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Dedication

I dedicate this paper to Dr. Robert Miller. He was a very caring and giving man who fought prostate cancer and passed on before his time.

Acknowledgements

Thank you Professor April Gardner for your endless proof readings, thoughts, and ideas; you have made writing this paper an enjoyable learning experience. I could not have done this project without you.

Table of Contents

Dedication.....	ii
Acknowledgements.....	iii
Table of Contents	iv
Background.....	1
Methods.....	4
Introduction.....	5
Literature Review.....	16
Conclusion	32
Tables	34
References.....	36
Abstract.....	48

Background

Prostate cancer is a well known disease that affects more than 2 million men in the United States according to the American Cancer Society ("American Cancer Society," 2010). In 2010, the ACS estimated that 217,730 new cases of prostate cancer will be diagnosed, and 32,050 men will die due to prostate cancer. It remains the second leading cause of cancer death in men in the United States ("American Cancer Society," 2010). Prostate cancer is an asymptomatic disease, but there are symptoms or side effects that are caused by each treatment option (Lev et al., 2009). These side effects, along with the increasing number of men living with this disease, have changed the definition regarding what is considered successful treatment.

Besides successful control of the disease, side effects are looked at closely with any prostate cancer treatment. The side effects differ depending on the treatment, but can range from pain, urinary retention, urethrorectal fistulas, and even perioperative mortality (Table 1). Impotence and incontinence are also side effects that have been important in defining successful treatment of prostate cancer because they can severely affect a patient's quality of life (QOL). The term trifecta is used to define the relationship of the cumulative outcomes of cancer control, continence, and potency following a radical prostatectomy and will be used to compare cryosurgery to other treatment options to see if cryosurgery is an acceptable treatment option for localized prostate cancer (Shikanov, Zorn, Zagaja, & Shalhav, 2009).

QOL issues like impotence and incontinence became important due to the increase and acceptance of prostate specific antigen (PSA) screening over the last decade (Bahn et al., 2002). PSA is a 33-kD androgen-regulated glycoprotein produced in the prostate gland, and the only tumor biomarker that is accepted for the detection, diagnosis, monitoring, and prognosis of prostate cancer (Goldman & Ausiello, 2008). PSA specificity is improved when PSA density,

which is defined as PSA value divided by prostate volume, is also used (Veneziano, Pavlica, Compagnone, & Martorana, 2005). This biomarker, along with the digital rectal exam, improves the detection of prostate cancer and reduces the death rate by 20% (Schroder et al., 2009).

Detecting prostate cancer at an earlier stage has made prostate cancer a more manageable disease because it has not yet spread outside of the prostate gland and is therefore considered localized. ("American Urological Association Foundation," 2008). Stage T1, nonpalpable disease, and stage T2, palpable disease, are both considered localized prostate cancer (Table 2).

The use of the Gleason score has also helped to predict the course of the disease ("American Urological Association Foundation," 2008). A pathologist determines a Gleason score by taking the sum of the two most common histologic patterns. A Gleason score less than 4 is considered well differentiated with a better outcome, and the scores increase with 5 to 7 being intermediate differentiation and scores 8 to 10 being poorly differentiated (Goldman & Ausiello, 2008). More localized treatment options for prostate cancer are now available due to the increasing diagnosis of localized prostate cancer and the ability to determine how well the disease can be managed.

The two most common treatment options have been radical prostatectomy and external beam radiotherapy. With the need to optimize the QOL of patients with prostate cancer, other treatment options have been investigated that are considered minimally invasive. Robotic radical prostatectomy, laparoscopic assisted radical prostatectomy, interstitial active surveillance, brachytherapy, and cryosurgery have all been found to be reliable treatment options; and high-intensity focused ultrasound is an option that is still being investigated with ongoing clinical trials (Long et al., 2001). It is important to know how cryosurgery compares to the other localized prostate cancer treatments because if it is shown to score higher within the trifecta

categories of cancer control, continence, and potency, then it is an option that should be offered to patients.

Methods

This review focused on cryosurgery as a reliable treatment option for localized prostate cancer. Search engines included Pubmed and CINAHL. Search terms included prostate cancer, prostate adenocarcinoma, cryosurgery, cryoablation, and third generation. Only articles that analyzed data using the third generation cryosurgery treatment technique were included. Articles that did not include third generation surgical technique were used for historical information only. Articles that did not separate data pertaining to primary verses salvage cryosurgery were not included.

Introduction

The prostate gland is located just anterior to the rectum and beneath the urinary bladder and supplies the liquid to the semen that helps to nourish and protect the sperm cells ("American Cancer Society," 2010). The prostate gland is also where testosterone is converted to dihydrotestosterone (DHT), the androgen responsible for the growth and development of the prostate gland and prostate cancer (Rosenberg, Froehner, Albala, & Miner, 2010). Proliferative inflammatory atrophy (PIA) is a precursor to prostate cancer thought to be caused by damage to the epithelium. This damage can arise due to inflammation, infection, or carcinogen exposure (Nelson, De Marzo, DeWeese, & Isaacs, 2004; Tindall & Rittmaster, 2008). If the damage to the epithelium is not corrected, there can be damage to the DNA and a change in the gene that cannot be repaired. The change in the gene will result in prostatic intraepithelial neoplasia (PIN) and localized prostate cancer (Nelson, et al., 2004; Rittmaster, 2008). Approximately 97% of these prostate tumors are adenocarcinomas (Holund, 1980).

Different risk factors are thought to be the cause of prostate cancer. Khan, Afaq, and Mukhtar (2010) discussed studies showing that obesity, processed meat, and total fat consumption can cause prostate cancer. Increasing age has been shown to be a factor with 50% of men older than 50 years having prostate cancer in autopsy studies (Holund, 1980). The last major factor is genetics. A male has a 2.57-fold lifetime risk of acquiring prostate cancer if he had a first degree relative with cancer. If there are more than two first degree relatives with prostate cancer, then there is an increase to a 5-fold lifetime risk (Zeegers, Jellema, & Ostrer, 2003).

The remainder of this introduction will define the treatment options available for localized prostate cancer, as well as discuss the advantages, disadvantages, and patient criteria

for each option. The treatment options include active surveillance, radical prostatectomy, robotic radical prostatectomy, laparoscopic assisted radical prostatectomy, high-intensity focused ultrasound, brachytherapy, external beam radiotherapy, and cryosurgery.

Active Surveillance

Active surveillance (AS) is an option for localized prostate cancer because 60% of prostate specific antigen-detected prostate cancers are overdiagnosed, meaning patients are diagnosed with a condition that will not continue on to cause any symptoms or death (Welch & Black, 2010). If the patient is only offered a curative approach, he will have increased morbidity and mortality associated with each treatment option. AS is a treatment protocol to help decrease that morbidity and mortality of prostate cancer. The protocol enables a patient to make the decision when to treat his prostate cancer. Treatment could be due to personal choice or if the cancer develops further during the surveillance time. Surveillance includes regular physical examinations, PSA measurement, and biopsy after one year and then three years following the diagnosis (Hayes et al., 2010). Unless the patient chooses to undergo intervention, the events that would trigger the patient to proceed with a curative surgery would be a Gleason score of 7 or greater or PSA doubling time (Singh, Trabulsi, & Gomella, 2010).

The advantage of AS is that there are no adverse effects as noted with the other treatment options. Van den Bergh, Roemeling, et al. (2009) and Klotz et al. (2010) report a 10 year prostate cancer specific survival rate of 100% and 97% respectively, so delaying treatment with AS does not increase mortality. AS was associated with the greatest quality-adjusted life expectancy (QALE) when compared to radical prostatectomy, intensity-modulated radiation therapy, and brachytherapy (Hayes, et al., 2010). QALE is an outcome measure that incorporates treatment complications, adverse effects, and quality-adjusted life-years (Hayes, et al., 2010).

Some of the disadvantages of AS include depression and anxiety due to the fact that this is not a cure and includes a need for increased biopsies (van den Bergh, Essink-Bot, et al., 2009).

This protocol requires that appropriate candidates are selected. Some of the criteria to predict the candidates with low risk prostate cancer that will likely benefit from AS include PSA density < 0.15ng/mL, PSA <10, clinical stage T2a or less, Gleason score 6 or less, and a life expectancy of less than 10 years (Bastian et al., 2009; Singh, et al., 2010).

Radical Prostatectomy

Radical prostatectomy (RP) is an invasive, open surgical procedure to remove the prostate gland with cure being the main goal. This procedure made much advancement over the last 100 years. There have been nine different surgical sites attempted with retropubic, suprapubic, transurethral, and perineal being the most popular (Sriprasad, Feneley, & Thompson, 2009). RP has become the gold standard for localized prostate cancer due to its many advantages. The biggest advantages are that the removed specimen can undergo pathologic staging and post-operatively the patient can have routine PSA testing. Following a RP, the patient is considered cured with a PSA level less than 0.2 ng/mL (Babaian et al., 2008). A definitive PSA level makes it easier to monitor for the return of prostate cancer and to assure the patient that all of the cancer has been removed. There are some disadvantages to RP which include a hospital stay, a visible incision, and invasiveness that can lead to higher morbidity and mortality (Zerbib, Zelefsky, Higano, & Carroll, 2008).

The increased morbidity and mortality that accompanies an invasive surgery is one reason there has been a movement to more minimally invasive procedure options that include laparoscopic radical prostatectomy (LARP) and robotic procedures. LARP is a surgical procedure that removes the prostate gland using a laparoscope and laparoscopic instruments

through multiple small incisions instead of one large incision (Schuessler, Schulam, Clayman, & Kavoussi, 1997). LARP is more criticized because it has a difficult learning curve and long operating times (Singh, et al., 2010). Advantages to LARP are that patients who had prior abdominal surgery, prior hormonal therapy, or are morbidly obese can still choose this as a treatment option (Eden, Chang, Gianduzzo, & Moon, 2006; Gonzalgo, Patil, Su, & Patel, 2008).

Robotic RP is another minimally invasive procedure performed with the da Vinci system. The da Vinci system is a robotic tower and remote console that is controlled by the surgeon outside of the surgical suite (Jamal, Patel, & Sooriakumaran, 2008). Robotic RP is shown to have decreased blood loss, shorter hospital stay, and faster convalescence compared to the traditional open RP (Zerbib, et al., 2008). The disadvantages are that the patient must have access to the da Vinci system, there is increased cost, and some insurances do not pay for the procedure if it is performed with robotics (Barbash & Glied, 2010).

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is another treatment option for localized prostate cancer. It is currently undergoing trials in the United States and considered an investigational treatment option. There are increasing studies in Europe that show it is an effective approach for patients that do not wish or are not suitable candidates to undergo other treatment options (Crouzet et al., 2010; Lukka et al., 2010). This procedure works by placing a transducer in the rectum that emits focused ultrasound waves to produce temperatures of 85 degrees centigrade at a specific focal point within the prostate gland (Gelet et al., 1993). The resulting temperature causes cellular disruption and coagulative necrosis at the focal point (Crouzet, et al., 2010).

Besides being an investigative treatment, other disadvantages to HIFU include that it is difficult to ablate the entire prostate and to treat anterior tumors (Marberger et al., 2008). Since 2000, the standard of care has been to perform a transurethral resection of the prostate (TURP) before the HIFU (Crouzet, et al., 2010; Vallancien, Prapotnich, Cathelineau, Baumert, & Rozet, 2004). Debulking the anterior and lateral parts of the prostate gland with TURP prior to HIFU enables the acoustic waves to ablate more of the prostate gland. This allows for better cancer control and decreases urinary complications because the patient will return to normal micturition sooner than without performing the TURP (Chaussy & Thuroff, 2003).

Advantages of HIFU are the ability to know if the treatment was effective within three to six months and if the treatment was not effective, the ability to either repeat the procedure or choose a different treatment option (Blana, Walter, Rogenhofer, & Wieland, 2004; Crouzet, et al., 2010). Since there are a limited number of randomized controlled studies involving this procedure, there is not certain patient criterion for when to consider this therapy. Most case series included only stage T1 or T2, a gland volume of less than 40 ml, no previous radical treatment for prostate cancer, and a life expectancy of less than 10 years (Crouzet, et al., 2010; Uchida et al., 2006).

Brachytherapy

Brachytherapy (BT) is a type of radiation treatment that was first attempted over 100 years ago (Aronowitz, 2008). Before 1951, radon implants were used until sources were unavailable during a procedure and a urologist substituted colloidal gold (Kerr, Flocks, Elkins, & Culp, 1953). The substitution was a success and made radiogold the first isotope seed used. Advancements in the procedure have led to the use of iodine-125 and palladium-103 isotope seeds as standard of care today. The isotope seeds are permanently implanted in the prostate

gland using transrectal ultrasound imaging. Since the implant is permanent, the treatment can take its course over weeks to months by emitting either low-dose or high-dose rate energy waves. Therefore the radiation dose is administered once instead of over multiple sessions (Gonzalvo, et al., 2008; Horwitz, Uzzo, Miller, & Theodorescu, 2003). Improvements in imaging have helped radiologists to accurately place the isotope seeds, which results in better outcomes for the patient and less complications.

The advantages of BT are that it is a convenient procedure because the patient undergoes the administration of the radiation one time, and it can be used to treat adenocarcinomas of the anterior prostate. There is also the advantage that the radiologist can safely use a greater dose of radiation because there is less scatter, and it is considered low-energy radiation. This allows for a better cancer control rate (Zerbib, et al., 2008). Some of the disadvantages of this procedure are that BT is not a treatment option for prostate glands larger than 50 to 60 cm³, if the patient has undergone a previous TURP, or if the patient has voiding symptoms such as irritation or obstruction (Gonzalvo, et al., 2008).

External Beam Radiotherapy

External beam radiotherapy (EBRT) is another type of radiation treatment. This treatment option has advanced from the four-field conformal radiotherapy (CRT4) to the standard of care used today which includes two different options for administering the radiotherapy: 3-dimensional conformal therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) (Namiki, Ishidoya, Kawamura, Tochigi, & Arai, 2010). This technology helps radiologists to increase the accuracy when delivering the radiation dose, which results in a decreased risk to the surrounding tissue. These advancements have also allowed the radiation

dose to increase from 68.5 gray (Gy) to the higher doses used today of ≤ 79 Gy and 81 Gy (Donnelly et al., 2010; Singh, et al., 2010).

The main advantage of this procedure is that it is an option for more advanced adenocarcinomas without the increased risk of morbidity from surgery. Namiki, et al. (2010) found this treatment option was chosen by patients who were older and had more comorbidities and therefore would have had an increased risk of morbidity with surgery. Disadvantages of this procedure are the inconvenience of having radiotherapy 5 days a week for at least 7 to 9 weeks depending on the radiation dose, and that radiation makes it more difficult to undergo a secondary therapy if there is a treatment failure (Zerbib, et al., 2008; Zietman et al., 2005). Zerbib, et al. (2008) discussed that 20% to 50% of patients experience rectal morbidity and/or urinary symptoms that require the use of medication. Rectal morbidity includes discomfort, tenesmus, diarrhea, and incontinence. Urinary symptoms include frequency, nocturia, urgency, dysuria, and incontinence. Both the rectal and urinary symptoms appear most commonly during the third week of treatment and usually resolve within days to weeks, but the symptoms can be permanent. EBRT is contraindicated if the patient has had previous radiotherapy, inflammatory bowel disease, or urinary obstructive symptoms (Zerbib, et al., 2008).

Cryosurgery

Cryosurgery is defined as the therapeutic use of cold and is a form of cryotherapy. Cryosurgery is a minimally invasive procedure that uses cryoprobes to target specific tissue, like the prostate gland, and causes necrosis by administering below freezing temperatures through the cryoprobes (Gage, 1998). The necrosis occurs due to both immediate and delayed effects. The immediate effect is due to the cooling and warming of the cells which is followed by the delayed effect of vascular stasis (Gage & Baust, 1998). Larson, Robertson, Corica, and Bostwick (2000)

found that a temperature below -40 degrees Celsius is the goal for prostate cancer when using the double freeze technique. The double freeze technique is used because it results in a significantly larger area of necrosis.

James Arnott first described the benefits of this type of treatment in 1845, but it was not until the 1960s that Soanes and Gonder first used it to treat prostate cancer using the perineal approach (Gage, 1998; Soanes & Gonder, 1968). Cryosurgery was then largely abandoned due to high morbidity that included incontinence, sloughing and rectourethral fistulas (Han et al., 2003). In 1988, Onik et al. (1993) reintroduced cryosurgery by incorporating the use of 2-dimensional transrectal ultrasound (TRUS). TRUS allowed for real time monitoring during the procedure which resulted in decreased complications. The procedure was also performed percutaneously with multiple probes for the first time instead of the previous perineal approach or with a single cryoprobe.

There was still great hesitancy to use the procedure as a treatment option because in the mid 1990s, there was another increase in morbidity with the use of urethral warmers that were not approved by the United States Food and Drug Administration (Ellis, 2002). Urethral warmers are devices that are inserted into the urethral meatus by way of the bladder, and their purpose is to protect the urethra. The urethral warmers help to maintain the normal temperature of the urethra when the prostate is frozen (Cohen & Miller, 1994) The lack of an acceptable urethral warmer caused urethral sloughing due to the inability to prevent the freezing of the urethra. The necrotic tissue from the urethra led to obstruction and urinary retention. This resulted in a high rate of dissatisfaction because patients would then have to undergo catheterization (Cohen & Miller, 1994). Cohen and Miller (1994) had a role in decreasing this

morbidity with the introduction of a new urethral warmer that was approved by the United States Food and Drug Administration.

Cryosurgery for prostate cancer has made other great strides due to technological advancements that include temperature monitoring with thermocouples by Wong, Chinn, Chinn, Chinn, and Tom (1997), the use of liquid nitrogen in the second generation system to gas driven probes in the third generation system, and the move from 2-dimensional to 3-dimensional TRUS (Chin, Downey, Mulligan, & Fenster, 1998; Wong, et al., 1997). The third generation systems use the Joule-Thompson effect, allowing argon gas to freeze the tissue and helium gas to thaw the tissue (Han & Beldegrun, 2004). This transition from liquid to gas also allows the use of smaller diameter probes which in turn gives the surgeon the ability to insert more probes. Lee et al. (1999) showed that the 8-cryoprobe system was superior to the previous 5 probe system. All the technological advancements have proven to be beneficial for cryosurgery. In 1999 cryosurgery became accepted by Medicare for reimbursement and in 1996 the American Urological Association (AUA) removed the investigational label (Han & Beldegrun, 2004; Shinohara, 2003).

Advantages of cryosurgery include that it can be an option for low-, intermediate-, and high-risk patients, patients with a history of pelvic surgery, and patients that have multiple comorbidities including obesity. Cryosurgery also has a shorter hospital stay than open radical prostatectomy and has small blood loss (Babaian, et al., 2008; Ellis, 2002). Onik et al. (1993) showed that the huge advantage cryosurgery has over the other treatment options is the ability to repeat the procedure without an increase in morbidity. The major disadvantage is that immediately following the procedure, 100% of the patients will experience erectile dysfunction due to freezing of the neurovascular bundle (Babaian, et al., 2008). Some patients have a return

of function within months to years of the procedure. Other disadvantages include that there are less reliable results in glands greater than 40 grams, previous TURP is a contraindication for the procedure, there are few long term studies, and there is not an established definition on what the post operative PSA value should be to indicate treatment success (Babaian, et al., 2008; Hubosky et al., 2007).

Throughout the literature, many different definitions of PSA value were used to indicate treatment success or failure for cryosurgery. Multiple authors used PSA nadir of >0.1 ng/mL, a PSA threshold of >0.4 ng/mL, or the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of three consecutive rises in PSA as definitions of failure (Ellis, Manny, & Rewcastle, 2007; Hubosky, et al., 2007). Lambert, Bolte, Masson, and Katz (2007) used their own criteria to define biochemical recurrence as PSA nadir of greater than 50% of the PSA level before treatment or a PSA nadir plus 2 ng/mL. Bahn et al. (2002) used yet another definition of 0.5 ng/mL and 1.0 ng/mL as the PSA cutoff to define biochemical relapse. All of these definitions make it difficult to analyze retrospective studies and to compare cryosurgery to the other treatment options.

There are many treatment options available to patients with prostate cancer. Each of these treatment options has disadvantages and advantages. It is important to understand how each of these options will affect the patient's QOL so that the best care can be given to the patient. The advancement in technology has allowed cryosurgery to be accepted as a treatment option for prostate cancer, but there have been only two randomized trials comparing cryosurgery to other treatment options. This paper will look at the randomized trials, prospective trials, and retrospective trials to compare third generation cryosurgery to the other treatment

options in order to determine if cryosurgery is an acceptable treatment option for localized prostate cancer.

Literature Review

Primary Cryosurgery Patient Criteria

As with any other procedure, patient selection for cryosurgery is very important. Cryosurgery was recognized by the AUA as a reliable treatment option in 1996, but it was not until 2008 that the AUA published patient criteria for cryosurgery. The criteria included documented prostate cancer confined to the prostate gland, appropriate neoadjuvant or concomitant hormonal therapy if the prostate gland is greater than 40 grams, and a contraindication of having a previous TURP (Babaian, et al., 2008). Since cryosurgery is a minimally invasive surgery with very low morbidity, there are few patients that are excluded from choosing this as a treatment option. Cryosurgery can be a treatment option for low-, intermediate-, and high-risk patients. The optimal patient with the best outcome is one that undergoes the procedure when he is stratified as low risk (Shinohara, 2003).

The way the patients were stratified varied among the articles. Most of the articles reviewed were stratified according to D'Amico et al. (2003). If the patient had a PSA level of ≤ 10 ng/mL, Gleason score of 7, or 2002 American Joint Committee on Cancer (AJCC) category of T2a or less, they were considered low risk. If the patient had a PSA level between 10 ng/mL and 20 ng/mL PSA level, a Gleason score greater than 7 or a 2002 AJCC category greater than T2a; they were considered intermediate risk. High-risk patient definitions varied among the studies. D'Amico et al. (2003) considered a high-risk patient one that had a PSA level greater than 20 ng/mL, Gleason score of 8-10, or 2002 AJCC category of T2c disease. Bahn et al. (2002) and Long et al. (2001) considered a patient having any two of three items from the intermediate list as a high-risk patient. Ellis (2002) and Cytron, Paz, Kravchick, Shumalinski, and Moore (2003) did not use the D'Amico et al. stratification and instead divided the patients

into favorable and unfavorable risk groups. Patients with a PSA level <10 ng/mL, a Gleason score ≤ 6 , and \leq T2a stage were considered favorable with all other patients being considered unfavorable. Cresswell, Asterling, Chaudhary, Sheikh, and Greene (2006) also used a different way to stratify patients by placing patients with a PSA level <10 ng/mL and Gleason score ≤ 7 into the low-risk category and patients with a PSA level ≥ 10 ng/mL and Gleason score > 7 into the high-risk category. Prepelica, Okeke, Murphy, and Katz (2005) and El Hayek et al. (2008) also separated the patients into low and high-risk categories with high-risk patients defined as PSA level ≥ 10 ng/mL and Gleason score ≥ 8 and all other patients were considered low risk.

Cancer Control Using PSA

Cryosurgery is considered a curative treatment option, and surgeons use PSA as one way to determine if the procedure was successful. There have been two randomized trials with cryosurgery, and both of them are in comparison to external beam radiotherapy (EBRT). Chin et al. (2008) were the first authors to report a randomized trial with a mean follow-up of 37 months. There were 31 patients in the EBRT arm and 33 patients in the cryosurgery arm. Using the ASTRO definition of three consecutive increases in the serum PSA, 64% (21) and 45% (14) of the cryosurgery and the EBRT arms respectively were considered biochemical failures. There was no statistical difference in overall survival at four years between the cryosurgery arm and the EBRT arm. They found the 4-year biochemical disease-free survival was statistically significant with the cryosurgery arm having a biochemical disease-free survival rate of 13% (4) and the EBRT arm having a rate of 47% (15) using the ASTRO definition of three consecutive increases in the serum PSA following nadir as failure ($p=.0277$). Chin et al. (2008) also reported that during the study, a total of 6 patients died. Two patients died from prostate cancer, one from each arm of the study, and four from unrelated causes.

Chin et al. (2008) concluded that cryosurgery was considered suboptimal in the treatment of local prostate cancer, but there were many issues with the trial. They were only able to accrue 64 of the planned 150 patients for the study due to the changing standard of care after writing the trial protocol. The trial's EBRT protocol used 66 Gy, compared to 79-81 Gy used today. The study does not state the dates of the trial, but the author did state in e-mail communication that the study was done with third generation cryosurgery.

The longest study to date is a randomized trial comparing EBRT to cryosurgery by Donnelly et al. (2010) and Robinson et al. (2009) with a median follow-up of 100 months. These two articles analyzed the same patient data, but Donnelly et al. (2010) focused on disease progression and survival, whereas Robinson et al. (2009) focused on quality of life issues. There were 122 patients in each arm of the trial, but due to patients declining the treatment option randomized for them, 114 patients were analyzed for the EBRT arm and 117 patients were analyzed for the cryosurgery arm. The EBRT radiation dose changed with the standard of care over the course of the study. In 1997, at the start of the study, the radiation dose was 68 Gy, then was increased to 70 Gy in 2000, and finally increased to 73.5 Gy in 2002. All cryosurgery procedures were performed with the third generation technique. The authors allowed patients with early PSA failure in the cryosurgery arm to undergo a second cryosurgery procedure without considering the patient a failure because of the advantage that cryosurgery can be repeated. Only one patient underwent a second cryosurgery procedure.

Donnelly et al. (2010) reported that at 36 months the cryosurgery arm had a failure rate of 17.1% (20) and the EBRT arm had a failure rate of 13.2% (15) using the definition of biochemical failure as a PSA nadir + 2 ng/mL. Using the definition of biochemical failure as 2 consecutive increases in PSA to a value >1.0 ng/mL, both arms had higher failure rates. The cryosurgery arm had a failure rate of 23.9% (28) and the EBRT arm had a failure rate of 23.7%

(27). The authors did not state if there was any statistical difference between the cryosurgery arm and the EBRT for failure rate at 36 months.

The failure rates at 60 months using the definition of biochemical failure as two consecutive increases in PSA to a value >1.0 ng/mL were 31% (37) and 37.7% (43) for the cryosurgery arm and the EBRT arm respectively. Using the definition of biochemical failure as a PSA nadir +2 ng/mL, the failure rates at 60 months were 25% (30) and 25.1% (29) for the cryosurgery arm and the EBRT arm respectively. The authors did not state if there was any statistical difference between the cryosurgery and the EBRT for the failure rate at 60 months.

The failure rates at 80 months using the definition of biochemical failure as two consecutive increases in PSA to a value >1.0 ng/mL, the cryosurgery arm had a failure rate of 33.2% (39) and the EBRT arm had a failure rate of 43.9% (50). Using the definition of biochemical failure as a PSA nadir +2 ng/mL at 80 months, the failure rates were 27% (32) and 31.7% (37) for the cryosurgery arm and the EBRT arm respectively. The authors stated that the results favored the cryosurgery arm at 80 months, but did not state if there was a statistical difference.

During the median 100 month follow-up, ten patients of the 244 total patients died from prostate cancer, with five patients from each arm of the study. The 5-year overall survival rates were not statistically different with rates of 89.7% (105) and 88.3% (101) in the cryosurgery and EBRT arms respectively ($p=.78$).

There were seven retrospective articles that only analyzed cryosurgery. Jones et al. (2008) performed a retrospective study using data that 27 physicians submitted to the COLD (Cryo On-Line Data) Registry. This included 1,198 consecutive patients with a mean follow-up of 24.4 months. Of the 1,198 patients, 112 patients had at least a 5-year follow-up with complete data. They found that 77.1% (87) had a 5-year biochemical disease free survival (bDFS) using the ASTRO definition of three consecutive increases in the PSA. Using the Phoenix definition of a nadir +2, the 5-year bDFS rate was 72.9% (82).

Hubosky et al. (2007) performed a retrospective study with 81 patients and a mean follow-up of 11 months. They analyzed data from 74 of the 81 patients and found that 82% (61) of the patients reached a PSA nadir of ≤ 0.1 ng/mL. Using the PSA threshold level 0.4 ng/mL and the ASTRO definition, the biochemical free rates were 70% (52) and 94% (70) respectively.

Prepelica et al. (2005) performed a retrospective study that included 65 patients and had a median follow-up of 35 months. They found that 83.3% (55) were considered free of biochemical recurrence using the ASTRO definition of three consecutive increases in the PSA level. They also found that two years after the cryosurgery procedure, 94.44% (62) and 80.55% (53) had a PSA nadir of < 4.0 ng/mL and < 1.0 ng/mL respectively.

Ellis (2002) performed a retrospective study that included 75 patients with a median follow-up of three months. They found that 84% (63) had a PSA nadir of < 0.4 ng/mL. A PSA nadir of < 0.4 ng/mL has been shown to be an excellent predictor of long-term biochemical survival by Shinohara, Rhee, Presti, and Carroll (1997), but this was analyzed using the second generation cryosurgery technique. The major limitation of the Ellis (2002) study was the short follow-up time of three months.

The second longest trial is a seven year study by Bahn et al. (2002). They retrospectively analyzed 590 patients with a mean and median follow-up of 5.43 years and 5.72 years respectively. This data included patients that had undergone both second and third generation cryosurgery. It was reported at seven years that 61% (56), 68% (119), and 61% (192) of low-, medium-, and high-risk patients had a PSA threshold 0.5 ng/mL and considered free from biochemical relapse. The combined-risk group percentage using PSA threshold 0.5 ng/mL as success was 62% (360). Using the PSA threshold level of 1.0 ng/mL as biochemical failure, 87% (80), 79% (138), and 71% (223) of low-, medium-, and high-risk patients were considered free from biochemical relapse. The combined-risk group percentage using ≤ 1.0 ng/mL as success was 76% (442). Bahn et al. (2002) further analyzed the data according to the ASTRO definition of three successive increases of PSA level as biochemical failure with 92% (85), 89% (156), and

89% (279) of low-, medium-, and high-risk patients considered free from biochemical relapse. The combined-risk group percentage, using this definition of failure was 89.5% (520).

Long et al. (2001) retrospectively studied 975 patients with a median follow-up of 24 months that also included both second and third generation cryosurgery. The 5-year biochemical free survival rate was 52% (507) and 63% (614) for PSA threshold of 0.5 ng/mL and 1.0 mg/mL respectively.

There were five prospective articles that analyzed cryosurgery. El Hayek et al. (2008) performed a prospective study that included 44 patients with a median follow-up of 41 months. There were 13 patients that were considered to be low-risk using a Gleason score ≤ 7 , PSA ≤ 10 ng/mL, stage $\leq T2$, and 24 patients that were considered to be high-risk using a Gleason score ≥ 8 , PSA > 10 and stage $> T2$. They found in the low-risk group that 92% (12) and 86% (11) were considered free of PSA relapse using PSA < 1 ng/mL at 12 and 24 months respectively. In the high-risk group, the PSA failure rate was 39% (10) and 52.9% (13) at 12 and 24 months respectively using PSA < 1 ng/mL. Using a PSA cut-off of 0.5 ng/mL, in the low-risk group, 74% (10) and 74% (10) remained disease free at 12 and 24 months respectively. Using a PSA cut-off of 0.5 ng/mL, in the high-risk group, 22% (6) and 18% (5) remained disease free at 12 and 24 months, respectively. El Hayek et al. (2008) also used the PSA cut-off of 0.2 ng/mL and found that in the low-risk group 74% (10) and 69% (9) remained disease free at 12 and 24 months, respectively. For the high-risk group, 22% (6) and 18% (5) remained disease free at 12 and 24 months respectively using the PSA cut-off of 0.2 ng/mL.

Polascik, Nosnik, Mayes, and Mouraviev (2007) performed a prospective study that included 50 patients with a median follow-up time of 18 months. They reported that 90% (45) were considered a biochemical success using a PSA level of < 0.5 ng/mL. Cresswell et al. (2006) performed a prospective study that included 31 patients that underwent primary cryosurgery but only acquired enough data for 29 patients. They had a median follow-up of nine months. They found that 79% (23) were considered to have a complete response using a PSA level < 0.5 ng/mL.

Han et al. (2003) performed a prospective study that included 106 patients with at least a mean follow-up of 12 months. At three months, they found an 81% (96) success rate using $PSA \leq 0.4$ ng/mL as biochemical success. At twelve months, the biochemical recurrence-free survival was 75% (79).

De La Taille (2000) performed a prospective study that included a total of 35 patients with a mean follow-up of 8.3 months, but only 16 patients underwent cryosurgery as the primary procedure. Using a PSA level of ≤ 0.2 ng/mL, 62.5% (10) were considered a biochemical success. The biochemical recurrence free-survival rate at nine months was 45% (7) for patients undergoing primary treatment. De La Taille (2000) reported higher rates of failure for cryosurgery, but this could be due to the recent move to third generation cryosurgery or the small sample size.

Cryosurgery success rates were reported as high as 94% using a PSA nadir of <4.0 ng/mL and as low as 18% using the PSA cut-off of 0.2 ng/mL. From the two randomized controlled studies, Chin et al. (2008) found that cryosurgery was a suboptimal therapy in comparison to EBRT, but they were only able to accrue 64 patients for the study and only had a mean follow-up of 37 months. Donnelly et al. (2010) also performed a randomized trial comparing cryosurgery to EBRT with a mean follow-up of 100 months and reported that for patients with localized prostate cancer cryosurgery outcomes were better than EBRT outcomes at 84 months. With the lack of randomized controlled studies and no universal biochemical failure definition, it is very difficult to compare cryosurgery to the other treatment options. It was found that cryosurgery is an acceptable alternative for short term cancer control, but there needs to be longer studies to determine how effective the procedure is for long term cancer control. There also needs to be more randomized controlled studies to compare cryosurgery to the other treatment options.

Cancer Control using Biopsy

Repeat biopsy after cryosurgery was previously common practice. With the advancement in technology and more study results, most surgeons choose to perform a post-treatment biopsy

if the patient is considered a biochemical failure. Donnelly et al. (2010) chose to biopsy both the cryosurgery and EBRT arms of their randomized trial, and at 36 months found 7.7% (7) and 28.9% (22) had positive biopsies respectively. There was a statistical difference seen with the EBRT arm having more positive biopsies ($p < .0001$). Even though at 36 months the cryosurgery arm had a higher biochemical failure rate of 17.1% (20) compared to 13.2% (15) in the EBRT arm, it does not correlate to the return of prostate cancer with EBRT having statistically significant more positive biopsies.

Jones et al. (2008) also performed biopsies on 336 of the 1,198 patients that underwent cryosurgery. Of the 336 patients, 129 patients were biopsied due to biochemical failure using the ASTRO or Phoenix failure definitions, and they found that 38% (49) had a positive biopsy. Of the 207 patients that underwent a biopsy at the discretion of the treating physician without biochemical failure, 14.5% (30) had a positive biopsy. This shows that biochemical failure using the ASTRO or Phoenix definition does not necessarily correlate to cryosurgery failure, and there needs to be more research into finding a better PSA threshold to predict cryosurgery failure. This also shows that even if a patient does not have biochemical failure using a certain definition that he may still not be disease free. Following cryosurgery, both patient and clinician need to be vigilante, and the patient must have follow-up PSA levels to look for increases that may show that the prostate cancer is still present.

Incontinence

Incontinence is the second part of the trifecta and important for quality of life. Robinson et al. (2009) found a significant difference in mean urinary function scores at three months. The cryosurgery arm and EBRT arm had mean urinary function scores of 69.4 and 90.7 respectively ($P < .0001$). The urinary function score was calculated using the Prostate Cancer Index, which is a questionnaire developed by Litwin et al. (1995). To calculate the urinary function score, the answered questionnaire is converted linearly to a 0 to 100 score range with 100 being the highest possible score and meaning a better outcome. At 36 months the scores were no longer

significant with the cryosurgery arm and EBRT arm having mean urinary function scores of 93.0 and 88.6 respectively ($p=.043$). The cryosurgery arm had better QOL regarding urinary function at 36 months, but both groups reported a return to their baseline level of urinary function.

Chin et al. (2008) reported that there was no statistical difference with a mean follow-up of 36 months between the EBRT arm and cryosurgery arm. They reported that 7% (2) in the cryosurgery arm and 3% (1) in the EBRT arm had incontinence.

Out of the retrospective and prospective trials, Jones et al. (2008) reported that incontinence occurred in 4.8% (58) and 2.9% (35) used pads following the procedure. El Hayek et al. (2008) reported that 22.7% (10) patients had urgency within the first six months and 13.5% (5) reported urinary incontinence using the definition of using one or more pads daily. Hubosky et al. (2007) found a 2% (2) incontinence rate using the definition of the use of a pad. Polascik et al. (2007) reported an incontinence rate of 3.7% (2) using the definition of requiring one to two pads per day. Prepelica et al. (2005) reported that 3.08% (2) of patients were considered incontinent using the definition of having to use a pad daily. Han et al. (2003) reported an incontinence rate of 4.3% (5) that required the use of pads, and 5.1% (6) had urge incontinence. Bahn et al. (2002) found that 15.9% (85) of the patients treated with cryosurgery were considered incontinent using the definition of any leakage of urine. This was reduced to 4.3% (23) if the incontinence required the use of a pad. Ellis (2002) defined incontinence as severe, requiring greater than two pads per day, or mild, requiring less than two pads per day. They found that 1.4% (1) and 4% (3) developed severe and mild incontinence respectively. Long et al. (2001) reported an overall incontinence rate of 7.5% (73). De La Taille (2000) reported no incontinence out of 35 patients.

Cryosurgery is shown to be comparable to radical prostatectomy, brachytherapy, and EBRT. The highest incontinence rate reported from the prospective and retrospective studies was by Bahn et al. (2002) as 15.9% (85), but this study included both second and third

generation cryosurgery. Table 3 shows incontinence rates of other treatment options from 2000 to 2006 (Ellis, et al., 2007).

Impotence

The third part of the trifecta and another important quality of life issue is impotence. Robinson et al. (2009) found a significant difference between the EBRT arm and cryosurgery arm potency results with a sexual function score of 16.0 and 36.7 for cryosurgery and EBRT respectively ($p < .001$). Of the 56 men in the cryosurgery arm that had been potent before surgery, 14% (8) reported spontaneous erections. At 36 months, when both assisted, use of medications or devices, and unassisted intercourse was included, 29.1% (14) patients were considered potent. Of the 57 men in the EBRT arm that had been potent before surgery, 66.7% (38) reported spontaneous erections. At 36 months, when both assisted, use of medications or devices, and unassisted intercourse was included, 29.8% (14) patients were considered potent. This showed that following cryosurgery, patients had a chance of regaining potency, whereas patients that underwent EBRT had an increased risk of impotence over time.

Robinson et al. (2009) also reported the mean sexual function score using the same Prostate Cancer Index questionnaire used for urinary incontinence. The questionnaire answers were converted linearly, 0 to 100, with 100 being the highest possible score and representing the best outcome (Litwin, et al., 1995). Cryosurgery patients had a mean sexual function score of 16 versus a mean sexual function score of 36.7 for the EBRT arm ($p < .001$). Neither the EBRT arm nor the cryosurgery arm was able to return to baseline sexual function (Robinson et al., 2009).

Chin et al. (2008) reported that 29% (10) in the cryosurgery arm had new onset erectile dysfunction, but they did not report the number of patients in the EBRT arm that had erectile dysfunction. They did state there was no statistical difference between the EBRT arm and the cryosurgery arm for new onset erectile dysfunction.

For the retrospective and prospective articles that only included cryosurgery, Jones et al. (2008) reported that 25.2% (90) patients were potent following the procedure. Only 8.8% (32) were able to have intercourse without any assistance from pharmaceuticals or devices. 16.4% (58) were potent with assistance from pharmaceuticals or devices. El Hayek et al. (2008) reported that of 28 patients that were potent prior to cryosurgery, 96.4% (27) reported erectile dysfunction following the procedure. Polascik et al. (2007) reported that 12% (6) patients remained potent following cryosurgery. Of the six patients, three required the use of 5-phosphodiesterase inhibitors. Cresswell et al. (2006) reported that 13 out of 29 patients were potent prior to cryosurgery, and all were unable to have an erection following the procedure. Four of the 13 (30.8%) regained partial erectile function between three to nine months following the procedure. Interestingly, two patients that reported erectile dysfunction before the procedure were able to achieve partial erections within the year following surgery.

Han et al. (2003) reported an 87% (95) impotence rate. In the Ellis (2002) study, before cryosurgery, 34 of the 75 patients were potent. They found that 17.6% (6) remained potent following cryosurgery. Bahn et al. (2002) found that within an average of 16.4 months, 5.1% (19) recovered their potency. Long et al. (2001) found an impotence rate of 93%, but did not state how many patients were potent before the procedure.

Table 4 compares the impotence rates between the different treatment options for prostate cancer. Whole gland cryosurgery does not compare well with brachytherapy or EBRT, and is not an acceptable treatment option for men who are potent prior to the procedure and wish to remain potent following the procedure. One of the main reasons that cryosurgery has a high rate of impotence is that during the procedure, the neurovascular bundle is frozen for adequate cancer control. This is also the reason that Robinson et al. (2009) found that over time, patients may eventually see a return of potency because the neurovascular bundle is only damaged and can repair itself.

Impotence is a major disadvantage to cryosurgery and the patient needs to be aware of this before choosing cryosurgery as his treatment option. If it is important to the patient to be potent following the surgery, then other treatment options should be discussed between the surgeon and the patient.

Other Complications of Cryosurgery

Other complications of cryosurgery were seen, but at very low rates. Chin et al. (2008) was the only randomized trial that compared the complications with cryosurgery to EBRT. They reported a significant difference in gastrointestinal side effects with 100% (31) of the EBRT arm and 45% (15) of the cryosurgery arm experiencing adverse effects that included proctalgia, hematochezia/melena, diarrhea, constipation, and fecal incontinence ($P < 0.001$). There was no significant difference in genitourinary side effects overall with 79% (24) from the EBRT arm and 81% (27) from the cryosurgery arm reporting frequency/urgency, poor stream, incontinence, hematuria, perineal/genital pain, or new onset erectile dysfunction. Out of the adverse genitourinary effects, there was statistical significance for perineal/genital pain with 3% (1) of patients from the EBRT arm and 32% (11) of patients from the cryosurgery arm reporting this side effect ($P = 0.006$).

The rate of rectourethral fistulas was reviewed in the studies because this was one complication that caused hesitancy among clinicians and patients to choose cryosurgery as a treatment option. Bahn et al. (2002) reported that out of 590 patients, rectourethral fistulas occurred in 0.004% (2) patients and this included patients that had the second generation or third generation cryosurgery procedure. Hubosky et al. (2007) reported a higher rectourethral fistula rate than Bahn et al. (2002) of 1% (1). This was surprising because Bahn et al. (2002) included patients that had second or third generation cryosurgery and Huboskey et al. (2007) only included patients that had third generation cryosurgery. Jones et al. (2008) reported a rectourethral fistula rate of 0.4% (5). Polascik et al. (2007) reported that there were no cases of rectourethral fistulas out of 50 patients. Prepelica et al. (2005) reported no occurrences of

rectourethral fistulas out of 65 patients. Ellis (2002) reported no rectourethral fistulas out of 75 patients, but one patient developed a scrotal abscess followed by Fournier gangrene. This was treated successfully with surgical and medical management.

Urethral sloughing was another complication that advancements in technology helped to decrease the complication rate. Jones et al. (2008) observed urinary retention in 3.6% (43) patients, and 2.1% (25) of patients underwent a TURP to remove sloughed tissue. Hubosky et al. (2007) reported only two of 89 patients (2%) experienced urethral sloughing. Polascik et al. (2007) reported no cases of chronic urinary retention or urethral strictures out of 50 patients. Prepelica et al. (2005) reported that 1.5% (1) had voiding complications following the procedure. Han et al. (2003) reported a urethral sloughing complication rate of 5.8% (5). Ellis (2002) reported a rate of 6.7% (5) for patients that experienced urethral sloughing, all five patients experienced urinary retention due to the urethral sloughing, and one patient underwent the TURP procedure.

Polascik et al. (2007) reported that there were no cases of chronic pelvic pain out of 50 patients. Prepelica et al. (2005) reported their most common complication, with a rate of 5.9% (4), as scrotal swelling and pelvic pain. Han et al. (2003) also analyzed pelvic pain and scrotal swelling and found these complications to occur at a rate of 5.9% (7). De La Taille (2000) reported a 12% (2) complication rate for swelling from cryosurgery.

El Hayek et al. (2008) reported the most common complication as mild hematuria with 16.21% (6) patients reporting this complication. Prepelica et al. (2005) reported no occurrences of hematuria out of 65 patients.

As technology advanced, there was a decrease in complications of pelvic pain, urethral sloughing, and rectourethral fistulas. The clinician must inform the patient that these complications are the most common and may occur. The clinician and patient must also discuss the possibility of having a TURP procedure after the cryosurgery procedure if urethral sloughing occurs.

Unilateral or Subtotal Prostatectomy

Unilateral or subtotal prostatectomy using cryosurgery is considered an investigational treatment option for unilateral, focal prostate cancer. Onik, Vaughan, Lotenfoe, Dineen, and Brady (2008) were the pioneers for this procedure, naming it the “male lumpectomy.” The patient criteria for this procedure differs from whole gland cryosurgery in that it is appropriate to attempt this procedure on men with good potency, and this procedure is only appropriate for men with low risk disease (Eggerer et al., 2007; Ritch & Katz, 2009).

The reason that this procedure is on the horizon is that it has been shown to have high potency rates. Onik et al. (2008) performed a prospective study that included 48 patients and a mean follow up of 4.5 years. They chose patients that had a positive biopsy in only one lobe of the prostate gland, and patients that wished to retain potency and continence. Of the 40 patients that were potent before a single unilateral cryosurgery procedure, 90% (36) remained potent postoperatively. Lambert et al. (2007) performed a retrospective study of 25 patients with a median follow-up of 28 months. Twenty-four of the 25 patients were potent before the unilateral cryosurgery procedure, and 71% (17) patients retained their potency postoperatively, with only seven patients needing assistance with phosphodiesterase-5 inhibitors. Ellis et al. (2007) performed a retrospective study that included 60 patients with a mean follow-up of 15.2 months. Fifty-five patients were potent before undergoing unilateral cryosurgery, and 72.7% (40) were potent following the procedure. These potency rates are far better than the rates reported for whole gland cryosurgery, with 29.9% (14) and 50% (6) being the best reported potency rates following whole gland cryosurgery (Donnelly, et al., 2010; Polascik, et al., 2007).

The continence rates for the unilateral prostatectomy were also remarkable with 100% (25), 100% (48), and 96.4% (53) patients remaining continent following the procedure (Ellis, et al., 2007; Lambert, et al., 2007; G. Onik, et al., 2008).

The last part of the trifecta, cancer control, is more difficult to analyze for this procedure because the surgeon is leaving more of the prostate gland. The PSA level for biochemical

disease free survival has not been defined, and there is a lack of long term studies for this procedure. Onik et al. (2008) analyzed data from 48 patients with at least a two year follow-up using the ASTRO definition of three successive increases of PSA level as biochemical failure. The results showed 94% (45) of patients had stable PSA levels. Of the four patients that had biochemical failure, the biopsy revealed they had disease in a portion of the gland that did not undergo treatment. These patients were able to undergo whole gland cryosurgery. Onik et al. (2008) were also able to perform routine biopsies at one year in 24 of the 48 patients. They reported that all 24 patients had negative biopsies. Lambert et al. (2007) followed 25 patients with a median follow-up of 28 months. Using a PSA threshold of 1.0 ng/mL, 36% (9) were free of biochemical recurrence. They then defined failure as a PSA nadir greater than 50% and found 84% (21) were free of biochemical recurrence. Ellis et al. (2007) followed 60 patients with a mean follow-up of 15.2 months. Using the ASTRO criteria for biochemical failure, 80.4% (48) of the patients were considered free from biochemical disease.

The disadvantage of this procedure is that the surgeon needs to select appropriate candidates. All of the patients that choose to undergo unilateral cryosurgery can expect to have routine follow-up that includes PSA levels every three months for at least the first year after surgery and then every six months thereafter (Lambert, et al., 2007). Onik et al. (2008) required the patients to obtain PSA levels every three months for the first two years, then every six months thereafter. The patient will also be required to undergo multiple follow-up biopsies because this procedure is not considered a cure for prostate cancer due to the possibility that the cancer can still return in the other lobe. So like AS, subtotal prostatectomy patients must be compliant with follow-up care and may have increased anxiety and depression (Ellis, et al., 2007).

Before a patient chooses unilateral cryosurgery as their treatment option, a discussion must occur so that the patient is fully aware of the risks of an investigational treatment option. The first concern is whether or not the patient is considered to have low-risk disease and the

disease has to be confined to one lobe (Lambert, et al., 2007). If the patient meets these criteria, then a discussion has to occur about the risks of having a unilateral cryosurgery procedure. The major risk is the possibility of the cancer returning to the other lobe which would require further surgery. The patient would also have to be compliant with all biopsies and follow-up care. If the patient meets the criteria and understands the risks and benefits associated with the procedure, then he can make a knowledgeable choice when choosing his treatment option.

Conclusion

Cryosurgery has made much technological advancement since it was first used to treat prostate cancer in the 1960s. This has allowed a decrease in the amount of procedure associated complications that include rectourethral fistula, urethral sloughing, pelvic pain, and hematuria. With the decline of these complications, in order for cryosurgery to be considered an acceptable treatment option for prostate cancer, the trifecta of cancer control, incontinence, and impotence has to be considered carefully.

In regard to cancer control, it is difficult to compare cryosurgery to the other treatment options of radical prostatectomy, brachytherapy, high-intensity focused ultrasound (HIFU), and external beam radiotherapy (EBRT). The reason for this is a lack of randomized controlled studies and no universal definition for biochemical failure. In conclusion, prospective and retrospective studies have shown cryosurgery to be an acceptable treatment option in regards to cancer control, but there still needs to be more research looking into the long term results of cryosurgery, and there needs to be more randomized controlled studies comparing cryosurgery to radical prostatectomy, brachytherapy, and HIFU. In order to properly follow-up with patients that choose cryosurgery, there also needs to be more research to find an acceptable universal biochemical failure definition.

For the second part of the trifecta, cryosurgery showed excellent results in regards to urinary incontinence, and cryosurgery was found to be significantly better than EBRT regarding urinary function. This is a major quality of life (QOL) issue that can be very important when a patient chooses a treatment option. Even though the rates for urinary incontinence are low following cryosurgery, there still needs to be a discussion between the clinician and the patient that this could be a complication from the procedure.

For the third part of the trifecta, cryosurgery did not compare well in regards to potency. It was found that cryosurgery is an unacceptable treatment option if a patient is potent prior to cryosurgery and wishes to remain potent following the procedure. EBRT was found to be

significantly better than cryosurgery regarding potency. Impotence is another QOL issue that needs to be discussed between the clinician and the patient, and if it is important to the patient, another treatment option should be utilized.

Unilateral cryosurgery is a new investigational treatment available for men that choose cryosurgery and wish to remain potent. This procedure shows excellent results in regards to urinary incontinence and potency. The downfall of this procedure is the lack of a universal biochemical failure definition. Since only half of the gland is frozen, it is also important to have an adequate biochemical failure definition, and it also important that the surgeon select appropriate candidates due to the amount of follow-up care. If the patient meets the criteria for unilateral cryosurgery and understands the risks and benefits associated with the procedure, then he can make a knowledgeable choice regarding his treatment options.

In conclusion, cryosurgery is found to be an acceptable treatment for localized prostate cancer, but it does not meet all three trifecta areas of cancer control, incontinence, and potency. Cryosurgery has shown to have acceptable success rates for cancer control and low rates for post-procedure incontinence, but is not acceptable compared to the other treatment options for post-procedure potency. To date, there is not a treatment option that fulfills the trifecta but with ongoing research and technological advances, it is possible that unilateral cryosurgery may be the treatment option for localized prostate cancer in the future.

Tables

Table 1. Side effects associated with each treatment option.

	AS	RP	Robotic RP	HIFU	Brachytherapy	EBRT	Cryosurgery
Pain						✓	✓
Urinary Retention							✓
Urethrorectal Fistulas							✓
Perioperative Mortality		✓	✓				
Urethral sloughing							✓
Incontinence		✓	✓	✓	✓	✓	✓
Impotence		✓	✓	✓	✓	✓	✓
Surgical Risks*		✓	✓	✓	✓	✓	✓
Bladder Neck Contractures		✓	✓				
Rectal Injury		✓	✓		✓		✓
Urethral Strictures		✓		✓			
Bowel function decreased					✓		

*Surgical risks include infection, bleeding, reaction to anesthesia

Table 2. Prostate cancer staging. Goldman & Ausiello, 2008

T1	Nonpalpable tumor detected on pathologic examination.
T1a and T1b	Detected after transurethral resection for benign hypertrophy.
T1c	Detected from biopsy for elevated PSA level.
T2	Palpable tumor confined to the prostate gland.
T2a	Palpable tumor confined in one lobe of the prostate gland or tumor extends
T2b	Palpable tumor confined to two lobes of the prostate gland or tumor
T3	Tumor extends through the prostatic capsule.
T4	Tumor invades the adjacent structures.

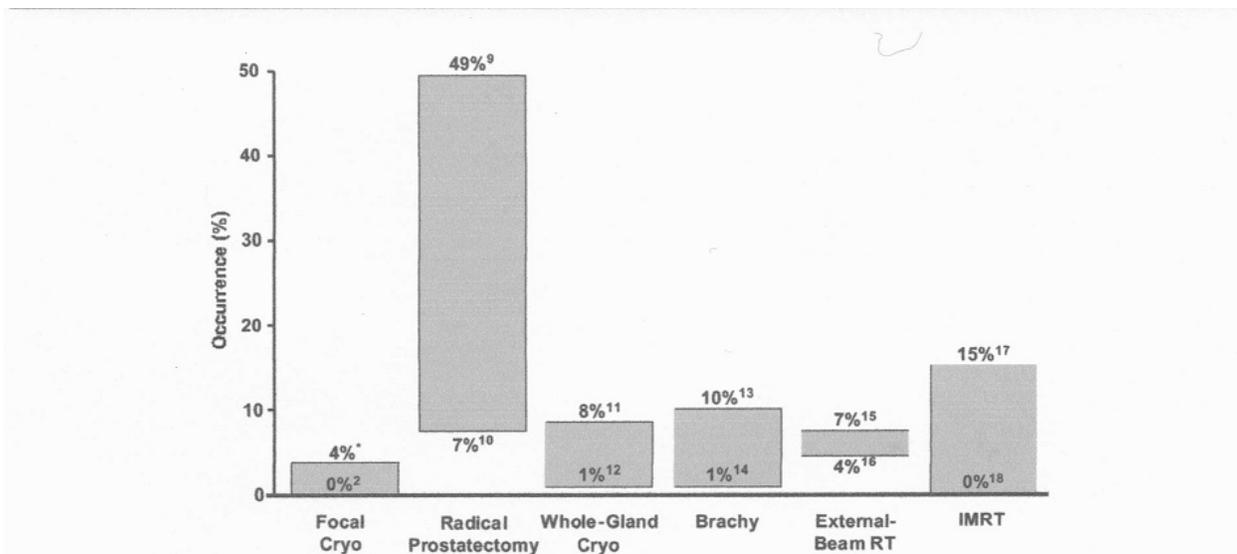
Table 3. Ellis et al., 2007

Figure 2. Comparison of published incontinence rates that appear in the literature from 2000 to 2006 for focal cryoablation (Cryo), radical prostatectomy, whole-gland Cryo, brachytherapy (Brachy), external-beam radiation therapy (RT), and intensity modulated radiation therapy (IMRT).^{7,9-18} *Indicates results for the current series.

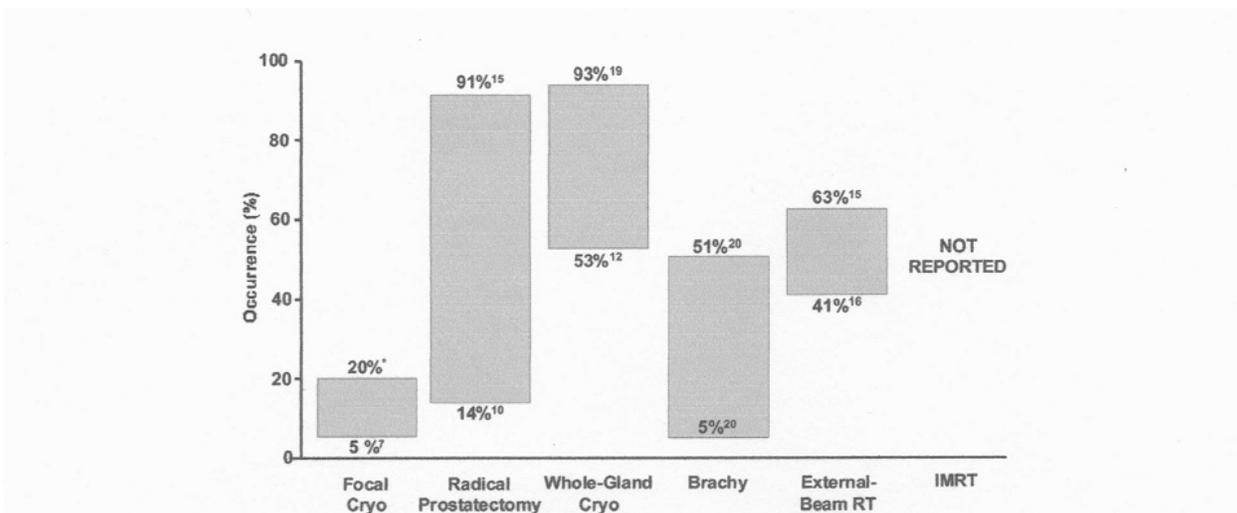
Table 4. Ellis et al., 2007

Figure 4/ Comparison of published impotence rates that appear in the literature from 2000 to 2006 for focal cryoablation (Cryo), radical prostatectomy, whole-gland Cryo, brachytherapy (Brachy), external-beam radiation therapy (RT), and intensity-modulated radiation therapy (IMRT).^{7,10,12,15,16,19,20} *Indicates results for the current series.

From "Focal Cryosurgery Followed by Penile Rehabilitation as Primary Treatment for Localized Prostate Cancer: Initial Results," by D. S. Ellis, T. B. Manny, and J. C. Rewcastle, 2007, *Urology*, Volume 70(6 Suppl), 9-15. Copyright 2007 by Elsevier. Reprinted with permission.

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Abstract

Objective: The purpose of this literature review was to compare third generation cryosurgery to other prostate cancer treatment options to evaluate prostate cancer recurrence, urinary incontinence, and potency outcomes.

Methods: Sources for this literature review were located by searching PubMed, The American Cancer Society and the American Urological Association.

Results: There were 13 research articles reviewed that included retrospective, prospective, and randomized studies.

Conclusion: Cryosurgery outcomes for cancer control and urinary incontinence compare to other prostate cancer treatment options. Cryosurgery is not an acceptable option for men who want to remain potent following surgery. Unilateral cryosurgery is an investigational treatment with high potency rates and excellent urinary continence results, but without an established definition for biochemical recurrence. More randomized trials need to be performed to determine an acceptable value for biochemical recurrence for cryosurgery and unilateral cryosurgery.