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Prostate cancer is the uncontrolled growth of the prostate gland cells. It is the most common cancer found in American men other than non-melanoma skin cancer. This disease will affect 1 in 6 men during their lifetime. With early diagnosis and treatment, prostate cancer has a cure rate of 90 %. Currently, there are several treatment options available for prostate cancer. The most common forms of treatment for early and intermediate stage prostate cancers are surgery, radiation therapy, hormone deprivation therapy, and active surveillance. New treatment modalities including CyberKnife radiosurgery are currently being tested to gather data on safety and efficacy. Although the CyberKnife system gained clearance from the Food and Drug Administration in 2001 to treat tumors anywhere in the body where radiation treatment is indicated, long term

data has not accrued on this device to assess its safety and efficacy. Investigational new treatments such as the CyberKnife must undergo clinical trials even after it is approved to determine long term effects of the procedure. As an intern with a CyberKnife, prostate cancer clinical trial, the author assisted in initiating the clinical trial at a major institution and observed the many aspects of clinical research with a focus on the role of a clinical research coordinator. Through this experience, the author researched the key components in a protocol and the background information necessary to compose a clinical trial protocol in the area of prostate cancer.

REVIEW OF THE CURRENT TREATMENT OPTIONS FOR PROSTATE CANCER, EVOLUTION OF RADIOSURGERY, AND INITIATION OF A CYBERKNIFE PROSTATE CANCER TRIAL

Julieanna Angel Camarena, B.S.

APPROVED:

Michael W Ogbeby
Major Professor

John L. Cochenderfer, Ph.D.
Committee Member

Betsy Steen
Committee Member

Patricia A. Gwartz
Committee Member

Chair, Department of Biomedical Sciences

Dean, Graduate School of Biomedical Sciences

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Julieanna Angel Camarena, B.S.

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CHAPTER I

INTRODUCTION

I completed my six month clinical research internship through the Baylor Research Institute (BRI) at Baylor University Medical Center (BUMC) in Dallas. BUMC is a large campus where numerous clinical trials are conducted. Research has grown so large here, that Baylor Research Institute was established in 1982 to oversee the different areas of research. I am based in the Clinical Trials Office with research nurses conducting various clinical trials. While in the Clinical Trials Office, I have been exposed to various aspects of research such as patient follow up appointments, monitor visits, site-initiation visits, the consent process, as well as managerial aspects of clinical research, such as ordering supplies, and diplomatically communicating between a sponsor, principal investigator, and research coordinator.

When I am not in the Clinical Trials Office, I am in the Radiosurgery Center with Dr. Brian Berger and Dr. John O'Connor. I am acting as research coordinator with the clinical trials that they are conducting. The Radiosurgery Center is an outpatient clinic where patients with various cancers can be treated with radiation therapy by either the Gamma Knife or the CyberKnife. This is also where the doctors screen patients and obtain consent, if the patient meets eligibility criteria.

The Radiosurgery Center currently is conducting three clinical trials. The first uses the CyberKnife for the treatment of non-small cell lung cancer. The second trial uses CyberKnife to treat renal cell carcinoma, and the third also uses CyberKnife for the

treatment of prostate cancer. I kept the Institutional Review Board (IRB) up to date on the lung and renal studies, as well as communicated with the sponsor on the lung trial. Due to the timing of my internship, I was able to initiate the CyberKnife clinical trial for the treatment of low and intermediate risk prostate cancer.

Prior to my arrival at Baylor, the Radiosurgery Center had a prostate cancer clinical trial using the CyberKnife, but no patients were enrolled. This was because current literature deemed the radiation doses used during the CyberKnife treatments too high. Instead of enrolling patients under this study's protocol, I closed out the old study and initiated a new protocol that used more conservative CyberKnife radiation doses. The new study is a prospective evaluation of CyberKnife stereotactic radiosurgery in the treatment of low and intermediate risk prostate cancers. This study was designed to estimate the rates of acute and late toxicities observed after CyberKnife stereotactic radiosurgery for the treatment of low and intermediate risk prostate cancers for comparison with traditional forms of radiation therapy. The study also documented rates of failure, quality of life, disease-free survival, and amount of work required for treatment to compare to other forms of prostate cancer treatments.

Common treatment options for clinically diagnosed prostate cancer are active surveillance, androgen deprivation therapy, surgery, and radiation therapy. Within these treatment options are various forms. For example, radiation therapy encompasses external beam radiation and brachytherapy. With so many options, physicians and patients must turn to literature to determine which treatment is best for the patient's unique situation. Since there are new treatment options emerging every day, it is difficult

to evaluate the effectiveness of newer treatments that have not been researched as extensively.

The clinical trial that I initiated incorporated ideas from various pieces of literature and past clinical trials in the protocol. It is important to understand the basic science behind a clinical trial, so I have reviewed this in full during this internship experience. I have detailed the most common forms of prostate cancer treatments and their related problems. I have also reviewed the evolution of radiosurgery to get a better understanding of the CyberKnife technology and the need for its clinical trials. By reviewing these topics, I have achieved a better understanding of the basis for clinical trials for the treatment of prostate cancer and how clinical trial protocols are developed. Initiating this study has helped me to understand the IRB process as well as what is involved in a study's start up.

CHAPTER II

BACKGROUND

Prostate cancer is the uncontrolled growth of the prostate gland cells. It is the most common cancer found in American men other than non-melanoma skin cancer.[1] This disease will affect 1 in 6 men during their lifetime. With early diagnosis and treatment, prostate cancer has a cure rate of 90 %.[2] It is not usually lethal, but it is a heterogeneous disease ranging from asymptomatic to a rapidly fatal systemic malignancy.[3]

Prostate cancer has a high morbidity, but the etiology is vastly unknown. Advancing age, race, and a family history of prostate cancer are the only established risk factors. Other risk factors such as androgens, diet, physical activity, sexual factors, inflammation, and obesity have been studied, but their influence on prostate cancer is ambiguous. It is estimated that as much as 42% of the risk of prostate cancer may be accounted for by genetic influences, which means environmental factors, such as diet, also play a role.[4] Epidemiologically, prostate cancer can be divided into hereditary and sporadic forms, but molecularly are indistinguishable, unlike many other cancers. The highly penetrant inherited genes conferring the prostate cancer phenotype have not yet been identified, but several polymorphisms have been associated both with increased risk of prostate cancer and with increased risk of progression.[3]

Although prostate cancer can be seen in younger men, over 60% of all diagnosed prostate cancers are found in men aged 65 years or older.[5] It is infrequent but possible

for prostate cancer to have symptoms. When symptomatic, prostate cancer can cause urinary urgency, nocturia, frequency, and hesitancy. These symptoms may also be caused by benign prostatic hyperplasia (BPH), a non-cancerous enlargement of the prostate, and are more likely to be caused by BPH than by cancer.[1] Commonly, prostate cancer is asymptomatic and diagnosed by Prostate Specific Antigen (PSA) screenings, Digital Rectal Exams (DRE), and confirmed by a prostate tissue biopsy.

PSA can be measured by a simple blood test and can be used as an early detection test for prostate malignancies. It was approved by the Food and Drug Administration in 1992 for the detection of prostate cancer in men. PSA, being a chemical naturally produced in a normal prostate gland, can be excreted into the blood at variable levels, thus causing serum values to vary.[6] In the presence of prostate cancer or BPH, PSA serum levels become elevated. Malignant prostate tissue generates more PSA than normal tissue, most likely because of the increased cellularity associated with cancer. Increased cellularity can also account for the increased PSA levels found in BPH. Also, cancerous tissue can disrupt the prostate-blood barrier, which will increase the PSA serum concentration.[1] For younger men, normal PSA levels are less than 2.5 ng/mL. Men older than 65 should have a normal serum PSA level below 4 ng/mL.[7] In men with a serum PSA in the range of 4 to 10 ng/mL, a prostate biopsy is usually advised. A man with a PSA level greater than 10 ng/mL should also get his prostate biopsied, but there is a greater chance the cancer has spread further than the prostate.[1] Since serum PSA levels can fluctuate, it is important to confirm this test with other exams.

Digital rectal exams can be used to detect tumors in the posterior and lateral portions of the prostate gland. By palpating the prostate through the rectum, prostate cancer can sometimes be felt. All men with a hardened prostate, asymmetry, or palpable nodule should be further analyzed to rule out prostate cancer.[1] This type of exam can be used to determine the clinical stage of the prostate cancer. Clinical stage is based off of the TNM staging system set forth by the American Joint Committee on Cancer (AJCC). The T represents the extent of the tumor, N signifies the extent of spread to the lymph nodes, and M is the presence of metastasis.[8] The TNM Staging system is summarized in Table 1.

Table 1. 2002 AJCC TNM Staging System for Prostate Cancer

Clinical tumor (cT) stage	
Stage cT1:	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in five percent or less of tissue resected
T1b	Tumor incidental histologic finding in more than five percent of tissue resected
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA)
Stage cT2*	Tumor confined within the prostate
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involving both lobes
Stage cT3	Tumor extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades the seminal vesicle(s)
Stage cT4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.
Pathologic Tumor (pT) Stage	
Stage pT2	Organ confined
pT2a	Unilateral, involving one-half of one lobe or less
pT2b	Unilateral, involving more than one-half of one lobe, but not both lobes
pT2c	Bilateral
Stage pT3	Extraprostatic extension
pT3a	Extraprostatic extension
pT3b	Seminal vesicle invasion
Stage pT4	Invasion of bladder, rectum
Regional lymph nodes	
NX	Regional lymph nodes not assessed
N0	No regional lymph nodes in metastases
N1	Metastases in regional lymph nodes
Distant metastases	
M0	No distant metastases
M1	Distant metastases present
M1a	Non-regional lymph nodes
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Data from the *AJCC Cancer Staging Manual, Sixth Edition*[8]

A prostate biopsy can also be performed, which is the standard diagnosis.

Prostate biopsies are usually done transrectally without sedation or analgesia, but with

local anesthetic and an antibiotic regimen. A biopsy needle takes 12 to 14 prostate tissue samples through the rectum. Once taken, a pathologist can confirm the presence of prostate cancer in the tissue samples.[9] Since biopsy tissue volumes are small and cancer develops in random locations, repeat biopsies may be required to confirm or rule out prostate cancer if the first biopsy attempt is negative. Pathologists analyze the histology of the sample and grade it by a Gleason score. This grading system uses numbers to characterize the stage of differentiation of the biopsied tissue, ranging from 1 to 5. The lower the number, the more it appears like normal tissue. The higher the number, the more irregular the tissue. A Gleason score is the sum of the 2 most encountered tissue types and will range from 2 to 10.[10] Figure 1 shows an illustration of the Gleason grade from 1 to 5.

Figure 1. Gleason Grade Scoring System

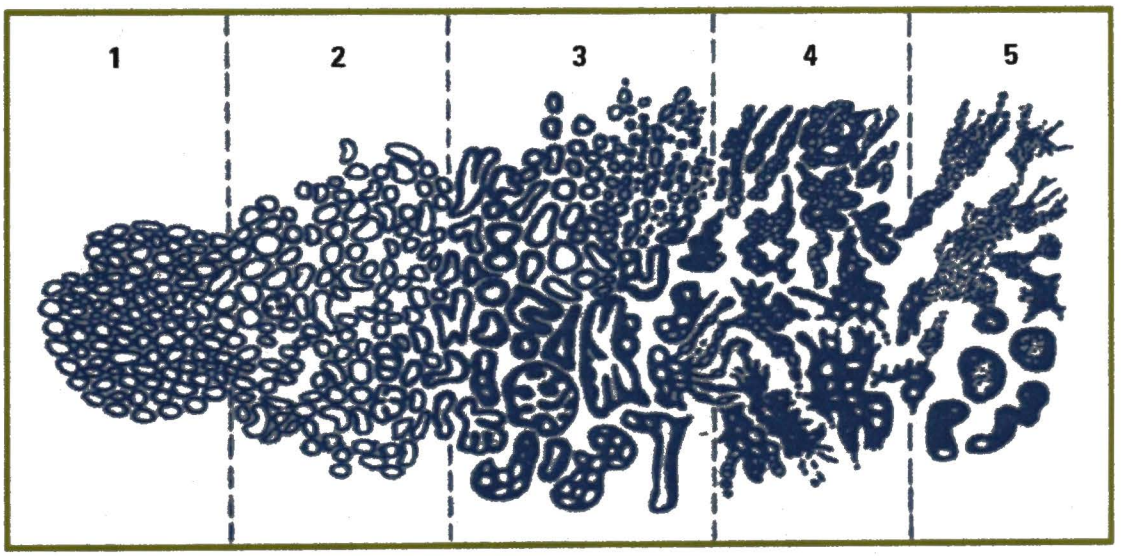


Figure from Urologic Pathology: The Prostate[11]

Although PSA, clinical stage, and Gleason score are important factors individually, combining all these factors into one predictive model allows a better

assessment of the extent of the disease and treatment outcome. The Partin model is the most common model used to predict the likelihood of prostate-confined cancer.[12] When prostate cancer is organ-confined, it is potentially curable, but non-organ confined disease is often fatal, and therapy is palliative. The Partin model can be seen in Table 2.

Table 2. Partin model predicting the probability of organ-confined prostate cancer

Gleason score	Clinical Stage T1c	Clinical Stage T2a	Clinical Stage T2b	Clinical Stage T2c
Prediction of probability of organ-confined disease:*				
Serum PSA = 0.0-2.5 ng/mL				
2-4	95 (89-99)	91 (79-98)	88 (73-97)	86 (71-97)
5-6	90 (88-93)	81 (77-85)	75 (69-81)	73 (63-81)
3 + 4 = 7	79 (74-85)	64 (56-71)	54 (46-63	51 (38-63)
4 + 3 = 7	71 (62-79)	53 (43-63)	43 (33-54)	39 (26-54)
8-10	66 (54-76)	47 (35-59)	37 (26-49)	34 (21-48)
Serum PSA = 2.6-4.0 ng/mL				
2-4	92 (82-98)	85 (69-96)	80 (61-95)	78 (58-94)
5-6	84 (81-86)	71 (66-75)	63 (57-69)	61 (50-70)
3 + 4 = 7	68 (62-74)	50 (43-57)	41 (33-48)	38 (27-50)
4 + 3 = 7	58 (48-67)	39 (30-48)	30 (22-39)	27 (18-40)
8-10	52 (41-63)	33 (24-44)	25 (17-34)	23 (14-34)
Serum PSA = 4.1-6.0 ng/mL				
2-4	90 (78-98)	81 (63-95)	75 (55-93)	73 (52-93)
5-6	80 (78-83)	66 (62-70)	57 (52-63)	55 (44-64)
3 + 4 = 7	63 (58-68)	44 (39-50)	35 (29-40)	31 (23-41)
4 + 3 = 7	52 (43-60)	33 (25-41)	25 (18-32)	21 (14-31)
8-10	46 (36-56)	28 (20-37)	21 (14-29)	18 (11-28)
Serum PSA 6.1-10 ng/mL				
2-4	87 (73-97)	76 (56-94)	69 (47-91)	67 (45-91)
5-6	75 (72-77)	58 (54-61)	49 (43-54)	46 (36-56)
3 + 4 = 7	54 (49-59)	35 (30-40)	26 (22-31)	24 (17-32)
4 + 3 = 7	43 (35-51)	25 (19-32)	19 (14-25)	16 (10-24)
8-10	37 (28-46)	21 (15-28)	15 (10-21)	13 (8-20)
Serum PSA >10 ng/mL				
2-4	80 (61-95)	65 (43-89)	57 (35-86)	54 (32-85)
5-6	62 (58-64)	42 (38-46)	33 (28-38)	30 (21-38)
3 + 4 = 7	37 (32-42)	20 (17-24)	14 (11-17)	11 (7-17)
4 + 3 = 7	27 (21-34)	14 (10-18)	9 (6-13)	7 (4-12)
8-10	22 (16-30)	11 (7-15)	7 (4-10)	6 (3-10)

PSA: prostate specific antigen.
* All numbers represent percent predictive probabilities (95 percent confidence interval).
Data From: *Partin, AW, et al. Urology 2001; 58:845.* [13]

Currently, these tests are being used to detect cancer at an early stage, while it is still organ confined. Thus, most prostate cancer research is being focused on treatment options for low-risk and intermediate-risk patients. Low-risk is characterized as a clinical stage T1c-T2a, Gleason score ≤ 6, and PSA < 10 ng/mL. Intermediate-risk is classified as a clinical stage T2b, Gleason score 7, and PSA ranging from 10-20 ng/mL.[14] Low-risk and intermediate-risk men with prostate cancer have the most choice in treatment options. It is not always clear which treatment option is the best and the pros and cons of each treatment must be weighed. Through prostate cancer research, many treatment forms are improving to a higher benefit to harm ratio. Understanding the current treatment options available for early stage prostate cancer and the evolution of radiosurgery is essential for improving the design of current and future prostate cancer clinical trials.

Specific Aim

My current research interest sprung from my family's multi-generational history of prostate cancer. Several years ago, my father faced it, and in the near future, my brother will most likely have to battle it as well. My overall goal of this internship was to learn about prostate cancer and the clinical trials that have potential to be promising treatment options. Also, I foresee myself as a physician conducting clinical trials. My second goal was to understand how clinical trials are conducted, with an emphasis on the rules and regulations followed, what roles the clinical research coordinator (CRC) plays, and the dynamic between the principal investigator and the CRC. Lastly, I wanted to learn how a protocol is developed. By researching the scientific background and current

medical developments for prostate cancer, I would understand how a prostate cancer trial using the CyberKnife is devised and evaluated for safety and efficacy.

Significance

Men at low and intermediate-risk for prostate cancer can choose between numerous treatment options. With so many options, physicians and patients must turn to literature to determine which treatment is best for the patient's unique situation. Since there are new treatment options emerging every day, it is difficult to evaluate the effectiveness of newer treatments that have not been researched as extensively. I will review the potential problems associated with each treatment option as well as determine which treatments are better suited to particular circumstances. Within these options, I will heavily research the evolution of radiosurgery up to the CyberKnife, explain its significance in the treatment of prostate cancer, and detail my experience initiating its use in a prostate cancer trial.

Materials and Methods

For the literature review of prostate cancer, prostate cancer treatment options, and radiosurgery history, peer-reviewed journal articles were retrieved from sources such as PubMed and UpToDate. In addition, I have accessed resources from credible websites of health organizations such as the Prostate Cancer Foundation, the American Cancer Society, the Centers for Disease Control, the National Cancer Institute, and the National Institutes of Health. I also used the United States FDA website as well as www.ClinicalTrials.org. The keywords used for my searches were "Prostate Cancer",

"CyberKnife," "Radiosurgery History," "Prostate Cancer Treatment," and "Prostate Cancer Radiosurgery."

My involvement in the initiation of a CyberKnife clinical trial for the treatment of prostate cancer has helped me to understand the foundations of a protocol and its implementation. I have learned from this experience specifically through shadowing the Principal Investigator, Brian Berger, M.D., the Director of Clinical Research at Baylor Research Institute, Betsy Stein, and the Clinical Trials Office Research Manager and research nurse, Mary Sams, throughout their daily activities. All have helped me through the process of initiating a clinical trial and obtaining exposure to clinical research management.

Results

Prostate Cancer Treatment Options

Active Surveillance

Active surveillance is one option for a newly diagnosed prostate cancer and is sometimes called, "watchful waiting." Since prostate cancer is a slow growing malignancy, it is not always necessary to seek treatment. Active surveillance exploits this reality of prostate cancer and nothing is done to prevent cancer growth. The active surveillance approach is characterized by (1) identifying patients who have a low likelihood of disease progression during their lifetime, based on clinical and pathologic features of the disease and patient age and comorbidity; (2) monitoring closely over time, (3) establishing reasonable criteria for intervention, which will both identify more aggressive disease in a timely fashion, and not result in excessive treatment, and (4)

meeting the communication challenge to reduce the psychological burden of living with untreated cancer.[15]

Typically, elderly men and men with highly comorbid conditions are advised to take this approach. Men with an estimated life expectancy beyond 15 years are not advised to choose active surveillance.[16] It is also an option for men with screen-detected, low-volume cancer. This is characterized by a Gleason score of 6 or less, a PSA value of 10 ng/mL or less, and a stage T1c or T2a disease.[17] The rationale for active surveillance is to prevent over-treatment and avoid or delay the risks and complications associated with definitive forms of treatment. Also, the majority of men who initially choose active surveillance with the intent of seeking treatment when the cancer progresses do so within 2 to 3 years due to persistently rising PSA level.[14] For appropriately selected men, active surveillance with a delayed treatment intervention does not compromise cure rates.[18]

The main complication associated with active surveillance is the eventual progression and metastasis of prostate cancer. Also, genitourinary symptoms typical of prostate cancer therapies frequently occur among men using the active surveillance approach and can negatively affect their quality of life that pertain to physical function, general health, vitality, bodily pain, and sexual function.[19] In a study comparing the quality of life of active surveillance to radical prostatectomy, the active surveillance group had higher incidences of urinary obstruction (44% vs. 28%), and lower rates of erectile dysfunction (45% vs. 80%) as well as urinary leakage (21% vs. 49%).[20]

Active surveillance may be appropriate for a portion of the population diagnosed with prostate cancer, but it does not even treat the disease. Also, it is possible to miss the

treatment window to prevent prostate cancer metastasis. Since most prostate cancer is found at an early stage when it is potentially curative, it is commonplace for physicians to advise seeking more definitive treatment options. Palliative treatments, such as androgen deprivation therapy, are sometimes used for local or metastatic progression when and if it occurs during active surveillance.

Androgen Deprivation Therapy

Androgen deprivation therapy is a practice designed to treat prostate cancer by reducing levels of the male hormones, androgens, in the body. The major androgens targeted are testosterone and dihydrotestosterone (DHT). Androgens, which are produced mainly in the testicles, stimulate prostate cancer cells to grow. By lowering androgen levels, often the prostate cancer will shrink or grow more slowly. Hormone levels can be lowered by either surgical castration (removal of the testes), drugs that decrease the levels of androgens (luteinizing hormone releasing hormone therapy), or drugs that block androgen receptors (anti-androgen therapy). However, hormone therapy does not change the overall prognosis of prostate cancer.[21]

Most often, men with metastatic prostate cancer use androgen deprivation therapy. Its use for advanced prostate cancer provides important quality-of-life benefits, including reductions of bone pain, pathological fracture, spinal cord compression, and urethral obstruction. However, it is not clear whether there is an improvement in long-term survival.[22] It can also be used in conjunction with other treatments such as active surveillance, surgery, and radiation therapy to improve the outcome. As a co-therapy, androgen deprivation is short term. For active surveillance, androgen deprivation will

slow the growth of the cancer. It can be used before surgery or radiation therapy to shrink the cancer and improve the treatment's effectiveness. It is also an option if the prostate cancer was not cured after the first definitive treatment attempt.[21] Androgen deprivation is becoming more acceptable prior to receiving radiation therapy in men with locally advanced disease, such as prostate cancer in the prostate capsule or the lymph nodes. A European study that compared radiation therapy with androgen deprivation therapy to solely radiation therapy found the overall survival at 5 years was 78% for the combined treatment group and 62% ($P<.001$) for radiation therapy alone group. Among the surviving patients, 74% and 40% were clinically disease-free at 5 years in the combined treatment and radiation-only groups, respectively ($P<.001$).[23]

Although androgen deprivation therapy may have its benefits, it also has numerous side effects. One set of side effects, labeled as the "castration syndrome," is hot flashes, loss of libido, and erectile dysfunction. Other side effects include obesity, decrease in muscular strength and mass, fatigue, a decline in physical activity and general vitality, mood changes, depression, and sometimes, gynecomastia.[24] Since androgens activate erythropoiesis, androgen deprivation can also result in anemia. Within 3-6 months of therapy, hematocrit and hemoglobin levels decrease.[25] Another complication of androgen deprivation therapy is rapid bone loss, the long term effect of osteoporosis, and an increased risk of debilitating bone fractures. Testosterone is converted to estrogen to inhibit osteoclasts and their role in bone resorption. Low levels of testosterone lead to less estrogen control of osteoclasts, which degrade bone, and little estrogen to maintain

proper function of osteoblasts, which build bone.[26] All of these complications significantly decrease ones quality of life without the potential of curing the disease.

Radical Prostatectomy

The surgical approach is an attempt to cure prostate cancer by radical prostatectomy. Approximately 40% of men diagnosed with clinically localized prostate cancer choose this definitive treatment option.[27] Most urologic surgeons perform an operation called radical retropubic prostatectomy, but less common approaches exist such as perineal and laproscopic prostatectomies, sometimes with robotic assistance.[21] The laproscopic approach uses several small incisions, long small instruments, and a camera. The retropubic and perineal approach is an "open" surgery and is illustrated in Figure 2.

Figure 2. Incision site for radical retropubic prostatectomy (left) and radical perineal prostatectomy (right)

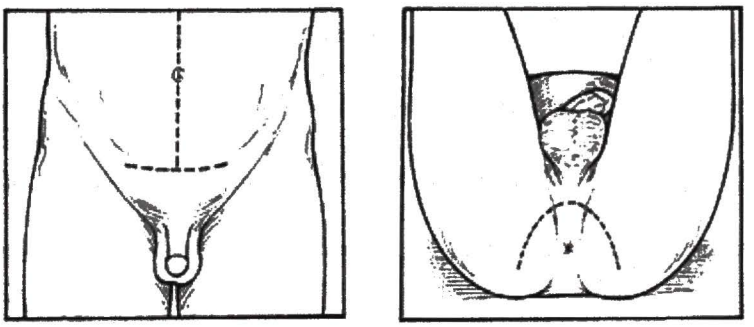


Figure from the American Cancer Society[21]

Radical prostatectomies can be performed under general, epidural, or spinal anesthesia. Pre-incision, a Foley catheter is placed in the urethra for urinary drainage and remains there during the recovery period. Men with low-risk prostate cancer have a less than 1% risk of lymph node metastasis. In men with a higher risk prostate cancer, a lymphadenectomy may be performed along with the prostatectomy. If cancerous cells

are found in the lymph nodes, the surgeon will not continue with the surgery because it will not cure the patient. Once the patient is sedated and the surgeon has made the required incisions, the important structures are identified such as the bladder, seminal vesicles, urethra, dorsal vein complex, neurovascular bundles, distal sphincter, and the prostate. The prostate and seminal vesicles are then removed, the associated blood vessels are tied off, and the urethra and bladder are anastomosed. A drain is placed in the obturator fossa to allow blood and other fluids to leave the surgical space during recovery and the incision is sutured. The average time for this procedure is 110 minutes, and with the addition of a lymphadenectomy, the average time increases to 125 minutes.[28]

Radical prostatectomy is an option for patients with localized prostate cancer who have a long life expectancy and no or minor comorbidities. Men with hypertension, diabetes mellitus, or coronary heart disease are still qualified for this surgery as long as the conditions are maintained properly and have a normal exercise capacity. Higher risk comorbidities, such as cardiovascular disease, can be assessed by a cardiac evaluation performed prior to surgery.[28] By removing the source of the cancer, men with prostate cancer can potentially be cured of their disease.

Risks from surgery include myocardial infarction, and thromboembolic, infectious, and neurologic complications. The morbidity rate of these complications is less than 10% and is more common in older men or those who have received prior irradiation.[29] Post surgery complications are of most concern to patients. It has been shown that

selection of an experienced surgeon with a good knowledge of functional pelvic anatomy is a good predictive factor for surgical outcomes and a reduction in complications.[30]

One common complication from this surgery is incontinence. This may happen for several reasons. The external urethral sphincter is paramount in preserving continence. Damage to this structure at the apex of the prostate will lead to post-operative urinary incontinence.[30] The internal urethral sphincter is located at the bladder neck, just above the base of the prostate, and damage to it can also lead to incontinence. A "no-touch" approach to this structure leads to improvements in continence.[31] The internal urethral sphincter is also associated with stress incontinence. This is when urine leakage happens during laughing, coughing, sneezing, or exercise. Continence has been shown to improve with pelvic floor muscle training. Contraction of these muscles increase their strength and endurance.[32] Also, medications exist to improve this condition such as Flomax and Hytrin.[10] Incontinence tends to improve over time, but severe post-prostatectomy incontinence can be managed with the placement of an artificial urinary sphincter.[28]

Another major complication from radical prostatectomy is impotence. Some men qualify for a nerve-sparing prostatectomy who do not have prostate cancer outside of the prostate gland.[33] The main issue with preserving erectile function is dissecting the prostate without the use of thermal energy and avoiding the nerve branches directed towards the corpora cavernosa.[31] The prostatic nerve plexus contains parasympathetic fibers that give rise to the cavernous nerves that control erection. [34] If these nerves are severed or damaged, erectile function can not be regained. Although the ability to get a

rigid penis for intercourse is lost, penile feeling and orgasm remain normal. Also, there are several medications currently on the market to treat erectile dysfunction if this happens.[35] Figure 3 depicts the prostate and bladder relationship associated with incontinence as well as the prostate nerve innervations associated with impotence.

Fig 3. Pelvic anatomy

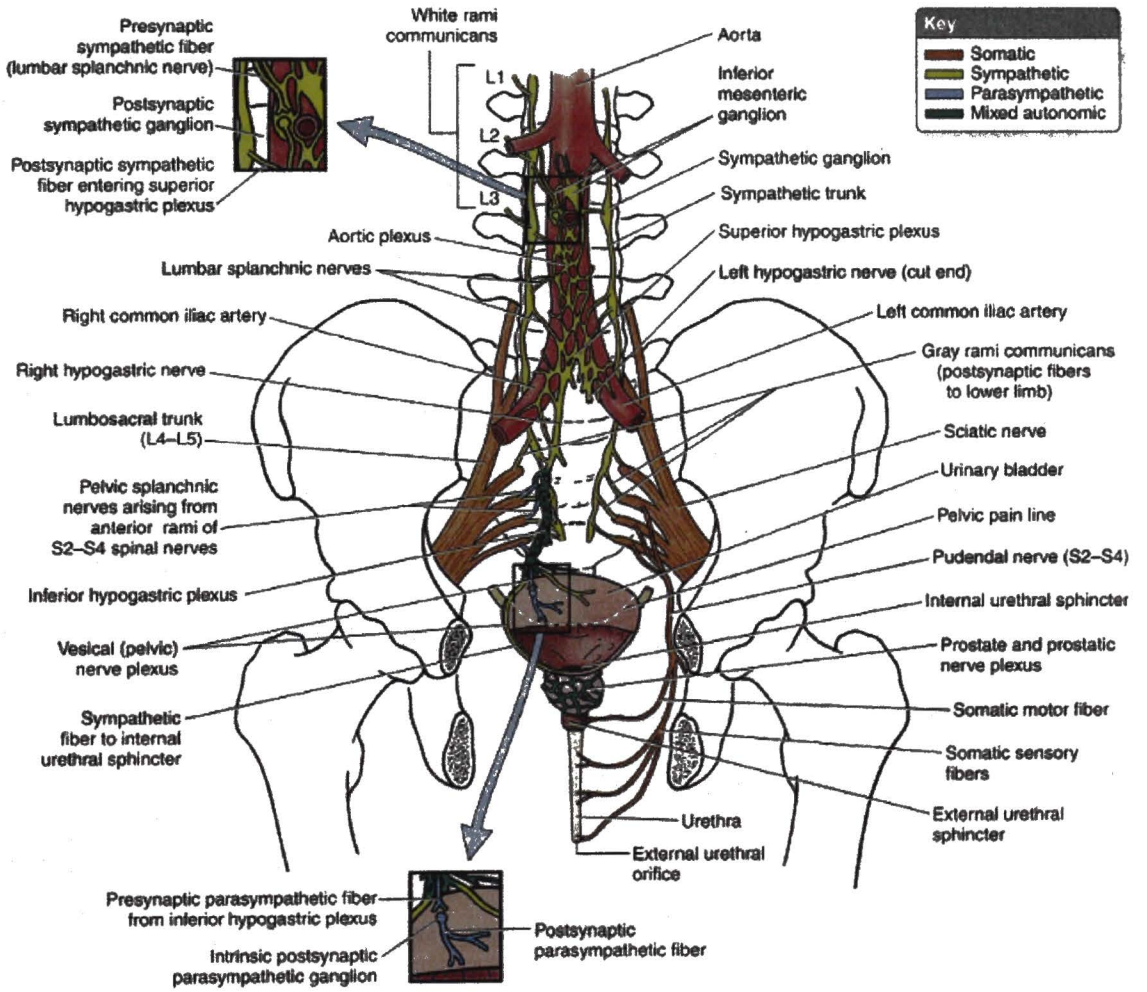


Figure from *Essential Clinical Anatomy.*[34]

Radiation Therapy

Radiation therapy is the most diverse form of treatment for prostate cancer. This therapy combats cancer by accurately delivering toxic doses of high-energy rays or particles to cancer cells as a way to kill them. Cancerous cells have abnormal DNA and continue to duplicate themselves without repairing the DNA. When a normal, healthy cell has damaged DNA, it has repair mechanisms to correct the damage or it can undergo apoptosis if the damage is irreparable. By focusing energy to the cancerous cells, the DNA becomes extremely damaged to the point that it can not replicate anymore.[21] By exploiting a cancer cell's weakness, radiation therapy is a viable option for treating prostate cancer.

Radiation therapy can be given in several ways. The most common are external beam radiation therapy (EBRT) and brachytherapy. EBRT encompasses conventional external beam radiation therapy, 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and conformal proton beam radiation therapy.[36] 3D-CRT became available when computers allowed for a 3-dimensional radiation therapy planning system and computer-controlled radiation delivery. This form of radiation therapy utilizes a set of fixed radiation beams chosen to match the shape and size of the prostate gland. Intensity modulated radiation therapy improved on this concept by allowing manipulation of the intensity of the radiation beams used for therapy. Changing the intensity allows less radiation to normal tissues and higher levels of radiation to the cancerous tissue.[37] Proton beam radiation therapy is very similar to 3D-CRT, but uses protons instead of x-rays. Protons can go through normal tissue without

damaging it, but can release a large amount of energy to the target where it is aimed, such as the prostate. This form of radiation therapy has not been researched very extensively, is expensive, and most insurance companies do not cover it.[21] The unit of measurement used to determine the amount of radiation absorbed by human tissue is called the Gray. Several studies concur that radiation doses must be greater than 70 Gy for external beam radiation to be a curative treatment for clinically localized prostate cancer.[36] Typically, approximately 2 Gy of radiation is given per treatment session to achieve this large amount of radiation.

Another form of radiation therapy is called brachytherapy. This is a slightly invasive form of radiation therapy performed with light general or spinal anesthesia. Radioactive, rice-sized pellets are placed into the prostate gland to emit radiation to the cancerous cells for a specified period of time and eventually dissipate. Imaging technology has improved the efficacy and long-term results of this treatment. Initially, doctors would place the pellets in the prostate randomly, and portions of the prostate would not receive adequate doses of radiation. Ultrasound guidance is now used during seed placement in a transperineal approach to ensure even spacing between pellets.[14]Typically, these pellets are made of iodine-125 [I-125] or palladium-103 [Pd-103]. These are low energy radioactive sources, which have a limited tissue penetration and placed accordingly to allow a sharp dose drop off at the edge of the prostate.[38] According to the National Cancer Institute, 22% of men treated for prostate cancer in the year 2000 received brachytherapy.[39]

Radiation therapy is usually advised to elderly men seeking definitive treatment of their localized prostate cancer. This is because it avoids the risks associated with anesthesia as well as the blood loss and recovery period associated with surgery. [40] External beam radiation therapy is an outpatient procedure, and normal activity can usually be maintained during treatment. It is administered daily for approximately 5 to 8 weeks, which can be inconvenient, but avoids prolonged hospitalization as seen with surgery.[41] Brachytherapy is ideal for treating localized prostate cancer in men whose prostate gland volume is not very large. Seed placement creates inflammation and swelling in the prostate gland, which could lead to urinary complications. Since brachytherapy will only exaggerate an enlarged prostate, these men should choose another treatment option.[42]

Radiation therapy complications can be grouped into 3 categories: Urinary, sexual, and gastrointestinal. Higher rates of urinary complications are seen after brachytherapy, but occur in both types of radiation therapy. These symptoms include urinary frequency, pain during urination, and urinary urgency.[14, 43] Urinary incontinence is a less frequent side effect after radiation therapy than after a radical prostatectomy. Sexual dysfunction is comparable to surgery, but radiation therapy provides a slightly lower rate of impotence.[44] Unlike surgery, gastrointestinal side effects are more frequently seen after radiation therapy. This is due to the prostate's close proximity to the rectum. Proctitis results from acute intestinal toxicity effects and severity is proportionate to the amount of bowel in the radiation field.[45] Symptoms of proctitis are abdominal cramping, feelings of incomplete defecation, as well as urgency and frequency of defecation.[44] Another

gastrointestinal side effect more commonly seen after brachytherapy is rectal bleeding.[46] Persistent diarrhea, formation of a secondary malignancy as a result of radiation, and death are extremely rare side effects of radiation therapy.[14]

Evolution of Radiosurgery and the CyberKnife

An improvement on radiation therapy for prostate cancer is radiosurgery. Radiosurgery is a precise, non-invasive method that delivers high doses of radiation to small tumors in a concentrated time period. It has over a 30 year history in treating brain tumors, but it is more recently being used to treat other areas of the body, like the prostate.[47] Lars Leksell, a Swedish neurosurgeon, first conceived the idea of radiosurgery in 1952, and the first patient was treated with radiosurgery in 1967 by a device called the Gamma Knife. The Gamma Knife was originally designed to treat functional disorders, but was later applied to intracranial lesions and arteriovenous malformations. Dade Lunsford, an American neurosurgeon, introduced the Gamma Knife to the United States by installing it at the University of Pittsburgh in 1987.[48]

The Gamma Knife is produced by Elekta, a Swedish medical systems company founded by Leksell. It is only used to treat abnormalities in the cranial region. A metal frame is required to be screwed on to the patient's head as a frame of reference for the device and for immobilization of the target area.[47] The current device contains 201 Cobalt-60 [Co-60] sources contained in a shielded array as the device's radiation source. Gamma radiation is focused through apertures (collimators) within a hemispheric helmet that attaches to the metal frame.[49]

The Gamma Knife was eventually improved upon by the use of imaging and computing technology, but linear accelerators expanded radiosurgery beyond this device. The next radiosurgical device using a linear accelerator, the X-Knife, was established in Philadelphia during August of 1991. Several technical and software problems were resolved by the mid-nineties which allowed tighter isocentric rotation (clockwise and counter-clockwise), a mobile linear accelerator system, accurate fusion of CT/MRI images for treatment planning, automated treatment planning, and treatment fractionation. The next advance in radiosurgery was the addition of an automated tertiary microleaf collimator. This allowed the emitted radiation to adapt to the shape of the target, and the next radiosurgical machine was born, the Novalis Shaped Beam Radiosurgery Unit. During this time, radiosurgery was limited to the cranial region, but John Adler began researching robotic technology and developed a radiosurgical device that could deliver radiation to intracranial as well as extracranial regions. This was the first of its kind as well as the first robotic linear accelerator available for commercial purchase.[48] It was named the CyberKnife, and the first patient was treated with it at Stanford University in 1994.[50] Other similar radiosurgery devices have come out on the market since the CyberKnife inception, such as a Novalis version and the Isolac. Figure 4 illustrates the CyberKnife Robotic Radiosurgery System.

Figure 4. CyberKnife Robotic Radiosurgery System in motion

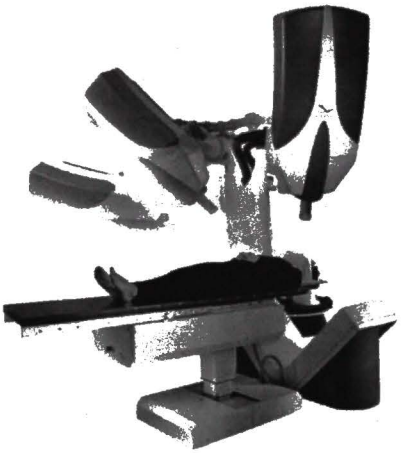


Figure from Accuray, Inc.[51]

CyberKnife is a robotic radiosurgery device manufactured and distributed by Accuray, Inc. of Sunnyvale, CA. The CyberKnife system gained clearance from the Food and Drug Administration in 1999 to treat tumors in the head, neck, and upper spinal region, then again in 2001 to treat tumors anywhere in the body where radiation treatment is indicated.[51] This device manipulates a 120 kg weight, 6-MV linear accelerator attached to a computer-controlled robotic arm with 6 degrees of freedom. The need for a frame is eliminated by the 2 ceiling mounted diagnostic x-ray cameras with corresponding orthogonal, floor-mounted amorphous silicon detectors that track patient movement by real-time digital imaging. Also, boney landmarks and radiopaque fiducials with known geometric distances can be identified to help track patient movement. The CyberKnife can track the prostate by the gold seeds (fiducials) placed in the prostate prior to treatment and the pubic bone. Once the target is found, the linear accelerator accurately delivers photon radiation and has an absolute accuracy that deviates no more than 1 to 1.5 mm from the desired target.[52] This accuracy allows for reproducible dose delivery that can be fractionated, or divided over several days.

The typical treatment course for prostate cancer treated with the CyberKnife is as follows. Patients must meet with a urologist and a radiation oncologist to determine eligibility. For example, due to radiation toxicity, patients who have received radiation therapy to the pelvic region probably would not qualify. Also patients whose weight exceeds 350 lbs are not eligible due to weight constraints on the CyberKnife machine. After meeting eligibility criteria and deciding on treatment with the CyberKnife, 3-4 small gold seeds (fiducials) will be placed into or around the prostate tumor by the urologist. Approximately 1 week later and after the swelling from the fiducial placement has gone down, an immobilization device is made to minimize changes in body position during treatment. This is a Vac-loc bag in which the patient lays on top, and when the air is suctioned out of it, the bag conforms to the patient's body. Next, CT/MRI scans are taken of the pelvis with a 1.25 mm slice thickness. These are high resolution images used for treatment planning which are taken while laying on the Vac-loc bag to ensure the same body position during treatment. During the planning stage, critical structures are identified and the computer is told which structures need radiation and which to avoid. Once this stage is complete, treatment can begin. The dose schedule commonly being accepted is a hypo-fractionated treatment regimen. Five separate CyberKnife treatments of 7.25 Gy are given within a two week period equaling a total dose of 36.25 Gy. Each treatment session takes approximately 1.5-2 hours.[53]

CyberKnife radiotherapy is an emerging treatment option for localized prostate cancer. The rationale behind this treatment option is that it has a much shorter treatment course than conventionally fractionated radiation therapy, it does not require general

anesthesia or the recovery period associated with surgery, it offers extreme precision, and it may yield an increase in local tumor control. A clear dose response exists for localized prostate cancer radiotherapy and a hypo-fractionated radiation regimen may allow for biologically equivalent dose escalation without increasing normal tissue toxicity.[54]

In other words, by hypo-fractionation, the use of large dose-per-fraction amounts of radiation, the therapeutic ratio can increase.[54] This has to do with the low α/β ratio for prostate cancer. Cells react differently to the amount of radiation they receive and to the rate of radiation delivery. The α/β ratio characterizes the intrinsic radiosensitivity to repair capacity.[55] Prostatic tumors contain significantly low proportions of proliferating cells, which have a high sensitivity to dose fraction size.[56] Prostate cancer is slow growing and acts more like normal tissue than other cancers when comparing growth patterns. As most cancers are fast growing and have many proliferating cells, they are treated with smaller doses of radiation to spare the normal, surrounding tissue. Since prostate cancer growth is similar to normal tissue, it stands to reason that some prostate cancer will be spared along with the normal tissue when treated in this fashion.[57] The low α/β ratio of 1.5 Gy means that prostatic tumors have an increased sensitivity to radiation fraction size. This allows a radiation dose change from approximately 2 Gy used in conformal radiation therapy to 7.25 Gy used in CyberKnife treatments. Hypofractionation leads to high tumor control rates, and with careful treatment planning and delivery, it is associated with minimal acute and late rectal and urinary toxicity.[58]

Currently, there is limited research on the safety and efficacy of CyberKnife treatment for localized prostate cancer. This is the major risk associated with this

treatment option, because not all of the long term side effects have been discovered. Common acute side effects include fatigue, urinary and rectal irritative symptoms such as burning with urination, increased urinary frequency/urgency, loose stools, flatus, and diarrhea. Long term side effects may include urethral stricture, rectal and bladder bleeding, as well as impotence. Ulceration and/or inflammation to the rectum and bladder are also possible, which could require surgical correction. Similar to other radiation therapies, patients have a very small risk of a secondary malignancy caused by radiation exposure.[59] Other long term side effects are yet to be determined.

Prostate Cancer Treatment Comparison

Radiation therapy and prostatectomy are the two most common treatment options for prostate cancer. It is surprising that there have not been any modern, published studies comparing these two modes of treatment. More research needs to be done to determine the most successful treatment option. The only data available for comparison are published observational studies. Even these are not the best comparisons, because several factors affect the data. For example, elderly populations are encouraged to undergo radiation therapy. Sexual function tends to decline in this age bracket, which can skew the data.[36] Also, the end point for comparison is debatable. For this comparison, I have chosen to use biochemical disease-free survival after 5 years.

A part of determining biochemical disease-free survival is measuring PSA nadir. This is the lowest PSA level achieved after treatment. For radical prostatectomy, PSA nadir is achieved within 1-2 months. If the surgery was performed successfully, there should not be any prostate gland to produce prostate specific antigen, thus PSA nadir can

be detected early. Since prostate tissue remains after radiation therapy, a longer time frame is needed to reach PSA nadir. For external beam radiation therapy, PSA nadir may not be reached for 1 to 2 years after treatment. Brachytherapy PSA nadir can take longer than 1 to 2 years.[60] After radiation therapy, PSA nadir must be reached before someone can be declared as a PSA failure. According to ASTRO, the American Society for Therapeutic Radiology and Oncology, the definition of biochemical recurrence after external beam radiation therapy is three consecutive PSA increases, with the date of failure backdated to the midpoint between the PSA nadir and the first of the three increases. The American Urological Association considers biochemical recurrence after radical prostatectomy to be a PSA level of 0.2 ng/mL or greater, with a second confirmatory PSA level of 0.2 ng/mL or greater.[61]

By measuring biochemical recurrence, biochemical disease-free survival can be measured. Since it may take several years to determine biochemical recurrence, I have chosen the endpoint of biochemical-disease free survival after 5 years to compare treatment options. The following table summarizes clinical trials comparing the 5 year biochemical disease free survival for definitive forms of prostate cancer treatment.

Table 3. Five year biochemical disease free survival after definitive treatment for localized prostate cancer

Author	Treatment	Number of Patients	5 Year Biochemical Disease-Free Survival
Kupelian, et. al[62]	Radical Retropubic (97%) or Perineal (3%) Prostatectomy	1034	81%
Han, et. al[63]	Radical Retropubic Prostatectomy	2091	84%
Perez, et. al [64]	Standard Radiation Therapy	68	53%
Cheung, et. al[65]	3-Dimensional Conformal Radiation Therapy (78 Gy)	235	81%
Zelefsky, et. al[66]	3-Dimensional Conformal Radiation Therapy (70.2 Gy median dose)	137	88%
Kupelian, et. al[67]	Hypofractionated Intensity Modulated Radiation Therapy (70 Gy at 2.5 Gy/fraction)	36	97%
Zelefsky, et. al[68]	High Dose Intensity Modulated Radiation Therapy (81 Gy at 1.8 Gy/fraction)	203	85%
Zietman, et. al [69]	High Dose Photon Radiation Therapy with a Proton Radiation Boost (79.2 Gy)	116	80.5%
Schour, et. al [69]	High Dose Rate Brachytherapy (43.5 Gy)	117	96%
Ghilezan, et al [70]	High Dose Rate Brachytherapy (38 Gy)	95	98%
Madsen, et al [58]	Isolac Stereotactic Hypofractionated Accurate Radiotherapy (33.5 Gy at 6.7 Gy/fraction)	40	70%*

*4 year biochemical disease-free survival was used because this is a new technique and data has not yet matured

Initiation of a CyberKnife Clinical Trial for Prostate Cancer at Baylor University Medical Center

The CyberKnife clinical trial for the treatment of localized prostate cancer is a sponsored research study; thus, no proprietary information will be disclosed regarding the

protocol or the endpoint. I will focus on how the CyberKnife was approved by the FDA and my experience initiating its use in a prostate cancer clinical trial.

FDA Device Applications

Prior to my involvement with this research, the makers of CyberKnife, Accuray, Inc., had to apply to the Food and Drug Administration for an investigational device expemption (IDE). According to the regulations under 21 CFR 812, an IDE allows the use of a device in a clinical study to gather information about safety and efficacy. From 1994 to 1999, CyberKnife was used to treat patients under this IDE for the treatment of lesions in the head and neck. In 1999, the company applied for a Premarket Notification 510(k) to market a device that would provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions of the brain, base of skull, cervico-thoracic spine, head, and neck. This notification is frequently required of Class II devices, such as the CyberKnife. On July 11, 2001, the FDA received another Premarket Notification 510(k) to market the CyberKnife as a device that provides treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions anywhere in the body when radiation treatment is indicated.[71] The approval was made possible by the upgraded tracking system that allows for 3-D and 6-D tracking of the target along the x. y, and z axis as well as the rotations about each axis. Another improvement was the x-ray imaging technology with increased resolution and sensitivity. These improvements allowed CyberKnife technology to be used in a variety of targets located throughout the body.[72]

Protocol Acquisition

Although the CyberKnife has been approved by the FDA to treat lesions, tumors, and conditions anywhere in the body when radiation treatment is indicated, there is not enough long term research to compare it to other forms of prostate cancer treatment. As stated earlier, the only prostate cancer treatment data available for comparison is published, observational studies. To compare CyberKnife to other published studies, a protocol was devised by a sponsor to gather data on the CyberKnife treatment of prostate cancer.

A sponsor wants to pick a site that is knowledgeable about the study subject, has the proper equipment to implement their study, and a staff able to perform the required tasks in the protocol. Before the sponsor of this clinical trial sent an official protocol, a quality assurance test was performed to determine if each site was capable of performing such a study. Our site was sent an anonymous dataset of CT images to create a treatment plan for this person's prostate cancer. For the treatment plan, several restrictions were given to ensure that the prostate received an appropriate radiation dose and other structures like the penile bulb received minimal amounts of radiation. After completing the test, the data was submitted back to the sponsor and reviewed by the national Principal Investigator and Physicist. Our site was asked to perform the quality assurance test again, which we submitted shortly after the request. After a month of no correspondence from the sponsor, our site inquired about the study protocol. We received it in early November.

Baylor's IRB and Approval Process

Before a clinical trial can be implemented, it must go through an Institutional Review Board. Information about an IRB's composition, operation, and responsibility can be found on the FDA website under 21 CFR 56. Within Baylor Research Institute is the Office of Research Subject Protection. This group provides staff support for the IRB, maintains IRB records, and informs researchers of federal and institutional regulations and guidelines governing IRB activities. The IRB is composed of Baylor physicians, PhDs, a registered pharmacist, and non-affiliated members including a physician scientist, an attorney, a lay person and a minister.[73]

To initiate a clinical trial at Baylor, a project summary must be submitted to the Baylor IRB. This summary includes information about Research Staff contact information, funding information, objective of the study, study design, eligibility criteria, risks, study population, where the study materials will be stored and where the study will take place, study benefits, and details of the informed consent process. Other forms must accompany the project summary such as financial disclosures for all the study staff, a review of scientific and scholarly validity signed by an administrator, and the Informed Consent Document. One of the more difficult tasks is obtaining signatures from everyone. Since study staff and administrators have daily tasks to complete as well as initiating new studies, coordinating form drop-offs and obtaining signatures in a timely manner can be laborious.

Prior to submitting the project summary to the IRB, the Informed Consent document must be reviewed and approved by the study sponsor. This is because once the

IRB approves an Informed Consent document, it can not be changed without a Revision to IRB Approved Study Form, which would create more work for the research coordinator and also the IRB. The Baylor Research Institute has a template for the Informed Consent document with instructions on how to make it pertain to a specific study. This template ensures that all of Baylor's Informed Consent documents have all required elements as stated in 21 CFR 50. I submitted the Informed Consent document to the sponsor for review and got a reply shortly after with suggested modifications. Sometimes this process can take a couple weeks, but it only took 2 days for this study.

For the project summary, information is asked about radiation exposure, which includes CT scans as well as therapeutic radiation. For studies that involve radiation, another committee, the Radiation Safety Committee, must approve of the study as well. They have their own process for study submissions. They meet on a quarterly basis, so I had to wait until January before receiving approval for the CyberKnife Prostate Study. Although the Radiation Safety Committee met later than the IRB committee, the project was still approved at the IRB meeting pending the Radiation Safety Committee's approval. Later, it was approved by this committee.

The IRB meeting went very smoothly. Other CyberKnife trials have gone through the IRB previously, which helped members of the IRB to understand what the CyberKnife is and how it works. The IRB did not have many questions for Dr. Berger, the Principal Investigator, and once the questions were finished, we were asked to leave so the IRB could vote on the study. A few weeks later, we were informed that the

prostate study was approved pending modifications to the Informed Consent document. I edited the Informed Consent document and resubmitted it.

Beyond Informed Consent, A Supplement

The CyberKnife is a very complex machine to explain. At the request of Dr. Scott, the Urologist on the study, I created a patient information sheet about the treatment of prostate cancer with the CyberKnife. Frequently, his patients ask for information about the CyberKnife, but they can not always afford to set up an appointment to receive the information. Dr. Scott does not mind sending the information, but the only materials he has are bulky and costly to mail. I created a patient handout to give additional information about the CyberKnife that is not found in the Informed Consent document.

This handout went through several revisions before Dr. Berger approved of the document. I also set up several meetings with Dr. Scott and Dr. Berger to go over the format and to make sure both of their requests were met. We finally agreed upon a full size, 8.5 x 11 in. format to give to patients and potential subjects, because it would be distributed to an older population with weakening eye sight. This process took several months to complete, but will benefit the patient or potential subject tremendously.

Although this document would be handed out to all patients considering CyberKnife treatment for their prostate cancer, subjects would also receive it. Any extra documents a subject receives must be reviewed by the legal department of BRI and later be approved by the IRB. I began the process of legal review and made their necessary edits. Once this was complete, Dr. Berger was undecided about which organization to

format and print these handouts. After being unhappy with BRI's format attempt, he decided to take the handout to his physician organization.

Several months went by without any progress, so I decided to ask the organization for him. It was difficult to find the appropriate correspondent, but once she was found, we promptly set up meetings to discuss the handout as well as other handouts I had completed for Dr. Berger's additional clinical trials. These documents were ultimately sent back to BRI and had to go through the legal review again, because they involved research. For the second time, they were approved. This document can be seen in Appendix B. We are currently waiting for the prototypes from the print shop. Once these are received, I can submit to the IRB for review before dispersing them to patients and potential subjects.

Budget

I coordinated a meeting with Betsy Stein and Dr. Berger to go over items that needed to be included in the study budget. After this meeting Betsy and I met to plan the budget. Once this was finished, it was submitted to the Office of Sponsored Research. They negotiate the study contract as well as the budget with the study's sponsor.

Later, we heard back from the sponsor and the study budget was higher than what they wanted to pay. After talking with Dr. Berger, changes were made to the budget to meet the sponsor's proposition. Once the budget was set, the contract was sent to the sponsor for review. Just before the last day of my internship, we received the contract and I promptly took it to Dr. Berger to sign.

Contract

I contacted the sponsor to coordinate a site initiation visit and to confirm that everything is in order to begin the study without delays. Dr. Berger found a potential study subject and asked me to find out when we would be able to enroll the subject. The Office of Sponsored Research holds the IRB approval letter and approved Informed Consent document until the contract is signed by all parties. For this study, the contract must be signed by the Principal Investigator, the Institution at which the research is taking place, and the Sponsor. This potential subject was not eligible because the contract would not be signed in time.

Unfortunately, this is the furthest the clinical trial has gone. The Baylor Radiosurgery Center would like to continue with this clinical trial at a later time.

Study Design

The study I attempted to initiate at Baylor was a 5 year, prospective, homogenous radiation dose, multi-center clinical trial to evaluate the safety and efficacy of the treatment of low and intermediate risk prostate cancer with the CyberKnife. Although the CyberKnife is approved by the FDA to treat prostate cancer, data collection is needed to determine efficacy and the long-term side effects. Approximately 30 subjects were expected to enroll at this site as part of a total multi-site enrollment of 300 subjects. The safety endpoint was to estimate the rates of acute and late toxicities to the gastrointestinal and genitourinary tracts. Efficacy endpoints measured the 5-year biochemical disease free survival, as well as documented rates of failure, quality of life, and amount of work required for treatment to compare to other forms of prostate cancer treatments.

Eligible subjects must have a histologically proven prostate adenocarcinoma, a PSA less than 20, a Gleason score less than 7, and a Clinical stage between T1b and T2b. Subjects who have had prior difinitive treatment of their prostate cancer or who have had an invasive malignancy other than prostate cancer or skin cancer are ineligible. Also, subjects who have implanted hardware in the pelvis such as a hip replacement are ineligible, because it may prohibit appropriate treatment delivery. Before a subject can enroll in any clinical trial, the subject must review, approve, and sign an Informed Consent document.

After this process and meeting all eligibility requirements, the subject can begin the treatment process. First fiducials are placed into or around the prostate tumor. Approximately one week later, an immobilization device is made to fit the subjects anatomy and CT/MRI scans are taken to begin the treatment planning stage. Approximately one week after the CT/MRI scans, treatment begins. Each subject receives the same amount of radiation over a 5 day period. After the last treatment session, follow up appointments are scheduled at 1 week, 1 month, every 3 months for 1 year, then every 6 months for a total of 5 years. At these appointments, subjects will be asked to complete several questionnares and they can be evaluated for any Adverse Events or Serious Adverse Events.

Discussion

Several factors are involved with initiating a successful clinical trial. The CyberKnife clinical trial for the treatment of low and intermediate risk prostate cancer has a lot of potential for being a successful clinical trial. This study was unlike many studies because it was not testing a new drug, device, or procedure to get approved by the FDA. The CyberKnife gained FDA approval in 2001, but long term data have not been collected. This clinical trial is very similar to a Phase IV drug clinical trial. For a drug clinical trial that has reached Phase IV, the drug is FDA approved, but different doses or a different schedule may be used than was performed in previous phases.[71]

Typically drug clinical trials have four distinct phases. A Phase I clinical trial is conducted in healthy volunteers to assess safety. Approximately 20-80 volunteers are monitored to determine the drugs' side effects and how it is metabolized and excreted. If the drug is determined to have an acceptable toxicity level, it can enter into Phase II. Usually a Phase II trial has several hundred volunteers and examines the effectiveness of the drug. Once the drugs' efficacy is confirmed, it can begin a Phase III clinical trial. The number of subjects in these trials can range from the hundreds to thousands. A Phase III trial studies safety and efficacy with variable doses in different populations. After Phase III, the FDA can choose to approve or reject the drug. The next phase, after a drugs' approval, is the postmarketing phase, Phase IV.[71]

One of the main goals of this study was to obtain long term data on the CyberKnife treatment of prostate cancer as well as use this data to compare it to other

prostate cancer treatments. For a successful trial like this, a key component is a well written protocol.

Clinical trial protocols must have well researched background information as a basis for conducting such a trial. It is difficult to sift through so much information that may or may not be relevant, but once this information is found and synthesized, it serves as a foundation for the protocol. Research can be done to fill in these data gaps and create a solid foundation. This is what the CyberKnife prostate cancer clinical trial is attempting. Through several peer reviewed journal articles, the sponsor has researched prostate cancer treatments as well as radiosurgery advancements, such as I have done. From this information, the gaps can be identified and a protocol can be devised to determine the required information. Also, if this foundation is not strong, finding Principal Investigators and sites willing to conduct the research will be difficult for the sponsor. This would waste the sponsor's time and money.

Another main component in successful research is a knowledgeable research staff that can work as a team. The Baylor Research Institute does a great job in creating a fluid environment for research. The several departments of BRI work together from the beginning of a trial to the closure. Research coordinators work closely with this organization to get studies approved, receive help with budgeting, negotiate contracts, obtain yearly IRB approval, perform audits, help with study closures, and find extra resources if a budget does not cover research costs. Another important factor is that the Principal Investigator, sponsor, and research coordinators work well together. A study

can be conducted more smoothly when each member of the research team has respect for each party contributing to the research.

The most important component of a successful trial is devoted subjects and research personnel. Without these two groups working together, information can not be collected, which leads to a shortage of data to make substantial conclusions. While at Baylor, I witnessed a multi-site clinical trial shut down due to a lack of data, which resulted in wasted time and resources. BRI has a marketing department to help coordinators advertise their studies and increase enrollment. It also sends out monthly recruitment/retention tips. Subject retention is a more critical part of the research process. Lack of subject follow up can also result in a clinical trial closure.

I was sad to see the CyberKnife prostate cancer trial not reach start up. Events were out of my control, which led to its abrupt stop. The Principal Investigator has decided to leave Baylor and does not want to continue this process. Perhaps when he leaves, the trial can continue under a different Principal Investigator. Since all the work has been done already, it should not take as long to go through the approval process. It had a lot of potential, and I hope the sponsor's research endeavor is successful.

Summary

Currently, men diagnosed with low and intermediate risk, localized prostate cancer can choose from a plethora of treatment options. So many options can be seen as a benefit, but caregivers may find this difficult when they are asked to recommend various treatment options. They must know about new advances in medicine and technology to give appropriate advice.

Radiation therapy has evolved a long way from the first attempts at treating prostate cancer. The CyberKnife is a great example of how technology changes a mode of treatment.

Although the CyberKnife is FDA approved, limited research has been done on the resulting side effects of treatment for prostate cancer, and the long term effects are still unknown. In theory, it sounds like a great treatment option, but only long term data can prove this. Through my research, I have gained a better grasp of how a clinical trial protocol is developed.

My internship at Baylor has also helped me to understand the various aspects of clinical research. I was able to "float" into different research departments, which allowed me to see different stages of clinical trials and not just the initiation process. I have gained experience in initiating a clinical trial, completing CRFs, maintaining regulatory documents, reporting to the IRB and sponsor, communicating with potential subjects, and creating documents to help potential subjects understand a clinical trial. I have also observed managerial aspects of clinical research such as documenting staff work hours, meeting with research teams to give and receive updates, and working with a monitor and sponsor to close a study after the original research coordinator has resigned.

CHAPTER III

INTERNSHIP EXPERIENCE

Description of Internship Site

I completed a clinical research internship at Baylor University Medical Center in Dallas through the Baylor Research Institute. Betsy Stein, Director of BRI, supervised me through this wonderful experience from August 15, 2007 through February 14, 2008. The Baylor Research Institute oversees over 650 different clinical trials at BUMC. This is done through several departments that are beneficial to researchers.

For example, the budget department will negotiate the clinical trial's study contract with the sponsor or can help find extra funding for unforeseen expenses. The Institutional Review Board is another department of BRI. They make sure that subject rights are upheld. This group can reject or accept a new study, annually reviews current studies, and monitors advertisements and media coverage for clinical trials. When a study is about to be closed out or be audited, BRI can send someone from Research Quality Assurance to review the study to make sure it is up to date, organized, and conducted according to protocol. BRI also houses a marketing department that will put a study on the Baylor website and help researchers advertise their studies to increase subject enrollment.

In addition, BRI organizes classes for their research coordinators. I have attended classes on IRB forms, budgeting, and the consent process. BRI also keeps it's

researchers up to date by hosting a monthly coordinators meeting. Past topics were saving data on a Baylor drive that is backed up every night, future changes with the IRB, and how to "audit" yourself. BRI understands the importance of the clinical researcher. Through departmental help and education, BRI ensures that research is done properly throughout the Baylor system.

Journal Summary

I was housed in the Clinical Trials Office, which was in close proximity to the Baylor Radiosurgery Center. Whenever I was needed at the Radiosurgery Center, I was able to respond within a few minutes. I learned many things while at the Radiosurgery Center, but an overwhelming amount of information was learned in other areas of research.

Approximately the same time I arrived at Baylor, a new manager, Mary Sams, began working at the Clinical Trials Office. We attended several classes and orientations together, and she quickly took me under her wing to learn about clinical research. When things were slow at the Radiosurgery Center, I would help with her studies, attend meetings, and tag along when she needed to distribute materials or collect signatures. For one study, I worked on the Informed Consent, and for another, I created a spreadsheet to help with invoicing a sponsor. I also had the opportunity to observe a pre-initiation monitor visit. Prior to site selection, the monitor visited to tour the site and determine if Baylor has the capabilities to perform the study. Being housed in the same office allowed me to see managerial aspects of a research team. Mary was designated to order supplies, perform job reviews for the Clinical Trials Office staff, reply to sponsors when a

coordinator could not be reached, as well as work on her own studies. Three other research nurses were housed in the same office by the names of Lupe Burmia, Laurie Jones, and Rene Gale. My desk was in an open area, so I was able to observe their day to day activities. This included monitor visits, patient consenting, patient follow ups, and sponsor correspondence. I also helped each of these research nurses when I had free time.

Lupe and Laurie worked together on several studies, but a gastric bypass study took up a majority of their time. Frequently they were needed in the GI lab, and they spent a lot of time there. When one of their follow up appointments would show up early, I would receive them and notify Laurie or Lupe that one of their subjects was waiting to be seen. Usually at these follow up appointments, vital signs would be taken and the subject's history would be updated. I also helped them initiate a spine study. I worked on the IRB submission and Informed Consents.

Rene worked on a breast cancer study that examined pathology. One day I accompanied her to the pathology lab to assist. She explained that we were shipping ductal lavage specimens. These specimens had to be kept in below freezing coolers to preserve the ductal cells. We ordered dry ice and when it arrived, promptly packed the specimens in Styrofoam coolers inside shipping boxes. After the specimens were picked up for delivery, we notified the sponsor that the specimens had been shipped. I also observed this study's close out. Prior to the last monitor visit, Kita Cathey from Research Quality Assurance performed an audit on the study. This took several days, but the data had been cleaned up prior to the actual close out monitor visit.

For a while, the Radiosurgery Center had little for me to do on their studies, because we were waiting for the new CyberKnife prostate cancer clinical trial protocol. During this time, I floated to other departments and helped out when I could. I followed a previous UNTHSC Clinical Research Management student, Lucy Kang, for a few days while she worked on her cardiac stent clinical trials. My first task there was to help archive a study, so I packed up a closed out study into boxes to send to a storage area. Later, Lucy showed me around the Baylor Jack and Jane Hamilton Heart and Vascular Hospital, where she consents subjects for her studies. She explained the process, and how she has to wake up very early to consent patients pre-operatively and before they have been medicated. When we got back to her office, I saw how patients get randomized through a telephone system. On another occasion, I observed a monitor visit and helped the monitor do inventory. At this visit I was able to interact with a monitor and understand what happens during monitor visits.

Once we received the CyberKnife prostate protocol, I worked hard and quickly on submitting it to the IRB. I learned the process as well as what forms needed to be submitted. The IRB has a pre-review deadline, which allows coordinators to submit a study and receive feedback on what should be changed prior to the actual IRB submission. While I was waiting to hear back from the IRB, I searched for administrators that needed to approve the study. I am not sure why I was so shocked, but the fastest way to get an administrators signature of approval is being friendly with their assistant. Small talk goes a long way. After I received the pre-review IRB suggestions, I made all necessary edits and submitted the CyberKnife prostate clinical trial to the IRB for an actual review.

Throughout the entire internship I worked on a CyberKnife lung study, a renal study, and an outdated prostate study. I would frequently be asked to change the staff on these studies or amend the protocol. I made several revisions to the Informed Consents as a result and submitted all changes to the IRB. I also had to submit a study packet to the IRB for their annual reviews. This required a lot of copying and took several days to put together. I can not count the numerous revisions I have submitted to the IRB, but I did complete 3 continuing reviews.

From time to time, the sponsor of the lung study would contact me for updates on their studies. This study gave me the most exposure to clinical research. I would fill out case report forms, copy source documents, blacken any identifying information before sending the documents to the sponsor, and make sure the subjects were up to date with their follow up appointments and questionnaires. I also created a spreadsheet that indicated when each subject was due for their follow up appointments. Although the case report forms were long and tedious, I enjoyed going through the patient charts and documenting their progress. I also communicated with the sponsor whenever they had questions. For example, one time I was asked to find out when our last payment was received for the study. After finding the appropriate person that handles this, I confirmed with the sponsor when the last payment was received.

When I was not working on the lung trial or other CyberKnife trials, I volunteered in departments that were under staffed. For half a week, I spent time with the endocrine group. I helped with a weight loss study they were conducting. I screened phone calls

off of their hotline and created a spreadsheet of potential subjects, their contact information, and their current medications.

Another group I volunteered with was the dermatology group. They were conducting several psoriasis studies. I frequently helped with time sheets. For two separate studies, I went through subject binders to total the amount of time a certain sub-investigator worked. This particular sub-investigator was not employed through BRI, so had to be paid separately. On another occasion, I created an employee time sheet that totaled the hours worked automatically. I also helped put together packets for a newly initiated trial. The subject was required to fill out an Informed Consent, tax documents, and several questionnaires. This packet also included note pages for the research coordinator to take vital signs and the subject's medical history. I was also able to watch the first subject's consent process and appointment. This study was different from the CyberKnife trials, because the Principal Investigator usually consents the subject.

Towards the end of my internship, I was invited to attend a site-initiation meeting. The UNTHSC Clinical Research Management student prior to me, Tory McFarlin, put together this meeting for the initiation of a new dendritic cell vaccine clinical trial. The first half of the meeting went over the background of dendritic cell vaccines and the statistical overview of the trial. The second half of the meeting explained procedures and how the study would be monitored. This was my very first site initiation meeting, and I am glad that I was able to take part in one.

Lastly, I worked closely with Betsy Stein, my on-site mentor. I accompanied her to several meetings about budgeting and giving and receiving updates to various research

groups. I also attended the monthly clinical research coordinators' meetings, where she would introduce new staff and scheduled speakers would present on clinical research topics. She also coordinated classes for research coordinators to learn more about good clinical practices, the informed consent process, budgeting, and the computer program used to manage all aspects of a clinical trial, StudyManager. We would meet weekly to review my journal entries and discuss my current research projects. She also gave me guidance when I did not know how to do certain things like initiating a study.

I was able to observe the pre-initiation process all the way through a study close out during my internship at Baylor. Although my own clinical trials that I worked on did not accrue new subjects, I was still able to examine all aspects of research from other clinical trials. This unique experience has strengthened my understanding and confirmed my interest in clinical research management. I especially have an extreme appreciation for clinical research coordinators and their role in conducting clinical trials. The invaluable knowledge I have gained from this internship will serve me well in my future endeavors as a principal investigator.

APPENDICES

Table of Contents

Appendix A

Acronyms/Abbreviations

3D-CRT	3-Dimensional Conformal Radiation Therapy
AJCC	American Joint Committee on Cancer
BPH	Benign Prostatic Hyperplasia
BRI	Baylor Research Institute
BUMC	Baylor University Medical Center
CFR	Code of Federal Regulations
CRC	Clinical Research Coordinator
CRF	Case Report Form
cT	Clinical Tumor
CT	Computed Tomography
DHT	Dihydrotestosterone
DRE	Digital Rectal Exam
EBRT	External Beam Radiation Therapy
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PSA	Prostate Specific Antigen
pT	Pathologic Tumor
TNM	Tumor Node Metastasis

Appendix B

Prostate Cancer Handout

CyberKnife® Radiosurgery for Prostate Cancer

Introduction: Prostate cancer will affect 1 in 6 men during their lifetime. With early diagnosis and treatment, prostate cancer has a cure rate of 90%. Currently, there are several treatment options available for prostate cancer. The most common forms of treatment for early and intermediate stage prostate cancers are surgery, radiation therapy, hormone deprivation therapy, and active surveillance. You should discuss the risks and benefits of each with your physician to determine the best treatment option for you.

Radiosurgery: Radiosurgery is a precise non-invasive method that delivers high doses of radiation to small tumors in a concentrated time period. It has over a 30 year history in treating brain tumors, but it is more recently being used to treat other areas of the body.[1] Since radiosurgery for prostate cancer is a new treatment, there is no long term data (5-10 year follow-up) on outcome and toxicity. However, in a recent published study of prostate radiosurgery from Madsen et al., excellent PSA control and no severe side effects were seen at a median follow up of 41 months.[2]

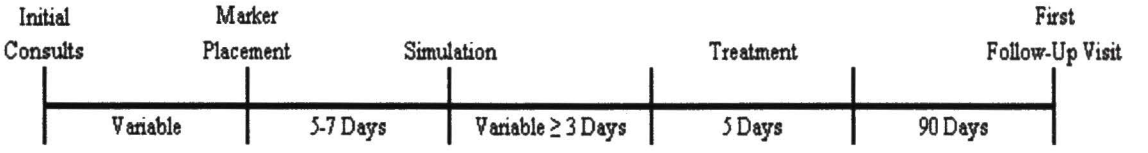
CyberKnife®: CyberKnife® is a robotic radiosurgery device made by Accuray. It uses image guidance to locate tumors precisely and deliver multiple beams of radiation therapy directly to the tumor site, while minimizing radiation exposure of the surrounding healthy tissue. The CyberKnife® system has clearance from the Food and Drug Administration to treat tumors anywhere in the body where radiation is required.

Radiosurgery vs. Radiotherapy: There are several advantages of radiosurgery over conventionally fractionated radiotherapy. Radiosurgery has a much shorter treatment course than radiotherapy, offers extreme precision, and may yield an increase in local tumor control. Radiosurgery has its disadvantages as well. There is potential for increased risk of late side effects to the bladder and rectum due to the high doses given each treatment. Also, until studies complete accrual and mature, there is lack of long term data on both efficacy and tolerance.

Side Effects: Side effects may result from CyberKnife® treatment. Common acute side effects include fatigue, urinary and rectal irritative symptoms such as burning with urination, increased urinary frequency/urgency, loose stools, flatus, and diarrhea. Long term side effects may include urethral stricture, rectal and bladder bleeding,

ulceration and/or inflammation to the rectum and bladder, which could require surgical correction, impotency, and a very small risk of a secondary malignancy caused by radiation.

Timeline:



1. Initial Consults: The radiation oncologist and urologist will determine eligibility.
2. Marker Placement: 3-4 small gold seeds (fiducials) will be placed into or around the tumor by the urologist.
3. Simulation: Immobilization device is made to minimize changes in body position during treatment. CT/MRI scans are taken of the pelvis.
4. Treatment: You will have five separate CyberKnife® treatments. Each treatment will take approximately 1.5-2 hours.
5. Follow-Up Visits: To assess the treatment's effectiveness and related side effects. These are scheduled for every three months for one year then every six months thereafter.

1. Quinn, A. M. (2002). CyberKnife®: A robotic radiosurgery system. *Clinical journal of oncology nursing, 6*(3), 149, 156.
2. Madsen, B. L., Hsi, R. A., Pham, H. T., Fowler, J. F., Esagui, L., & Corman, J. (2007). Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: First clinical trial results. *International journal of radiation oncology, biology, physics, 67*(4), 1099-1105.

For More Information Please Contact: Baylor Radiosurgery Center at [Redacted]

Appendix C

Example of Informed Consent Document

BAYLOR RESEARCH INSTITUTE
Baylor University Medical Center, Baylor Radiosurgery Center
Dallas, Texas

PARTICIPATION EXPLANATION AND CONSENT FORM

PROJECT TITLE: Prospective Evaluation of CyberKnife Stereotactic Radiosurgery for Low and Intermediate Risk Prostate Cancer: Homogenous Dose Distribution

INVESTIGATORS: Principal Investigator: [Redacted]
Sub-Investigator: [Redacted]
Sub-Investigator: [Redacted]

TELEPHONE NUMBER: [Redacted]

INTRODUCTION:

Before you say that you will be in this clinical trial (a kind of research study) you need to read this form. It is important for you to understand all the information in this form. This form will tell you what the clinical trial is about and how it will be done. It will tell you about some problems that might happen during the clinical trial. It will also tell you about the good things that might happen for you during the clinical trial. When you read a paper like this to learn about a clinical trial it is called "informed consent." The people who are doing this clinical trial are giving you very important information about the clinical trial. When you give your consent for something, it is the same as giving your permission. This consent form may contain words that you do not understand. Please talk with one of the doctors or their staff if you have questions. Do not sign this consent form unless all your questions have been answered and you feel comfortable with the information you have read. You will be given a copy of the form to keep.

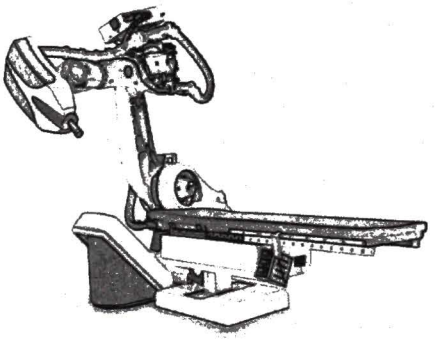
You are being asked to take part in this study because you have been diagnosed as having low or intermediate risk, early stage prostate cancer confined to one lobe of the prostate. This has been confirmed with a digital rectal exam that measures the Clinical Stage, a prostate tumor biopsy that measures the Gleason Score, and a blood test measuring the amount of Prostate Specific Antigen (PSA). A Gleason Score is the sum of 2 numbers, each ranging from 1-5, that characterizes the prostate's microscopic appearance. The higher the Gleason Score, the more aggressive the cancer is. PSA is a protein produced by prostate gland cells. PSA usually becomes elevated in the presence of prostate cancer. Low risk prostate cancer is defined as a Clinical Stage of T1b-T2a, Gleason Score of 2-6, and a PSA $\leq$ 10. Intermediate risk prostate cancer is defined as a Clinical Stage of T1b-

T2b, Gleason Score of 2-6, and a PSA ≤ 20 or a Clinical Stage of T1b-T2b, Gleason Score of 7, and a PSA ≤ 10.

Why Is This Study Being Done?

The purpose of this study is to find out what effects that a highly focused radiation treatment using the CyberKnife® system (made by Accuray Incorporated) has on patients with your condition and to evaluate the effect of this treatment on your quality of life over time.

Standard treatment for prostate cancer involves either surgery or radiation therapy (radiation therapy is a type of treatment for cancer that uses high energy x-rays). The CyberKnife system is a new type of radiation machine that uses a special system to precisely focus large doses of x-rays on the tumor. The device is designed to concentrate large doses of radiation onto the tumor so that injury from radiation to the nearby normal tissue will be minimal. The purpose of this evaluation is to see if this treatment will help patients with your condition and to evaluate the effect of this treatment on your quality of life over time. We are also conducting this study to demonstrate that CyberKnife based radiation treatments to prostate is an alternative to other forms of treatment for early stage prostate cancer.



What is the Status of the Devices or Procedures involved in this study?
The CyberKnife system is currently approved by the US Food and Drug Administration. The CyberKnife system previously has been used in the lung, brain, head and neck as well as other areas of the body. The CyberKnife system has market clearance from the U.S. Food and Drug Administration to treat tumors, lesions and conditions anywhere in the body when radiation therapy is required. However there is very limited experience treating patients with early stage prostate cancer with this device.

How Many People Will Take Part In The Study?

About 300 people will take part in this study worldwide/nationwide. About 30 of these people will take part at this location.

What Is Involved In The Study?

Prior to entry on this study, you will have had your PSA checked and your prostate biopsied within the last 12 months. The results of this biopsy showed that you have prostate cancer. In addition, you will have had a digital (finger) rectal exam to determine if the cancer could be felt. Based on the results of these tests and examination it has been determined that your prostate cancer is in an early stage and has not likely spread outside the prostate or anywhere else in your body.

If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen:

Preparation for CyberKnife radiation to the prostate:

Questionnaire: You will be asked to complete a short questionnaire before your CyberKnife treatment. This questionnaire will ask you to answer multiple choice questions that ask about your bowel, bladder and sexual functioning. It will also ask some general questions about your mood and how you feel about your cancer.

Marker Seed Placement: You will have a procedure to place 4 small gold seeds into the prostate. This procedure is commonly done in patients receiving standard external beam radiation for prostate cancer and is not an experimental procedure. These will be used to determine the location of the prostate during your CyberKnife treatment. This procedure is very similar to a prostate biopsy except the seeds are placed in the prostate instead of a biopsy being done. You will need to clean out your rectum with an enema and take antibiotics the day of the seed placement. An ultrasound probe is placed into the rectum. Needles containing the gold seeds are guided into the prostate and the seeds then deposited. Like with your biopsy, you will need to avoid aspirin and aspirin containing medications for a week before the seed placement.

Planning CT Scan: You will have a planning CT scan of the pelvis after the seeds have been placed into the prostate. This is a regular CT scan. This type of CT scan is standard procedure for patients receiving external beam irradiation. The images obtained during the scan will be used to plan the CyberKnife treatments.

CyberKnife Treatments: The CyberKnife treatment differs from standard external beam radiation. Treatment with CyberKnife has a much shorter overall treatment course and offers extreme precision. Each treatment fraction is, however, longer due to utilizing

many more beams and because the CyberKnife takes interval x-rays before turning on each beam to ensure proper positioning.

- Your course of radiation will consist of five separate CyberKnife treatments.
- These will be delivered within an 11 day period of time
- Each treatment will take 1.5-2.5 hours. You will lie on the treatment table, breath normally while you receive your radiation treatment. You can take short breaks at any time during your treatment.

Follow-Up Visits: After your CyberKnife treatment, you will need follow-up visits at the Baylor Radiosurgery Center to determine how effective the treatment was and if you are having any treatment related side effects. These visits will be scheduled for one month, three month, six month, and every six months thereafter for 5 years. This is the same schedule of follow-up visits that most patients have when they receive standard radiation for prostate cancer. The follow-up visits will include a rectal exam and blood test to measure your PSA level. This is the standard procedure for follow-up visits. In addition, you will be asked to complete a questionnaire. This questionnaire will ask about your bowel, bladder and sexual functioning and how you feel about your cancer treatment. It is very similar to the questionnaire you are asked to complete prior to CyberKnife treatment.

If it is suspected that your tumor is growing or if there are concerns about disease progression on your PSA exams, a prostate needle biopsy of the tumor may be performed. Two years after CyberKnife treatment, the study recommends but does not require a prostate biopsy.

How Long Will I Be In The Study?

You will be in the study for five years. After the initial consultation, taking part in this study requires separate visits for marker placement into the prostate and simulation (a planning CT scan of the pelvis after the seeds have been placed into the prostate). After the treatment, which will be five treatments over 11 days, a researcher will call you 1-2 weeks later to discuss how you are doing. You will also have follow up appointments in the Baylor Radiosurgery Center at 1, 3, and 6 months, then every six months for a total of 5 years.

The researcher may decide to take you off the study if any of the following occur:

- He/She feels that it is in your medical best interest.
- Your condition worsens.
- New information becomes available.
- If you are not tolerating the radiation treatment well.

You can stop taking part in this study at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the researcher and your regular doctor first.

What Are The Risks of The Study?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the CyberKnife radiation treatments are stopped, but in some cases side effects can be serious or long lasting and permanent. A risk to taking part in this study is the likelihood of receiving CyberKnife treatments that may not be effective in helping to treat your disease. This means that you may spend time and experience side effects of undergoing CyberKnife treatments that may not provide you with any health-related benefits.

Risks and side effects related to the CyberKnife radiation treatment we are studying include:

PLACEMENT OF GOLD SEEDS INTO THE PROSTATE
The biopsy and placement of the gold markers may cause some discomfort as these procedures require the use of small needles inserted into the prostate. Discomfort from these procedures will be minimized by the use of local numbing medications (anesthetics) and you may receive intravenous injection of small doses of medications to make you drowsy (sedatives). It is likely that a patient undergoing this procedure may experience discomfort from placement of the needles and minor bleeding because of injury to the small blood vessels in the path of the needle. The majority of cases do not require treatment and the bleeding resolves spontaneously. Other possible side effects which are rare include infection requiring antibiotic treatment and significant bleeding requiring transfusion and/or surgery.

RADIOLOGIC IMAGING FOR THE TREATMENT PLANNING
This research study may involve exposure to radiation from a CT scan as part of your screening visit. The radiation dose you will receive from this scan is equivalent to a uniform whole body exposure of 11mSv. This is nominal (very small) in comparison to the radiation dose from the therapeutic part of the radioactivity you will receive as part of the treatment. The radiation dose from the test dose is equivalent to 22% of the annual radiation exposure limit allowed for a radiation worker and exposure of this magnitude is considered to be comparable to other everyday risks.

CYBERKNIFE TREATMENT
The administration of radiation itself is painless and the only discomfort is expected to be from your having to lie very still during the treatment.

Possible side effects following CyberKnife treatment include irritation of the bladder or urethra (the tube that carries urine out of the bladder through the penis). This may lead to temporary symptoms including a reduced stream of urine, burning with urination, having to urinate more frequently, having to get to the bathroom quickly to urinate, and/or

getting up more at night to urinate. Other possible side effects include irritation to the rectum which may lead to temporary symptoms including an increase in frequency of stools, loose stools and/or more gas with bowel movements. Some patients have temporary mild fatigue, and some may develop temporary or permanent impotence (inability to have erections) or permanent accidental leakage of small amounts of urine. Other side effects which are less likely include temporary hair loss, redness or tanning of skin in the treatment area, permanent urinary urgency, permanent urinary frequency, need to move bowels urgently or frequently, and rectal or urinary bleeding. Rarely, some patients may experience the inability to control urine which could require a catheter. Very rarely, complications include uncontrollable leaking of the bladder, perforation of the rectum or bladder, abnormal communication to other organs, narrowing of the urethra, and obstruction of the bowl bladder or urethra. Any of these complications could lead to operative intervention including organ resection and/or colostomy. Also, it is rare but possible to develop a new cancer caused by the radiation exposure.

NOTE: **Since this CyberKnife treatment is new, there may also be other side effects that we cannot predict**

For more information about risks and side effects, ask the researcher.

Your doctor may be an investigator in this research study. If so, s/he is interested both in your medical care and in the conduct of this research. Before you sign up for this study or at any time during the research, you may discuss your care with another doctor who is not associated with this research project. You are not under any obligation to take part in any research study offered by your doctor.

Are There Benefits to Taking Part in The Study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope that the information learned from this study will benefit other patients with this disease in the future.

CyberKnife treatment to the prostate is done with the delivery of large doses of highly focused radiation instead of the more conventional approach which is done with low doses of radiation given daily over seven to nine weeks. The three important possible benefits to CyberKnife therapy are that the higher doses of radiation may be: 1) more damaging to the tumor and, therefore, lengthen the time to tumor progression 2) have a greater chance of prolonging your life, 3) less damaging to surrounding tissue 4) more convenient than treatments being given daily over seven to nine weeks 5) a minimally invasive procedure performed on an out-patient basis.

The possible benefits of taking part in the study are the same as receiving CyberKnife radiation treatments without being in the study.

What Other Options Are There?

Taking part in this study is voluntary. Instead of being in this study, you have the following options:

- Watchful-waiting: This is a program of close follow-up delaying definitive treatment of your cancer
- Surgery: This is the surgical removal of the prostate
- Brachytherapy: This is the placement of small radioactive seeds into the prostate
- External Beam Radiation: This is the use of a machine to deliver small amounts of radiation on a daily basis, five times a week for 7-8 weeks.
- Hormonal Therapy: The use of hormones to lower or block the male hormone, Testosterone, to suppress prostate cancer growth
- Cryotherapy: This is freezing the prostate.

These options may or may not be appropriate for you. You should discuss them with your physicians prior to your agreeing to take part in this experimental treatment for early stage prostate cancer.

Although CyberKnife has been approved for use anywhere in the body by the FDA, there is limited experience treating prostate cancer with CyberKnife. We do not intend to treat any patient "off trial" with CyberKnife for early stage prostate cancer.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about taking part in this study.

What About Confidentiality?

You have a right to privacy. This means that all the information about you from this study will only be shown to the people working on the study. The results of this study may be published in a scientific book or journal. If this is done, your name will not be used. All information about you from this research project will be kept in a locked office or other locked area. Information that is kept on computers will be kept safe from access by people who should not see it.

The privacy law requires that Baylor Research Institute get your permission before giving any of your health information to other people. There are people who need to review your information to make sure the study is done correctly. These people may look at or copy your information while they are doing this review. When you sign this form, you give permission to Baylor Research Institute to give other people information about your health as needed for the research project. These groups include people who work for Baylor Research Institute (including the Institutional Review Board), the US Food and

Drug Administration, the Office for Human Research Protections and the Association for the Accreditation of Human Research Protection Programs. This also includes the following groups of people who are working with the sponsor of the study: [Redacted], the study sponsor, members of [Redacted] Data Safety Monitoring Board, and [Redacted]. Even though we usually remove your name from the information, the people who get this information may be able to figure out who you are. The kinds of health information that might be given to these people include results from lab tests or other tests like x-rays. This information might also be notes written by your doctor from your medical record or notes written by your doctor asking for tests to be done on you. This information may include your type of cancer, other medical problems, and type of treatment.

You do not have to give this permission and it is all right to refuse to sign this form. Your doctor will still treat you and your insurance company will still pay your medical bills (according to their policy) even if you do not give your permission for us to release this information. However, since it is important for the people listed above to have access to your information, if you do not sign this form, you cannot be in the research study.

If you give permission to Baylor Research Institute to give other people information about your health and the other people are not part of the group that must obey this law, your health information will no longer be protected by the privacy law. However, we will take all reasonable measures to protect your information from being misused.

If you change your mind and later want to withdraw your permission, you may do so. You must notify Baylor Research Institute in writing at [Redacted]. If you decide to do this, it will not apply to information that was given before you withdrew your permission.

You may not be allowed to look at your health information during this study. However, at a later time, you will be able to look at this information. This later time will be sometime after the study is completed.

Unless permission is withdrawn, this permission will not expire at the end of the research study.

What Are the Costs?

Taking part in the study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

You and your insurance company will be charged for the CyberKnife therapy for your cancer. Tests and procedures associated with CyberKnife treatment will also be charged to you or your insurance company. Because neither the government nor the manufacturer of the CyberKnife is paying for this study, prior approval by your insurance company is

needed before you can take part in this study and receive CyberKnife treatment for your prostate cancer. The estimated cost of CyberKnife treatment for prostate cancer is about $20,000. You will be responsible for any co-payments or deductibles that are standard for your insurance coverage.

The sponsor of this study is paying Baylor Research Institute a specific amount of money for each person who agrees to take part in the study. This money is to cover the cost of doing the study and pay for such things as study supplies, research staff salaries, etc.

Will I Be Paid For Taking part in This Study?

You will not be paid for being in this study.

What if I am Injured or Become Ill While Taking part in this Study?

The people doing this research project will do everything they can to make sure you do not get hurt during the project. If you do get hurt, there are some things that you need to know:

- The people doing the research project have not set funds aside to pay you money if you are hurt.
- **Baylor Health Care System, Baylor Research Institute, Baylor University Medical Center** have not set funds aside to pay you money if you are hurt.
- [Redacted] has not set funds aside to pay you money if you are hurt.
- If you have an emergency illness during the project, the people working with you will provide emergency care. You or your insurance company may need to pay for the emergency care if that happens.
- You have not given up any of your legal rights by signing this form.

If you are injured as a direct result of your taking part in this study you should contact the Investigator at the number provided under the section "Whom Do I Call If I have Questions or Problems?" in this form. You will be offered the necessary care to treat your injury. You or your insurance company will be billed for medical care and/or hospitalization related to this injury. You will be responsible for all co-payments and deductibles required under your insurance. No other reimbursement will be voluntarily provided for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

What are My Rights As a Participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the

study at any time. If you agree to take part and then decide against it, you can withdraw for any reason. Deciding not to be in the study, or leaving the study early, will not result in any penalty or loss of benefits that you would otherwise receive.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

All of the people working on the project must be careful not to carelessly harm you. If you are hurt during this project, you have the right to seek legal counsel. Nothing in this consent form takes away that right if you are hurt during this research.

Whom Do I Call If I have Questions or Problems?

If you have complaints, concerns or questions about the study or have a research-related injury, contact [Redacted], Principal Investigator, at [Redacted].

For complaints, concerns or questions about your rights as a research subject or simply want to speak with someone who is not a member of the research team, [Redacted], IRB Chair, at [Redacted].

Statement of Person Obtaining Consent:

I have explained to _____ the purpose of the research project, the procedures required and the possible risks and benefits to the best of my ability. They have been encouraged to ask questions related to taking part.

_____ _____

Signature of Person Obtaining Consent Date and Time

Statement of Principal Investigator (if PI did not sign above):

As Principal Investigator of this study, I confirm that to the best of my knowledge this subject has voluntarily agreed to take part in this study and has had an opportunity to ask questions and has received answers to these questions. If another individual was responsible for obtaining informed consent, then this individual has signed above.

_____ _____

Signature of Principal Investigator Date and Time

Confirmation of Consent by Research Subject:

You are making a decision about being in this research study. You will be asked to give your written consent if you want to be in the study. Giving consent is like giving permission. You should not give your permission to be in this study until you have read and understood all the pages in this form. If you cannot read, then someone can read the form to you. Make sure that all your questions about this research project have been answered before you sign this form. When you sign this form, you are giving your permission to be in the study. By signing this form, you have not given up any of your legal rights or released anyone from liability for negligence.

_____ has explained to me the purpose of the research project, the study procedures that I will have, and the possible risks and discomforts that may happen. I have read (or have been read) this consent form. I have been given a chance to ask questions about the research study and the procedures involved. I believe that I have enough information to make my decision. I have also been told my other options. To the best of my knowledge, I am not in any other medical research. Therefore, I agree to give my consent to take part as a subject in this research project.

_____ _____

Signature of Subject Date and Time

Appendix D

Daily Internship Journal

Daily Journal

August 15, 2007

Today was my first day. I mostly oriented myself with the office and its policies. I reviewed part of the new employee handbook, but did not get to finish, as it is very long. I also began my IRB online education program. I took a series of quizzes on Baylor Research Institute's (BRI) IRB policies. There were seven lessons:

Introduction to the IRB Process (2007)

Definitions and Examples of Research (2007)

Exemptions and Expedited Review (2007)

Recruiting, Screening, Consenting and Retaining Subjects (2007)

Risk Assessment in Research (2007)

Principal Investigator Reporting Responsibility (2007)

Special Considerations for Vulnerable Subjects (2007)

August 16, 2007

I finished the IRB lessons today. Again, I reviewed the New Employee Handbook and read the protocols for the studies Dr. Berger is conducting. Around lunchtime, I attended my first IRB meeting. It was actually pretty interesting. The IRB consists of a group of people knowledgeable in their fields, and the meeting had a structured format. The first order of business was amendment voting. The IRB approved or disapproved minor changes in study protocols.

The second order of business was voting on new studies. There are lots of new studies trying to get approval. A representative(s) of the study attends the meeting to clarify any issues the IRB may have. At least two IRB members go through the protocol thoroughly and give their opinion and concerns. After this, the study representative has a chance to explain confusing parts of the study. Next, the representative is asked to leave the meeting while the committee votes on its approval. I did not realize how many different aspects the IRB must look at before they can approve a study. For example, billing issues was a major theme. How much will the sponsor cover and what will be out of pocket for the subject? Also, the protocol and consent form needs to be well written. Some topics may be unclear to the IRB or could potentially be confusing to a subject and must be changed before it is approved. The consent form needs to be at an appropriate reading level, have all the elements of consent, and must agree with procedures in the protocol.

One issue I had never considered is the property rights of specimens a subject gives to a study. The IRB wants to make sure that Baylor Health Care System will not get any lawsuits and must make sure certain statements are made in the consent form to prevent this. Semantics is very important.

August 17, 2007

I am interested in this property rights issue and will explore it a little more in detail today. *Moore v Regents of University of California* is a case about a man with a unique disease, hairy cell leukemia. His specimens turned out to be used for a financial endeavor by his physician. A cell line was developed from Moore's T-lymphocytes, and

the University patented this line. Moore was not aware of his physician's financial interests, and eventually the case was settled pre-trial.

Another interesting case is *Washington University v Catalona*. Dr. Catalona invented the PSA test and was a well respected prostate cancer surgeon. He formed a prostate tissue bank while at Washington University. Eventually, there was conflict with the school, and Dr. Catalona took a position at Northwestern University School of Medicine in Chicago. He wanted to take his tissue bank with him, and asked the donors for their permission. This action was not approved by Washington University, which began a lawsuit against Catalona. Washington University, Catalona, as well as the donors each claimed property rights over the tissue. This case was decided by the court of appeals that Washington University had the property rights to the tissue, because Dr. Catalona signed numerous agreements acknowledging the University's ownership of the biological samples. Donors do not have property rights once it is given and have fewer rights on what it done to that tissue.

These are very gray areas in medicine and clinical research. BRI is aware of these types of issues and are trying to minimize these conflicts through their IRB.

August 20, 2007

Today I attended an IRB Forms class. It was very informative and I learned which forms to fill out and how. The handout will be very helpful to me. I know not to leave questions blank, because it is unclear if I have nothing to say or that I just forgot to fill it out. I also learned what the IRB committee is looking for in their forms, and what

is acceptable as an alternative form. I was awarded a certificate of completion on "How to Complete IRB Forms." I can't wait to use it!

August 21, 2007

In the morning, I attended a Clinical Research Coordinators meeting. Betsy Stein was the speaker, and she presented on "Business Practice Diagnostics: Practical Strategies for Investigative Sites." She talked about problem solving to improve a site's operational and financial performance. One interesting topic was budget management. Baylor has a great budgeting template to figure out study costs, and study coordinators should take advantage of it. Also, StudyManager is available, which is software to help organize and manage clinical trials. These are wonderful resources I would like to take advantage of while I am here.

After the meeting, I went to the CyberKnife clinic and visited with Dr. O'Connor and Dr. Berger. There was a representative of Accuray there as well, who provided lunch. I got to listen to their future plans with the CyberKnife and who should be contacted about these plans. Eventually, they would like to radiate tumors in the spine. After lunch, Dr. Berger and I talked about the different areas I would be able to help, and asked about my personal goals of this internship. I am glad that everyone has taken an interest in my involvement.

Later in the afternoon, I sat in on a dermatology budget meeting. It was interesting to hear all the aspects of budgeting that were overlooked. If a sponsor's budget is too low, an investigator can ask for a different amount. I guess it is common for a sponsor to overlook Administration and Up-Front fees in their proposed budgets.

The administration fee must be able to pay for the CCRC or Research Nurse's time. Typically, the contract rate for a CCRC is $65/hour and a Research Nurse is $70/hour. For the up-front fee, a PI should ask for it as non-refundable, just in case the study ends early. This fee goes toward salary, supplies used for enrollment, and study start-up like an IRB submission.

August 22, 2007

This morning I was designated to make protocol and consent form changes to the prostate cancer study. Electronic versions were difficult to find, but I have enough information to make these changes. I completed the changes to the consent form and began filing the IRB revision form (Form 7). Dr. Berger will have to help me finish the Form 7, because I do not know his plan to reconsent former subjects in the study. I also began revising the protocol today.

August 23, 2007

I worked on revising the prostate study's protocol. I met with Dr. Berger and discussed the new prostate study protocol from the study sponsor, the maker of CyberKnife. First, they sent an anonymized data set and potential study sites are asked to develop a treatment plan. I will need to get with Hahn Pham, the dosimetrist, to help plan a treatment for this "patient." Once our team accomplishes this task, we will send it back to the study PI and physics chair, who will look over it. This is a quality assurance test. If we pass, the study sponsor will send us a copy of the final protocol, the consent form and a clinical trial agreement. I am really excited that I get to have a major role in this process and will get to see the entire approval process.

During the afternoon, I drove out to UNTHSC to look at previous students' internship practicum reports. One of my friends was at the library working on her proposal as well. After talking with her and reading the reports, I realized BRI is definitely the best internship site. The most interesting report that I saw was from a previous student at BRI. It was well written, and she was obviously interested and very involved in her internship.

August 24, 2007

I am still working on the protocol revisions. Dr. Berger asked me to wait on a few revisions; I suppose to calculate radiation doses on certain organs. We will be meeting at 11. I made the necessary revisions. We will be starting a new prostate cancer study protocol soon.

August 27, 2007

This morning I had a meeting with Betsy Stein to go over the protocol revisions. There were a few points that we needed clarification, so we set up a meeting with Dr. Berger around 11. Unfortunately, we decided at the meeting that all the revisions I had been making would not be necessary anymore. At least I got a better understanding of IRB Form 7 and the revision process. I began helping with the Quality Assurance Test for the new prostate cancer study. Dr. Koneru is doing a fellowship with the CyberKnife center and also helping to plan treatments for the "fake patient." Dr. Scott, the urologist, and Dr. Berger spent a good amount of time planning as well. I got to draw a couple bladder cross sections for this treatment plan. Playing video games when I was younger

definitely would have helped with the coordination necessary to do this. Dr. Koneru was a lot faster at drawing.

August 28, 2007

I began my day in the Radiosurgical Center. Dr. Scott was working on the plan early, and then Dr. Berger took over. I have learned a lot of information about different radiation techniques and how to read the different densities in an MRI and CT scans. We worked on the plan all morning, and it is still not complete. Hopefully tomorrow we will start planning the radiation intensity aspects. It is very labor intensive. I also visited the MRI specialists today to help read an MRI. Sometimes they can be very tricky. For example, on the "fake" patient, it is difficult to define the penile bulb. Dr. Scott was helpful, but we still needed to consult Netter and another anatomy book.

August 29, 2007

Today was the same thing. Hahn Pham began to plan the doses today, but at the end of the day, Dr. Berger changed the original plan, so Hahn will have to start all over again tomorrow. Dr. Scott was there again helping us, and showed me the probe and machinery used to put the fiducials necessary for the machine to orient itself. I researched different articles that may be helpful on my proposal as well as worked on my HIPAA training.

August 30, 2007

Dr. O'Connor wanted to be added to the renal and prostate study as a Sub-investigator. No one has been enrolled on these studies, so the paperwork is less difficult. I had to track down an electronic version of the renal consent form and could not. I did

find a paper version, and revised the prostate consent form to match. Luckily, they were very similar and even had the same typos. I made those corrections, added Dr. O'Connor, and filed a Form 7.

The treatment plan for the new protocol is close to finish. We did miss one guideline though. Hahn will have to go back and make sure the plan meets all the criteria. Dr. Berger is taking tomorrow off and asked me to make sure the plan gets sent once it is done.

August 31, 2007

This morning I finished adding Dr. O'Connor to the renal cell protocol and packaged it for the IRB committee. Today I was responsible for sending the QA Test through Fed Ex. When I went to the CyberKnife Center, I was surprised to see Dr. Berger reviewing the treatment plan, because he was supposed to take today off. Fortunately, he was able to sign the renal cell protocol change, and I was able to send it to the IRB. Dr. Berger explained to me that there were still some inconsistencies in the treatment, so Hahn would have to make those revisions before sending the QA Test. Today was the deadline for each site to send their QA Test to the study sponsor, so I waited patiently for the final treatment plan.

When we received the packet containing our QA Test information from the study sponsor, we had to figure out how to import the information given to us into our computers. Although our sponsor sent directions for importing the data, they were incorrect. Surprisingly, they excluded instructions for exporting the data they need to review our QA Test. They did enclose a blank CD in each site's packet though. I did not

realize how difficult and complex the CyberKnife software could be. It is nothing like Microsoft Windows.

Hahn's treatment plan revisions did not take long, but the directions were not clear on what data the National Principal Investigator needed to review our QA Test. Hahn and I made several phone calls to and the study staff, but since Monday is Labor Day, few people were in their office. Eventually, we established communication with the study sponsor's Technical Help Desk. The Help Desk seemed very flustered and we asked why. They were very busy because they were receiving phone calls from all the sites about importing and exporting the QA Test data without any notice from the study sponsor's staff. They too were unable to locate study personnel to explain what kind of information they needed from each site. Since we were unable to find help, we had to guess what information was needed, and burned it to the enclosed CD.

Once the package was ready to send, I took it to Edith, the office receptionist, to schedule a Fed Ex pickup. Unfortunately, it was already too late in the day to schedule a pickup. I went to the Fed Ex website to find the closest drop off, and sent the package from a location near my home.

September 3

Labor Day

September 4

Dr. Berger was busy seeing patients today and did not assign me any tasks. I spent the entire day reviewing Baylor and UNTHSC journal databases for proposal information. I found about 16 articles that may or may not be helpful. They are all about

the CyberKnife, and some have an emphasis on prostate cancer. Dr. O'Connor has talked to me before about journal articles, and offered the use of the radiosurgery center's account for obtaining articles that Baylor does not have access. If I could not find an article at Baylor, UNTHSC would usually have it and vice versa. I am not sure what I want to cover in my proposal, so I picked very general search terms. I plan to review these articles through the remainder of the week.

September 5

This morning I received an email from Dr. Berger wanting me to meet him in the Radiosurgery Center. The study sponsor sent instructions on how to export the information they need for the QA Test. It had already been burned to CD, and I needed to send it to the National Principal Investigator. It is a good thing I kept the Senders copy of the package sent on Friday. It was the only documentation of their Fed Ex Account #. Once again, I located the closest Fed Ex drop off and it is on N. Washington and Gaston. I searched all over the hospital, and found it next to the post office. I also brainstormed research proposal ideas and am excited about my project.

September 6, 2007

I reviewed journal articles. Some of them are a little too technical for my understanding, so I had to consult other on-line sources to get a stronger background. I will figure out as much as I can, but I will have to ask Dr. Berger or Dr. O'Connor to explain a few things to me.

September 7, 2007

Today I worked on my proposal ideas and reviewed journal articles. I also spent some time in the Radiosurgery Center observing prostate treatment plans.

September 10, 2007

Dr. O'Connor and Dr. Berger were eager to help me find resources for my proposal. I explained that a lot of the sources I have reviewed were a little too technical, so they have shown me a few textbooks to get a better foundation. Dr. Berger will attend a conference in October that provides a very informative DVD about radiosurgery. Usually at the conference, there is a lecture on the history of radiosurgery. Dr. Scott, Dr. Berger, Dr. Koneru, and I also did treatment plans for prostate cancer. During some of the down time, Dr. Koneru explained the different types of radiation treatments available. He also has a subscription to a journal review service, and found some articles for me that will help with the different prostate cancer treatment options. Treatment is very different for advanced and early stage prostate cancers. Since CyberKnife is used for early stage prostate cancers, I have decided to focus my research to those treatments.

September 11, 2007

Dr. Scott would like some information to give his patients about the CyberKnife trials at the Radiosurgery Center. I worked on that this morning. Nanette Myers, the business development specialist at BRI, will help me with this task. I have found the information needed for the Baylor website, and marketing can help with a handout.

September 12, 2007

Today I asked Dr. O'Connor to check the information that will be posted on the Baylor website for the prostate and renal clinical trials. I had to make a few minor changes, but it is ready for review by the Legal department. I talked with Dr. Berger, and he would like information to hand to patients about the CyberKnife clinical trials. When I talked to Dr. Scott, he was more interested in CyberKnife information. I will have to talk to Betsy to figure out what I need to do.

I also helped with the treatment planning of a patient with prostate cancer. Dr. Koneru explained some of the technical aspects of radiation to me. I learned about BED, biologic equivalent dose, and why it is important. In traditional forms of radiation, 1-2 Gy of radiation is given per session, up to around 70 Gy total. Since the CyberKnife uses higher concentrations of radiation, there is a special equation to estimate the amount of radiation given in "traditional" terms. This equation is:

$BED = dose_{total}\,[1+[dose_{per\ fraction}/(\alpha/\beta)]]$.

The α/β value is either 10 to determine acute effects or 3 to determine late effects. Traditional radiation has a higher rate of acute effects, and CyberKnife treatments calculate a higher rate of late effects. That is why we need to test CyberKnife treatments. It is a fairly new device with little data on long term effects.

September 13, 2007

This week the Radiosurgery Center is really busy. Most of the treatment planning that I can help with was already completed, so I decided to work on my proposal. I

worked on it all day and part of the night, and sent it to Dr. Oglesby, my major professor, for review.

September 14, 2007

This morning I had a BRI New Employee Orientation meeting. According to the Baylor map, BRI and the Baylor Institute for Immunology Research (BIIR) are in the same building. When I got to the BRI office, I realized the address was not the same as BIIR. I had forgotten that the BRI offices used to be housed in the same building as BIIR, but have moved since. Luckily, BIIR was not far away, and I was not late. I also met Tory at this meeting. He was the UNTHSC grad student at Baylor before me. He was recently hired and is working in the same department in which he did his internship.

After the orientation, I had a meeting with Betsy. She showed me how to use StudyManager. I have a site for the CyberKnife on the web edition of StudyManager. This will be helpful because I can use it to make a schedule of patient visits for the lung cancer protocol.

September 17, 2007

I was out of town for a wedding.

September 18, 2007

I attended the monthly Clinical Research Coordinator meeting. We learned how to back up files. I do not have a U drive, but I can call to request one. If I were to store my files on this drive, they would automatically be backed up nightly.

I have been waiting on information from Dr. Berger to make a prostate cancer handout, but he has been extremely busy lately. I decided to just gather the necessary information on my own. It is turning out nicely.

I also spent time in the Radiosurgery Center. They were treating a patient with prostate cancer with the CyberKnife. When the man came out of the treatment room, I realized that I recognized the patient. A few weeks earlier, Dr. Berger let me sit in on a patient consultation. He was the same patient from this consultation. Today was the first time I have seen a patient through an entire treatment cycle. I saw him in the consultation, the staff and I planned his treatment last week, and now he is actually receiving the treatment. I have spent so much time treatment planning on computers lately; it was nice to see how it is used to treat an actual human being.

September 19, 2007

Today I went to the Radiosurgery Center. It is Dr. Koneru's last day, so I am trying to learn as much about radiology as I can from him, before his departure. I also worked on the prostate cancer handout. I will get Dr. Berger to look it over to make sure it is what he wants.

Dr. Berger wants something different. I will reconcile the differences with Dr. Scott and Dr. O'Connor. This may be difficult since Dr. Berger will be away on vacation. I have attempted to set up a meeting with Dr. Scott to discuss this further.

September 20, 2007

I had a morning meeting with Betsy. She has advised me on what to do about the patient information handout. Today Dr. Steinman, one of four winners of this year's

Lasker Award, will be lecturing at Baylor. According to the Lasker Foundation, the Lasker Award is known as "America's Nobels" and is the most coveted award in medical science. This claim is fairly valid because in the last 60 years, over 70 Lasker Award winners subsequently received a Nobel Prize. I have not attended a lecture in a couple months and am looking forward to it.

To prepare for Dr. Steinman's presentation, I read up on dendritic cells. I was hoping it would help me to understand his lecture better. It is interesting how dendritic cells can manipulate the immune system. They can hyperactivate the immune system and be used for infectious diseases, or they can be suppressive, which would be useful for organ transplant procedures.

After the lecture, I worked on the handout using the guidelines Dr. Berger had suggested. I had to do a bit of research to cover all the information he requested.

September 21, 2007

I had a morning meeting with Dr. Scott to reconcile the differences in information for the handout. He had a lot of good suggestions, and I made the necessary changes.

September 24, 2007

I remembered that the handout did not have any contact information, so I added it. I also reviewed journal articles.

September 25, 2007

I completed my HIPAA training today and began the Safety training. I also began the protocol summary sheets today. I will have to check with Dr. Scott to find out what information should be included for each summary.

September 26, 2007

I had a morning meeting with Dr. Scott. He requested a few more changes to the protocol handout and told me what he thought should be included in the protocol summary sheets. I worked on the protocol summary sheets for the majority of the day. I also had a meeting with Betsy.

After lunch, I helped Renee, one of the study coordinators in the Clinical Trials Office, ship some specimens. Since she was shipping different types of body fluids, she explained how to label those shipping boxes. Also, some specimens had to be packed in dry ice. Labeling for those boxes can be complicated, because you have to list addresses and phone numbers of the shipper and shippee, as well as how much dry ice is being shipped. While talking to the delivery man, I learned that for medical use, you can ship boxes up to 50 lbs with dry ice, but only 5 lbs for non medical shipments.

I also set up my StudyManager account and entered the 3 CyberKnife trials into the system.

September 27, 2007

This morning I worked on the protocol summary sheets. I also attended 2 budget training classes today. There are so many things that need to be accounted for in the budget. For example, when specimens are examined in the pathology lab, a fee is charged for the lab work (technical fee) and another is charged for the specimen evaluation (professional fee). Baylor has a nice, easy to understand template to configure a study budget. They also have staff that can help the study coordinator plan the budget or look over the budget to make sure that all direct, indirect, and hidden fees are

accounted for. After the classes, I finished working on the protocol summary sheets and sent them to Dr. O'Connor for review.

September 28, 2007

Today I was invited to work with Lucy at the Baylor Jack and Jane Hamilton Heart and Vascular Hospital. Lucy completed UNTHSC's CRM program with her internship here at Baylor. Later, she was hired at Baylor as a clinical research coordinator in the same area as her internship, interventional cardiology. This week was a little slow for them, so they were archiving previous study information. They will be starting a couple of new trials soon, and needed to make room in the office for those materials.

After we boxed up old material and rearranged, Lucy showed me how they randomize patients. She received a phone call from another site whose study coordinator had taken the day off. The doctor was trying to schedule an appointment for a new subject but needed to know which group in which the subject was randomized, because there are different appointments for each group. I do not know how often other sites ask for help, but it seemed odd. The randomization process involved calling an automated system, giving subject information, and writing down which group the subject was assigned. It did not take long at all.

Later, Lucy gave me a tour of the Heart Hospital and showed me how they consent patients. Mondays and Fridays are their biggest consenting days, because there are two doctors that are screening potential subjects as opposed to one doctor on other days. They try to recruit about 16 subjects on their big days. Lucy explained that they

have to start at around 6:30 AM to catch potential subjects before their surgeries. You can not consent a patient once he/she has received drugs in preparation for surgery. That is why they have a small window early in the morning to consent patients.

Lucy taught me a lot and made me realize how different our studies are. I hope to come in early next week to observe the consent process.

October 1, 2007

Today I heard back about my proposal draft. I edited what was necessary and sent it to my committee for review.

I also received an email from Nanette Myers, about the prostate cancer handout. Legal reviewed it and requested some changes. I made those changes and sent it to Dr. Scott for review. I plan to meet with him soon to discuss the changes.

October 2, 2007

This morning I had a meeting with Dr. Scott to go over the changes. I made them and will have them reviewed by legal again. I also made some minor editing changes to my proposal draft.

The remainder of the day was spent entering data into StudyManager. It was a little more complicated than I was expecting. I will consult the StudyManager manual for my future attempts.

October 3, 2007

My morning meeting with Betsy went well. Before the meeting I worked on an Excel spreadsheet to help the Clinical Trials Office invoice a sponsor. For this study, the contract agreement says to invoice the sponsor according to groups of procedures

completed, and the sponsor will pay in installments. This is less clear for invoicing screen failures. I will attempt to make a spreadsheet to show what can be invoiced and for how much. I worked on this in the morning and at the end of the day.

Today, I also joined Lucy in the heart hospital. Patient recruitment for her current study is still on hold, and she does not think they will be recruiting next week either. She was reviewing the new protocol and was preparing questions for the initial site visit.

Also today, she had a monitor visit. At another site, there was trouble with packaging, so the sponsor implemented an emergency monitor visit to check inventory. Lucy is working on several drug eluting stent trials, so the study devices are stored in the cath lab. Since this is also storage for other medical devices, there are several rules in place to make sure they are stored in a sterile environment. For example, the lab must have on file a copy of the results from your most current TB test. Checking inventory proved to be a difficult task, because the monitor did not have his TB record with him. Thankfully, the cath lab worked with us, and we were able to check inventory. The monitor read off the lot and serial numbers for each device, and I checked them off in the inventory log. I would say I played an active role in this site monitor visit.

October 4, 2007

All day I attended the GCP Fundamentals training. It was taught by Barbara Richardson from MedTrials. She also taught my clinical research class at UNTHSC. It was good hearing the information again, because now I have a better understanding of what she is teaching, just through personal experience. For example, I had never seen a case report form until I began my internship. Now, I understand what they are and that

the abbreviations and the drug names (generic/trade) recorded on them should be used consistently at that site to avoid confusion.

October 5, 2007

Today I heard back about my proposal from Dr. Gwirtz. I edited the proposal more. I also worked on the invoice spreadsheet. I had to make sure that all protocol procedures were accounted for and that the price of each procedure was correct. Since the sponsor owes BRI a large sum of money, it is important that we bill the sponsor for all completed procedures at the same cost agreed upon in the contract.

October 8, 2007

I worked on my proposal and am figuring out how to submit the proposal to the graduate office. I drove to campus to attain signatures from my committee members during the second half of the day.

October 9, 2007

Today I got my last signature and faxed a copy to the graduate office. I also sent the original in the mail. Today Dr. Berger returned from vacation, so I dropped off the handouts I have been creating. I will see him tomorrow.

I also attended 2 meetings with Betsy. The first meeting was with the dendritic group. They discussed study updates and Baylor Health Care System (BHCS) initiatives. An interesting change is in the interviewing process for screening potential employees. Baylor will soon switch to a behavioral interview, which has a higher success rate than the previous system for determining work ethic. The second meeting was about sponsor invoicing. The pulmonary group is owed a large sum of money from several sponsors for

the studies that they are conducting. The most difficult part of invoicing is determining the amount of procedures performed. I have seen several budget contracts where the sponsor requests to be invoiced per group of procedures. This system is more beneficial to the sponsor, because this adds more work for the study coordinator, and it is least likely to be done. StudyManager can be used to keep track of the procedures needing to be invoiced, but it is not a very user-friendly program, which is most likely why study coordinators fall behind on their invoicing.

October 10, 2007

Today I met with Dr. Berger and we reviewed the handouts. Overall, I will not have to make too many changes, but I will have to find more journal article references. It will be a challenge to interpret the journal articles and translate them into a grade school reading level, but I am up for the task. I have been reviewing journal articles all day and revising the fact sheets.

October 11, 2007

Dr. Berger invited me to the GI Tumor Board at 6:30 AM. It was really interesting hearing about the different cases. Next tumor board, I will review my histology before hand. Afterwards, I revised the prostate handout until my meeting with Betsy. Mary in the Clinical Trials Office is working on a new study and will have to give a tour of the site for the initial monitor visit. Since it is a GI study, she requested a tour of the GI lab so she will know where to take the monitor. I tagged along for the tour and spoke with one of the doctors that presented at the Tumor Board. After the tour, I stopped by the Radiosurgery Center and talked with Dr. Berger about the handouts. He

made more revisions and I worked on them the rest of the day. Once again, I returned to the Radiosurgery Center at the end of the day so Dr. Berger could review the revised handout. It took about an hour and a half for him to tell me exactly what he wanted for the next version.

October 12, 2007

I have worked on the handout all morning and part of the afternoon. I also created a spreadsheet for the Radiosurgery Center. Dr. Berger wanted a schedule of all the follow-ups for the patients on the non-small cell lung cancer study. Dr. Berger had a very busy schedule, so he was not able to go over the new handout with me.

October 15, 2007

I found Dr. Berger and he had more revisions for me. We have gone over this handout sheet 3 times today, and each time, he finds something new he wants to change. As always, I revised the sheet each time and wait for his new corrections.

October 16, 2007

This morning was the monthly Clinical Research Coordinator meeting. Nanette Myers gave a presentation titled, "Promoting Your Research Site – What Do Sponsors Want?" It was really interesting to find out what sponsors look for in a site. I had never thought about how sponsors select investigators before. Often times, they are re-used, but they are frequently found through word of mouth methods, like from Clinical Research Associates, selection firms, or by being key opinion leaders, or published. Sponsors are also concerned about how timely they can get the study going. The IRB process takes time and so does the budgeting contract. Most importantly, sponsors care

about a site's enrollment. If a site is too busy with studies, the site should not accept any more studies especially from a new sponsor, because it can leave a bad impression if the study fails. I learned a lot from this meeting and will keep the handouts for future reference.

I also met with Dr. Berger to talk about the handout. Dr. Berger has finished making changes, but we are waiting to hear Dr. Scott's input. I emailed Dr. Scott but was not able to meet with him to discuss the handout.

October 17, 2007

I attended a cultural competency seminar at UTA. It was over healthcare of the Mexican-American population. I am very concerned about their healthcare, and plan to use clinical research to combat the health disparities within that population. I was very pleased with the conference because all the speakers were great communicators and very knowledgeable. There were 6 time slots for lectures, and during 2 of those slots, participants were allowed to pick which lecture they wanted to attend. The lectures I attended were: Structure of Medical Care in Mexico, Tips to Approach the Latino Patient in the Office, Language Barriers, Healers Witchcraft and Health, Informed Consent, and Health Literacy-Preview and Working with Interpreters.

One of the most interesting talks that most relates to clinical research management was the health literacy lecture. I learned that the average American reads at an 8th grade reading level. We watched a video that interviewed several patients with health literacy problems. Most of them were ashamed and try very hard to hide the fact that they are not good readers. One woman said that she was given about 5 forms to sign, and since she

was ashamed that she could not read very well, she signed them without reading them. The next time she returned for her follow-up appointment, the nurse asked, "How are you feeling after your hysterectomy?" The woman said she felt so stupid for feeling ashamed and for letting someone take out a piece of her body without her knowledge. Especially in our litigious society, it is important that patients/subjects understand the informed consent document. This document protects a patient/subject's rights when he/she can understand it, but can do the opposite when the patient does not understand it. Now I have a better comprehension of why patient information needs to be written at a grade school reading level.

October 18, 2007

My meeting with Betsy went well this morning. Dr. Berger had consulted with Dr. Scott yesterday on the handout sheet. Both doctors had minor changes. I am almost done! I also began working on the protocol summary sheets again.

October 19, 2007

I had a meeting with Dr. O'Connor this morning to discuss future research plans. I also finished the first draft of all 3 protocol summary sheets today. I dropped them off at the Radiosurgery Center, and Dr. Berger will have them reviewed by Monday. He says he will not be as strict on these handouts, but I will believe it when I see it. Even though there are 3 handouts this time, I do not think they will take as long, because I have a better understanding of Dr. Berger's writing style.

October 22, 2007

Over email, Dr. Berger and Dr. Scott agreed to take the prostate handout through Health Texas, instead of through Baylor University Medical Center. Although Health Texas is part of Baylor, it is a physician practice management group with funds to pay for patient education materials. I emailed the final version to Dr. Berger, and he will send it through Health Texas. I also began working with Dr. O'Connor more. He has helped me understand patient records and has explained where to locate side effects, which may be considered adverse events.

October 23, 2007

Today I had a medical school interview and filed my "Intent to Graduate" form at the Graduate School Office.

October 24, 2007

Today I explored the different areas of the Radiosurgery Center where patient information can be found. There are several computer based media to find patient records like MRI and CT scans as well as radiology reports. These are used by the Radiosurgery Center to plan treatments.

I also had lunch with Lucy today. We talked about the differences in device trials and drug trials. For drug trials, clinical researchers are looking for adverse reactions to the drugs. For device trials, clinical researchers look for complications in the device's function. She was saying that all her experience is in device trials, and she does not think she would be able to switch to drug trials later in her career. I had never thought about the differences between the two types of clinical trials.

October 25, 2007

I had a meeting with Betsy, but spent most of the day in the Radiosurgery Center. I have become familiar with patient records. I have scanned through several of them to learn what kind of side effects patients feel after their CyberKnife treatments. Almost half of the patients have no complaints, but the most common side effect was fatigue.

I also had a chance to sit in on a few consultations. One of them today was the gentleman with prostate cancer that I have been following from consultation through treatment. Today was his one month follow-up appointment. Although he is not on the prostate cancer protocol, many of the same restrictions were used on his treatment plan. It was interesting to see what kind of side effects I should expect to see in future subjects. His chief complaint is fatigue. He has felt very tired since treatment, but this week he is feeling slightly better and has a little more energy. He also experienced bowel and bladder irritation, but it has also improved. I am very happy to hear that his side effects were minor. The one month follow-up appointment is just to see how the patient is doing and to prescribe medication if he is having any complaints. The three month follow-up will not be as pleasant, because it requires a blood draw and a digital rectal exam. We plan to see him again just before Christmas.

October 26, 2007

Today I finished the project Dr. O'Connor had me help with involving patient records. We looked at large abdominal tumors and the side effects of CyberKnife treatment. I learned where to locate patient information, how to read radiology reports, and where to look for patient side effects. I also brushed up on Microsoft Excel's

formula tool. I had not used it since undergraduate statistics. I used it to calculate BED. Reading these records has given me practice for when our new prostate cancer trial begins.

I also attended 2 research staff meetings with Betsy. The first group we met with was with Interventional Cardiology, Lucy's group. The second meeting was with the Baylor Sammons Breast Center. This group is very busy right now, because it is Breast Cancer Awareness month. At both meetings, the research staff updated Betsy on their current research. Betsy also updated the staff on new Baylor initiatives. She had good news to spread to her staff today, so after the meetings, we spread the good word. Betsy has staff everywhere, and it was a good chance for me to meet other researchers in different departments.

October 29, 2007

Today I reviewed the directions on how to write my internship practicum report. I also did a search for newly published articles. I reviewed journal articles the rest of the day.

October 30, 2007

Mary had a pre-initiation site visit today. We met the monitor at the PI's office to start the visit. After a few minutes of questions, we left to go to Mary's office. There, the monitor asked several questions about the doctors involved in the study, instruments in the GI lab, and estimated subject numbers. Monitors need to know a lot of information about the site in order to select the best sites for their studies. Following the question/answer session, Mary and I took the monitor to the GI lab for a tour. Since this

study involves injecting a drug into a GI tumor, we also took the monitor to tour the pharmacy's investigational research area. She seemed very impressed with the site's amenities. For her next visit if our site is chosen, she will have to tour areas in the Texas Oncology building. This monitor said that she used to work there, so she should already have an idea about what to expect. For monitor visits prior to study initiation, coordinators have a large responsibility to coordinate meeting times with all areas involved in the study. They must also gather paper work from everyone, like CVs from the people involved in the research, licensing, and lab normal values.

A lot of work goes into coordinating prior to site approval. This takes up a large amount of the coordinators time before the site receives any payment. If the site is not chosen, the site does not get paid for the coordinator's time. BRI really pushes for their coordinators to make their sites attractive to sponsors. During the monthly coordinator meetings, they give tips on how to do this. Although BRI is a non-profit sector of Baylor, they still must make enough money to break even. When coordinators put in their time and effort for a study that does not get approved, BRI must compensate for this loss.

October 31, 2007

Today is Halloween! Baylor has several festivities going on today. I started my morning at the Red Cross Blood Drive. It was held in Beasley Auditorium. It was well thought out, because they were playing "scary movies" while people were waiting and donating blood. Most of the chairs were facing the screen, so donors were able to watch as well. After donating blood, I spent the day in the Radiosurgery Center. They were hosting Trick or Treaters from the Baylor Day Care Center. The staff dressed in costume,

and I dressed as an angel. The children had fun Trick or Treating. Soon after, we had our potluck lunch. There was way too much food!

After lunch, Tamara Bynum taught a class on how to work with different people's personalities. It was a fun and informative class. Everyone had to take a "quiz" to find out their own personality style, which was categorized into one of four color groups. Once everyone had their own color, we learned the most effective ways of working with each color group. For example, the red group was characterized as assertive and active. I was classified as blue, which is the creative group. When I work with people that I recognize as red, I should be concise and to the point. Since the staff at the Radiosurgery Center did this class together, we know each other's "color" and know how to work efficiently with each other.

November 1, 2007

I had my weekly meeting with Betsy this morning. I had found an article in the New York Times titled, "Participants Left Uninformed in Some Halted Medical Trials." It brings up an issue for device trials not found in drug trials. Although clinical researchers are not required to disclose test results to participants, they are required to inform patients of emerging product dangers. My question is what happens to the subjects when their installed devices are not approved. Since these devices are not approved, logically, it would seem that there is a problem with the device. Betsy has set up a lunch with Elizabeth Cothran, the director of the IRB, for next week. I will be able to get an IRB opinion of this matter over lunch.

November 2, 2007

I started working on a consent form for one of the drug trials at the clinical trials office. Although the sponsor provides a consent form, it is important that it looks like a "Baylor" consent form. It is easier for the IRB to review and ensures that all necessary material is included.

November 5, 2007

I worked on the consent form today.

November 6, 2007

I was in the Radiosurgery Center all day. Today Dr. Berger saw follow-ups for his patients with prostate cancer and lung cancer. He also had a consultation for a patient with prostate cancer that may be eligible for the prostate cancer trial. This man has some time to decide what kind of treatment he prefers. Although treatment is ultimately the patient's choice, it is difficult for a physician to say what treatment option is the best. Gleason score, PSA, and Stage can be used to determine risk of metastasis into the seminal vesicles, lymph nodes, and prostate capsule. These may be helpful for some patients to determine what the best treatment option would be, but can also blur the lines too. For example the patient today has an intermediate risk of cancer spread to his seminal vesicles. Some oncologists would recommend that his pelvis gets radiation as well, while others may think that solely the prostate should get irradiated. There is no right answer because it is difficult to tell where the cancer has spread. These are difficult choices for a patient during a stressful time. Also, we received the new prostate protocol at the end of the day!

November 7, 2007

Out of the office

November 8, 2007

Out of the office

November 9, 2007

My email and Baylor access has been cut off, and I spent the afternoon attaining access. It was not very difficult. I also helped Dr. O'Connor in the Radiosurgery Center today with his project on large abdominal tumors. While I was waiting for my computer access, I read a journal article about the history of radiosurgery. Fortunately, by the end of the day, I gained access to my computer files.

November 11, 2007

Since I had to take a couple days off last week, I worked on the consent form from home today. The IRB submission deadline is Tuesday at 8:00AM. I need to make sure the consent is complete by tomorrow, so Mary and I can go over it before submission.

November 12, 2007

I finished the consent form today. I had many issues with the formatting and basically had to retype several sections of the consent. It was aggravating, but happens.

My lunch meeting with Betsy and Elizabeth was rescheduled for today. I had the opportunity to find out from an IRB standpoint what happens beyond device trials. My concern is what happens to subjects who participated in device trials whose devices never gained FDA approval. Elizabeth told me that all devices are registered and tracked. In

the event that a device has a serious complication, the device can be recalled. Frequently, removal of the device would add a greater risk than leaving it. Also, devices may not be approved for reasons other than malfunctioning. A sponsor may stop a trial because the device functions equally to an already approved device, but not better. Since the cost of conducting a clinical trial is so high, a sponsor would not want to continue a study that will not be profitable. The article that got me interested in this subject made it sound like once a clinical trial is dropped, a subject's health is no longer followed. Usually, an IRB will not approve a study that does not agree to follow the subject's health.

November 13, 2007

The monthly coordinator meeting was today. MedTrials presented about "Liability and Risk Management in Clinical Trials." We heard some horrible stories about research misconduct. One PI would make up patients and use his staff's stored urine for the required tests. Research coordinators have also been held liable for research misconduct also. A couple of the PI's coordinators were barred from clinical research for 5 years. There was also another case where a research coordinator would enroll subjects that did not meet eligibility criteria. Since one of those patients died, he was charged with criminally negligent homicide. Eventually, the FDA permanently disbarred him from research, he was sentenced to 71 months in prison and owed several sponsors $639,000. This presentation made me realize that research coordinators had more liability than I had thought.

I also went to the Radiosurgery Center today. Dr. Berger and I had a consult with a patient with lung cancer. Unfortunately, he is not eligible for the lung cancer trial.

I will be working on the CRFs for the lung trial in the next few days. The sponsor is switching to an electronic database and is requesting all CRFs to begin data entry into the system. Mary has helped me to figure out what I need to do, and I will start tomorrow.

November 14, 2007

This morning I went with Mary to the GI lab for one of her new studies. She has been working with the different oncologists involved in the study. She must get signatures from them agreeing to certain procedures as standard of care. Although one doctor signed the paperwork for standard of care procedures, when Mary picked up the document, his research nurse told her that the doctor just signed the paper even though that is not a standard of care procedure he normally does. Since this conflict has the potential to cause problems later in the study, Mary had to inform the PI in the GI lab.

After the GI visit, I went to the Radiosurgery Center to work on the lung trial CRFs. I pulled patient charts and found source documents. Surprisingly, most patients had not completed their follow-up appointments. I will find out more about this tomorrow. I also called the national clinical study manager to let her know that we are making sure all CRFs are up to date and to expect them in the near future. She clarified some issues for me, and asked why we had not enrolled any new subjects. We ended the conversation with her asking for more subjects. Personally, I dislike telephone conversations, but realized that I have to get over it in order to do this job correctly.

November 15, 2007

I worked on the lung trial CRFs all day. I talked to Erika Resendez, Dr. Berger's medical assistant about the missed follow-up appointments. One of the subjects is

scheduled for Tuesday next week and the others will be scheduled soon. I also had my weekly meeting with Betsy. She went over the different forms I need to complete and submit to the IRB to initiate the new prostate clinical trial. I will work on these as soon as I finish the lung CRFs.

November 16, 2007

I worked all morning on the lung CRFs. The past couple weeks I have been organizing a tour of Baylor for Dr. Oglesby, which happened today. Lucy and Tory, his previous students, gave tours of their departments, and Dr. Berger gave a tour of the Radiosurgery Center. Dr. Berger spent a lot of time with us explaining the CyberKnife and Gamma Knife and how they work. It was a great visit, and after Dr. Oglesby left Baylor, I continued working on lung CRFs. I thought they would be done today, but I could only send one set. On my way home, I dropped it and another package at Fed Ex.

November 19, 2007

I worked on CRFs all morning and part of the afternoon in the Radiosurgery Center. When I returned to the Clinical Trials Office, Mary informed me that I had missed a few emails earlier that day. When I checked my email, I found out that the prostate and renal clinical trials were up for continuing review by the IRB. All appropriate documents were due November 12. If the appropriate forms did not reach the IRB by Wednesday, the 21st, his studies would miss the annual review and would be put on hold. Fortunately, I was able to fill out the required IRB Forms by the end of the day. When I went to the Radiosurgery Center to get Dr. Berger's signature, the doors were locked. I knocked and waited patiently, but everyone was in the very back and did not

hear. So I gave up on the signature and decided to try tomorrow. As I was walking away, Dr. Giller, the neurosurgeon at the Radiosurgery Center, left for the day, and I was able to catch the door before it locked again. Luckily, the second doors to the Radiosurgery Center are glass, and someone was able to see me to let me in the back of the suite. Dr. Berger approved of the final version and signed the forms.

After obtaining his signature, I tried to drop the forms off at the Baylor Research Institute. Most everyone had left, but Betsy was still there and told me where to drop off the forms. Unfortunately, I did not realize I had to gather more forms to turn into the IRB, and I would have to finish tomorrow.

November 20, 2007

In my hastiness to turn in the Continuing Review forms to the IRB, I missed one of the email attachments with instructions on what to submit to the IRB. I spent all morning and half of the afternoon compiling these documents for each study: 4 copies of the Continuing Review Form, 4 copies of the project summary, 4 copies of the current Informed Consent with highlighted revisions, 3 copies of the protocol, financial disclosure forms for study personnel, and a clean copy of the Informed Consent. Fortunately, as I had finished typing the financial disclosure forms for each doctor on each study, I ran into Dr. Scott, one of the investigators not normally in the Radiosurgery Center. This saved me some time, not having to track him down for a signature. After all necessary documents were compiled and signed, I hand delivered them to Janet Collinson, the administrative assistant at BRI. I was also able to talk with Jan Harrell, an IRB coordinator, about a few questions Dr. Berger wanted me to ask the IRB.

The small remainder of the day was spent on the lung trial CRFs. I had collected, compiled, and copied all appropriate information, but still needed to organize it, and get it ready to send to Fed Ex. Mary did not realize how late we were both working, and offered to help me. She found the shipping supplies for me, while I filled out the address form. Once again, on my way home, I dropped it off at Fed Ex.

It was also Thanksgiving at the Radiosurgery Center. Edith organized a lunch for everyone. All staff at the Radiosurgery Center chipped in to buy a barbecue lunch, since most of us would be eating traditional Thanksgiving food in a couple of days. It was nice hearing about everyone's holiday plans, but we were all so busy that it ended up being a short lunch.

November 21, 2007

I thought the day before Thanksgiving would be a fairly easy day, because I had just finished 2 big projects that have been stressing me out. This morning Dr. Berger and I had a meeting about the new prostate protocol. I told him that Betsy and I had a meeting about what I need to do to initiate this trial. The plan did not include the clinical trial agreement, which made me confused at this meeting. He seemed slightly aggravated that I had not done anything with this contract and hastily signed investigator signature lines for me to turn into BRI. Many of the fields were blank and he forgot to initial each page. I emailed Betsy for guidance. I do not think he fully understands the initiation process and would have liked to have it all done today.

I also received an alarming email from the sponsor as well. Several things need to be done before initiation. Betsy helped me reply to this email diplomatically, because I was unsure how to respond.

While I was at the airport and on the plane to my Thanksgiving destination, I knocked out 3 journal articles for my internship practicum report. I learned a couple more differences between the Gamma Knife and CyberKnife and learned who the "big players" were in the evolution of radiosurgery.

November 22 & 23, 2007

Thanksgiving Holiday.

November 26, 2007

Betsy and I had a meeting to clarify what I need to do for this IRB submission and we reviewed the previous project summary form. I have a much better idea of what I need to do to this form. I finished the informed consent form for the new prostate protocol today. I think it is important to do this first because once Dr. Berger approves it, I need to send it to the sponsor for approval. Once the sponsor approves of it, I can submit it to the IRB. I handed a copy to Dr. Berger for him to review and sent an electronic version to Betsy for her review.

November 27, 2007

I worked on the project summary form all day. On my way out, I stopped at BRI for a meeting with Betsy. She found several errors and areas that need revision on the informed consent document. Dr. Berger has not gone over his copy yet.

November 28, 2007

I worked on the project summary form all day. I predict it will be finished tomorrow though. I also corresponded with the sponsor on a few questions I had.

The Radiosurgery Center had a State Inspector visit today. Chuck Lazzare, the Radiation Safety Officer, thought it would be best for me to stay away from the Radiosurgery Center today. I complied, so do not know if Dr. Berger has reviewed the informed consent document. I was able to contact his medical assistant to set up a budget meeting for this new trial with Betsy.

November 29, 2007

I had my weekly meeting with Betsy. She clarified a few questions I had, and told me what to do to prepare for the budget meeting. I finished the IRB Form 1, Project Summary today and took it to the Radiosurgery Center for Dr. Berger's review. He was busy seeing patients and asked that I return later. When I returned, he was still too busy and suggested I set up a meeting through his medical assistant. We are scheduled to meet at 9:00 AM tomorrow to go over the informed consent and project summary. I also began revising the informed consent based off of Betsy's editing suggestions.

November 30, 2007

This mornings meeting with Dr. Berger was short, but we finished reviewing the new prostate consent form. I plan to go back later in the day to review the project summary. I finished editing Dr. Berger's and Betsy's changes to the informed consent and corresponded with the sponsor to ask the last few questions and where to send the consent for review. She responded quickly and I was able to send the informed consent

to the sponsor. I was told to expect a turnover of 2 business days for their review. I have a few more IRB forms to complete before the submission.

While I was waiting for Dr. Berger's schedule to clear up, I contacted the Radiation Safety Committee to get details on their submission process. Since the new protocol involves CT scans and radiation therapy, the Radiation Safety Committee must also approve of the study. I also created the contact information attachment that the IRB requires for study personnel as well as filled out the Financial Disclosure Forms for each person.

December 3, 2007

Since I had ended last Friday waiting for e-mail responses from the sponsor and the Radiation Safety Committee, they were waiting in my inbox this morning. I received the informed consent from the sponsor, and made their suggested corrections. I also began compiling a packet for the Radiation Safety Committee. I have to submit to them, the project summary, an informed consent, and an application with signatures. I collected signatures from Dr. Berger and Dr. Scott, and had planned to turn it in at the end of the day.

I also had the opportunity to review the project summary with Dr. Berger. I made his corrections earlier in the day. I received Betsy's corrections in the afternoon, but was not able to complete them in time to submit it to the Radiation Safety Committee like I had planned.

I also contacted HealthTexas about the information sheets I drafted. Dr. Berger said that he would contact HealthTexas to get them approved and published, but he has

not. I took it upon myself to contact them and found the appropriate person to help guide me through the process.

December 4, 2007

I finished editing Betsy's corrections to the project summary application. Today was also an online treatment plan training session for the new prostate protocol. I thought it started at 9, but when I tried to log in, I realized it was scheduled for 9:00 AM Pacific Time! Fortunately, my time zone (Central Time) is 2 hours in the future than Pacific Time. I will try to be more aware of the sponsor's time zone from now on. I had forgotten that they are on a different schedule.

Today at the Radiosurgery Center one of the lung trial subjects had a 2 year follow-up. I had to make sure that the subject received the questionnaires and that Dr. Berger dictated certain things in his progress notes.

After lunch, I decided to hand deliver the Radiation Safety Committee application, because it would get there faster than inter-department mail. I checked the Baylor map, and the only building on Elm Street is the Main Street Annex. That building was locked and I realized that the address was in the 3800s and I needed to be in 2600s. Since it was nice weather outside, I decided to walk it instead of driving there. I had no idea that I was going into Deep Ellum though. I just learned that Deep Ellum is a twist on "deep Elm Street." I met a friendly homeless person and saw some interesting shops and bars on my way. At first, I was mildly frightened of Deep Ellum, because I am a small person walking alone in a "high crime" area. It wasn't so bad, but I would not do it again without daylight. I did take note of the shops and restaurants and will have to come back

one day to try them. As I left my destination, I saw the Baylor bus outside but did not catch it. I found a less shady path back to Baylor, and finished my day responding to emails.

December 5, 2007

This morning Dr. Berger, Betsy, and I met for a budgeting meeting. This meeting was to determine which procedures where "standard of care." Procedures that are not considered "standard of care" get billed to the sponsor.

After the meeting, Betsy gave me a list of documents I need to include in the IRB submission. Our goal is to make the Dec. 10th IRB pre-review deadline. Before the meeting, Dr. Berger sent me an email with a few corrections to make on the project summary. I had made those changes and returned the final version for him to sign. I also contacted Benny Bolin to determine if he is the appropriate administrator to approve the project summary.

December 6, 2007

Sick.

December 7, 2007

Today I attended the class, "Ensuring Success in the Informed Consent Process: An Interactive Workshop for Research Coordinators." It was taught by Barbara Richardson from MedTrials. She kept my attention by asking questions to keep us focused instead of an entire day of lecture. We went over the required elements of an informed consent document and how to ensure that the subject comprehends the material. One of the main themes discussed was that coercion does not allow for an effective

informed consent process. Most subjects just assume that a trial is safe, when in all reality, it is not. This is one key idea that coordinators or PI's must make clear to potential subjects. The class also discussed how to respond to an FDA Form 483 (warning letter.) The response should address the problem, and include the problems extent, how it happened, a plan to fix it, and any supporting documents. Also, it is a good idea to send the response to the sponsor before sending it to the FDA.

After class, I worked on the editing suggestions from the Radiation Safety Committee. This clinical trial will have to be approved by the full committee, which meets January 11, 2008.

December 10, 2007

Today was the IRB pre-review deadline. I attempted to get everything in the morning, but Dr. Berger was too busy to get to me. I had to run around campus collecting signatures from everyone else involved in the study too, which kept me occupied. I tried all day to meet with Dr. Berger, but he had several meetings and patient today. Finally, around 4:00 PM he was available. This put me in a bad position, and I worried that I would not be able to make the 5:00 PM deadline. Once I got to his office, there was a line of 4 people trying to talk with him. Fortunately, Dr. Scott and Dr. O'Connor let me go ahead of them.

Dr. Berger did not realize that today was a deadline. I didn't think I needed to tell him, since everything was ready to go last week. All I needed was his signatures. I asked for the project summary IRB form, and he claimed that I never gave it to him. Luckily, I had an extra copy with me. He wanted to review it again, and found minor

spelling errors he wanted corrected before signing it. I rushed back to the Clinical Trials Office to fix it and rushed back down. The doors were locked, but Hahn saw me to let me back to his office. When I got back, he had found his copy of the project summary. I hurried to BRI and turned in the IRB submission by 5:00 PM.

December 11, 2007

This morning Betsy and I had our weekly meeting. After the meeting, she told me about a research group that needed help today. She took me to meet Jennifer Thomas, a research manager working with diabetes and weight loss. Today on the 12 o'clock news, there was going to be a news story about their research, and they were expecting a high volume of people to call for more information. Jennifer asked me to return after lunch to help with these calls.

When I returned, Jennifer had me take calls off of their hotline and put the information left on the messages in a database. I assume the news story aired around 12:20, because the messages started a couple minutes after. I worked for 4 hours straight, screened over 180 messages, and only got to the messages left at 12:30. Jennifer and a couple of other people planned to take more messages off the hotline later that night. There was also going to be another airing of the news story at 5:00, but it did not air for some reason.

December 12, 2007

I reported to Jennifer in the morning to see if they still needed help. They did, but wanted me to come back tomorrow to help. I decided to work on the renal protocol the rest of the day. Dr. Berger had said he would go through the older version and the newer

version to find the differences, but has not. I decided to go ahead and find them, so I can get going on the IRB forms. I found 3 differences, but could not get a hold of him to discuss these differences.

December 13, 2007

I received an email from Jeff Fiedler, the physicist at the Radiosurgery Center this morning. He was asking for the names of the clinical trials in which the Radiosurgery Center was participating. I gave him the list of Dr. Berger's studies, but realized that I was not sure if Dr. Giller had any studies.

I was able to meet with Dr. Berger today to discuss the protocol differences. They are minor changes, but he would like me to make those changes on the current protocol and get it going through the IRB. I asked him to send me an electronic version of the protocol, and sent an email reminder.

I also returned to Jennifer's office to help with their studies. There were new messages left on the hotline, so I was asked to take them off and enter them into the database. There were about 30 messages, which seemed like a small feat after last Tuesday.

December 14, 2007

Again, I returned to Jennifer's office to help with the calls. The messages that were taken off the hotline were written on paper, and I would transfer them to the database. Once I had finished, everyone was eating pizza in the break room, and I was invited to eat also.

I also talked with Jeff about the studies today. He needed the names so the Radiosurgery Center would be properly charged. Betsy wanted to know if this charge needed to be included in the new prostate protocol's study budget. It did not need to be included.

Elizabeth Cothran, the IRB director, sent me her edits for this new protocol, and I worked on them. There was not many, so once I was finished, I took them to Dr. Berger for approval. He did. Now I am just waiting on administrator signatures.

BUMC and BRI both had their Christmas parties at the end of the day.

December 17, 2007

I prepared for the marketing meeting with HealthTexas today. I met Pam Zippi, who does marketing for HealthTexas, and Carolyn Adelman, who does marketing for Baylor. The meeting discussion was over the next marketing meeting and who should attend. At the end of the meeting, we discussed how the prostate handout and protocol summaries should look like. Dr. Berger wants a certain "look," but he was very vague on his expectations. I can't wait to see how Carolyn will present the material. After the meeting, I sent Carolyn the handouts electronically.

December 18, 2007

After talking with Dr. Berger about his renal trial protocol changes, I brought up how the protocol summary that I sent to Carolyn would have to be changed as well. This also reminded me that the IRB number would not be the same for the prostate trial protocol summary. I quickly emailed Carolyn about the changes and not to work on

those two protocol summaries until the changes are approved by the IRB. Thankfully, she had not worked on them yet.

I also went around to the administrator assistants to bug them about the IRB forms that I am waiting to collect. I asked Mary how to do this, and she said to start up a conversation with them to get on their good sides. So I asked them about their holiday plans, where they are from, and how they ended up in Texas. After a while, I smoothly asked about the IRB forms, and successfully acquired one. The other one was not ready yet, but the assistant gave me the administrator's office number to leave a message. I decided to email instead. It should be ready by Thursday AM.

I also talked to Dr. Berger about the renal protocol changes. I can't change the protocol until he sends me the electronic version. Originally, he sent me the PDF because he could not find the word document. He admitted that he knew I would not be able to do anything with it. I can't understand why he would do that. I also blocked off his schedule during the IRB meeting on January 3.

December 19, 2007

I compiled the IRB paperwork for the submission. There must be 3 copies of each item, 1 copy highlighted, only 1 staple per packet, and several other rules that I must follow. It takes a while to compile all the copies of each item. I will have to organize them once I get my last administrator signature, but as for now, I have the right number of copies of everything else. I read the submission instructions and plan to have it all ready tomorrow.

December 20, 2007

This morning I had my weekly meeting with Betsy. We discussed my thesis and the upcoming IRB meeting. I also picked up the signature page for the project summary IRB form. This was the last piece to make the IRB submission complete. After organizing all the IRB documents into "packets," I turned it in to BRI. The remainder of the day was spent on my thesis.

December 21, 2007

Today I responded to emails. Also there was confusion on some paperwork that I submitted, so I spent the remainder of the day straightening it out. Although I had turned it in to the appropriate office, the wrong person ended up with it. By the end of the day, I was told that my file had been located, and that it would be processed soon. I also gathered more materials for my thesis.

December 24, 2007

Christmas Eve

December 25, 2007

Christmas

December 26, 2007

I worked on my thesis today.

December 27, 2007

I worked on the renal protocol changes and my thesis today. I gave the protocol changes to Dr. Berger for him to review as well as the Form 7. I need to turn that in by

Friday next week. We also talked about an email we received about the prostate handout and lung protocol summary.

December 28, 2007

I worked on my thesis today.

December 31, 2007

New Years Eve

January 1, 2008

New Years Day

January 2, 2008

I worked on my thesis today. I had a few emails to respond to as well.

January 3, 2008

This morning I had my weekly meeting with Betsy. We talked about the upcoming IRB meeting and processing time of expedited IRB protocol changes. I was under the impression that the renal protocol changes had to be submitted by the IRB copy deadline, but it actually gets processed whenever the IRB receives it. I hope to get the renal protocol changes to the IRB soon.

I also attended today's IRB meeting. Our new prostate protocol was under review today. I sent a reminder email to Dr. Berger about it in the morning. It was a good thing, because he had forgotten about it. He spent the remainder of the morning reviewing literature and the protocol, just in case the IRB had any questions. Fortunately, there were none. It sounded like it would be accepted pending minor changes to the consent form. Before the meeting, Dr. Berger showed me a typo in the IRB project summary as

well as an inconsistency in the section on eligibility. We asked the IRB what to do about it, and were told, "If the project summary is approved with minor changes, then fix it in the new submission. If the project summary is approved without changes, then submit a Form 7." After the IRB discussed and reviewed our submission, Dr. Berger and I had to leave the room so the IRB could vote. Once the IRB voted, I was invited to come back to the meeting, but Dr. Berger had to get back to treating patients.

Following the IRB meeting, I went to Betsy's office to work on the prostate trial budget. After taking out the dosimetrist's, physicist's, and a large amount of Dr. Berger's time, the study budget became closer to what the sponsor wanted to pay, but still over. Lori Taccino, who works in the Office of Sponsored Research, will negotiate with the sponsor on budget. Hopefully everything will go through nicely.

After all these meetings, I had to run to the Department of Public Safety to get a change in my badge. I was recently granted access to the Radiosurgery Suite and needed this change reflected on my badge. It will be nice not having to disrupt the busy nurses to let me through to talk to Dr. Berger.

January 4, 2008

Today's major event was turning in the renal protocol change into the IRB. I had given it to Dr. Berger last week for him to review. I received an email from him earlier in the week letting me know that he wanted to change a few things. We went over those changes today at the end of the day. After making the necessary changes, Dr. Berger approved the protocol and IRB form, by signing them. I turned the forms into the IRB 1 minute till 5:00 PM.

January 7, 2008

I thought that I would be helping out dermatology today, but I never heard from them. I worked on my thesis instead.

January 8, 2008

Nanette needed some information about Dr. Berger's trials. She heard about a story being published in one of the Baylor publications and is concerned that it may need IRB approval. I had the opportunity to talk with Dr. Berger about this, and he did not know of any story. He suggested asking Carolyn Adelman in Baylor marketing. I emailed, and she quickly responded with a Gamma Knife story. I responded to Nanette, and after I sent it, I had another email from Carolyn. She said that they are working on a story currently, and will send it to Nanette once it is finished. I forwarded that email.

I also had a chance to talk with Dr. Berger about what I will be doing for the remainder of the internship. He would like me to make sure everything is in place for the prostate trial before I leave.

January 9, 2008

I had my weekly meeting with Betsy. This morning, we were informed that the sponsor of the new prostate trial will not negotiate on budget. Dr. Berger really wants to do this study because it will add credibility to the Radiosurgery Center and the procedure. I am really helping out on this study by not getting paid. If I were not here, Dr. Berger would have to pay a research coordinator or manager to file the submission and to start up this study. With the sponsor's proposed budget, there is little money to pay for a

research coordinator's time. Most of the work for this study will go to Dr. Berger, his nurses, and the rest of his staff. A research coordinator will have to be used sparingly.

Also this morning, Carolyn Adelman forwarded the news story that will be published in the March issue of BaylorHealth Magazine. It mentions the prostate trial and therefore needs IRB approval. I worked on the Form 7 today and will drop it off at BRI on my way home from work.

Before lunch, Laurie Jones, a coordinator in the Clinical Trials Office, asked for some help on an IRB submission. It is a spine study. Mary helped me figure out which doctor is conducting the study. I will start on it tomorrow.

After lunch, I received an email from the sponsor of the lung trial. They wanted the newly updated Case Report Forms and my contact information. I went through the Case Report Form books, organized, went through patient charts, and looked at the most recent appointments. Unfortunately, there is nothing new to tell them since I last sent in Case Report Forms. I am expecting a phone call from the sponsor tomorrow to follow up on this email. One subject had to cancel the last appointment and is now past due. Another subject is due for a follow up very soon. I will remind the Radiosurgery Center about these patients to ensure that they get an appointment in the near future.

January 10, 2008

Today I helped out in dermatology. They are slightly understaffed right now and need any extra help they can get. At first, Mary deHaas was busy with patients, so I was told to review protocols. I spent the first 3 hours reading different protocols and informed consents. Once Mary was done with patients, I was given charts to

review. One of the sub-investigators is employed through Texas Dermatology, thus does not get paid through BRI. I had to review patient charts to see which visits she conducted so that the sub-investigator would be paid accordingly. About half way through the charts, I took a lunch break, and made sure to save my work. When I got back, somehow, my work had not saved, and I had to restart from scratch. Also, during lunch, my car got towed, so things were not going very well anyways. The remainder of the day was spent finishing the chart review.

January 11, 2008

This morning the dermatology department needed me early in the morning. Once I was there, I began another chart review for a different study to see how many visits the sub-investigator has conducted. That did not take very long, so the remainder of the morning was spent moving boxes and rearranging their storage space. After lunch, I worked on my thesis.

January 14, 2008

Today I worked on Laurie's IRB submission. I was having trouble finding information and had to ask Laurie for help. There are a few questions we will have to ask the sponsor to finish filling out the IRB Project Summary Form. This form took the entire day.

January 15, 2008

I attended the monthly clinical research coordinators meeting in the morning. Elizabeth Cothran, director of the IRB, presented and updated us on IRB news. Soon

Baylor will switch to an electronic IRB submission. This is exciting news because it will cut down on paper use.

After the meeting, I went to the Radiosurgery Center. Dr. Berger heard back about the new prostate protocol from the IRB, which requested changes to the consent form. One request was to explain the difference between standard external beam radiation and CyberKnife treatment. I did my best to explain it, but I knew Dr. Berger would give a better explanation. I waited for him to review the changes, but he was busy with patients. Since he did not have time for me, he said he would review it and have the changes by tomorrow.

The remainder of the day I worked on my thesis.

January 16, 2008

Today I went to Fort Worth for a meeting with Dr. Gwirtz and the current CRM students. It was an opportunity to ask questions about our theses. After the meeting, I went to the graduate office to go over previous students' theses. It was really helpful, and now I have a better idea on how to format mine.

After going over theses, I went to the library to check my Baylor email and voicemail. I had forgotten to tell Dr. Berger about my meeting in Fort Worth, and he was expecting me to submit the informed consent changes. I rushed back to Dallas, changed the consent form, changed it again, and then submitted it to the IRB.

January 17, 2008

I had my weekly meeting with Betsy. After the meeting, I went to the Radiosurgery Center. One of the subjects on the lung trial had an appointment on

Wednesday, but was not given the follow-up questionnaires. I went through the patient record to find the subject's address to mail off the questionnaires. I did not know that this could be done, so I went through the remaining subject's charts to make sure everything was up to date. One subject had not returned for a follow-up, so I took note of the subject's address. I asked Edith in the Radiosurgery Center about postage paid return envelopes. The Radiosurgery Center does not have any. Mary Sams had a site initiation today and was busy, so I was not able to ask her about return postage. I was not comfortable sending the questionnaires without return postage, so I decided to wait on sending them. The remainder of my day was spent on my thesis.

January 18, 2008

I asked Mary about return postage today. She called around and found out that Patricia Phipps has postage paid return envelopes. I created letters for the 2 subjects explaining the contents of the letters and to please complete the questionnaires and return them in the postage paid envelope. I was going to use a post-it note, but realized a letter would be more professional. I traveled to BRI to pick up the envelopes in Patricia Phipps office. She requested I write "Attn:Angel Camarena" on the return envelopes so she could send them my way when they return. I also worked on my thesis today.

January 21, 2008

This morning I worked on my thesis. In the afternoon, I worked on Laurie's IRB submission. I had finished the Form 1, but did not have all the information to fill in several blanks. I sent it to Laurie to review and to guide me on where to find the missing information. I also began the Informed Consent document today.

January 22, 2008

This morning I worked on my thesis. In the afternoon, I worked on Laurie's IRB submission. I almost finished the Informed Consent document, but had to skip a couple sections because I was missing information. I did finish the Spanish Short Form Consent. I emailed Laurie to get help with the missing information.

January 23, 2008

I finished the "Scientific Validity" Form for Laurie's IRB submission today. She forwarded my questions to the sponsor and received a rapid response. I was able to complete the Informed Consent Document and almost the Form 1. It needs to be submitted to the radiation safety committee. They will be able to tell us the amount of radiation subjects will be exposed to during x-rays and MRIs. I also do not know who the Baylor Administrator will be to approve this study. Lastly some sort of study procedure happens on the 6th floor of the Truett building. I was not able to list it in the Form 1. Except for these minor missing pieces, the Form 1 is almost complete, and should be ready for submission soon. I was able to meet up with Lucy to talk about the thesis and defense process. I also worked on my thesis for a couple hours today.

January 24, 2008

Mary deHaas asked me to help out in dermatology today. I created a potential subject database. I used screen fail forms, phone messages, and patient referrals to gather contact information. Being able to pull potential subjects from a database should help the department with subject enrollment in the future. Patient names are accompanied by their

phone numbers, date of birth, research interest, address, and if given, e-mail address. I also worked on my thesis.

January 25, 2008

I had my weekly meeting with Betsy this morning. I also planned a meeting with the Radiosurgery Center staff, Betsy, and me to discuss how to manage this study with the fewest coordinator hours. I helped Mary in dermatology again today. I was there for about an hour before she had time to give me something to do. When I was ready to leave to work on my thesis, she gave me a task. She wanted me to create a timesheet in Excel for her employees. The current timesheet is in paper format, and the weekly totals must be added manually. I created a timesheet in excel that automatically subtotals time for each week of the two week time period, and a grand total of hours worked. In the afternoon, I worked on my thesis.

January 28, 2008

I worked on my thesis all day.

January 29, 2008

This morning was the site initiation meeting at Baylor Institute for Immunology Research. It was divided into 2 parts. I stayed for the first morning session. The study is a phase II, randomized trial of a dendritic cell vaccine to treat melanoma. The first session went over the scientific overview of how the vaccine works, the clinical overview of how people have responded as a phase I trial, and a statistical overview of how the data will be analyzed. The second session was for the study staff, and went over

apheresis/blood product shipment procedures, vaccine shipment procedures, and monitoring of the clinical trial. I did not stay for the second session.

After this meeting, I went to the Clinical Trials Office to work on IRB forms. I have to close out the old prostate CyberKnife study, since the new one is replacing it. Dr. Berger also has a continuing review soon for the lung trial. I worked on those IRB forms as well. Hopefully, Dr. Berger will have time to sign off on them today. If not, tomorrow he does not see patients, and should have more time.

January 30, 2008

This morning I met with Dr. Berger to get signatures on IRB forms. Afterwards, I met Mary deHaas to help in dermatology. I created subject packets for a new psoriasis study that is beginning to enroll patients. There were several questionnaires, an informed consent, a notes page, a tax form, and BRI forms in each packet. Unfortunately, when I sent the packet through the copier, I assumed it automatically collated the packets for me. I collated 15 packets of 37 pages. Also that morning, the first patient was enrolling, and I observed the consent process and completion of the questionnaires. Dr. McCoy had to take part in the study paperwork as well, so while the subject was waiting in the exam room, we completed the questionnaires until he was able to fill out his portion. This study pays the subjects for each visit, and I have not worked with paying studies before. I was surprised to see that they had to fill out a tax form as part of the enrollment process. It was great to witness the consent and enrollment processes, since they are so different from the CyberKnife studies.

January 31, 2008

I worked on my thesis.

February 1, 2008

I worked on my thesis in the morning. In the afternoon, I visited Dr. Berger to find out if he responded to an email from BRI about the new prostate study contract. He responded while I was there, and we talked about a person that is interested in the lung CyberKnife study. I received contact information from someone whose mom has lung cancer. I tried to call today to see if I could help, but there was no response. I left a message saying that I will try again on Monday. This is the first time I have contacted someone with an interest in the CyberKnife studies. I am very fortunate to have made those patient information sheets detailing the study. It is understandable and summarizes the details of the study like eligibility and time commitment. I plan to use it as reference when I call again.

February 4, 2008

This morning I talked with a daughter of a potential research subject for the CyberKnife lung trial. I went through the inclusion and exclusion criteria with her and explained how the CyberKnife works. She also asked about how CyberKnife is different from Gamma Knife and traditional radiation therapy. I was able to tell her, but if I had been asked at the beginning of this internship, I would have had no idea! She was also trying to tell me that since this is a clinical trial, all expenses should be paid for by the study. I would have assumed this also, without experience in clinical research, but I had to explain that study procedures will have to be covered by the subject or the subject's

insurance. I was excited that I was able to answer all her questions, but referred her to the Radiosurgery Center to talk with Dr. Berger.

In the afternoon, I had my weekly meeting with Betsy. She answered several of my questions and approved my daily journal. Following this meeting was another meeting at the Radiosurgery Center. We met with the doctors and staff to go over the new prostate study. The staff informed us of past problems with study initiation, and I was given several tasks before my departure to help the study run smoothly.

February 5, 2008

I worked on my thesis and IRB forms for the CyberKnife studies. I closed out the old prostate study and added additional personnel to the lung study. Dr. Berger signed the close out form, but would not tell me why he would not sign the other form. He asked me come back tomorrow.

February 6, 2008

Today I worked on my thesis, CRFs for the lung study, and IRB forms. Again, Dr. Berger did not want to sign a form, but did sign the one adding personnel to the new prostate study. Mary came with me to the Radiosurgery Center to obtain the signatures. I also talked with the sponsor of the lung study today. I think they may have lost some data, so I will make copies of the data and send the copies.

February 7, 2008

I put the IRB continuing review packet together for the lung study. I had to create the financial disclosure forms for each person on the study, which are 7 people including me. I then had to distribute them to the appropriate people to obtain their signatures. I

collected 4 back today, and need the remaining 3 by Monday. It is not a difficult form to fill out, but looking up everyone's contact information took the most time. For this submission, I had to make 4 copies of the continuing review form, project summary, and informed consent. I also needed 3 copies of the protocol and formed all the documents into packets. This took the morning and most of the afternoon. The remainder of the afternoon was spent finishing up CRFs for the lung study. I completed them and dropped them at a Fed Ex box on my way home.

February 8, 2008

Today was another CRM student's defense in Fort Worth. I went back to UNTHSC to watch it and understand the process. Afterwards, I took care of work emails and mail messages. I also talked with Dr. Gwirtz about how to set up my defense. It is difficult coordinating with everyone, but I plan to have it set on Monday. After lunch, I returned to Dallas and picked up a Financial Disclosure form. My IRB submission is almost complete!

February 11, 2008

Today I returned back to UNTHSC to finish setting up my defense. While I was obtaining signatures, the power went out on campus. It extended my stay, but I was still able to return to Baylor in Dallas to pick up the financial disclosures and submit the continuing review to the IRB before the end of the day.

February 12, 2008

I was able to work on my thesis this morning. Dr. Berger saw a patient today that is eligible for the new prostate trial. Too bad the contract is not complete yet. Also, the

IRB contacted me because of some missing documents in the continuing review. I always forget about the Spanish Informed Consent. I delivered that to them in the afternoon.

February 13, 2008

This morning I was writing an email to Lori Taccino from the Office of Sponsored Research to find out about the prostate contract, when she emailed me to tell me it was ready. It was such a funny coincidence. I ran to BRI to pick it up, and tried to drop it off at the Radiosurgery Center, but Dr. Berger was not there in the morning. I gave it to his assistance and would check again in the afternoon. After lunch, I had a voicemail asking me to stop by the Radiosurgery Center and I did. I also talked with the sponsor about the site initiation visit. I am waiting on Dr. Berger to give a response. The remainder of the afternoon went to my thesis.

February 14, 2008

This morning I had my weekly meeting with Betsy. Her morning meetings ran a little late, so I accompanied her to her next meeting. During this meeting, I learned a new trick to use with the email program as well as what is new with the dendritic cell studies. We discussed the new prostate study contract and sponsor information. I worked on my thesis and replied to the sponsor of the lung trial and the prostate trial. For the lung trial, the sponsor had asked a few questions about study subjects that I researched in the Radiosurgery Center. One of the subjects is having insurance problems and can not come in for a follow up appointment until it is resolved. I was also just informed that one of the subjects did not make eligibility requirements, so should not be on the study. I will

soon get to learn what that process is like. The sponsor also asked about financial payments to make sure they were up to date. Mary told me who to contact about this, and I was able to respond with this information. Today is Valentine's Day as well as the end of my 6 month internship at Baylor. I will continue to work on the studies that I am involved with as needed, but will focus my time on completing my thesis and defense presentation.

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