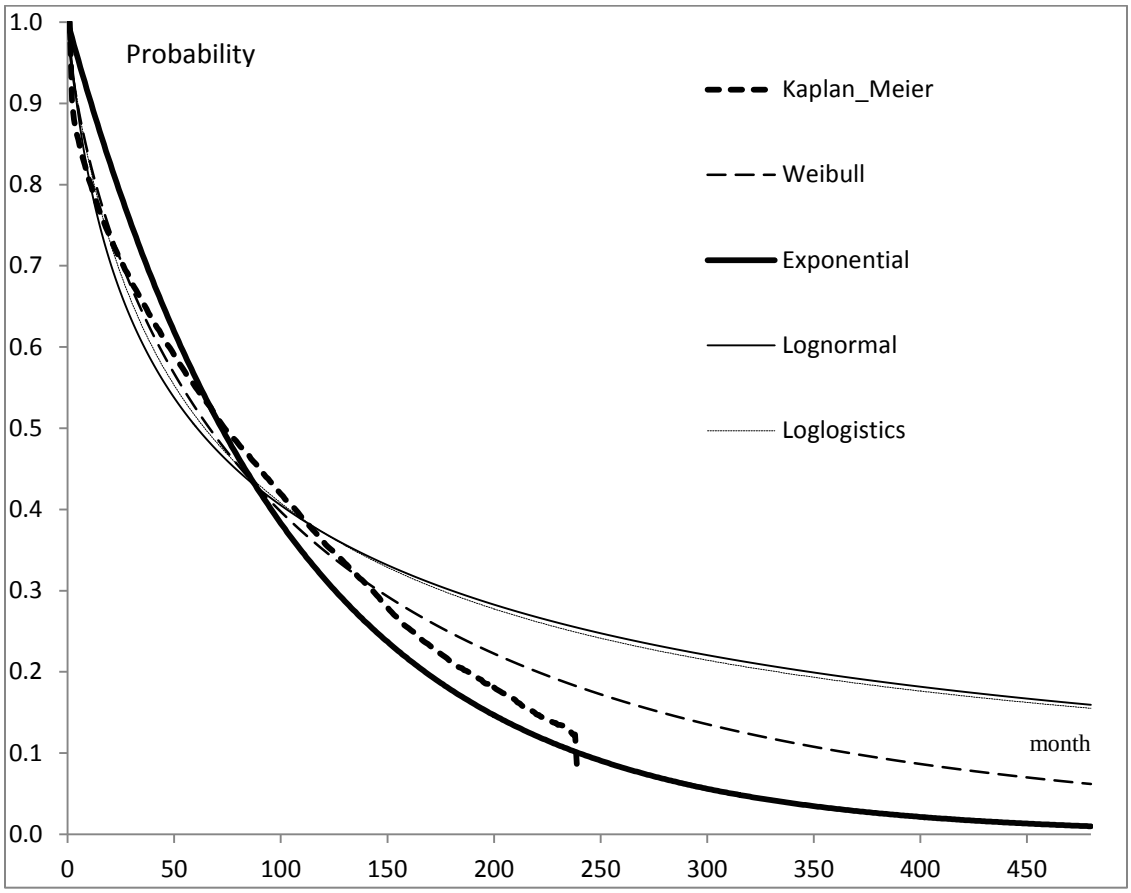

Panel B
Product-Limit Survival Estimates
With Number of Subjects at Risk
Metastasis free survival, stratified by severity
Locally advanced (highr=1): median 51(13,119) month
Clinical localized (highr=0):median 78(19,167) month
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 22055 11115 5415 1862 779 0
1 2039 951 485 256 136 0
0 50 100 150 200 250
Metastasis Free Survival
highr 0 1
Panel C
Product-Limit Survival Estimates
With Number of Subjects at Risk
Metastasis free survival, stratified by age
Age 65-74 (agec=0): median 99(23,199) month
Age ≥ 75(agec=1): median 46(12,105) month
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 16175 8895 4705 1804 836 0
1 7919 3171 1195 314 79 0
0 50 100 150 200 250
Metastasis Free Survival
agec 0 1





Note: NR= not reached, interquartile ranges were included in brackets

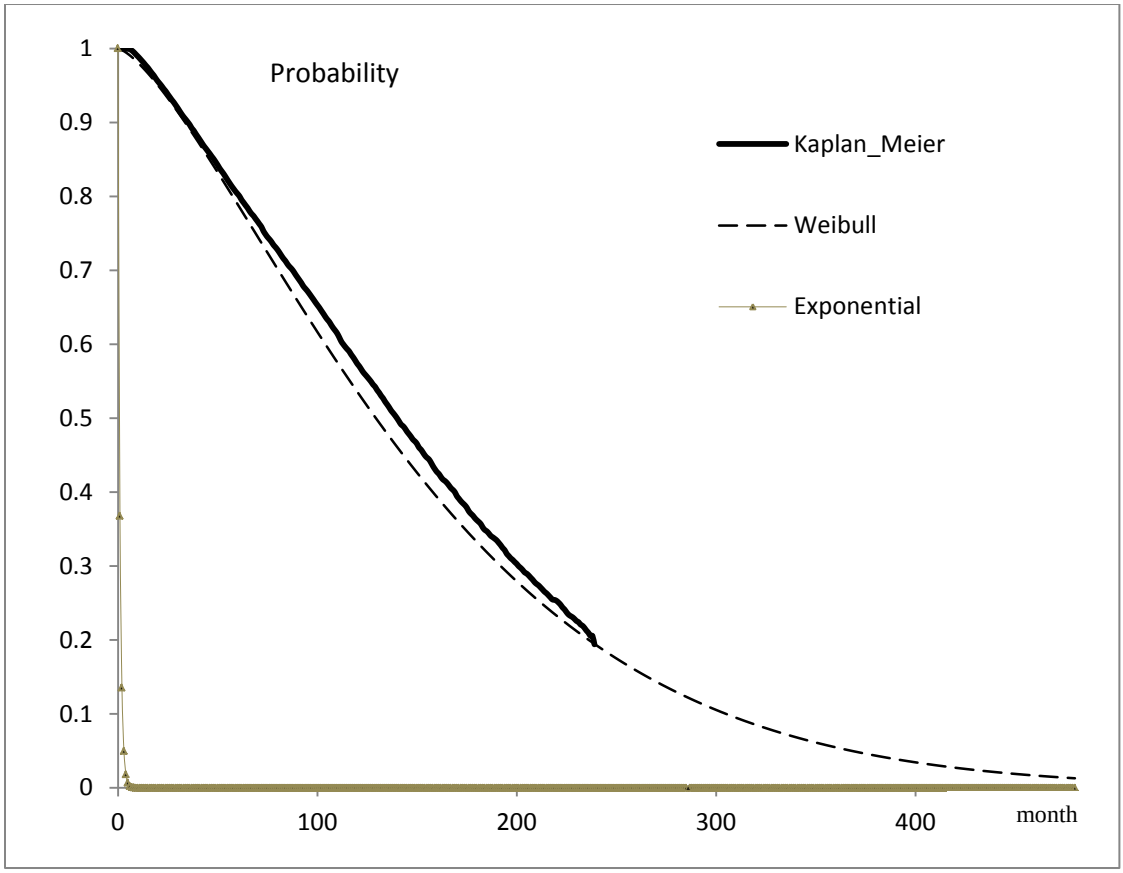
Figure 3.4) Parametric fitting of MFS



From the right side, log-normal remains at the top of five curve with fine continuous line; log-logistics curve is below the log-normal curve, with fine dotted line;Weibull is below log-logistics represented by a fine dashed line; Kaplan-meier curve is the thick dashed line; exponential is the one at the bottom with thick solid line.

From the figure, Weibull curve was closest to the Kaplan-Meier curve from time zero to month 150. After month 150, Kaplain-Meier curve is between the Weibull curve and exponential curve.

Figure 3.5) Parametric fitting of Overall Survival



From the right side, Kaplan-Meier curve is the thick solid line at the top. Weibull curve is the one next to it with dashed line. Exponential curve was the curve close to the Y axis and X axis, apparently not a good fit. Based on visual inspection, Weibull curve was close enough to simulate the Kaplan-Meier curve.

Chapter 4. Estimating the disease management costs by using SEER-Medicare Linked Database

4.1 Introduction

Published cost-effectiveness studies on localized prostate cancer reported different cost estimates (Table 2.4). However, those data were either not from US public payer perspective or not from the actual patient groups under the investigation. Some of them were outdated while others did not reflect the model structure. It might be misleading if plugging those estimates directly in the model without justification. The objective of this chapter is to evaluate the cost patterns in the SEER-Medicare Linked Database and to make a recommendation of cost inputs for the model.

4.2 Methods

In the previous chapter, 24,094 patients diagnosed with high-risk localized prostate cancer were identified. Their claims were analyzed in this chapter. Payment costs were analyzed by disease states (i.e., metastasis-free period, post metastasis period) and the event of death. State cost was defined as monthly average of the lump sum cost in specific disease state. Individual payments from 1991 to 2011 following index months (e.g., the first month when patients were treated with a prostatectomy, radiotherapy or ADT, or the first month the cancer spread) were summed up by each patient and month. The total amounts paid were analyzed to include payments from both Medicare and patients. Costs included hospital stays, emergency room, hospital outpatient visits and physician offices visits. Claims associated with home health services [Home Health (HHA)], hospice, equipment, and durable event costs [Durable Medical Equipment (DME), Part D Event (PDE)] were not included because of data availability. For patients who died, the cost for the last year was summarized as the end of life cost. Price was adjusted for the 2013 calendar year by consumer price index of medical care service (Bureau of Labor Statistics. 2015).

To understand the treatment pattern, the frequencies of major medical interventions (see definition in Table 4.1) were analyzed, e.g., radiation, surgical, and hormone therapies, frequency of hospitalization. They were reported by first and second year; and the stage of metastasis-free and post-metastasis for patients who had at least a history of two years at different disease state.

In this cohort, 58.7% of patients were still alive at the time of the study cutoff date (December, 2011). Records collected after the cutoff time were excluded. Due to substantial number of exclusions, the average cost per month for the full sample was biased because patients had variable follow-up. Bang and Tsiatis (2000) recommended a nonparametric estimator of the inverse probability, which reduced the first year costs and elevated the subsequent cost estimators. With high volume of patient claims, a simple solution was to focus only on the records of those who died before the cutoff date. Adjustment was performed in a subgroup of patients who died during this period. Summary statistics are reported by two methods. Lastly, a multivariate linear regression model of the overall mean cost, with selected variables including disease state (post metastasis versus metastasis free), year of disease state (first year versus subsequent year), disease severity (locally advanced versus high risk localized), age (older than 75versus 65-74), diagnosis period (post 2000 versus before 2000), and having a prostatectomy, was conducted to understand the differences among those variables.

4.3 Results

Initial demographic, clinical, and social economic patient characteristics are described in Chapter 3 (Table 3.1). Metastasis-free and post-metastasis costs were reported first as time series starting from the index month (Figure 4.1-4.2) by two methods. The average costs for both states were L shaped, i.e., high in the first year, after which they dropped and remained low in the subsequent years. Near the tails of the time series, average costs became volatile especially for the post

metastasis state, though the trends were still steady. As time went by, the sample size reduced substantially (see numbers under figures). For instance, the total sample of metastasis free dropped from 18,192 at time zero to 506 at month 200, with 1% of patients left. Consequently, the costs estimates near the tails were not reliable. In both Figures 4.1 and 4.2, mean costs were also reported by censor adjusted (dotted line) and unadjusted (solid line) methods. With adjustment, the average monthly cost increased at the tails regardless of disease states. This pattern was consistent with Bang and Tsiatis (2000), although they used a non-parametric statistical reweighting method.

To understand the reason why first year cost was substantially higher compared to the costs in subsequent years, a patient cohort with 6,163 patients was identified with at least two-year history of metastasis-free. The other cohort comprising 15,125 patients had at least a two-year history of metastasis. There were 1,944 patients in both cohorts. Table 4.2 summarizes the number of patients who had at least one medical intervention each year by disease state, namely, brachytherapy, CRT, IMRT, proton, cryotherapy, radical prostatectomy, orchiectomy and LHRHa. Patients with 1, 2, or more hospital stays were also reported. In the same disease state, patients in the first year following their index months obtained more intensive medical care. However, substantially less patients were treated in the second year, which explained observed cost differences. Of course, patients who had a surgery, such as radical prostatectomy and orchiectomy had no needs to repeat those surgeries in subsequent years. The reduction of other treatments might imply that the disease was under control. Similar pattern emerged in the post-metastasis state. More treatments were given in the first year. In addition, more patients received LHRHa in the post-metastasis phase than in the metastasis free phase, regardless of whether it was the first year. In summary, the medical resource utilization pattern indicated the treatment modality differed either in the first or second year and either before or after metastasis.

Table 4.3 reported descriptive statistics of all costs estimates. Costs did not follow a normal distribution. Medians were below the means. For instance, the median and mean of monthly average cost during the first year for the metastasis-free state were $258.5 and $2,751.8, respectively. The cost distributions were positively skewed. Except for the end of life cost, the standard deviation was about twice the size of the mean, indicating substantial dispersion of the cost data. As expected, censor adjusted results were higher compared to the unadjusted, except for the first year costs. For the first year costs, adjustment reduced the cost estimate by less than 15%. For subsequent years, the adjustment caused the cost estimate to increase by no more than 30%.

Generalized linear regression model showed that the censor adjusted overall mean costs differed significantly across age, severity, diagnosis period, disease state and year of disease state (Table 4.4). The costs were higher for the first year of disease state versus subsequent years, locally advanced versus high risk localized, post metastasis versus metastasis free, recent diagnosed versus diagnosed earlier, and age younger than 75 versus older. The overall costs were lower for patients treated with prostatectomy than treated with radiation or hormonal therapy

4.4 Discussions

This analysis proved that HRLPC patients experienced a significant cost burden, especially in the first year of active treatment, in the first year when cancer spread, and at the end of life. It also showed that during the subsequent year of the treatment, the costs were lower compared to those in the first year for both metastasis free and post metastasis states.

Monthly costs for both disease states were not evenly distributed. The first year was accompanied by higher costs, whereas the costs of subsequent years were substantially less. This pattern is

associated with intensive medical care in the first year of that disease state. Patients may be more actively seeking medical help when they are diagnosed or when they know that the tumor spread. With time, they learn to cope with their disease. For the index month in the first year, the adjusted average monthly cost was $2,579.2, which was translated into an annual cost of $30,950.4 if a patient was free of metastasis. Correspondingly, the cost of post metastasis was $25,743.6 in the first year. Referring to the review of cost in Chapter 2, the numbers were not comparable, as definitions differed. Annul direct medical costs reported by Copperberg et al. (2013) and Bayoumi et al. (2000) were lower. However, those studies as well as Parthan et al.'s (2012) study reported higher treatment costs separately as event costs. Roehrborn et al. (2009) used the same data sources for the period between 1991 and 2002 to analyze the cost pattern. They reported just the first year costs of treating prostate cancer. Each patient was ensured to have at least one-year survival. The costs of subsequent years were not discussed. They reported annual cost for stage 3 and stage 4 as $22,030 and $25,521, respectively, without adjusting for inflation (Roehrborn et al. 2009). Those numbers were not far off from the costs of both states during the first year in this study. In the medical resource use analysis, they reported 12.2% and 9.8% for stage 3 and 4 patients who were treated with IMRT. In this cohort, 11.2% of metastasis-free and 16.9% of post-metastasis were treated with IMRT patients in the first year. In addition, nearly one of eleven patients was treated with brachytherapy whereas in Roehrborn et al.2009, this rate was only 1%. As time frames of the studies differed, the cost pattern could have changed over the years. Cooperberg et al. (2013) reported higher end of life cost compared to this study, as it did not include HHA, hospice, equipment, and durable event costs.

One major drawback of this study was that the costs were only from MEDPAR, NCH - Carrier (physician/supplier) and Outpatient datasets, although the study was comprehensive in terms of physician office, skill nursing facility, hospital inpatients, and outpatient. It did not include HHA,

hospice, equipment, durable event costs, and Part D Event. HHA and hospice were needed in the end stage of patients' life because patient mobility was restricted. Part D applied to oral medicines, such as oral antiandrogen (e.g., bicalutamide), pain medication, or Antiemetic. Although their costs were not substantial, missing data on these variables biased the cost estimate toward the null, especially during the year of the end of life. Adjustment was not made because the share of those items in total patient costs was unknown. In addition, the SEER-Medicare linked Database did not include patients who had Veteran Affairs or private insurances. As patients might be older than the general population, and we know age is important prognostics factor based on Chapter 3, we need to be cautious about interpreting the results.

The cost estimates defined by disease states are important data inputs for upcoming modeling exercises. This is the first study to analyze cost by disease states using SEER-Medicare for HRLPC patients. Although the definitions were not consistent, the cost estimates from this study did not differ substantially from the existing studies (Bayoumi et al. 2000; Cooperberg et al. 2013; Parthan et al. 2012; Roehrborn et al. 2009). One interesting finding is that the costs of subsequent year were substantially lower compared to those of first year, regardless of disease states. Further researches should be designed to understand the changing treatment pattern of this patient group across the treatment pathway.

In summary, this analysis showed that substantial expenses incurred for US Medicare HRLPC patients. Excessive disease management costs were observed for patients who started active treatment, when tumor spread, and at the end of life. Finally, although observational data analyses can retrieve information that experimental studies cannot generate, caution should be applied when analyzing and interpreting the results because of the potential bias.

Table 4.1) Diagnosis and procedure codes used to define the treatments

Treatment	Diagnosis and procedure codes
Brachytherapy	ICD-9-CM procedure codes: 9227 CPT codes:55860, 55865, 55862, 55859, 55875, C1715, C1717, C1719, C1728, C2634, C2635, C2636, C2638, C2639, C2640, C2641, Q3001, 77776, 77777, 77778, 77799, 77785, 77786, 77787
CRT	CPT codes:77407,77408, 77409, 77411, 77412, 77413, 77414, 77416
IMRT	CPT codes: 77418
Proton	CPT codes: 77520,77522, 77523,77525
Cryotherapy	ICD-9-CM procedure codes: 6062 CPT codes, 55873, G0160, G0161
Orchiectomy	CPT codes: 54520, 54521,54522,54530,54535
Prostatectomy	ICD-9-CM procedure codes: 603, 604,605 CPT code: 55821, 55801, 55810, 55812, 55815, 55831, 55840, 55842, 55845
LHRHa	HCPCS codes: J0128, J9202, J1950, J9225, J9217, J9218, J9219, J3315

Abbreviation: ICD= International Classification of Diseases, CPT=Current Procedural Terminology, HCPCS= Healthcare Common Procedure Coding, IMRT=Image-guided radiation therapy, CRT=conformal radiotherapy, LHRHa=Luteinizing hormone-releasing hormone agonists

Table 4.2) Medical resource utilization pattern

	Metastasis-free (N=15,125)				Post-metastasis(N=6,163)			
	Year 1		Year 2		Year 1		Year 2	
EBRT	99	0.7%	19	0.1%	30	0.5%	24	0.4%
Brachytherapy	1,126	7.4%	11	0.1%	554	9.0%	18	0.3%
CRT	3,475	23.0%	218	1.4%	1,486	24.1%	88	1.4%
IMRT	1,700	11.2%	138	0.9%	1,043	16.9%	53	0.9%
Proton	67	0.4%	5	0.0%	18	0.3%	0	0.0%
Cryotherapy	34	0.2%	7	0.1%	12	0.2%	4	0.1%
Prostatectomy	2,846	18.8%	7	0.1%	124	2.0%	1	0.0%
Orchiectomy	278	1.8%	71	0.5%	67	1.1%	23	0.4%
LHRHa	900	6.0%	481	3.2%	5,213	84.6%	3382	54.9%
Hospitalization								
1	3,673	24.3%	1269	8.4%	811	13.2%	717	11.6%
2	686	4.5%	437	2.9%	253	4.1%	288	4.7%
3+	811	5.4%	283	1.9%	329	5.3%	195	3.2%

Abbreviation: EBRT=External beam radiation therapy, CRT= conformal radiotherapy, IMRT=Intensity-modulated radiation therapy, LHRHa=luteinizing hormone-releasing hormone agonists

Note: The table reported unique patient counts for each procedure etc. Patients were required to have two years histories in their respective health states. Patients had less medical resource use in the second year in both metastasis-free and post-metastasis states.

Table 4.3) Summary statistics of costs

			Mean	SE	STD	Median	Range	IQR
First year	Metastasis-free	Raw	2,751.8	22.4	8,579.2	258.5	228,868	1,350
		Adjusted	2,579.2	29.7	7,096.0	263.0	153,616	1,470
	Post metastasis	Raw	636.6	2.6	2,124.7	168.1	183,314	407.5
		Adjusted	715.5	4.3	2,082.2	174.7	125,944	450.2
Subsequent years	Metastasis-free	Raw	2,509.9	27.3	7,415.5	654.3	191,583	1,685
		Adjusted	2,145.3	32.2	5,667.8	779.7	191,550	1,770
	Post metastasis	Raw	915.8	4.2	2,159.7	281.8	108,978	842.9
		Adjusted	1,198.5	7.9	2,519.5	407.3	105,829	1,258
Final Year		Raw	21,955.7	318.3	30,719.0	12165.4	577,556	23,654

Abbreviation SE=standard error, STD=standard deviation, IQR= interquartile range

Note: The units of costs were US dollars in 2013.

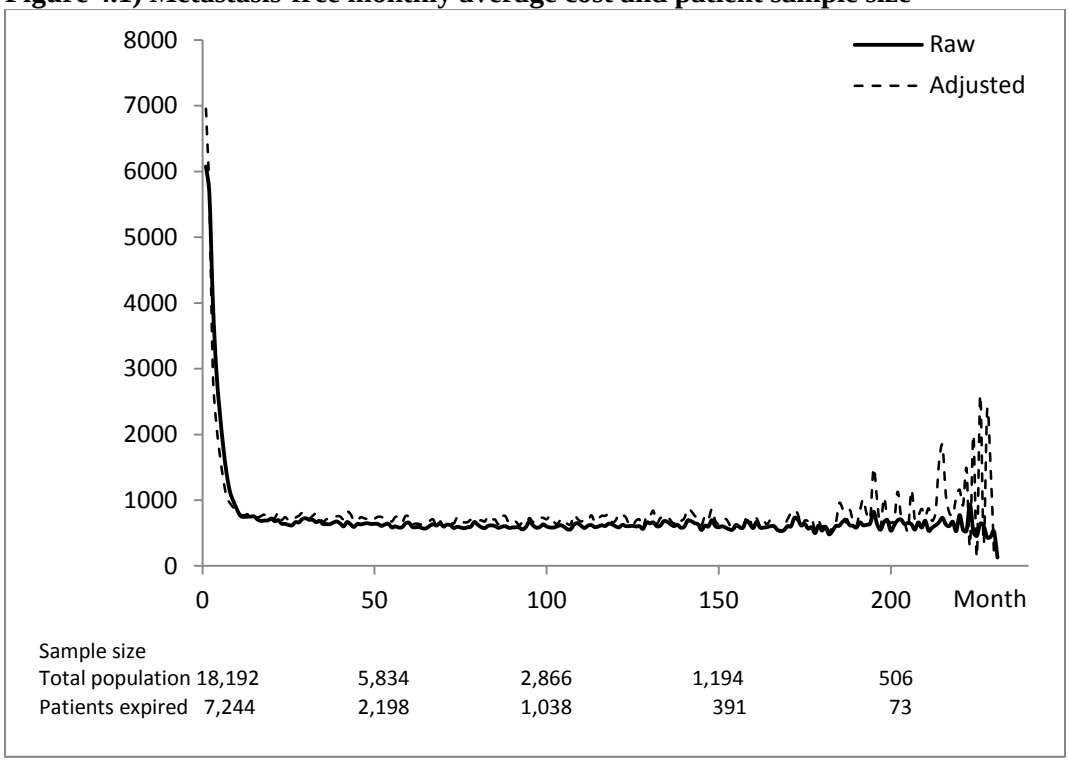
Adjustment made 1st year cost estimates lower and the subsequent year costs higher. Costs were positively skewed.

Table 4.4) Multivariate model of cost

	Parameter estimates	t Value	P value
Intercept	946.6	54.8	<.0001
Post Metastasis	231.4	19.1	<.0001
First year versus subsequent year	1493.4	107.7	<.0001
Locally advanced	39.6	2.4	0.0166
Age 75+	-169.8	-13.7	<.0001
Diagnosis after 2000	308.2	23.4	<.0001
Surgery	-183.7	-14.8	<.0001

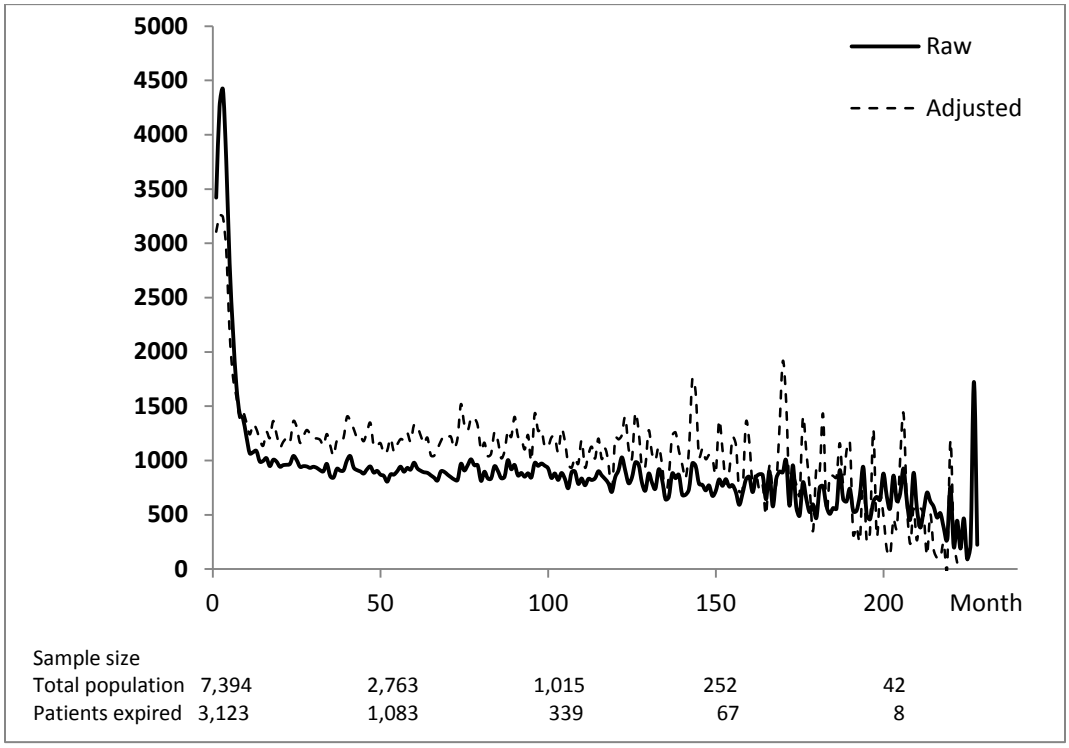
Note: F value= 2087.8, p value <0.001 adjusted R^2 =0.033
Study was conducted on the subset that all patients died in the study period.
Post metastasis, first year, locally advance, recent diagnosed, younger patients were associated with higher costs. Patients treated with surgery were associated with lower costs

Figure 4.1) Metastasis-free monthly average cost and patient sample size



Note: Costs were in US Dollars in 2013. Raw is in solid line based on total population. Adjusted is in dotted line based on the subgroup patients who expired.

Figure 4.2) Post-metastasis monthly average cost and patient sample size



Note: Costs were in US Dollars in 2013. Raw is in solid line based on total population. Adjusted is in dotted line based on the subgroup patients who expired.

Chapter 5. Methodology issues of modeling the CDX cost-effectiveness of targeted neoadjuvant or adjuvant chemotherapy among HRLPC patients

5.1 Overview

This chapter discusses some methodological issues associated with modeling personalized medicine in prostate cancer, i.e., using a CDX to select HRLPC patients for adjuvant or neoadjuvant chemotherapy. We are considering how chemo related treatments delay metastasis and extend survival as well as how utilities of patients are impacted. Relevant states and events are considered.

The idea of modeling either adjuvant or neoadjuvant is virtually the same, except of timing of the major treatment. Taking radical prostatectomy (RP) as an example, the procedure emerges at cycle 0 for adjuvant chemotherapy. For neoadjuvant treatment, RP is conducted after chemotherapy. The model structure is capable of simulating both situations. The difference is mainly in defining time zero, i.e., the time when patients enter the simulation. Such adjustment can be done at the stage of the data analysis, as was done in Chapter 3. From now on, adjuvant chemotherapy is used for demonstration.

5.2 Model structure

An "area under the curve" (AUC) model (Fleeman et al. 2011; Hoyle et al. 2011) uses survival curves to inform transition between states. This is a transition-based survival partition model instead of events based model. Transition between disease states is driven by a survival curve, which is time dependent. Time-to-events simulated by such model requires fewer assumptions because estimated probabilities match closely with observation. The AUC model may alternatively be described as semi-Markov model because it assumes that constant transition

probability is relaxed. The rationale for using AUC model is to regenerate predicted time-to-event curves closely to ensure internal validity.

The systematic review in Chapter 2 found that BFS, PFS, MFS, and OS have been frequently selected as endpoints of clinical trials conducted in neoadjuvant or adjuvant settings. Those endpoints are candidates for modeling, as they are major disease states along disease progression. BFS can largely be defined by patient PSA level and death events. But the actual definition varies in different studies. Disease progression usually involves bone progression when two or more new lesions are found on bone scan. Sometimes it is measured by lymph nodes. BFS or PFS is not available in a claim database as lab or imaging data are not usually available. Information may exist in patient charts, or it may be collected by a prospective study, e.g., RCT. Such information is usually not available to the public. Another challenge of using those surrogate endpoints is the lack of a standard definition. Without the data, neither PFS nor BFS is an optimal endpoint for modeling. Some models classify death into prostate cancer related death and all-cause mortality. If data show differences in cancer related death, it is worth to differentiate them in the model. For instance, if the end of life cost associated with prostate cancer differs from that of all-cause mortality, or if treatments show differences in cancer related mortality, it is a good idea to break them apart. Otherwise, it adds an unnecessary layer of complexity to track the cause of mortality.

In summary, this model describes three health states, i.e., metastasis-free, post-metastasis, and death. It can be easily extended to multiple states, including BFS or PFS, or the state of death can be broken into prostate cancer related death and all-cause mortality to refine the economic benefits of different treatment strategies as long as the data are available. The methodology of

modeling remains the same, except for the increasing the number of health states. Of course, a more complicate model structure means additional assumptions and uncertainty.

Since it is a US population based model, the definition of target population is based on the NCCN guideline, which defines high risk localized prostate cancer as either T3a, Gleason score 8-10, or PSA>20 ng/ml and locally advanced as stage equal or worse than T3b. This model considered both high risk localized and locally advanced patients. The data inputs are based on the reviews in Chapter 2 as well as the data analysis in Chapter 3 and Chapter 4 based on the SEER-Medicare Linked Database. Secondary data are leveraged to make auxiliary assumptions where real world evidences were lacking.

The base case model treats men with standard of care (SOC) (e.g., radiation, surgical or hormone therapies). Based on SOC, the intervention arm was chemotherapy plus SOC whereas control arm was placebo. As a background therapy, SOC changes as patient disease progresses. Depending on the disease stages, treatment may include additional surgery, radiotherapy, ADT deprivation, secondary anti-androgen and chemotherapy. By the end of 2011, new anti-androgen therapies, such as enzalutamide, immunological therapy (sipuleucel-T), and new radioactive therapy agent (radium Ra 223 dichloride), were not yet approved by FDA, except for abiraterone acetate. Detailed history of the treatment was ignored to keep the model structure simple. From now on, we call the intervention arm as chemotherapy and the comparator arm as SOC. This model is built using Microsoft Excel with Visual Basic for Application (VBA). Unlike using programming language, such as C++ or Java, Excel model has been widely accepted by the HTAs because of its transparency and simplicity. People can easily examine formula / macros imbedded in the spreadsheet.

Patients enter the model with different intervention choices, 1) No companion diagnostics and no chemotherapy, i.e., all patients were managed with standard of care, 2) Chemotherapy treatment, and 3) Selective chemotherapy treatment with assistance of a CDX which can be labeled as personalized medicine. At time zero, patients were free of metastasis. A CDx can test patients as either positive or negative. If positive, they received chemotherapy. Otherwise, they were treated with standard of care. As disease progresses, cancer can spread. Patients may die at any time. At each cycle, a patient may remain in his current health state, progress, or die, but cannot regress, i.e., metastasis patients cannot revert to the state of metastasis-free. Model cycle is monthly, which is consistent with how date was reported in SEER-Medicare Linked Database. As chemotherapy is dosed in cycles, it can be easily mapped to month. For a 60-year-old man diagnosed with HRLPC, if he can live up to 100 year old, there was only 480 cycles. Model structure is presented in Figure 5.1, which is consistent with the previous discussed PORT model (Fleming et al. 1993) with a few distinctions. First, the PORT model did not consider CDX. Second, the transition between states in PORT model was driven by transition probabilities. Third, this model does not include a castration resistant stage after metastasis, which was not the focus of the research question.

Generally, in a Markov-like cost-effectiveness model, events can happen at any time of that cycle. Counting membership only at the beginning or at the end of each cycle is a strong assumption. If life expectancy is not long enough, half cycle correction is necessary. For HRLPC patients, it is nice to have such correction although it is not compulsory due to relatively long life expectancy. Nevertheless, half cycle correction is conducted to be consistent with best practices of modeling (Briggs, Claxton & Sculpher 2006).

5.3 Modeling economic outcomes

For the base case model, metastasis-free survival and overall survival of the SOC arm were estimated using SAS PROC LIFEREG (SAS Institute Inc. 2008) to fit a parametric hazard function, such as exponential, Weibull, log-logistics or log-normal, as discussed in Chapter 3. The Kaplan-Meier curve can precisely describe what happened in the observed period, but not for extrapolation. With parametric survival function, lifetime simulation required by payers became possible.

The exponential function incorporates constant hazard. In the case of Weibull function, the hazard is monotonic. It can either increase or decrease, depending on the specifications of parameters. Log-logistic and log-normal distributions often have a long tail, showing a few patients that never die. Except exponential, Weibull, log-logistic and log-normal usually have two parameters. Taking Weibull function as an example, the probability density function is the following (SAS Institute Inc. 2008),

$$f(t) = \lambda\gamma t^{\gamma-1}e^{-\lambda t^{\gamma}} \quad , \qquad (1)$$

where t is the time while γ and λ are the Weibull shape and scale parameters, respectively. The hazard is $\lambda\gamma t^{\gamma-1}$. The survival function is $S(t) = e^{-\lambda t^{\gamma}}$. Given cycle T, the probability of survival S is expressed as $e^{-\lambda T^{\gamma}}$. If the probability is known as S, then time can be solved as

$$T=\left(\frac{-\ln(S)}{\lambda}\right)^{1/\gamma} \qquad (2)$$

The best fitting distribution function was chosen by visual inspection, Akaike Information Criterion (AIC), corrected Akaike information criterion (AICc), or Bayesian Information Criterion (BIC), though the best fit usually does not guarantee a close fit. The estimated curve may still deviate from the observation. Some models combine the Kaplan-Meier curve for the

trial period and conduct parametric extrapolation beyond the trial to achieve the best fit. When the data for both arms are available, it is feasible to adopt such two-step approach, which was accepted by some HTA agencies, such as NICE (2012b).

A neat feature of exponential or Weibull function is that survival curve of the intervention arm can be constructed with simple assumptions based on comparator arm. Letting HR be the hazard ratio for chemotherapy plus SOC versus SOC, if other parameters are the same as those of SOC, the survival function of the new intervention arm can be expressed as:

$$S'(t)=\exp(-HR.\lambda t^{\gamma}) \quad (3)$$

Both γ and λ are from the estimation of the SOC arm. Correspondingly, when the probability of survival (S') is given, the time can be expressed as the following.

$$T=\left(\frac{-\ln(S\prime)}{HR*\lambda}\right)^{1/\gamma} \quad (4)$$

To describe CDX, three parameters are needed, i.e., sensitivity (S), specificity (Sp), and prevalence of actual respondents (P). Prevalence is defined as the ratio of patients who responds to the chemotherapy versus to the total population (Annemans, Redekop, and Payne 2013). With above three parameters we can derive positive predicative value (PPV) and negative predictive value. Alternatively we can describe the performance of the test by S, Sp and PPV. Let us assume the total population of N (Figure 5.2). By definition, actual numbers of respondents and non-respondents are as P*N and (1-P)*N, respectively. True positive (TP), false positive (FP), false negative (FN), and true negative (TN) can be expressed as functions of N, P, S and Sp.

$$TP = P*S*N \quad (5)$$

$$FN= P*(1-S)*N \quad (6)$$

$$FP = (1-P)*(1-Sp)*N \quad (7)$$

$$TN= (1-P)*Sp*N \quad (8)$$

Each component is proportional to the size of total population. Such feature makes it easy to decompose total cohort into different segments. It does not matter whether one individual or one thousand patients are simulated because the sample size cancels out when calculating ICER.

For patients treated with SOC, let us assume that at one specific cycle, P_{MFS} and P_{OS} indicate the probability of metastasis free survival and overall survival, respectively. For a cohort with N patients, $N* (1-P_{os})$, $N*(P_{os}-P_{MFS})$, and $N*P_{MFS}$ are the numbers of patients who are dead, in post-metastasis, and metastasis free state, respectively. As metastasis free survival is a composite endpoint that includes overall survival, the value of P_{MFS} should be less or equal to P_{os} for that cycle.

The following equation should hold.

$$N* (1-P_{os})+N*(P_{os}-P_{MFS}) + N*P_{MFS}=N \quad (9)$$

The equation above means that for any cycle, the volumes of patients in each disease state add up to the total population. Such relationship also applies to chemo respondents. However, the probabilities differ because of different treatment effectiveness. Similarly, it holds for the general population treated by chemotherapy with or without CDX. Because overall survival is part of metastasis free survival, we should consider the correlation between the two variables at the time of estimating the survival functions.

Let us consider a simple case if we have a two health state model. One health state is alive and the other state is death. Let us assume the probabilities of survival of chemo respondents and SOC arm are Ec and E*s*, respectively. As patients entered the model, they were divided into four groups listed above. We now discuss how to calculate the cost, life year and QALY at certain cycles of each group by treating all patients with chemotherapy and the personalized medicine strategy. For the true positive patients, their probabilities at each disease state by definition follow those of chemo respondents, as they are responding to chemo. Regardless of whether they are under a CDX, their probabilities of survival are Ec. Cost and QALY calculation also follows those of chemo respondents. For the false positive patients, although they are treated with chemotherapy in both strategies, their survival probability follows SOC because they do not respond to chemo. When calculating both QALY and cost, we needed to apply cost and utility related to chemotherapy with survival probability of SOC. For false negative patients, their outcomes differ depending on the strategy used, that is, personalized medicine strategy and treating all patients with chemo. The calculations of life year, QALY and cost of the latter strategy are the same as those of chemo, as patients responded to chemo. Considering personalized medicine strategy, patients are assigned to SOC, as they tested negative. They have missed the chance to receive appropriate treatment. Their life year, QALY, and cost calculation follow SOC. For the true negative patients, because they are not chemo respondents, the life year of both treatment strategies follows that of SOC. The QALY and cost calculation differed across treatment strategies. Under personalized medicine strategy, the QALY and cost follow SOC because they are assigned with SOC. However, considering the strategy of treating all patients with chemo, QALY and cost are calculated the same way as those of chemo. In summary, under two different treatment strategies, the calculation of life year, QALY and cost did not differ for true positive and false positive except underlying survival probabilities, as in each situation,

patients were treated with chemo. For false negative and true negative patients, corresponding calculations were different due to different treatments and survival probabilities.

With formula 5-8, overall life year of treating all patients with chemotherapy can be expressed as follows,

$$(TP+FN)*Ec + (TN+FP)*Es = [p*S*N+P*(1-S)*N]*Ec+[(1-P)*(1-Sp)*N+Sp*(1-P)*N]*Es = N*P*Ec+N*(1-P)*Es \quad (10)$$

where Ec and Es stand for the survival probability of chemotherapy and standard of care, respectively. Formula 10 implies that for all patients being treated with chemo, those who were true negative and false positive did not respond to chemo, with treatment effectiveness following SOC. For personalized medicine strategy, only positive patients were treated with chemo. False positive (FP) patients did not respond. Their outcome followed Es. Both false negative and true negative patients were treated with SOC, and their outcomes followed Es. Overall, the effectiveness of targeted treatment can be expressed as follows,

$$TP*Ec + (FN+TN+FP)*Es= P*S*N*Ec + [P*(1-S)*N+ (1-P)*(1-Sp)*N+Sp*(1-P)*N]*Es = N*P*S*Ec+N*[1-P*S]*Es \quad (11)$$

Comparing formula (10) and (11), as sensitivity is always a number between 0 and 1, treating all patients with chemotherapy results in equivalent or better overall compared to a targeted treatment from the cohort perspective, assuming the effectiveness of chemotherapy is better than that of SOC. When treating all patients with chemo, false negative patients respond to the treatment. In contrast, they are assigned to SOC arm in the targeted approach. Those patients miss the chance to be optimally treated. The downside of treating everyone with chemotherapy is that many patients may have unnecessary side effects, and excessive medical resource use increases

the cost of administration and drugs. For patients who are not suitable for chemotherapy, it is a waste of limited resources. In addition, some patients may not tolerate the chemotherapy. In summary, the targeted treatment may have lower effectiveness from the perspective of a cohort, but it prevents unnecessary medical resource use and HRQOL deterioration.

Assuming Uc and Us represent the utility of chemotherapy and SOC, respectively, the QALY of CDX under the personalized medicine strategy is the following,

$$TP*Uc(Ec)+FP*Uc(Es)+(FN+TN)*Us(Es)$$

Uc(Ec) and Uc(Es) represent chemo related utility value calculation applied to the survival of chemo respondents and non-respondents, respectively. Us(Es) means the standard of care utility calculation is applied to the survival of standard of care. Because TP and FP will be treated with chemo, their utility follows chemo. Only the survival probability of TP follows chemo, since FP does not respond. When plugging in formula (5-8), the QALY of CDX can be rewritten as the following,

$$\{Uc(Ec)*P*S+Uc(Es)*(1-P)*(1-Sp)+Us(Es)*[P*(1-S)+(1-P)*Sp]\}*N \quad (12)$$

Similarly, assuming Cc and Cs represent the cost of chemo and SOC, respectively, the cost of CDX strategy is,

$$\{Cc(Ec)*P*S+Cc(Es)*(1-P)*(1-Sp)+Cs(Es)*[P*(1-S)+(1-P)*Sp]\}*N \quad (13)$$

The notation of Cc(Ec), Cc(Es), and Cs(Es) follow the same logic as utility.

Because both false positive and true negative patients are not chemo respondents, the QALY of treating all with chemotherapy is expressed as

(TP+FN)*Uc(Ec)+(FP+TN)*Uc(Es)

When we plug in formula (5-8), we have

[Uc(Ec)*P+Uc(Es)*(1-P)]*N (14)

Similarly, the cost of treating all patients is

[Cc(Ec)*P+Cc(Es)*(1-P)]*N (15)

By definition, $0 \leq P \leq 1$, $0 \leq S \leq 1$ and $0 \leq Sp \leq 1$, those conditions ensure that each component of formula from 12 to 15 is non-negative. Table 5.1 summarizes the discussion above. In the case of three health state model, we decompose Ec into probability of metastasis free and that of post metastasis. The logic of calculating life year, QALY and cost is still the same as above.

Total life year is calculated by summing the columns of each state and divide the sums by 12 months. To calculate QALY, utility at each state is used to multiply life year. Cost calculation is conducted in a similar manner. If the cost is related to each state, we need to multiply life year with the average cost of that state. If the cost is an event (e.g., death), it adds to the cost of that cycle, depending on when the event takes place. For example, the cost of CDX happens in cycle 1, as everyone is tested with a CDX in cycle 1. It is important to track when events happen because discounting affects the results.

The Markov like model calculates cost and benefit by taking discounting into consideration, i.e., the formula for life year is,

$$LY = \sum_{k=0}^{n} \frac{LY_k}{(1+r)^k} \quad (16)$$

Where LY is the net present value of life year, LY_k is the future value of life years at cycle K. The same approach is applicable to calculate QALYs and costs (World Health Organization. 2003).

$$QALY = \sum_{k=0}^{n} \frac{QALY_k}{(1+r)^k} \quad (17)$$

$$Cost = \sum_{k=0}^{n} \frac{Cost_k}{(1+r)^k} \quad (18)$$

5.3.1 An example demonstrating how to model CDX

Assuming a survival curve of standard of care, which can be described as Weibull function (λ equals to 0.012 and γ equals to 1.39) and the hazard ratio of chemotherapy versus SOC of 0.75, prevalence of 0.2, and sensitivity of 0.9, we then obtain the survival probability of SOC arm is $e^{-\lambda t^{\gamma}} = e^{-0.012*2^{1.39}}$=0.969 for cycle 2 (model start from cycle 0). For patients responding to chemo, the survival probability is $e^{-\lambda t^{\gamma}} = e^{-0.012*0.75*2^{1.39}}$=0.977. Comparing 97.7% to 96.9% in cycle 2, 0.8% more patients survive if they all respond to chemotherapy. In reality, the cohort also includes non-respondents. Considering prevalence and sensitivity of the CDX, the survival probability of the cohort treated with chemotherapy is (1-0.2)*0.969+0.2*0.977=0.971 based on formula (10) given the specification of other parameters. For the cohort treated with personalized medicine, the survival probability is (1-0.2*0.9)*0.969 + 0.2*0.9*0.977 = 0.970 based on formula (11). From a cohort perspective, 0.1% more patients survive if everyone is treated with chemotherapy compared to those exposed to personalized medicine in cycle 2. Although cohort with targeted treatment is slightly worse off compared to the cohort that treats everyone with chemo, both treatment choices achieve better outcomes compared to SOC under current assumptions.

Figure 5.3 provides an example of overall survival curves for three different treatment strategies. The effectiveness of treating everyone with chemotherapy (dotted line) and the effectiveness of selected treatment (solid line) almost overlap. The reason is that the difference in survival of two chemo strategies is P*(1-S)*(Ec-Es). Given the parameters of prevalence, sensitivities between 0 and 1, and high probability of survival by chemotherapy, this difference is only a small proportion of Ec-Es, since P*(1-S) is a small fraction.

5.3.2 Example of model layout and half cycle correction

For each treatment strategy, the sum of the probabilities at each disease state equals to 1. As long as chemotherapy delays disease progression (metastasis) or death, the probability of metastasis-free survival in each cycle is higher compared to that of SOC in the corresponding cycle.

With raw estimation, the next step is to conduct the half circle correction, i.e., keep cycle 1 as is, starting from cycle 2 and onward and taking the average probability of previous cycle and the probability of current cycle as the new probability of the current cycle. For example (Table 5.2 Panel A), in the half-cycle correction, the new probability of cycle 2 in the metastasis-free state was 0.956 (the cell of cycle 2 of metastasis-free of SOC arm), which equals to the average of 1 and 0.912 (the probability of previous cycle 1 and cycle 2, respectively, in the corresponding stage and arm, Table 5.2 panel B).

5.4 Modeling Uncertainty

The model explores different assumptions of base case, such as treatment profile of chemotherapy for HRLPC patients, CDX, utility value of disease stages, utility decrement associate with chemo agent and CDX, costs, and the like. The results are first presented in a one-way sensitivity analysis.

Probabilistic sensitivity analysis aims to capture stochastic uncertainty in the model. The uncertainty in the individual parameters is characterized by probability distributions, and it is analyzed using Monte Carlo simulation. As effectiveness estimation involves multiple parameters, Cholesky decomposition provides correlated draw from a multivariate normal distribution. Detailed mathematical derivation can be found in Briggs et al. (2006). In brief, a lower triangular matrix T has to be found so that T*T' (T' was the transpose of matrix T) equals to the covariance matrix V, which is generated from regression. Once matrix T is derived, we can derive a correlated vector X= $\begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$, so that

$$X = Y + Tz \tag{19}$$

where Y= $\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$ is the vector of parameter mean values, and z= $\begin{pmatrix} z_1 \\ z_2 \end{pmatrix}$ is the vector of independent standard normal variate. X is the correlated vector, which has a mean of Y and covariance matrix of V.

For example, in the case of 2 × 2 matrix, T can be expressed as a lower triangle matrix $\begin{pmatrix} a & 0 \\ b & c \end{pmatrix}$. The transpose of T is $\begin{pmatrix} a & b \\ 0 & c \end{pmatrix}$. By definition, because T*T'=V, the following relationship holds:

$$\begin{pmatrix} a & 0 \\ b & c \end{pmatrix}\begin{pmatrix} a & b \\ 0 & c \end{pmatrix}=\begin{pmatrix} var(x_1) & cov(x_1,x_2) \\ cov(x_1,x_2) & var(x_2) \end{pmatrix} \tag{20}$$

where the right side of equation is the covariance matrix V.

By definition, $var(x_1) = se^2(x_1)$ and $cov(x_1, x_2) = \rho * se(x_1)se(x_2)$

When solving the above equation, we obtain the following,

$$\begin{pmatrix} a & 0 \\ b & c \end{pmatrix} = \begin{pmatrix} se(x_1) & 0 \\ \rho * se(x_2) & \sqrt{1-\rho^2} * se(x_2) \end{pmatrix} \quad (21)$$

By combining (19) and (21), the correlated vector is

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu_1 + se(x_1) * z_1 \\ \mu_2 + \rho * se(x_2) * z_1 + \sqrt{1-\rho^2} * se(x_2) * z_2 \end{pmatrix} \quad (22)$$

The following example helps explain how correlated draw is conducted. Based on the patient level data, a parametric survival curve can be generated. For example, with intercept of 3.1760, scale of 0.7180, and the following covariance matrix, we can conduct Cholesky decomposition.

	Est. Covariance Matrix	
	Intercept	Scale
Intercept	0.002081	0.000245
Scale	0.000245	0.000638

Based on (21), 'a' equals to square root of 0.002081, which is 0.046, 'b' equals to $cov(x_1, x_2)$ divided by $se(x_1)$, i.e., 0.000245/0.045618, which equals to 0.005, 'c' is the square root of the difference between $var(x_2)$ and b^2, which is 0.025. The correlated vector X is expressed as

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu_1 + 0.046z_1 \\ \mu_2 + 0.005z_1 + 0.025z_2 \end{pmatrix} = \begin{pmatrix} 3.176 + 0.046z_1 \\ 0.718 + 0.005z_1 + 0.025z_2 \end{pmatrix}$$

Now, the vector is correlated because both x_1 and x_2 share component z_1**.** When we conduct probabilistic sensitivity analysis, the new intercept and scale parameters are 3.176+0.046 z_1 and 0.718+0.005 z_1+0.025 z_2 respectively, where z_1 and z_2 are random variables. In application, their values are generated with random seeds between 0 and 1 with Excel function RAND (). With Cholesky decomposition, probabilistic sensitivity analysis considers the covariance matrix of

multivariate analysis. The model uses the covariance matrix of SOC for both chemo respondent and SOC.

It is optimal for probabilistic analysis if a variable takes value between 0 and 1, as Beta distribution is restricted between 0 and 1. Beta distribution can be described with α and β. The mean is μ = α / (α+ β) with variance of $se^2 = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$, where both α and β are non-negative and the sum of α+ β>0. By rearranging above equations, we get

$$\alpha = \mu\left(\frac{\mu(1-\mu)}{se^2} - 1\right)$$

$$\beta = (1-\mu)\left(\frac{\mu(1-\mu)}{se^2} - 1\right) \quad (23)$$

Given mean value and standard error, α and β can be derived.

For example, a patient utility has a mean value of 0.773 and standard error of 0.005. Plugging in formula (23), we get α=4,607.6 and β=1,350.7. The uncertainty for parameters of prevalence, sensitivity, and specificity follows similar calculation as utility because the ranges of all those parameters are between 0 and 1.

Costs are constrained as non-negative amount. Gamma distribution is usually used when the cost is skewed. Like Beta distribution, Gamma distribution is characterized by two parameters. With mean $\mu=\alpha\beta$ and variance $se^2 = \alpha\beta^2$,

$$\alpha = \mu^2/se^2,\ \beta = se^2/\mu \quad (24)$$

Both α and β are non-negative. As an example, if a cost variable has a mean of 4,393.81 and

standard error of 292.44, with formula (24), we can derive α=225.74 and β=19.46. A summary of functions used for probabilistic sensitivity analysis is shown in Table 5.3.

The incremental cost-effectiveness ratio is calculated as $\Delta C/\Delta B$, where the numerator is the incremental cost and the denominator is the incremental benefit. Payers impose a WTP threshold λ for decision-making. For instance, such thresholds are £20,000-£30,000/QALY for NICE (2012c). As long as the net monetary benefit (NB) is positive, the new intervention is cost-effective. The net monetary benefit can be expressed as $NB= \lambda \Delta B-\Delta C$.

Using the concept of net monetary benefit, we can calculate the cost-effectiveness acceptance curve (CEAC, see Briggs et al. 2006). Given a willingness to pay threshold λ, for each interaction of the simulation, we can calculate the net monetary benefit for each treatment arm. The one with the highest NB is most cost-effective, so its probability of cost-effectiveness is labeled as 1. For other treatment, the probabilities of cost-effectiveness are 0. For multiple iterations, e.g., 1,000, we can calculate the average probability for each arm, which is the probability of cost-effectiveness for each arm under given λ. By changing λ, we can derive a curve representing the probability of cost-effectiveness for each treatment arm. At each λ, we can determine which treatment arm is the most cost-effective choice by choosing the product with the highest probability. The CEAC provides an overview of relative cost-effectiveness for all treatment arms under consideration.

Following the calculation of NB, the value of information theory (Briggs et al. 2006) was developed to address whether to adopt a technology and whether more information is required to make the decision. If there are "j" alternative treatments with unknown parameter θ, the optimal decision is the intervention, which gives the maximum expected NB, i.e., $Max_j E_\theta NB(j,\theta)$. With perfect information, the decision makers have to know how uncertainty would resolve before

making a decision. They need to select the intervention that maximizes the net monetary benefit given a θ. Mathematically, $Max_j NB(j,\theta)$. As we do not know the true value of θ, the Expected Value of Perfect Information (EVPI) is calculated by averaging the maximum net monetary benefit over the joint distribution of θ (Briggs et al. 2006),

$$\text{EVPI}=E_\theta Max_j NB(j,\theta) - Max_j E_\theta NB(j,\theta) \quad (25)$$

To make the above formula intuitive, Table 5.4 shows a numeric example with 5 iterations of NB for three treatments (A, B, and C). The expectation of column "Treatment A" is to take the average of five iterations from 11 to 15, with the result of 13. Using the same approach, the expectations of treatment B and C are 13.4 and 13.8, respectively. Those are $E_\theta NB(j,\theta)$ of the equation 25 with j being 1, 2, and 3. Among the expectations of three treatments, treatment C has the highest expectation 13.8. Hence, we find out $Max_j E_\theta NB(j,\theta)$. $Max_j NB(j,\theta)$ is the highest NB of each row, summarized at the last column. $E_\theta Max_j NB(j,\theta)$ is the average of last column, which equals to 14.8. EVPI is calculated by using 14.8 minus 13.8; hence, it equals to 1 in this example.

When the threshold of WTP is low, the new intervention is not expected to be cost-effective. Accordingly, no new information is required. EVPI becomes high usually at the time when one CEAC begins to cross the other CEAC, as more information is needed to make a decision. The model calculates the EVPI for a population of 40,000 people, as we do not have a precise estimator of prevalence of this patient group. The EVPI associated with future patients is discounted to provide the total EVPI for the population of current and future patients.

5.5 **The method of calculating cost-effectiveness price, a deviation from base case**

In this section, the assumption that CDX test was free of charge is relaxed because the diagnostics manufacturers often are separate entities from drug companies. A cost-effective price of CDX was derived by back calculation method. To make a technology cost-effective, net monetary benefit should be positive. Otherwise, it is not cost-effective by definition. Hence,

$$\lambda \Delta B - \Delta C \geq C_{CDx} > 0 \quad (26)$$

Inequality (26) provides the range of the price that a companion diagnostics can charge. As long as the test price falls into this inequality, the personalized medicine strategy is cost-effective compared with SOC. From now on, let us call upper limit of this range as cost-effective price of CDx. Since CDX is given when patients enter the simulation, no discounting adjustment is needed. As long as the price of CDX falls into the above the range, the treatment strategy with CDX is more likely to be cost-effective compared with SOC. The price calculation considered willingness to pay thresholds of both $50,000 /QALY and $100,000 /QALY.

The uncertainty around the cost-effective price is driven by net monetary benefit. Based on the probabilistic sensitivity analysis, we can find the 95% CI of NB. Since the price of CDX takes away the net benefit, it is also the CI of the cost-effective price. Sensitivity analyses can be conducted, since many factors, including prevalence, sensitivity, specificity, and treatment effectiveness, influence the cost-effective price of CDX.

5.6 Some comments to the model

Here, a relative simple model is derived to demonstrate how to assess CDX. The strengths of this type of model are intuitive and transparent. The model does not require many assumptions. Still, a few assumptions have to be made. First assumption is that patient outcome can be projected based on observation period. However, parametric fitting with observation has its drawback in terms of

predicting. We frequently see the survival curves change their trajectories at different times of reading due to cross-over, subsequent therapy, stopping rules, and patient dropout in the clinical trials, especially in the case of oncology drugs. The second assumption is to keep non-chemo responders in the treatment. In reality, those patients may quickly stop chemotherapy after a few cycles based on physicians' discretion. The third assumption is that the CDX is tested only once. No further adjustment is made. For instance, there is no cross-over allowed. Moreover, as MFS is a composite endpoint that includes OS, correlation between OS and MFS is endogenous. The current model does not consider such correlation for extrapolation, which may cause internal inconsistency. Additionally, as reported in Chapter 3, the overall survival outcome differs significantly across age, cancer severity, treatment modality, and even diagnosis period, which indicates that HRLPC is a heterogeneous group. If we want to understand a particular subgroup, the model needs to be built based on those risk factors. Lastly, with recently launched new agents for treating mCRPC, the medical spending in late stage prostate cancer has a different pattern compared to the period under examination. A simple model may not be necessarily correct to describe the changing treatment and cost patterns.

In summary, since trial results or individual patient level data are not available for CDX in the adjuvant or neoadjuvant chemotherapy setting, the model structure is sufficiently capable of answering the research questions proposed in Chapter 1. When patient level data become available, data analysis, including survival analysis, can be re-evaluated to allow more sophisticate modeling.

Table 5.1) Life year, QALY, and cost calculation

	True Positive	False Positive	False Negative	True Negative	Total
Life year					
Personalized medicine	Ec	Es	Es	Es	Ec*P*S+Es*(1-P*S)
Chemo	Ec	Es	Ec	Es	Ec*P+Es*(1-P)
SOC	Es	Es	Es	Es	Es
QALY					
Personalized medicine	Uc(Ec)	Uc(Es)	Us(Es)	Us(Es)	Uc(Ec)P*S+Uc(Es)*(1-P)*(1-Sp)+Us(Es)*[P*(1-S)+(1-P)*Sp]
Chemo	Uc(Ec)	Uc(Es)	Uc(Ec)	Uc(Es)	Uc(Ec)*p+Uc(Es)*(1-P)
SOC	Us(Es)	Us(Es)	Us(Es)	Us(Es)	Us(Es)
Cost					
Personalized medicine	Cc(Ec)	Cc(Es)	Cs(Es)	Cs(Es)	Cc(Ec)*P*S+Cc(Es)*(1-P)*(1-Sp)+Cs(Es)*[P*(1-S)+(1-P)*Sp]
Chemo	Cc(Ec)	Cc(Es)	Cc(Ec)	Cc(Es)	Cc(EC)*P+Cc(Es)*(1-P)
SOC	Cs(Es)	Cs(Es)	Cs(Es)	Cs(Es)	Cs(Es)

Note: Ec, survival probability of chemo respondents, Es, survival probability of SOC, Uc(Ec), utility of chemo applied to chemo respondents, Uc(Es), utility of chemo applied to non-respondents, Us(Es), utility of SOC, Cc(Ec), costs of chemo applied to chemo respondents, Cc(Es), costs of chemo applied to non-respondents, Cs(Es), costs of SOC, P, prevalence, S, sensitivity, Sp, specificity
Personalized medicine refers to treating patients with chemo by CDX
Patients treated with chemo were penalized with lower utility per chemo related AE

Table 5.2) Example of probabilities at different states by cycles

Panel a) Layout of disease state

	SOC			Personalized medicine			Chemo		
Cycle	Metastasis-free	Metastasis	Death	Metastasis-free	Metastasis	Death	Metastasis-free	Metastasis	Death
1	1.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000
2	0.912	0.085	0.002	0.913	0.086	0.001	0.914	0.086	0.000
3	0.904	0.090	0.005	0.907	0.090	0.003	0.910	0.089	0.001

Panel b) Half cycle correction

	SOC			Personalized medicine			Chemo		
Cycle	Metastasis-free	Metastasis	Death	Metastasis-free	Metastasis	Death	Metastasis-free	Metastasis	Death
1	1.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000
2	0.956	0.043	0.001	0.957	0.043	0.000	0.957	0.043	0.000
3	0.908	0.088	0.004	0.910	0.088	0.002	0.912	0.088	0.001

Abbreviation, SOC=standard of care
Personalized medicine refers to treating patients with chemo by CDX
Half cycle correction was conducted by taking average of values of previous and current cycles.

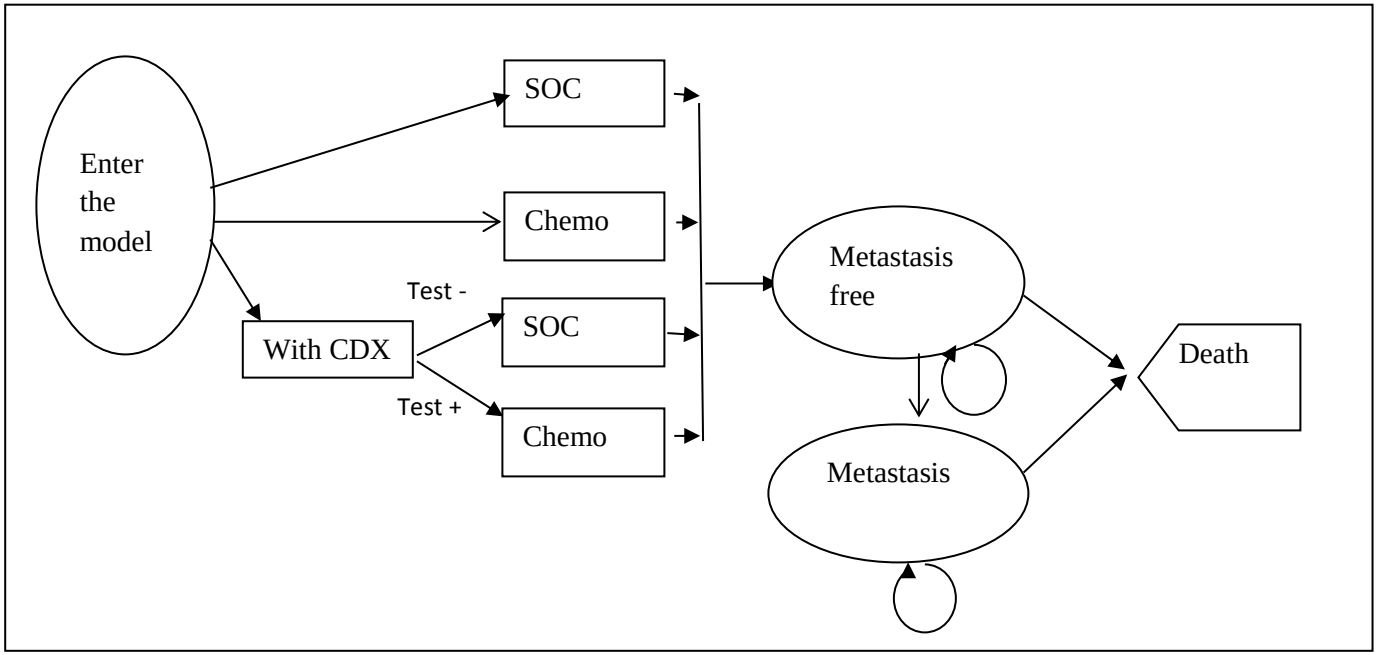
Table 5.3) Model parameters varied in probabilistic sensitivity analysis

Parameter	**Distribution**
Parameters of the survival equations	Multivariate normal (Cholesky decomposition)
Utilities (metastasis-free, post metastasis, chemo or CDX decrement)	Beta
Prevalence	Beta
Sensitivity	Beta
Specificity	Beta
Costs	
State costs (first year & subsequent years)	Gamma
End of life costs	Gamma

Table 5.4) An example of calculation EVPI

Net Monetary Benefit (units, $)	Treatment A	Treatment B	Treatment C	Optimal choice	Maximum NB	EVPI
Iteration 1	11	16	17	C	17	
Iteration 2	12	14	13	B	14	
Iteration 3	13	11	12	A	13	
Iteration 4	14	12	11	A	14	
Iteration 5	15	14	16	C	16	
Expectation	13	13.4	13.8	13.8	14.8	1

Figure 5.1) Schematic of the health economics model



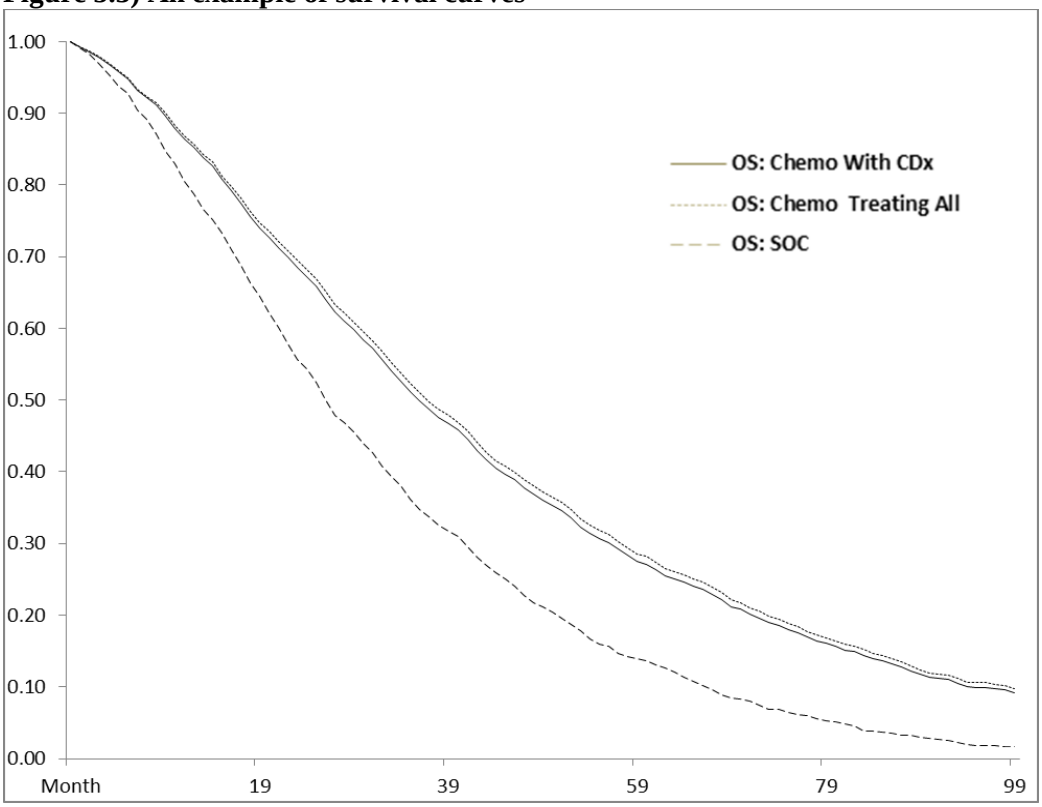
Abbreviation: CDX=Companion diagnostics; SOC= standard of care

Note: Patients enter the model with three different treatment strategies, i.e., SOC, treating all with chemotherapy, personalized medicine (treating CDX tested positive patients with chemo). At the beginning of simulation, patients are free of metastasis. With disease progression, they metastasize or die.

Figure 5.2) Relationship between tested respondents and actual respondents

Tested	Actual respondents		
Respondents	Positive	Negative	Total
Positive	TP	FP	
Negative	FN	TN	
Total	p*N	(1-p)*N	N

Figure 5.3) An example of survival curves



Chapter 6. Cost-effectiveness of treating patients with CDX

The objective of this chapter is to analyze the cost-effectiveness of treating HRLPC patients with two chemo related regimens, personalized medicine or treating all patients with chemo compared to standard of care (SOC), from the US public payer perspective. Personalized medicine means selecting patients for chemo treatment by CDX. A base case analysis was presented along with a number of sensitivity analyses (both deterministic and probabilistic sensitivity analyses). Key clinical assumptions of chemotherapy were based on the CHAARTED study (Sweeney et al. 2014). Assumptions of companion diagnostics test were based on the reviews in Chapter 2. Based on the base case, the cost-effective price of the companion diagnostics is discussed in the following sections.

6.1 Input assumptions

Base case patient characteristics were discussed in Chapter 3 (see Table 3.1). A 30-year simulation was conducted based on the NICE (2012c) guideline. The model was flexible to simulate a shorter time horizon by restricting cycles to the right period. The assumption of CDX testing was based on Table 2.6, which showed a wide range for prevalence of gene mutation. KRAS mutation presented in 40% of CRC patients, and BEAFV600E mutation presented in 40% of metastatic myeloma patients in Table 2.6. The 40% prevalence of above biomarkers was used for demonstration. In the sensitivity analysis, both 10% and 70% were tested for the prevalence, respectively. The ranges of sensitivity and specificity in Table 2.6 were 85-100% and 92-100%, respectively. The sensitivity and specificity were set to be 93% and 95%, respectively, taking the midpoints of the mentioned ranges. Therefore, the simulated CDX had a good performance. In the base case, the cost of CDX was set to be 0 because drug companies might own it. Some healthcare systems allow drug manufacturer to pay for CDX (The European Personalised

medicine association, 2014). Since a CDX device is most likely to be used to analyze serum or urine specimen, it is mostly non-invasive, one-time collection process. The utility decrement of CDX was assumed to be 0 in the base case. Sensitivity analysis tested whether utility decrement was up to 0.04.

There are several assumptions of the outcome of the SOC. Theoretically, the probability of metastasis-free survival (MFS) should drop faster compared to that of overall survival (OS) in both observed period as well as projection period, since MFS is a composite endpoint including both death and metastasis. MFS curve was lower than the OS curve in the observed period; however, they crossed at the projection period. As we discussed in Chapter 3, the projection of MFS and that of OS were considered separately because negative Hessian matrices complicated the computation of the results. In the model, projected MFS was forced to follow the trajectory of predicted OS when two lines crossed. With the survival curves of MFS and OS of SOC, corresponding curves of chemotherapy for full responders could be constructed. In Chapter 2, a meta-analysis of the OS benefits of chemotherapy for mCRPC patients showed the pooled hazard ratio of 0.691. HR of 0.7 was assumed for the base case. Since clinical communities (Ellis et al. 2014) agreed that a HR of 0.8 defined a clinical minimum improvement, a HR of 0.7 is a decent improvement for HRLPC patients.

The treatment cycle of chemotherapy was assumed to follow the CHAARTED study with 6 cycles where each cycle included three weeks of docetaxel treatment (Sweeney, 2014). Mazta, Cong, and Chung (2013) showed that chemotherapy was associated with significant disutility. Disutilities of 30-minute infusion and 2-hour infusion were 0.03 and 0.04, respectively. Since docetaxel was administered as IV for 1 hour on day 1(Clinicaltrial.gov, 2015a), the disutility of docetaxel was assumed to be 0.03 in the base case. Sensitivity analyses of 0 (no disutility) and

disutility of 0.078 were tested. The later value was from docetaxel associated grade 3/4 AE in post chemo mCRPC stage (National center for pharmacoeconomics, 2012). The monthly treatment cost of docetaxel was derived as follows. The average body surface area of adult men is 1.90m^2 (Mosteller, 1987). The total dose of docetaxel (75mg/m^2, Sweeney 2014) was 143mg (product of 75 mg/$m^2$and 1.9 m^2). From the CMS payment rate for HCPCS Code J9171, 1mg of docetaxel was $4.53 (CMS, 2014a). Therefore, one cycle of docetaxel costs $648 (product of 143mg and $4.53/mg). In the simulation, $648 was used as monthly cost, considering some patients may need additional rest time. Costs associated with the management of chemo-related AE were not considered in the base case. The sensitivity analysis considered the scenario that the cost was doubled to accommodate the costs of AE and that the cost was the same as a branded chemo agent (e.g., $8,820 per month of cabazitaxel, Q1group 2015). In addition, both 3-cycle and 12-cycle treatment durations were considered in the sensitivity analysis.

The base case utility used the mean value in Table 2.5, i.e., the utility of metastasis-free and utility of metastasis of 0.80 and 0.68, respectively. The first year and subsequent management cost of metastasis free and post metastasis were selected from Table 4.3. End of life costs were based on the review in Table 2.4. Costs were standardized to calendar year 2013. Hence, the cost-effectiveness results were presented as real rather than nominal price. As state costs included the treatment costs and service fees, the treatment cost of SOC was set to be 0 to prevent double counting. In the sensitivity analysis, the cost values were reduced or inflated by 30%. The rationale is that the differences between adjusted and unadjusted cost estimates in Chapter 4 are no greater than 30%.

The willingness to pay (WTP) threshold in US is unclear. $50,000 /QALY was used, e.g., Kowada et al. (2013), but $100,000 /QALY was also considered (Shiroiwa et al. 2010).

According to the World Health Organization (WHO) Cost-effectiveness and strategic planning (WHO-CHOICE) program (World Health Organization, 2002), a new intervention is very cost-effective when the ICER measured by cost per Disability-Adjusted Life Year (DALY) is less than one GDP per capita or cost-effective when ICER is between one and three folds of GDP per capita, and it is not cost-effective when ICER is 3-fold greater than is GDP per capita. The GDP per capita of US in 2013 was $53,143 (The World Bank, 2015). The willingness to pay thresholds of $50,000 /QALY and $100,000 /QALY are about one and two folds of GDP per capita, respectively, both being more stringent than the WHO-CHOICE recommendation. One caveat is that QALY and DALY are not interchangeable (Anand & Hanson, 1997). The results reported by cost per QALY and cost per DALY are not always the same. To be conservative and consistent with most decision criteria used in the existing studies, both WTP thresholds of $50,000 /QALY and $100,000/QALY were considered in this study. A $50,000/QALY is also equivalent to the WTP threshold £30,000/QALY set by NICE (2012c). In addition, discounting rates for both utility and cost were 3.5%, following the NICE guidance (2012c). Sensitivity analyses considered both 5% and 0.

6.2 Base case results

6.2.1 Cost-effectiveness estimates

Based on Chapter 3, the overall survival curve and metastasis-free survival curve for patients who received SOC, chemo, or personalized medicine are presented in Figure 6.1. The median OS rates of SOC, chemo, or personalized medicine were 10.3, 11.6, and 11.5 years, respectively. In this chapter, both strategies, i.e., treating all with chemotherapy and personalized medicine, were considered an active treatment. Active treatments improved the overall median survival by roughly 15 months. The main cost-effectiveness results of base case are presented in Table 6.2.

The total discounted costs for treating all patients with chemo, personalized medicine, and SOC were $155,532.5, $153,049.9, and $147,687, respectively. The corresponding discounted total life years were 10.2, 10.1, and 9.5 years, respectively. Discounted QALYs were 7.8, 7.8, and 7.3, respectively. Compared to SOC, treating patients with personalized medicine was associated with incremental QALYs and costs of 0.5 and $5,362.9, respectively, with incremental cost-effectiveness ratio (ICER) as $9,786.5/QALY. In contrast, treating all patients with chemo was associated with incremental QALYs and costs of 0.6 and $7,845.6, respectively, with ICER of $13,498.2/QALY. Both treatment strategies were cost-effective compared to SOC. The net monetary benefits (NB) under $100,000/QALY threshold were $50,277.2 and $49,436.2 for personalized medicine and treating all with chemotherapy strategy, respectively. The NBs under $50,000 WTP threshold were $21,215.8 and $22,036.63, respectively. The personalized medicine strategy always came with higher NBs, offering better value for the money.

6.2.2 One Way Sensitivity analysis and Probabilistic sensitivity analysis

In contrast to a regular cost-effectiveness analysis based on an established technology, this study had substantial uncertainty because of the lack of data. Sensitivity analysis was conducted using varying prevalence, sensitivity and specificity, hazard ratios of chemo respondent versus SOC, costs and utility values. One-way sensitivity analysis tornado diagram of personalized medicine strategy versus SOC graph are reported in Figure 6.2, showing the change in ICER from base case. Detailed results for both active treatment strategies and SOC are reported in Table 6.3. Numerically, the ICER of personalized medicine strategy was always less than the ICER of treating all with chemotherapy. By analyzing net monetary benefits, personalized medicine strategy was always cost-effective compared to treating all patients across all scenarios.

The variation in utilities and costs were further investigated. For instance, if the disutility of chemo as 0.078 a value used for grade 3/4 chemo associated of mCRPC, was plugged in the model, the ICER increased to $9,953.9/QALY. The state costs and the end of life costs for the cohort were also tested. If the first year management cost of the metastasis-free increased by 30% ($3,353.0 versus $2,579.2, which was higher than the unadjusted estimator $2,751), the ICER increased to $9,960.8/QALY. If the first year cost of the post-metastasis was $2,574 instead of $2,145 used in the model, the ICER decreased to $9,697.3/QALY. A 30% change in the magnitude of state costs had limited effect on the ICER. Lower prevalence showed a large difference in cost-effectiveness between treating all with chemotherapy and personalized medicine, whereas the gap narrowed under a higher prevalence. Personalized medicine strategy is very useful when the prevalence is low. Sensitivity and specificity influenced the ICER of personalized medicine versus SOC, whereas they did not change the ICER of treating all with chemotherapy versus SOC because treatment decision was not based on test. The model results were also sensitive to discounting rate. However, discounting is required in a standard model, as we have to consider future inflation.

As chemo related AE was not considered in the base case, a scenario in which the cost of chemo was doubled was considered. The ICERs of treating all with chemotherapy and personalized medicine versus SOC were $19,836.3 /QALY and $12,510.2 /QALY, respectively. Although both ICERs increased, they were still under the WTP threshold of $50,000/QALY. If the price of chemo was the same as that of cabazitaxel, ICER of treating all with chemotherapy and personalized medicine strategy versus SOC would increase to $93,426.4 and $44,134/QALY, respectively (Table 6.4). A branded chemo agent with only 6 months treatment duration might not be cost-effective under a more stringent WTP threshold if treating everyone. Personalized medicine strategy successfully reduced the ICER by more than half and made it cost-effective

under both WTP thresholds. When HR of Chemotherapy versus SOC equaled to 0.99, the ICER of personalized medicine versus SOC was $ 170,227.3/QALY. If the drug does not work, there is no reason for a personalized medicine strategy. If hazard ratio of chemo respondent versus SOC improved from 0.7 to 0.5, the cost-effectiveness results for both active treatments would improve further.

In summary, increases in prevalence, sensitivity, specificity, baseline utility, maintain costs for the post metastatic stage and end of life, and discounting rate of costs reduced the ICER. On the other hand, increases in discounting rate of benefit, cost of the metastasis-free state, costs of chemo, utility of post metastasis, disutility of CDX, and disutility of chemo treatment increased the ICER.

A probabilistic sensitivity analysis with one thousand iterations was conducted by changing model parameters simultaneously under their probability distributions. The uncertainty of key inputs was discussed in previous chapter. Figure 6.3 presented the incremental cost-effectiveness scatter plot for personalized medicine strategy, treating all with chemotherapy and SOC, with the horizontal axis representing incremental outcomes measured by QALYs and the vertical axis measured by costs. Each point of the figure represented one round of iteration. When compared to SOC, both active treatments were more expensive and improved health benefits measured by QALY. Most of those points fell under both referenced WTP thresholds ($50,000/QALY and $100,000/QALY), indicating in the base case that both active treatments were cost-effective versus SOC. However, the scatter plot did not quantify which of the two active treatments are economically more feasible.

The cost-effectiveness acceptance curve (CEAC) addressed the above question, indicating the probability of cost-effectiveness of an intervention under different WTP thresholds. It also

reported the cost-effectiveness of credible interval for different treatment options. Figure 6.4 shows the CEAC of personalized medicine strategy, treating all with chemotherapy and SOC. The horizontal axis represented the willingness to pay for each intervention in terms of cost per QALY while the vertical axis represented the probability of being cost-effective. SOC was presented as a thick solid line and personalized medicine strategy was a thick dotted line. Treating all patients with chemo was indicated as fine dotted line. Under WTP of $10,000/QALY, SOC dominated both active treatments. It is cost-effective to stay with SOC if the payers/patients lack financial resources. Beyond the WTP threshold of $10,000 per QALY, the probabilities of personalized medicine being cost-effective quickly became 100%. As shown in Figure 6.4, treating all patients with chemo is never cost-effective although it may be cost-effective compared with SOC in a pair comparison.

EVPI tells us when we should collect more information to make treatment decision. Given current information, we need more information on the following: 1) the expected cost-effectiveness of one option compared to the other and 2) the uncertainty of cost-effectiveness estimates. A high value at the EVPI curve indicates uncertainty in making choices. More information is needed to make a decision. From Figure 6.5, it was clear that SOC was cost-effective below $10,000/QALY. No more information was needed. If the payer cannot afford more expensive treatments, SOC treatment was the best choice. A high value was observed starting at WTP threshold of $10,000 per QALY, where the CEAC of personalized medicine exceeded that of SOC, indicating some level of uncertainty about the change. Subsequently, the EVPI dropped to 0 and remained 0 up to WTP of $20,000/QALY. Between $10,000/QALY and $20,000/QALY, it was clear that personalized medicine was cost-effective. Starting from $20,000/QALY, EVPI increased again, consistent with the increase in CEAC of treating all with chemotherapy starting. Although the strategy of treating all with chemotherapy was not cost-

effective compared with other treatment strategies, it still provided better benefits by eliminating false negative patients. More studies are needed to understand, which strategy is the best after WTP of $20,000/QALY.

6.3 Results of deriving cost-effective price of CDX

For the base case, the net monetary benefit (NB) under WTP threshold of $50,000 /QALY was $22,023.8, with CI of ($16,196.0, $27,451.8). The NB under WTP threshold of $100,000/QALY was $49,439.0, with CI of ($36,464.1, $61,206.4). The higher the willingness to pay, the higher the price a diagnostics manufacturer can ask for. Figure 6.6 showed the relationships between a cost-effective price and prevalence, with price shown on the vertical axis and prevalence on the horizontal axis. Higher prevalence was associated with higher price a CDX could charge. Similarly, higher WTP threshold was associated with higher price potential. Figures 6.7 through 6.10 showed the relationship between the cost-effective price of CDX and sensitivity, specificity, hazard ratio, and drug costs, respectively. Higher sensitivity and specificity, lower hazard ratio, and lower chemo monthly costs corresponded to higher cost-effective CDX price.

Considering CDX price as a dependent variable and prevalence as the independent variable, a linear regression was built between the cost-effective price under WTP $100,000/QALY and prevalence. For the price potential under the WTP threshold of $100,000 / QALY, increase in prevalence by 0.01 meant that the cost-effective price of CDX could increase by $1,242.3. Similar relationships under two different WTP thresholds and key clinical drivers are summarized in Table 6.5. Comparing the relationships between cost-effective price and other factors, CDX price was most sensitive to hazards ratio. One percent point reduction in HR caused $3,334 increase in price potential under WTP threshold of $100,000/QALY. The next influential factor was prevalence, followed by sensitivity and specificity.

The results of landmark CHAARTED study were remarkable, as they were based on a 6-cycle treatment of docetaxel (Sweeney et al 2014). We have seen it would not be cost-effective to treat all with chemo under WTP threshold of $50,000/QALY if docetaxel was replaced by cabazitaxel (Table 6.4). In an extreme example, cabazitaxel was given up to 12 months or to metastasis stage, whichever came first. In this scenario, the ICER of treating all patients with chemo was $174,941.5/QALY and the ICER of personalized medicine was $78,846.3/QALY. If the WTP threshold was $50,000/QALY, neither strategy would be cost-effective. In this situation, a diagnostics manufacturer could not charge a price for the CDX (Table 6.6). Although treating patient with chemo for 1 year was not common, Schmidt et al. (1996) treated HRLPC patients with EMP for up to 2 years. Both docetaxel (Tannock et al. 2004) and cabazitaxel (de Bono et al. 2010) were administered for up to 10 cycles in their pivotal studies.

6.4 Discussions

This study showed that both active treatment strategies would be cost-effective in comparison to SOC if we had an effective chemotherapy for high risk localized prostate cancer and the treatment duration was only 6 months. Given CDX free of charge, it was the most cost-effective choice for patients selected to the chemo treatment. The conclusion was highly sensitive to underlying assumptions. If any key parameters, such as the effectiveness, treatment duration, prevalence, duration, and costs, changed, the results would vary. In addition, based on probabilistic sensitivity analysis, even when personalized medicine strategy was cost-effective, substantial uncertainty remained. The EVPI exercise illustrated that we need to invest more on research to confirm the finding.

Further, it was demonstrated that numerous variables influence CDX price. The hazard ratio of chemo respondent versus SOC had substantial effect on the price. It was also sensitive to

prevalence, sensitivity, and specificity. Hence, a good drug, as measured by costs and effectiveness, as well as a good CDx test, as measured by performance, are important for making effective economic decisions. If the cost-effectiveness of a selective treatment was established, along with the treatment duration and price, diagnostics manufacturer would be able to accommodate the cost of CDX. As we see in Table 2.6, the price of CDX accounted only for a small fraction of the price of drug. For instance, the cost of BEAF V600E test ranged from $120 to $150, only 3% of the monthly cost of Vemurafenib. The costs of the CDX were not the key drivers of the cost-effectiveness of the companion diagnostics treatment strategy because CDX was a one-time, low cost item. Instead, the cost-effectiveness of personalized medicine versus SOC was driven primarily by the drug profile. If the effective intervention was a branded product, like cabazitaxel, and the treatment duration up to 1 year, it was most likely that the CDX was not cost-effective under a stringent WTP threshold. It may be difficult to justify a fair price for CDX.

The key findings of this study can be summarized as follows:

- Is it cost-effective to treat all HRLPC patients with neoadjuvant or adjuvant chemotherapy?

It depends. If we had a chemotherapy comparable to the base case, i.e., with limited treatment duration, generic price, and clinically meaningful treatment effect, treating all patients with chemo would be cost-effective. If the treatment duration is up to one year and treatment is expensive, then it may not be a cost-effective choice for HRLPC. Companies that are currently testing new agents, such as enzalutimide (Clinicaltrials.gov, 2015c) in HRLPC, have to justify the high ICER if drug is given for long period, such as two years, especially in the cost per QALY HTA countries.

- Would the above conclusion change if we had a companion diagnostics?

This study demonstrated that a companion diagnostics was always cost-effective in comparison to chemo as the main treatment for all. By teasing out non-respondents, the cost that the CDX saved outweighed the loss. Drug companies should always prioritize a CDX plan in the drug development to secure clinical effectiveness and cost-effectiveness. Both diagnostics manufacturer and drug companies need to coordinate the development of both drugs and CDx to fully optimize commercial success.

- What drives the economic value of a companion diagnostics device?

The cost-effective price of CDX depends on an array of multiple factors, e.g., the clinical benefits and risk profiles associated with new treatment, treatment duration and costs, prevalence of responders, sensitivity, and specificity. Utilities and costs also contribute. Among those factors, treatment effectiveness and associated costs play important roles in determining the value of CDX. Literally, the value of CDX relies heavily on the accompanying drug.

The current study is unique in that it provides an economic evaluation framework to assess counterfactual scenarios by combining the testing profile with AUC model. This methodology is consistent with the recommendation from a recent systematic review (Doble et al. 2015) of cost-effectiveness of companion diagnostics. This model considered the prevalence of genetic biomarkers, sensitivity, specificity, and time of the test.

The strengths of this model were simplicity and transparency. The transparency was achieved by writing VBA macros in open codes. Thus, users are able to check how the programs are written. It was straightforward because only three health states were considered. The OS is the ultimate goal for both regulatory and HTA agencies. The MFS is also important, since it is a possible

biomarker of overall survival (Schweizer et al.2013).Though FDA is not clear about the magnitude of MFS that would constitute a meaningful clinical benefit, it started to discuss the value of MFS (FDA, 2011). As more disease states require additional assumptions, the simple framework described in this study helped us clarify the key points.

In addition, the framework can be easily modified to evaluate the cost-effectiveness of any CDX in other interventions, such as novel anti-androgen, e.g., abiraterone acetate, enzalutamide, or immunotherapy, e.g., sipuleucel-T for HRLPC patients, or it can simulate CDX in other type of cancers, as discussed in previous chapter. For example, we can use it to evaluate the cost-effectiveness of Cobas 4800 BRAF V600 Mutation test for the vemurafenib treatment of patients with naïve melanoma. Without changing the model structure, we only need to replace the parameters of survival outcomes, costs associated with vemurafenib and dacarbazine, costs and utility values of disease states, and parameters associated with the Cobas 4800 BRAF V600 test. As Chapman et al. (2011) reported only PFS and OS, the MFS in the model needs to be replaced with PFS. The costs of treatment and test could be found on the last line of Table 2.6. With additional literature searches and data analysis, this model for adjuvant chemo of HRLPC can be converted into a model to evaluate Cobas 4800 BRAF V600 Mutation test.

This study has few limitations, as outlined below.

- A three health state model might oversimplify disease progression of HRLPC. If a trial only demonstrates clinical endpoints measured by surrogate endpoints, such as biochemical free survival or progression free survival, revision is needed.
- The model was not based on a head-to-head RCT. It is a typical early model that is useful for understanding the value of the upcoming technology. Users have to revise the data inputs if underlying disease changes.

- The use of companion diagnostics device in the model might not be consistent with clinical practice. For instance, when patients are unresponsive or intolerant to chemotherapy, physicians will stop the therapy. CDX may involve multiple tests. A dose response relationship with the biomarker might exist. Alternatively, physician may use patient's information to judge whether he needs a test, etc.
- Chemo agents used here might be too general. Chemotherapies might differ from each other based on their individual mechanism of actions, treatment effectiveness, safety, and costs. Although early results of a few large trials shed light on a promising chemo treatment, the agent that will eventually be feasible in clinical practice remains unclear in HRLPC. As Fizazi et al. (2014) demonstrated the usefulness of docetaxel and EMP in a subset of HRLPC patients, a combination of chemo might be useful.
- This study was based on SEER-Medicare linked database. Patients who were insured privately or treated in Veteran Affairs hospitals were not included. Additionally, SEER did not cover long-term care at home or in a nursing home. The sample was restricted to patients over 65 years of age. We need to be cautious about generalization.
- As this model was simulating ex-ante, a head-to-head study should be conducted to formally validate the model.

Although the study considered the perspective of US public payer such as Medicare, cost-effectiveness study was not used when making decisions. US payers like to understand the economic implication of new therapy, but their decisions are driven by comparing treatment effectiveness. The government would rather defer making decision on a cost-effective treatment to patients and physicians. As oncology medicines usually fall into categories of specialty drugs and highest tiers for co-pay, nowadays patients have to select cost-effective option. A CEA helps patients, the ultimate payer, to make decision.

Whether Medicare will use CEA for its decision is an ongoing debate. Medicare proposed a framework of CEA in 1989 (Neumann et al. 2005). The reasons for not implementing the framework include politics, process, leadership, or perhaps public opinion (Botta et al. 2014). As the US health spending as a percentage of the GDP keeps growing, physicians, patients and payers are all facing cost burden. Physicians and hospitals are calling for a cost-effective treatment for cancer patients (Kantarjian et al. 2013). Increasing numbers of payers are starting to explore the possible use of CEA. Payers and providers' roles are also blurring. A survey of 228 managed care plans conducted by Garber et al. (2004) indicated that 90% of plans considered cost and about 40% of plans considered formal CEA. Workshops with California health care organizations (Bryan et al. 2009) stated that 90% of them would apply CEA to Medicare and 75% would apply CEA to private insurances. With a growing pressure on cost containment, we cannot rule out that one day, CEA would be part of decision making in US.

Although this simulation study is a US based, it can be easily adapted to centralized healthcare systems in countries such as the UK, Canada, Australia, Sweden, Korea, and even France, where CEA is the key medical decision-making entity. By changing costs and country specific patients utility, the results of the model would be useful for national payers. My findings, which indicate that it is important to have a clinically effective short treatment to demonstrate the economic value of innovative therapy in HRLPC patients, that a personalized medicine strategy needs to be considered during drug development, and that the value of CDX is highly influenced by drug performance and costs, are transferable to different healthcare systems.

Further research can take on a deep dive on the survival outcome patterns identified in this study. For instance, it is valuable to compare radical prostatectomy versus other treatment modalities in this patient group. For the cost estimation, it is worthy to apply the nonparametric method

proposed by Bang and Tsiatis (2000) to validate the subgroup approach used in this analysis. We can test this model in an established CDX device.

In summary, a cost-effectiveness model was presented to understand the economic implication of different clinical strategies given the uncertainty regarding suitable candidates for chemotherapy in patients with high risk localized prostate cancer. The output of such framework can help policy makers evaluate the economic consequence of a new CDX to identify potential patients for chemotherapy. It can also be used by diagnostics manufacturers to determine whether the test under development can be profitable. At an early stage, such model can play important role in trial design.

Table 6.1) Base case assumption for data inputs

Parameter	Base case Value	Data source
Discount rate, benefit (%)	3.5	NICE (2012c)
Discount rate, cost (%)	3.5	NICE (2012c)
prevalence of chemo responders	0.4	Assumption based on Table 2.6
Sensitivity	0.93	Assumption based on Table 2.6
Specificity	0.95	Assumption based on Table 2.6
Utility, Metastasis free	0.8	Assumption based on Table 2.5
State cost, Metastasis free first year ($)	2579.2	From Table 4.3
State cost, Metastasis free following year ($)	715.5	From Table 4.3
Utility, metastasis	0.68	Assumption based on Table 2.5
State cost, Post metastasis first year ($)	2579.2	From Table 4.3
State cost, Post metastasis following year ($)	715.5	From Table 4.3
End of life cost ($)	46491.0	From Table 2.4
Cost of Chemo and SOC ($)	648.0	CMS (2014b)
Utility Chemo decrement	0.03	Mazta et al. (2013)
Max Number of Drug Cycles	6	Assumption based on Sweeney et al.2014
Hazard ratio for chemo responders versus SOC OS	0.7	Assumption based on Figure 2.3
Utility CDX decrement	0	Assumption

Table 6.2) Cost-effectiveness results, base case

		LY [a]	QALY	Cost
SOC	Metastasis free	7.0	5.6	79,979.1
	Metastasis	2.5	1.7	36,393.7
	End of life			31,314.1
	Total	9.5	7.3	147,687.0
Chemo treating all patients	Metastasis free	7.9	6.3	91,382.0
	Metastasis	2.3	1.6	34,134.6
	End of life			30,015.9
	Total	10.2	7.8	155,532.5
	Incremental vs. SOC	0.7	0.6	7,585.6
Personalized medicine [b]	Metastasis free	7.8	6.2	88,650.4
	Metastasis	2.3	1.6	34,292.7
	End of life			30,106.8
	Total	10.1	7.8	153,409.9
	Incremental vs. SOC	0.7	0.5	5,362.9

ICER [c]	Cost/LY	Cost/QALY
Treating all with chemotherapy vs. SOC	10,878.4	13,498.2
Personalized medicine vs. SOC	7,995.8	9,786.5

[a] LYs, QALYs and Costs were discounted

[b] Personalized medicine means selectively treating patients with chemo by CDX

[c] Total costs and QALYs of SOC were 7.3 and $147.687 respectively; Total costs and QALYs of chemo for all were 7.8 and $155,532.5 respectively; Total costs and QALYs of personalized medicine were 7.8 and $153,409.9. The increment costs and QALYs for treating all with chemotherapy versus SOC were $7585.6 and 0.6 with ICER as $13,498.2/QALY. The increment costs and QALYs for personalized medicine versus SOC were $5362.9 and 0.5 with ICER as $9,786.5/QALY.

Table 6.3) One-Way sensitivity analysis

Parameter	Base case Value	One way Sensitivity analysis		ICER of personalized medicine vs. SOC		ICER of treating all with chemotherapy vs. SOC	
		Low bound	High bound	Low bound	High bound	Low bound	High bound
Discount rate: benefit	0.035	0	0.05	5,217.4	12,352.5	7,150.6	17,098.3
Discount rate: cost	0.035	0	0.05	20,114.5	7,522.5	23,993.6	11,192.6
prevalence of chemo responders	0.40	0.10	0.70	10,831.3	9,637.9	34,946.9	10,686.9
Sensitivity	0.93	0.50	0.99	9,965.7	9,773.9	13,498.2	13,498.2
Specificity	0.95	0.50	0.99	11,672.0	9,620.2	13,498.2	13,498.2
Utility: Metastasis free	0.80	0.72	0.91	11,097.7	8,418.8	15,335.0	11,589.5
State cost: Metastasis free first year ($)	2579.2	2063.4	3095.0	9,670.3	9,902.7	13,380.5	13,616.0
State cost: Metastasis free following year ($)	715.5	572.4	858.6	7,282.7	12,290.3	10,959.9	16,036.6
Utility: metastasis	0.68	0.42	0.80	9,191.5	10,103.4	12,666.9	13,941.5
State cost: Post metastasis first year ($)	2145.3	1716.2	2574.4	9,875.7	9,697.3	13,588.7	13,407.8
State cost: Post metastasis following year ($)	1198.5	958.8	1438.2	10,464.1	9,108.9	14,185.2	12,811.3
End of life cost ($)	46491.0	21955.7	71026.3	10,949.2	8,623.8	14,676.9	12,319.5
Cost of Chemo and SOC ($)	648.0	1296.0	$8,820.0	12,510.2	44,134.4	19,836.3	93,426.4
Utility Chemo decrement	0.03	0.00	0.08	9,688.1	9,953.9	13,186.5	14,047.8
Max Number of Drug Cycles	6.0	3	12	8,419.3	12,400.4	10,310.7	19,636.6
Hazard ratio for chemo responders versus SOC OS	0.70	0.50	0.99	8,206.6	170,227.3	10,056.2	1,924,795.7
Utility CDX decrement	0.00001		0.04		10,556.9		13,498.2

Abbreviation, ICER=incremental cost-effectiveness ratio, CDX=companion diagnostics

The ICER of treating all patients with chemo is always higher than that of personalized medicine strategy. Personalized medicine means selectively treating patients with chemo by CDX

Table 6.4) A scenario Cabazitaxel (treated up to 6 months treatment) for HRLPC

		LY [a]	QALY	Cost
SOC	Metastasis free	7.0	5.6	79,979.1
	Metastasis	2.5	1.7	36,393.7
	End of life			31,314.1
	Total	9.5	7.3	147,687.0
Chemo treating all patients	Metastasis free	7.9	6.3	137,838.5
	Metastasis	2.3	1.6	34,134.6
	End of life			30,015.9
	Total	10.2	7.8	201989.0
	Incremental vs. SOC	0.7	0.6	54302.0
Personalized medicine [b]	Metastasis free	7.8	6.2	107472.7
	Metastasis	2.3	1.6	34,292.7
	End of life			30,106.8
	Total	10.1	7.8	171872.2
	Incremental vs. SOC	0.7	0.5	24185.3

ICER [c]	Cost/LY	Cost/QALY
Treating all with chemotherapy vs. SOC	75,293.7	93,426.4
CDX vs. SOC	36,058.7	44,134.4

[a] LYs, QALYs and Costs were discounted
[b] Personalized medicine means selectively treating patients with chemo by CDX
[c] Total costs and QALYs of SOC were 7.3 and $147.687 respectively; Total costs and QALYs of chemo for all were 7.8 and $201,989.0 respectively; Total costs and QALYs of personalized medicine were 7.8 and $153,409.9. The increment costs and QALYs for treating all with chemotherapy versus SOC were $54,302.0 and 0.6 with ICER as $93,426.4/QALY. The increment costs and QALYs for personalized medicine versus SOC were $24,185.3 and 0.5 with ICER as $44,134.4/QALY.

Table 6.5) Regression coefficients of selected factors versus cost-effective price of CDX under two WTP thresholds

Cost-effective price	WTP100,000/QALY	WTP50,000/QALY
Prevalence	124,227.0	55,639.0
Sensitivity	53,322.0	23,837.0
Specificity	3,044.7	2,620.9
HR of chemo respondent versus SOC	-333,397.0	-155,437.0

Note: HR of chemo respondent versus SOC has the biggest impact among selected variables to cost-effective price of both WTP thresholds. More impact is observed from the price under higher WTP threshold.
All models are statistically significant ($p<0.05$)

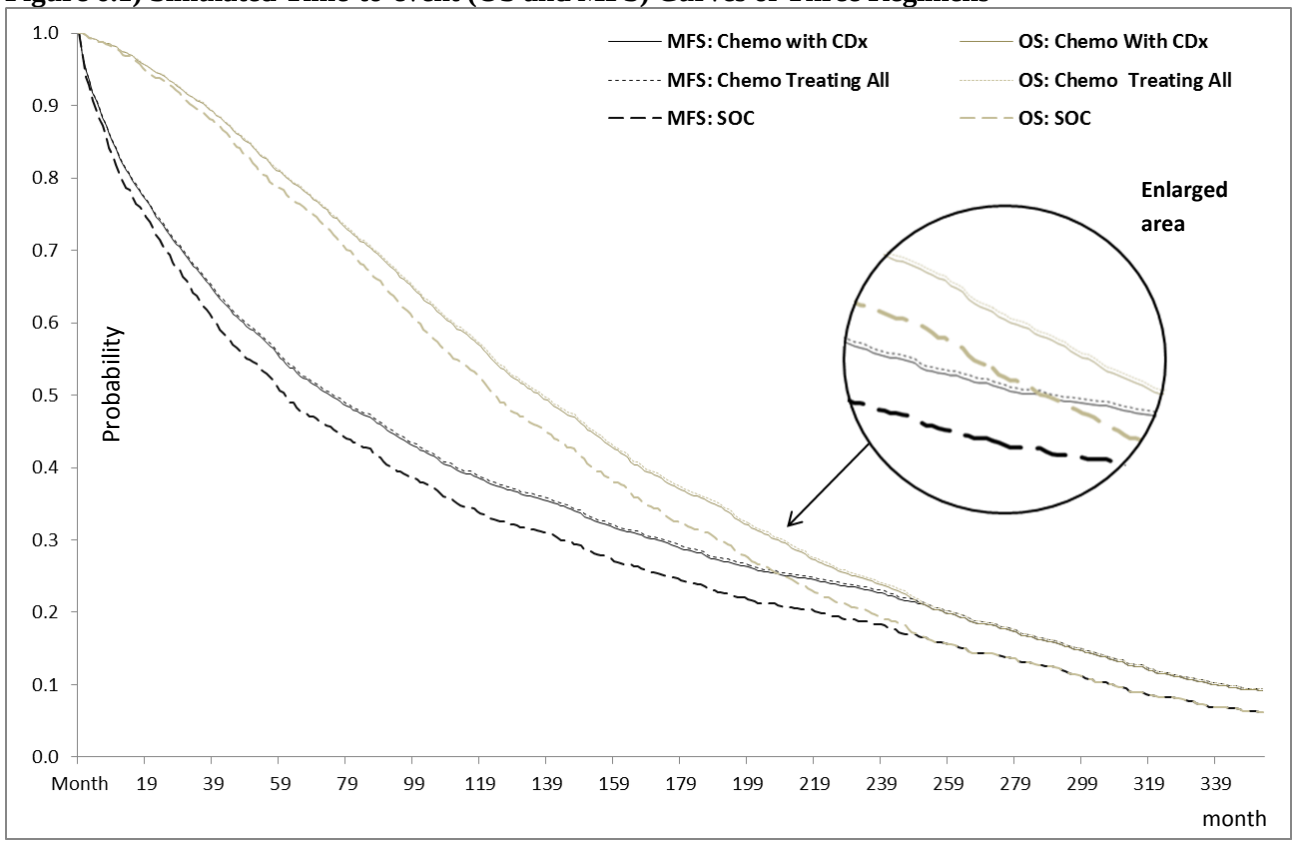
Table 6.6) A scenario cabazitaxel (treated up to 12 months treatment) for HRLPC

		LY [a]	QALY	Cost
SOC	Metastasis free	7.0	5.6	79,979.1
	Metastasis	2.5	1.7	36,393.7
	End of life			31,314.1
	Total	9.5	7.3	147,687.0
Chemo treating all patients	Metastasis free	7.9	6.3	182,978.9
	Metastasis	2.3	1.6	34,134.6
	End of life			30,015.9
	Total	10.2	7.8	247,129.4
	Incremental vs. SOC	0.7	0.6	99,442.5
Personalized medicine [b]	Metastasis free	7.8	6.2	126,078.7
	Metastasis	2.3	1.6	34,292.7
	End of life			30,106.8
	Total	10.1	7.8	190,478.2
	Incremental vs. SOC	0.7	0.5	42,791.2

ICER [c]	Cost/LY	Cost/QALY
Treating all with chemotherapy vs. SOC	127,884.2	174,941.5
CDX vs. SOC	63,799.1	78,846.3

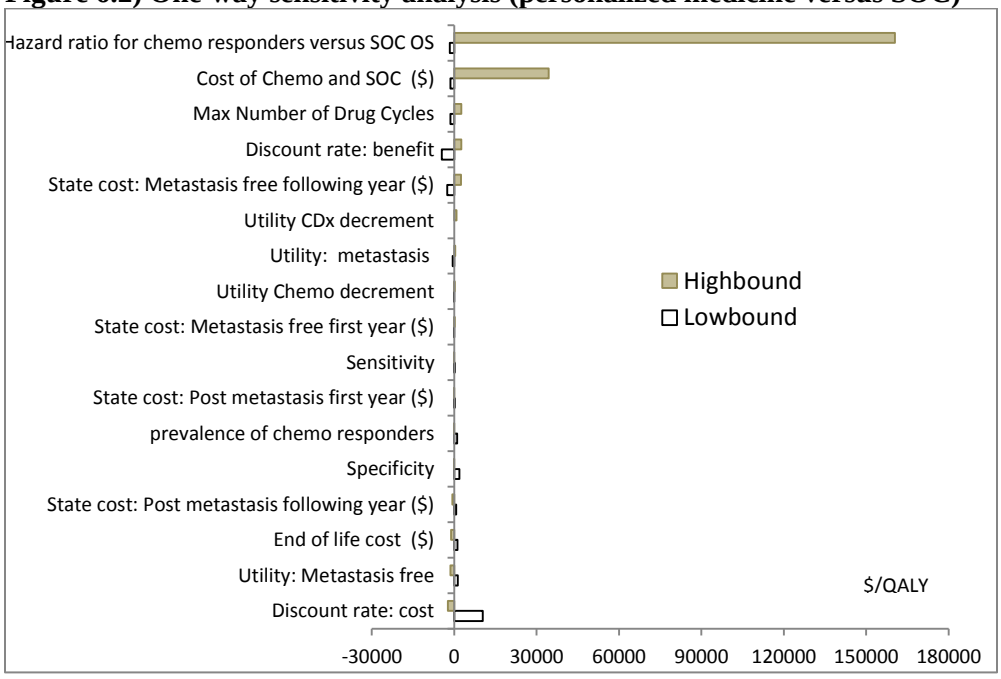
[a] LYs, QALYs and Costs were discounted. Cost is in 2013 price.
[b] Personalized medicine means selectively treating patients with chemo by CDX
[c] Total costs and QALYs of SOC were 7.3 and $147.687 respectively; total costs and QALYs of chemo for all were 7.8 and $247,129.4 respectively; total costs and QALYs of personalized medicine were 7.8 and $153,409.9. The increment costs and QALYs for treating all with chemotherapy versus SOC were $99,442.5 and 0.6 with ICER as $174,941.5/QALY. The increment costs and QALYs for personalized medicine versus SOC were $42,791.2 and 0.5 with ICER as $78,846.3/QALY.

Figure 6.1) Simulated Time-to-event (OS and MFS) Curves of Three Regimens



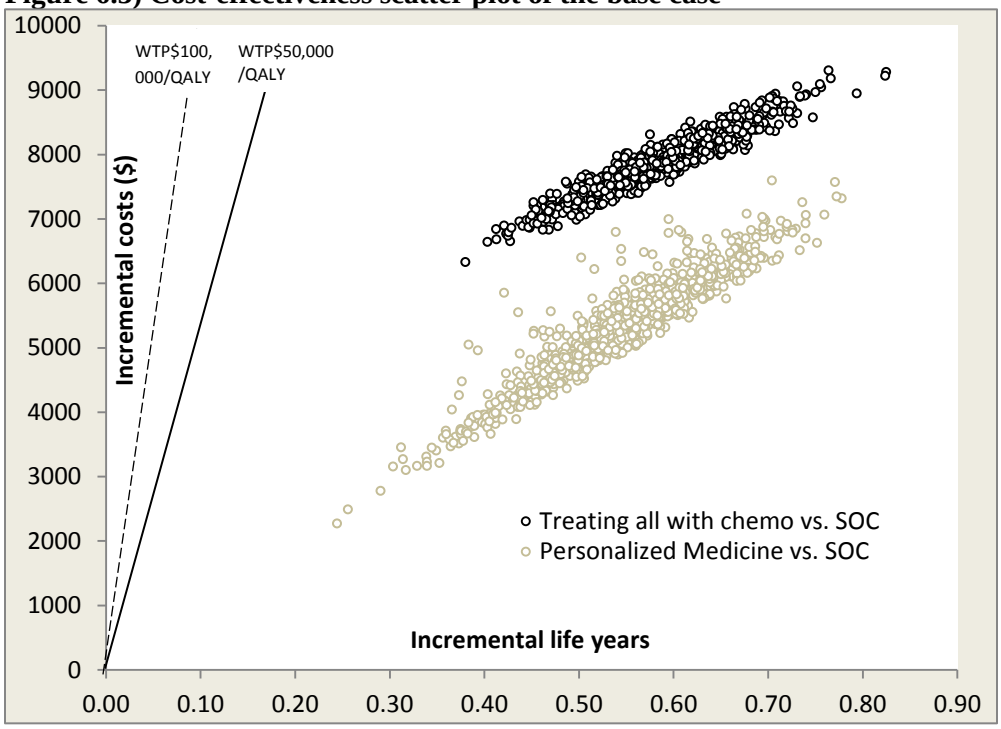
All OS curves are in black whereas all MFS curves are in gray. The small circle shows an enlarged area for better reading. For each type of survival outcome, treating all with chemotherapy has the best result. Its survival curve (dotted line) is at the top of three treatment strategies. The survival curves of treating by CDX (personalized medicine) are the solid lines, which almost overlap with the curves of treating all with chemotherapy (dotted line). The SOC curves (dashed line) are separated out from the others.

Figure 6.2) One-way sensitivity analysis (personalized medicine versus SOC)



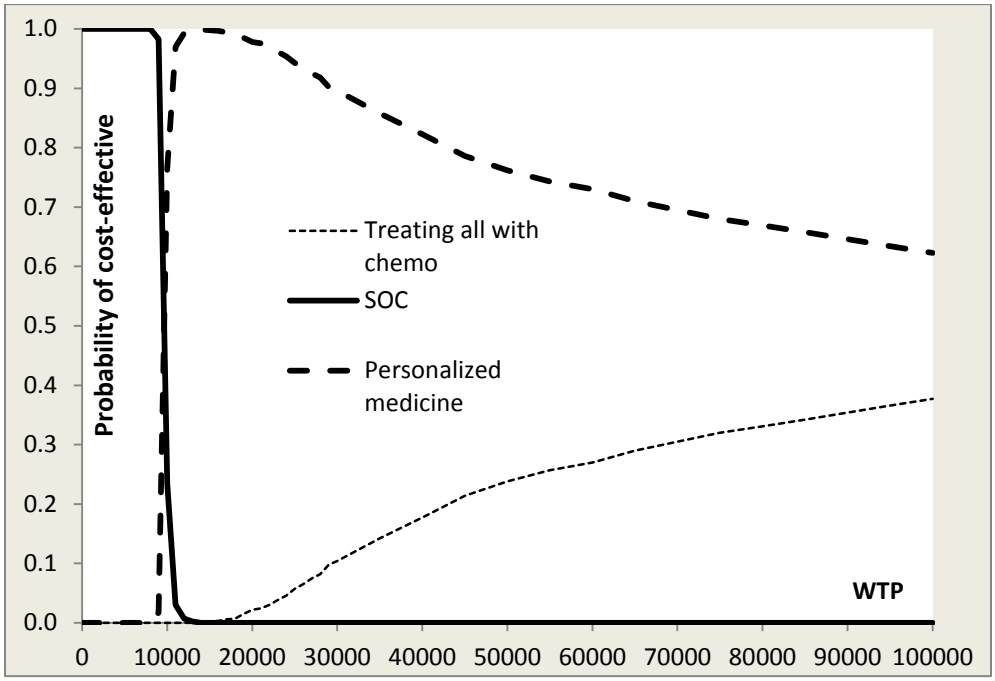
Note: When HR=0.95 then ICER increased to $170,223/QALY; When Cost followed that of Cabazitaxel, the ICER increased to $44,134.4. Other factors also influenced the results.

Figure 6.3) Cost-effectiveness scatter plot of the base case



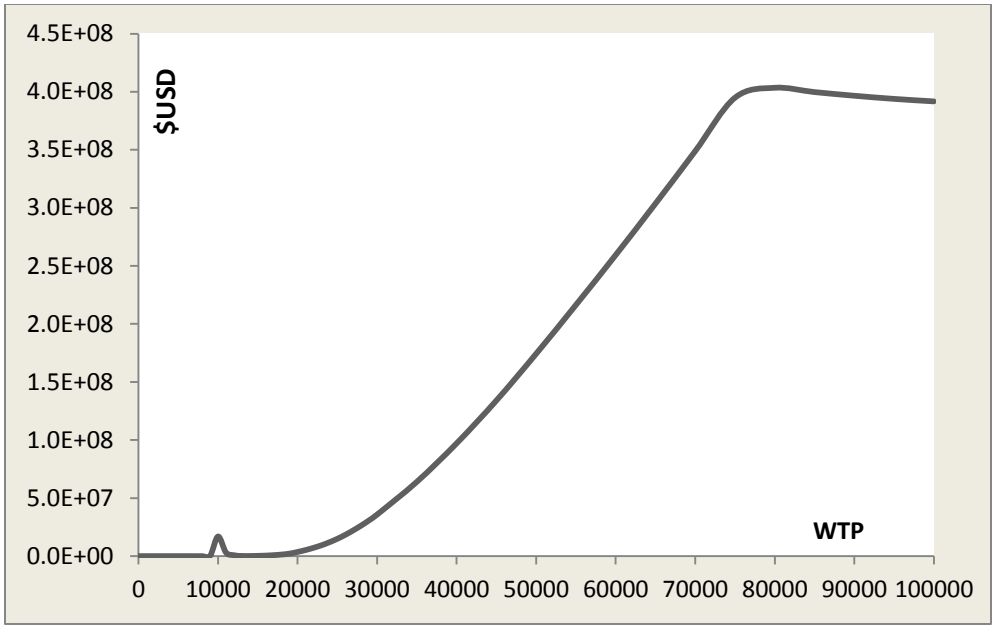
Note: Black dot represents a single probabilistic iteration comparing treating patients with personalized medicine (selectively treating patients with chemo by CDX) versus Standard of Care (SOC), whereas gray dots represent a single probabilistic iteration comparing treating all patients with chemo versus SOC. Almost all points were under the reference lines (WTP threshold 50,000/QALY (straight line) and 100,000/QALY(dashed line)), indicating base cases were cost-effective.

Figure 6.4) Cost-effectiveness acceptance curve of base case



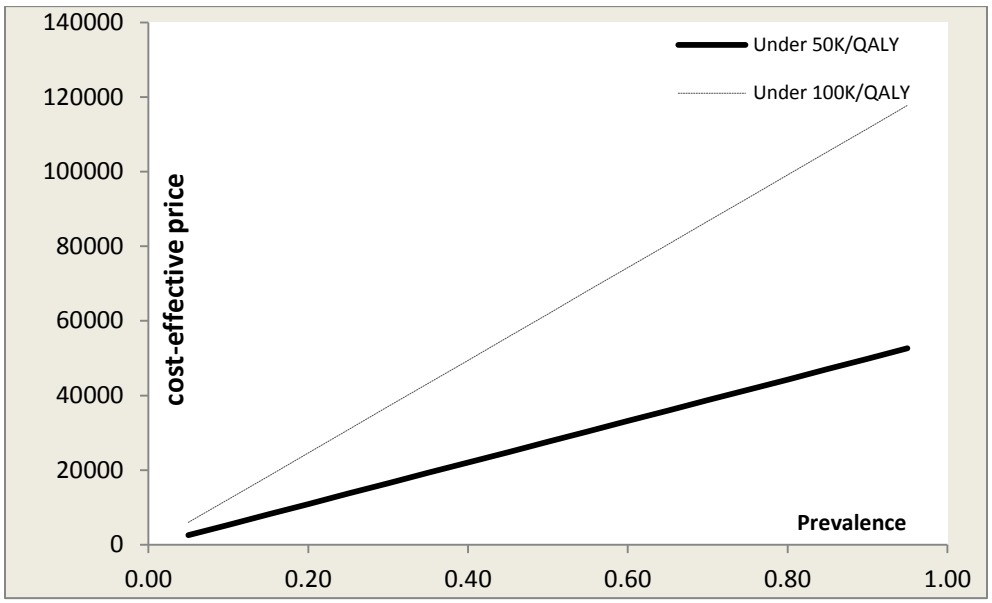
Note: Treating all patients with chemo had no chance to be cost-effective. It was dominated by SOC when WTP is less than $10,000/QALY and dominated by personalized medicine (selectively treating patients with chemo by CDX) when WTP is greater than $10,000/QALY.

Figure 6.5) Expected value of perfect information (EVPI) of base case



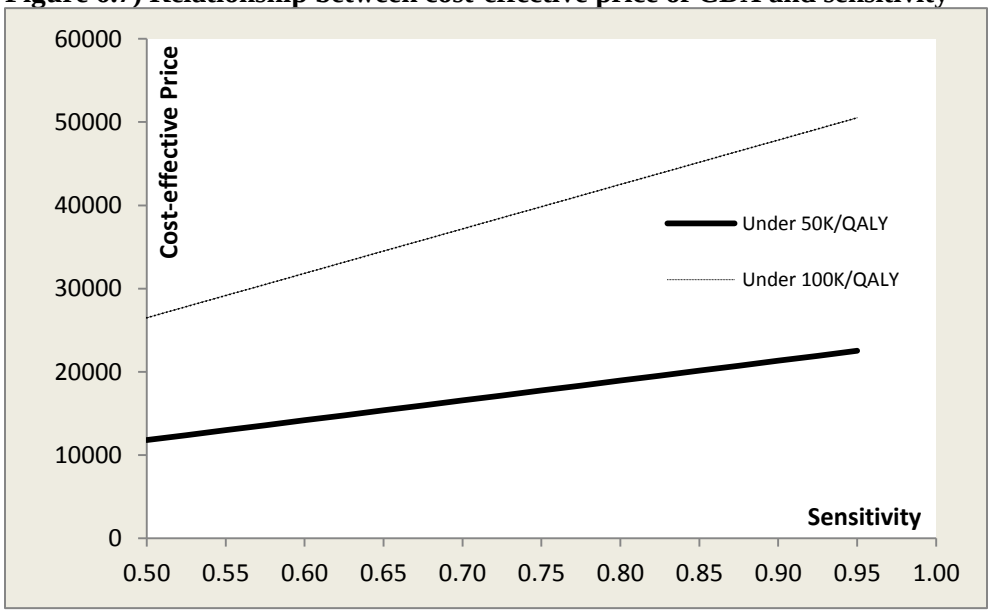
Note: EVPI increased at WTP $10,000/QALY where personalized medicine became cost-effective and then dropped to 0. It started to grow again with WTP after $20,000/QALY

Figure 6.6) Relationship between cost-effective price of CDX and prevalence



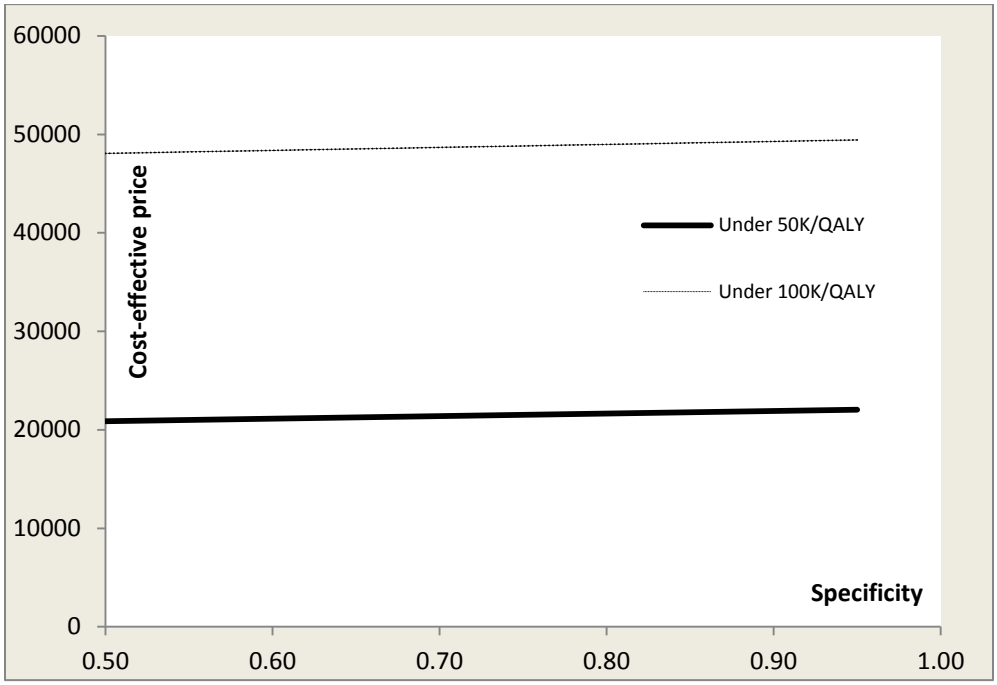
Note: Lower WTP cost-effective price is associated with lower WTP threshold. The cost-effective CDX price increases with prevalence

Figure 6.7) Relationship between cost-effective price of CDX and sensitivity



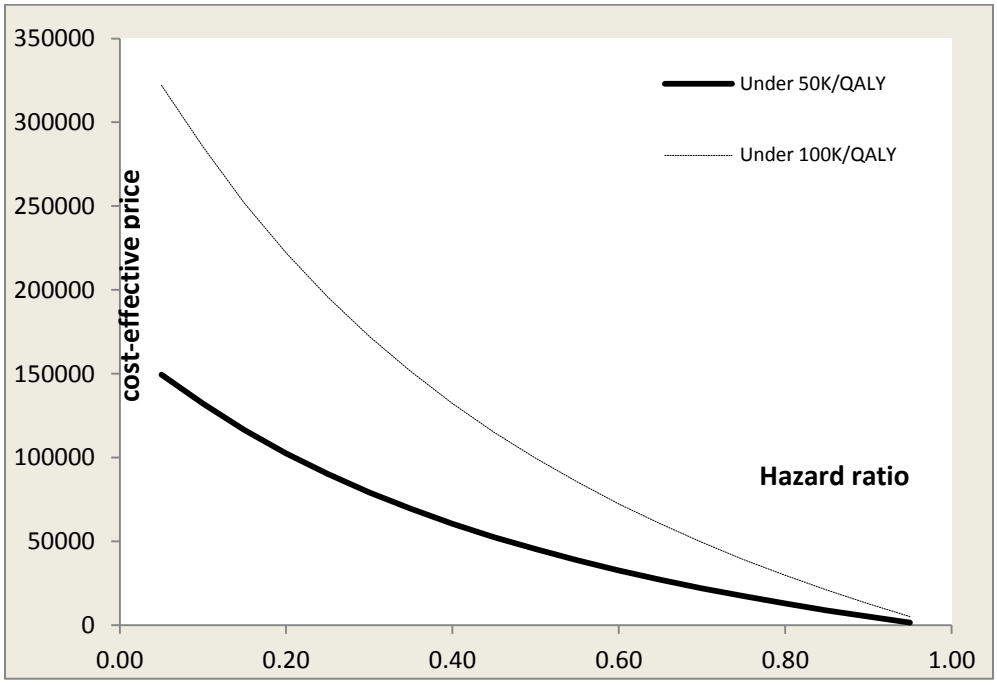
Note: The cost-effective CDX price increases with sensitivity

Figure 6.8) Relationship between the cost-effective price of CDX and specificity



Note: The cost-effective CDX price increases with specificity, but with lower slope than of sensitivity

Figure 6.9) Relationship between cost-effective price of CDX and hazard ratio of chemo respondent versus SOC



Note: The cost-effective CDX price exponentially decays with hazard ratio

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