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Review Article

Cryotherapy As Treatment of Curative Intent for Localized Adenocarcinoma of The Prostate Gland with A Focus on Low-risk and Medium – (Intermediate-) Risk Localized Adenocarcinoma of The Prostate Gland: A Review and Update

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Abstract:

Cryotherapy which is also referred to as cryosurgery or cryoablation refers to utilization of very cold temperatures to freeze various cells depending upon the pathology. Cryotherapy has tended to be utilized as treatment of curative intent for localized low-risk and intermediate risk carcinomas of the prostate gland. Cryotherapy has also been utilized for the treatment of post-cryotherapy failure prostate cancers with residual tumour or locally recurrent tumour that is confined to the prostate gland. Cryotherapy has also been utilized for the treatment of locally recurrent prostate cancers or localized prostate cancers that have remained following failure of radiotherapy to the prostate cancer of curative intent or radical prostatectomy of prostate for prostate at times. Because cryotherapy of prostate cancer is a minimally invasive treatment procedure, it can be utilized in the treatment of patients who have localized prostate cancer whose tumours could be treated by means of radical prostatectomy or radiotherapy (external beam radiotherapy or brachytherapy) who are considered not to be medically fit to undergo these procedures because of their co-morbidities. The most common treatment options for the management of localized adenocarcinomas of the prostate gland tend to involve radical prostatectomy or radical radiotherapy. Nevertheless, other treatment options for localized prostate cancer that have been undertaken sporadically include: Radiofrequency ablation of the prostate cancer, High intensity focussed ultrasound scan treatment of prostate cancer, irreversible electroporation of prostate cancer. Cryotherapy of prostate cancer as treatment of curative intent has tended to be published sporadically based upon case reports or case series and there has not been reports of an extensive clinical-trials on cryotherapy of localized adenocarcinoma of the prostate. Furthermore, there is no consensus opinion validated definition of biochemical failure pursuant to treatment of localized prostate cancer by cryotherapy. Nevertheless, one article has reported a prospective study with the undertaking of standardized follow-up protocol in which it a series of 108 patients who were diagnosed as having localized adenocarcinoma of prostate that was staged T1c to T2c were treated by primary cryoablation of curative intent and in which the median follow-up was 61 months. With regard to the results of this study, the criteria of biochemical recurrence had been unified based upon the American Society for Therapeutic Radiology and Oncology (ASTRO). The end points of the study included: biochemical progression-free survival (BPFS), cancer-specific survival, as well as overall survival. The complication rates were reported in the study. With regard to the results the biochemical progression-free survival rates were for low-, medium-, and high-risk prostate cancer patients 96.4%, 91.2%, and 62.2%, respectively. The Cancer-specific survival was 98.1%. The overall survival reached 94.4%. The complications that were encountered included incontinence in 5.6% of the patients, urinary tract obstruction in 1.9% of the patients, urethral sloughing in 5.6% of the patients, haematuria in 1.9% of the patients, perineal pain in 11.1% of the patients, and prostatorectal fistula in 0.9% of the patients. Erectile disfunction was found in 98.1% of the patients. The authors concluded that cryotherapy is an effective and minimally invasive treatment for primary carcinomas of the prostate gland in well-selected cases, and the treatment procedure is associated with low surgical risk and good results in terms of biochemical progression-free survival (BPFS), cancer-specific survival, and overall survival. Even though the results of this study had illustrated that the oncology outcome of high-risk prostate cancer was lower than the outcome of low-risk and

intermediate-risk prostate cancer more than 60% of patients who had high-risk prostate cancer had biochemical progression-free survival after a median follow-up of 61 months. At the moment cryotherapy is being utilized as treatment of curative option for some low-risk and intermediate (medium) -risk prostate cancer. Cryotherapy of the primary prostate cancer has been utilized for the palliative treatment of some advanced / metastatic prostate cancer which had temporarily ameliorated the general health of few reported patients. In the scenario of persistence of localized low-risk or intermediate- (medium-) risk localized prostate cancer that have persisted following cryotherapy of the prostate cancer, the cancer can be treated by means of either further cryotherapy, radical prostatectomy, radical radiotherapy, HIFU treatment, Irreversible electroporation, and radiofrequency ablation of prostate gland. The complications of erectile / sexual dysfunction, and urinary incontinence / voiding dysfunction following cryotherapy for prostate cancer tends to be more transient in comparison with following radical prostatectomy or radical radiotherapy. It may be that cryotherapy of localized prostate cancer of low-risk, and medium-risk patients may have a slightly inferior long-term oncology outcome in comparison with radical prostatectomy, radical radiotherapy and other minimally invasive treatment options of curative intent but this needs to be further investigated through a large global multicentre treatment comparative study of various treatment options with a long-term follow-up. Nevertheless, cryotherapy of prostate cancer does represent a minimally invasive alternative treatment for localized prostate cancer as treatment of curative intent and it can also be used to treat persistent/locally recurrent prostate cancer following radical radiotherapy and radical prostatectomy. Cryotherapy as treatment option is a safe and effective treatment option for localized low-risk and medium-risk prostate cancer.

Keywords: adenocarcinoma of prostate; prostate cancer; cryotherapy; cryoablation; cryosurgery; radical prostatectomy; radical radiotherapy; biochemical progression-free survival; low-risk; medium-risk; high-risk; incontinence; sexual dysfunction; survival

Introduction

The European Association of Urology guidelines on carcinoma of the prostate gland documented that cryotherapy represents a true treatment alternative for patients who have clinically localized carcinoma of the prostate gland [1] [2] The American Association of Urology in 2008 documented a best practice iteration which had confirmed cryotherapy as a valid therapeutic option for both primary as well as recurrent localized carcinoma of the prostate gland. [1] [3] It had been iterated that in 2005 within the United Kingdom, the National Institute of Clinical Excellence had approved utilization of cryotherapy for patients who have adenocarcinoma of the prostate gland, both as a primary therapy as well as salvage therapy pursuant to radiotherapy or hormone treatment. [4] National Institute of Clinical Excellence. Cryotherapy as a primary treatment for prostate cancer. 2005. [4] It has also been documented that in February 2008, the United Kingdom National Institute of Clinical Excellence guidelines on carcinoma of the prostate gland which was released had reversed the aforementioned decision and had suggested that the cryotherapy of prostate cancer should be undertaken within the setting of clinical trials. [1] It has also been stated that because of ongoing debate related to cryotherapy of prostate cancer, a further revision of the NICE guidelines had been made to allow United Kingdom Medical Practitioners to collect data on patients who are treated locally for funding requirements. [1]

It has been explained that cryotherapy does cause cell death via two principal mechanisms [1] [5] First of all as the temperature does fall, extracellular ice does crystalize which does tend to cause movement of water from the intracellular into the extra-cellular environment after an osmotic gradient. [1] As the temperature continues to fall, intra-cellular ice crystals tend to form, and this does cause direct damage to the intra-cellular organelle system as well as to the cell membrane. [1]

With regard to the second mechanism, this does relate to platelet aggregation as well as microthrombus formation within small blood vessels and this does tend to emanate in ischaemic change within the tissue area which is supplied by the affected blood vessels. These changes do emanate in the development of coagulative necrosis as well as they do cause a well-demarcated lesion. Furthermore, severe changes of temperature as well as ischaemic changes do induce apoptosis within cells at the periphery of the cryo-lesion. [1] [6] It has been iterated that the effectiveness of cellular destruction does depend upon rapid freezing [1] [7], the lowest temperature that is reached as well as slow thawing. This is stated to be generally achieved via two freeze-thaw cycles to a treat temperature of – 40 degrees centigrade. [1] [5].

In order to provide treatment of curative intent for the management of localized adenocarcinoma of the prostate gland, either the prostate gland containing the carcinoma should be completely excised through a surgical operation like radical prostatectomy or the tumour cells must be completely destroyed by the treatment option that has been provided and traditionally radical radiotherapy by means of external beam radiotherapy or brachytherapy have tended to be undertaken. Nevertheless, these days other treatment options that are minimally invasive are being undertaken as treatment with an aim of curative intent in various centres in the world but such treatment options are not being regarded as a universally accepted consensus opinion options of treatment. Cryotherapy of prostate cancer is one of the new non-invasive treatment options that are sporadically undertaken in some oncology centres in the world.

Cryotherapy is utilized for the treatment of various conditions in different parts of the body in various countries within the world. It does appear that cryotherapy as primary treatment of localized prostate cancer as well as salvage therapy pursuant to failure or recurrence of adenocarcinoma of the prostate gland tends to be undertaken mostly within the developed countries but not very often in some of the developing countries. Cryotherapy as treatment of curative intent for localized adenocarcinoma as well as salvage therapy for recurrent prostate cancer also tends to be undertaken within regional oncology centres in a number of developed countries and hence many clinicians that work within district hospitals and clinics as well as a number of clinicians who work within district hospitals in some developing countries may not be familiar with cryotherapy as a treatment option for prostate cancer. The ensuing article on cryotherapy as a treatment option for adenocarcinoma of the prostate gland is divided into two parts: (A) Overview which has discussed cryotherapy generally including cryotherapy as treatment for various conditions and (B) Miscellaneous Narrations And Discussions From Some Case Reports, Case Series And Studies Related To Cryotherapy As Treatment Of Curative Intent For Localized Adenocarcinoma Of The Prostate Gland As Well As Salvage Therapy For Failure Of Treatment Or Recurrence Pursuant To Radical Prostatectomy, Radiotherapy / Hormonal Therapy.

Aims

To review and update the literature on Cryotherapy of prostate cancer with a focus on localized low-risk and medium –(intermediate)-risk localized adenocarcinoma of the prostate gland.

Method

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PubMed. The search words that were used included: Cryotherapy; Cryotherapy of prostate cancer, cryotherapy of carcinoma of prostate cancer, cryotherapy of adenocarcinoma of the prostate; carcinoma of prostate; adenocarcinoma of prostate; focal treatment of prostate cancer. One hundred and thirty-six, (136) references were identified which were used to write the article which has been divided into two parts: (A) Overview which contains general discussions on (I) Cryotherapy in general, (II) adenocarcinoma of prostate, (III) cryotherapy of prostate cancer, and (B) Miscellaneous Narrations and Discussions Related to Some Case Reports, Case Series, And Studies Related to Cryotherapy of Prostate Cancer.

Results

(A) Overview

Cryotherapy

Definition and General Statements

- Cryotherapy is a terminology that is utilized for the utilization c a freezing chamber which usually tends to be -110 degrees i order to help muscles recover. [8]
- It has been stated that cryotherapy tends to be utilized for multipl applications [9]
- It has been documented that "Cryo" is a word which ha originated from the Greek language and does mean icy or col [8] [10]]
- Cryotherapy does refer to a procedure which exposes the body t temperatures that tend to be colder than minus 200 degrees fc about 3 minutes [10] [11]
- It has been documented that the practice of cryotherapy ha originated in Japan in the late 1970s when a Japanes rheumatologist utilized cold temperatures for the treatment of hi patients' painful joints [8] [10] [12]
- It has also been iterated that cryotherapy is also utilized for th treatment of cancer, in which cold temperatures are utilized t destroy cancer cells. [10] [13]
- Cryotherapy is stated to be at times referred to as cold therapy an it refers to the local or general utilization of low temperature i medical treatment. It has also been pointed out that cryotherapy could be utilized for the treatment of various tissue lesions [1] It has also been documented that the most common utilization of the term cryotherapy does refer to the surgical treatment, which is specifically referred to as cryotherapy or cryoablation and tha cryotherapy does refer to the application of extremely lo temperature for the purpose of destroying abnormal or disease tissue and cryotherapy is utilized most often to treat ski conditions [9] [10] 14]
- It has been documented that cryotherapy tends to be utilized in a effort to relieve muscle pain, sprains, as well as swelling tha ensues tissue damage or surgery, [10]
- It has been documented that that cryotherapy has tended to b commonly utilized to accelerate recovery in athletes pursuant to exercise for a number of decades as well as cryotherapy does decrease the temperature surface in order to minimize hypoxic cell death, accumulation of oedema, as well as muscle spasms, all of which eventually ameliorate discomfort as well as inflammation [10] [15]
- It has also been stated that cryotherapy could also involve a rang of treatments from the application of ice packs or immersion i ice baths which has generally been referred to as cold therapy, to the utilization of cold chambers. [10]
- It has been iterated that cryotherapy is widely utilized, but there is little evidence as to the efficacy of cryotherapy which had been replicated or demonstrated in large controlled studies. [[new 10]] The long-term side effects of cryotherapy had also not been studied [10] [16] [17]
- It has nevertheless been iterated that: results of a study had concluded that cryotherapy does have a positive impact upon the short-term recovery of athletes as well as cryotherapy had helped in the management of muscle soreness as well as facilitated recovery within the first 24 hours pursuant to a sporting-related activity. It has additionally been iterated that: athletes, who utilized cryotherapy within the first 24 hours for the alleviation of pain had recovered at a faster rate in comparison with athletes who did not utilize cryotherapy pursuant to their sport-related activity [10] [15]

Cryotherapy Chamber

Partial Body Cryotherapy (PBC).

- It has been documented that there are different types of cryochamber that exist and each chamber does have different mechanisms of action as well as utilization [10] It has been stated that the Partial Body Cryotherapy (PBC) does utilize nitrogen to decrease the temperature. This cryochamber is said to be an individual, tube-shaped enclosure which does cover a person's body with an open-top in order to keep the head at room temperature. [18]
- The second cryochamber tends to be referred to as the whole-body cryotherapy (WBC) and it does utilize electricity in order to reduce the temperature inside the chamber. In contrast to the first cryochamber, the user fully does enter the electricity operated chamber. [10]
- Partial-Body Cryotherapy is stated to be a specific type of low-temperature treatment which is utilized to reduce inflammation as well as painful effects [10] [19]
- It has been iterated that cryotherapy was developed in the 19970s by a rheumatologist from Japan called Toshima Yamaguchi [10] [20] [21] and that cryotherapy had been introduced to Europe, United States of America, as well as Australia in the 1980s [22] [23] The effect of cryotherapy on total antioxidative capacity in patients with active seropositive rheumatoid arthritis. [23]. and 1990s. [24]
- Both cryochambers are stated to decrease the skin temperature; however, WBC does reach lower temperatures in comparison with PBC and it might be considered to be more effective. [10] [25]

Mechanism of action

The ensuing summations have been made regarding the mechanism of action related to cryotherapy: [10]]

- In scenarios when the body is vulnerable to extreme cooling, the blood vessels tend to be narrowed and they then make less blood to flow to the areas of the swelling. [10]
- It has also been iterated that once outside the cryogenic chamber, the vessels do expand, and an increased presence of anti-inflammatory proteins (IL-10) tends to be established within the blood. [10] [26]
- It has also been documented that cryotherapy chamber does entail the exposure of individuals to freezing dry air that is lower than one hundred degrees centigrade (100 °C) for 2 minutes to 4 minutes. [10] [27]

Main utilizations [10]

Proponents say that cryotherapy may reduce pain as well as inflammation, help with mental disorders, support exercise recovery performance and does improve upon joint function. Cryotherapy chambers belong to the group of equipment that have been associated with sports rehabilitation and wellness.

- Weight loss [28]
- Reducing anxiety as well as depression [29]
- Reduction in the symptoms of eczema [30]

Cryosurgery

Medical cryotherapy gun.

Cryosurgery

Cryosurgery is a terminology that is utilized for the application of extreme cold in order to destroy abnormal or diseased tissue. The application of ultra-cold liquid does cause damage to the treated tissue as a result of intracellular ice formation. The degree of damage does depend upon the minimum temperature which is achieved and the rate of cooling. [31]

Cryosurgery is utilized to treat a number of diseases and disorders, most especially skin conditions like including warts, moles, skin tags as well as solar keratoses. Liquid nitrogen usually tends to be utilized to freeze the tissues at the cellular level. The procedure tends to be often utilized in view of the fact that it is relatively easy and quick to undertake, and it can be undertaken in the doctor's surgery, as well as cryosurgery is deemed to be associated with quite a low risk. It has been iterated that if a cancerous lesion is suspected then excision of the lesion rather than cryosurgery might be deemed more appropriate. [32]

Icepack treatment

Ice pack treatment is a treatment of cold temperatures to an injured area of the body. It has been iterated that even though the treatment is extensively utilized, and it had been agreed that Icepack therapy does alleviates symptoms, testing had produced conflicting results about the efficacy of Icepack therapy. [33] [34] [35] [36]

An ice pack tends to be placed over an injured area of the body and it is intended to absorb heat of a closed traumatic or oedematous injury by the use of conduction to transfer thermal energy. The physiological effects of cold application do include immediate vasoconstriction with reflexive vasodilatation, decreased local metabolism as well as enzymatic activity, as well as decreased demand for oxygen. Cold does tend to decrease muscle spindle fibre activity and does slow nerve conduction velocity; therefore, it is often utilized to decrease spasticity as well as and guarding of muscle. It is commonly used to alleviate the pain of minor injuries, as well as decrease muscle soreness. It has been stated that the use of ice packs in treatment does decrease the blood flow most rapidly at the beginning of the cooling period, [37] and this does occur as a result of vasoconstriction, the initial reflex sympathetic activity.

It had also been iterated that ice is not commonly utilized preceding rehabilitation or performance because of its known adverse effects to performance including decreased myotatic reflex as well as force production, and a decrease in balance immediately following ice pack therapy for 20 minutes. [38]

Nevertheless, if ice pack treatment is applied for less than 10 minutes, performance could occur without detrimental effects. It has furthermore been iterated that if the ice pack is removed at this time, athletes tend to be sent back to training or competition directly with no decrease in performance. [39]

Cryotherapy pursuant to total knee replacement

1. Total knee replacement (TKR) is a common intervention that tends to be provided for patients who have end-stage osteoarthritis of the knee. Post-operative total knee replacement surgical management does tend to include cryotherapy. Cryotherapy might slightly reduce the amount of blood loss as well as associated pain. Cryotherapy was generally safe and it was not associated with any serious adverse events. Cryotherapy could improve upon the range of movement at the knee in the first one to two weeks pursuant to surgery. Potential benefits of cryotherapy on blood loss, postoperative pain, and range of motion might be too small to justify its utilization, and the quality of the evidence was very low or low for all main outcomes. For this reason, it was stated that well-designed randomized trials are necessitated to improve upon the quality of the evidence and that the effectiveness of cryotherapy had not been clarified [40].

Cold spray anaesthetics

Freeze spray

Additional to their utilization in cryosurgery, several types of cold aerosol sprays tend to be utilized to achieve short-term pain relief. Ordinary spray cans that contain tetrafluoroethane, dimethyl ether, or substances that are similar, tend to be utilized to numb the skin preceding or possibly instead of local anaesthetic injections, and preceding other needles, small incisions, sutures, and other procedures. Other products that contain chloroethane are utilized to alleviate sports injuries, similar to ice pack therapy. [10]

Whole body cryotherapy

Cryotherapy patients during their preparation of c. 3 minutes.

It has been stated that an increasing amount of research has been undertaken on the effects of whole-body cryotherapy (WBC) upon exercise, beauty, and health and that results of research had often been inconsistent because the usage of the different types of cryo-chambers, and different periods of treatment. Nevertheless, it had become increasingly clear that WBC does have a positive effect upon muscle soreness and does increase the recovery time after exercise. [19] It had also been documented that some older papers had reported inconsistencies in the effects of whole-body cryotherapy. [10] [24]. It has additionally been iterated that the FDA had pointed out that the effects of whole-body cryotherapy does lack evidence and that whole-body cryotherapy needs to be researched more. [10] [41]

It has been iterated that cryotherapy is also increasingly being utilized as a non-drug treatment against rheumatoid arthritis, stress, anxiety, chronic pain, multiple sclerosis as well as fibromyalgia. [10] [42]. It has additionally been stated that studies for these, as well as other diseases including Alzheimer's disease and migraines are being undertaken even though more evidence does become available on the positive effects of Whole-Body Cryotherapy. [10] It has been iterated that the FDA had pointed out that the effects of Whole-Body Cryotherapy, lacks evidence and more research on the topic does need to be researched more. [43]

It has been explained that cryotherapy treatment does entail the exposure of individuals to extremely cold dry air (below −100 °C) for two to four minutes and that in order to achieve the sub-zero temperatures that are necessitated for WBC, two methods typically tend to be utilized including: liquid nitrogen and refrigerated cold air. It has been explained that during these exposures, individuals do tend to wear minimal clothing, which usually tend to consist of shorts for males, and shorts and a crop top for females. Gloves, a woollen headband covering the ears, and a nose and mouth mask, and furthermore, dry shoes and socks, tend to be commonly worn in order to reduce the risk of cold-related injury. It had been iterated that the first WBC chamber was built in Japan in the late 1970s, and this was introduced to Europe in the 1980s, and it has been utilized in the United States of America (USA) as well as within Australia over the preceding decade. [10] [24]

Adverse effects

It has been iterated that review articles on of whole-body cryotherapy had called for research studies to be undertaken in order to implement active surveillance of adverse events, which had been suspected to have been under-reported. [10] [24] It has been documented that if the cold temperatures are produced by evaporating liquid nitrogen, there is the risk of development of inert gas asphyxiation and also frostbite. [44] [45] Nevertheless, it has been stated that these risks are irrelevant within the electronically operated chambers. [10]

Partial body cryotherapy

With regard to partial body cryotherapy (PBC) devices which also do exist, it has been iterated that if the cold temperatures are produced by evaporating liquid nitrogen, there tends to be the risk of inert gas asphyxiation and also frostbite. [10] [45]

Definition / general statements related to adenocarcinoma of the prostate gland.

Distribution of Adenocarcinoma of The Prostate Gland: [46]

- It has been iterated that 95% of adenocarcinomas of the prostate had tended to be acinar type (of carcinoma and 5% of adenocarcinomas of the prostate gland tend to be ductal type of carcinoma [pathologyoutlines.com new [46]

- It has also been documented that 70% of prostate cancers tend to arise from peripheral zone of the prostate gland that is situated on the posterior and lateral aspect of the prostate gland. [pathologyoutlines.com [46]
- It has been pointed out that quite often prostate cancer does spare the transition zone of the prostate gland which is situated within the periurethral/anterior zone (TZ) of the prostate gland and that the involvement of the transition zone (TZ) by carcinoma of the prostate gland usually has tended to be the expansion of tumour from the peripheral zone of the prostate gland into the transition zone. [46]
- It has been documented that at radical prostatectomy, greater than 90% (>90%) of the prostate gland has tended to contain tumour but only 65% of the prostate glands have tended to contain prostate cancer tumour anteriorly. [46]
- It has been stated that anterior prostate cancer has tended to be associated with higher volume of prostate cancer tumour as well as resection margin positivity of tumour. [47], even though the oncology outcomes have tended to be similar to the oncology outcomes of posterior prostate cancers. [48]
- It has additionally been documented that the finding of prostate cancer tumour within biopsy has tended to entail a tumour that is clinically "significant" if the Gleason score is equal to or higher than 3+4=7 and if the length of the tumour is equal to or higher than 3 mm, within prostatectomy specimens, and the tumour is regarded as significant if the volume of the tumour is equal to or higher than 0.5 cc, or the stage of the tumour is equal to or higher than (≥) pT3a) [49]
- Extension of Tumour [46]
- Extra-prostatic extension (EPE) is most common, and has been defined as tumour in contact with extra-prostatic fat
- The prostate has a fibromuscular pseudo-capsule that is discontinuous at its apex, bladder base and anteriorly, so the "capsule" is not relevant in staging prostate cancer
- Local invasion occurs via seminal vesicles (if tumour infiltrates muscular wall) and bladder base; rarely via prostatic urethra
- Rectal invasion is rare due to tough Denonvillier's fascia which abuts pseudo-capsule; may present as anterior rectal mass, stricture or serosal implants
- Seminal vesicle invasion occurs via (a) direct spread along ejaculatory duct complex, (b) spread outside prostate, then into seminal vesicle, (c) isolated deposits of cancer in seminal vesicle with no contiguous primary cancer in the prostate. [50]
- Incidentally detected: [46]
- In cysto-prostatectomy specimens for bladder cancer, most studies had reported a 50% rate of incidental prostatic adenocarcinoma; 20% of the tumours were clinically significant [51]
- Epidemiology [46]
- It has been stated that adenocarcinoma of the prostate gland accounts for 300,000 cases per year in United States of America and the first most common cancer cause of after skin cancer, as well as it does cause 41,000 deaths per year and adenocarcinoma of the prostate gland is the cause of death after lung cancer.
- It has been documented that 20% of American men tend to be diagnosed as having carcinoma of the prostate gland their lifetimes, as well as 3% die of prostate cancer
- It has been stated that the **a**ge adjusted incidence of prostate cancer is increasing
- It has also been iterated that 99% of individuals who have clinical disease are aged over 50 years.
- It has been iterated also that a sizable minority of prostate cancers including those cancers that have been graded as Gleason score 3+3=6 (or less), had been shown almost never to metastasize to the lymph nodes [52] and lately it has been proposed to designate these lesions not even as cancer; however, by the terminology Indolent Lesion of Epithelial Origin (IDLE) [53]
    - Nevertheless, majority of pathologists endorse have endorsed that Gleason 3+3=6 cancer is still cancer [54]
- , and a variety of surgical and non-surgical management options are now available for low-grade cancer
    - Low grade or "latent" cancers do comprise of 20% in cancers in men who are in their 50's, and 70% in men in their 70's; and usually the pathologist should examine the entire gland to find the tumours.
- It has been iterated that clinical disease and high grade prostatic intraepithelial neoplasia (HGPIN) are more common in African-Americans in comparison with white men; and black men have higher stage prostate cancers at presentation, but the stage-adjusted survival is similar
- It has been documented that clinical prostate cancer disease is rare in Asians which does amount to 3 cases to 4 cases per 100,000 versus 50 cases to 60 cases per 100,000 within the United States of American white men; higher rates of prostate care was also found in Scandinavians; and all groups were found to have similar incidence of latent cancers, which had suggested the importance of environmental or other genetic factors
- It has also been documented that there tends to be no carcinoma of the prostate gland if prepubertal castration had been undertaken, as well as there tends to be a low incidence of prostate cancer associated with hyperestrogenism (liver cirrhosis)
- It has been iterated that carcinoma of the prostate gland is not associated with sexually transmitted disease, smoking, occupational exposure, diet, or nodular hyperplasia
- Sites [46]
- Prostatic apex is more often involved than the bladder base
- Peripheral zone is more often involved than transition zone or central zone
- Posterior peripheral zones are more often involved than anterior / lateral horns of the peripheral zones
- But bladder base, transitional / central zone and anterior / lateral horns of peripheral zones are more difficult to sample
- Clinical features [46]
- It has been stated that with regard to manifestations of carcinoma of the prostate gland, carcinoma of the prostate gland has tended to be detected by means of digital rectal examination (DRE), trans-urethral ultrasound scan images which does miss 30% of carcinomas of the prostate gland that are isolated, or based upon assessments for raised serum levels of prostate specific antigen (PSA) which could be either above 4 ng / dL, or increasing over time. [46]
- It has been iterated that there is some evidence which does favour the utilization of serum prostate specific antigen (PSA) that is higher than 2.5 ng / dL, as a cut-off point for prostate biopsies to miss fewer prostate cancers, particularly with regard to men who are older than 60 years. [46] [55]
- Diagnosis [46]
- It has been stated that these days, diagnosis of carcinoma of the prostate gland has most often been made based upon pathology examinations of specimens of needle biopsies of the prostate gland and on rare occasions diagnosis of carcinoma of the prostate gland has been made upon pathology examinations of trans-

urethral resection of prostate (TURP) specimens. [pathology outlines.com [46]

- Considering that trans-vesical prostatectomy and retropubic prostatectomies are undertaken in some parts of the world because of enlarged prostate glands associated with lower urinary tract symptoms for pre-operative diagnosis of benign prostate biopsies, on rare occasions some of the prostatectomy specimens could be found to contain areas of adenocarcinoma of the prostate gland. [46]

Reporting standards [pathologyoutlines.com [46]

- With regard to the standard of reporting of prostate biopsies b pathologists, it has been iterated that in a sample of prostate biops specimen from a single vial, the pathologist should report the fraction of cores that are involved by cancer [56] the percentage of each core tha contain cancer [57] and the length (in mm) of tumour on needle biops cores [58] all of these do tend to carry important prognostic value [59]
    - All reports on prostate cancer should list the fractio of cores or core fragments that contain cancer, and a least either the percentage of individual cor involvement or the length of the tumour (in mm c cm)
    - Many commercial urological pathology laboratorie and individual pathologists do tend to report bot percentage of tumour and the length of tumour
    - When there are intervening areas of benign prostate within th core biopsy, the tumour tends to be designated as multifocal c discontinuously involving the core, and one of those two term should appear in the diagnosis

Urine cytology:

With regard to utilization of urine cytology in the process of assessing prostat gland for the diagnosis of prostate gland the following points should b understood: [46]

- Urine cytology has not been used since 1980s and urine cytolog has been largely replaced by automated spring loaded 18-gaug biopsy
- Urine cytology is not useful for prostate cancer screening becaus it is difficult to identify well differentiated tumours wit utilization of urine cytology, and that it is easier fo poor/moderately differentiated tumours of the prostate gland.
- Core biopsy of prostate [46]
- High grade adenocarcinoma of the prostate gland versus hig grade urothelial carcinoma: It has been pointed out tha specimens of adenocarcinoma of adenocarcinoma of the prostat gland do contain oval nuclei with smooth borders; fine, powdery evenly distributed chromatin; large nucleolus (if present), n significant pleomorphism [60]
- normal seminal vesicle cells tend to be atypical and do simulat carcinoma but they tend to exhibit positive staining for MUC (MUC6+) [61

Transurethral resection of prostate (TURP) specimens:

- It has been stated that with regard to the finding within a TUR specimen of the prostate gland, this could either indicate a extensive spread by conventional adenocarcinoma of the prostat gland or central carcinoma of the prostate glan [pathologyoutlines.com [46]
- It has been recommended by Humphrey et al. that with the findin of prostate cancer in TURP specimens, complete sampling shoul be undertaken for patients who are younger than age 60 years [62
- With regard to the finding of prostate cancer in patients who ar older than 60 years of age, random sampling of 8 blocks of th TURP specimen should be undertaken by the pathologist [63]
- or 10 blocks (Humphrey book) can be undertaken; and if cance is detected, then complete submission would be needed. [46]
- It has also been recommended that if only high-grade PIN is found in the TURP specimen then the pathologist should embed all the tissue as well as obtain deeper levels. [46]

Frozen section diagnosis:

With regard to frozen section specimens related to the assessment of prostate cancer, the ensuing recommendations have been made for pathologists to undertake: [46]

Pathologists should look for architectural disarray or perineural invasion of the tumour.

With regard to lymph node frozen section/imprints, pathologists should be aware of the fact that 10% false negatives do exist

Laboratory tests [46]

Clinical screening: [46]

It has been pointed out that carcinomas of prostate gland do secrete 10x the prostate specific antigen (PSA) of normal tissue (in the past, and 50% had levels greater / higher than 10 mg / ml (> 10 mg/ml), BUT

The United States of America. Preventive Services Task Force (USPSTF) had issued a blanket "D" recommendation against all prostate-specific antigen (PSA) based early detection efforts for prostate cancer [64]

The American Urological Association (AUA) had counteracted the USPSTF statement [65] which had noted that this recommendation is based upon crucial misinterpretations of the risks and benefits of screening and had issued its own recommendation that men who are aged 55 years to 69 years should be offered biennial (every 2 year) screening and that men who are under the age of 40 years or over 69 years should not normally be screened. [46]

The overall impact of this controversy upon the volume of prostate biopsies prompted by an elevated PSA does seem to be minimal. [46]

Utilization of the PCA3 molecular urine assay [66]

in addition to the serum PSA tests does improve the sensitivity and specificity for cancer detection [46]

Radiology imaging [46]

It has been stated that utilization of trans-rectal ultrasound scan is the standard radiology imaging option that has tended to be utilized in the assessment of the prostate gland to identify abnormal areas within the prostate gland for biopsies of prostate gland and prostatic lesions to diagnose prostate cancer and utilization of magnetic resonance imaging (MRI) scan to guide needle biopsies was a new innovation [67]

Additionally globally now the usefulness of MRI scan in identifying abnormal areas within the prostate that need to be targeted for biopsy of prostatic lesions in order to ensure all abnormal looking areas are targeted for biopsy for more reliable diagnosis of prostate cancer as well as the location of the prostate gland has been realized and this has led to an increased utilization of MRI scanning of the prostate gland in the initial assessment of patients who have raised serum PSA levels in planning the assessment regarding the biopsies of prostates to ascertain if the prostate glands do contain cancer.

In district hospitals of countries that do not have facilities for CT scan and MRI scans, ultrasound scan of the abdomen and pelvis in addition to chest X-ray tend to be utilized for the initial staging and follow-up assessments of individuals who are diagnosed as having prostate cancer and in addition chest x-rays tend to be undertaken in these areas of the world.

CT scan-guided biopsies of the prostate as well as well as CT scan of thorax, abdomen and pelvis tend to be undertaken for the initial investigation, and staging of prostate cancer as well as follow-up assessments of patients who have undergone various types of treatment for prostate cancer including radical radiotherapy, radical prostatectomy, cryotherapy, irreversible electroporation and radiofrequency ablation of the prostate cancer.

CT scan also tends to be undertaken at regularly periodic intervals as further follow-up assessments of patients who have small low-risk prostate cancers that are being assessed regularly under active surveillance system as well as those patients who are undergoing watchful waiting for newly diagnosed prostate cancer to find out those who should in the future undergo treatment.

- MRI scan-guided biopsies of the prostate as well as well as MRI scan of thorax, abdomen and pelvis tend to be undertaken for the initial investigation, and staging of prostate cancer as well as follow-up assessments of patients who have undergone various types of treatment for prostate cancer including radical radiotherapy, radical prostatectomy, cryotherapy, irreversible electroporation and radiofrequency ablation of the prostate cancer.
- MRI scan also tends to be undertaken at regularly periodic intervals as further follow-up assessments of patients who have small low-risk prostate cancers that are being assessed regularly under active surveillance system as well as those patients who are undergoing watchful waiting for newly diagnosed prostate cancer to find out those who should in the future undergo treatment
- Isotope bone scan tends to be undertaken for patients whose serum PSA levels are higher than 20 ng/dL to ascertain if the patients do have bone metastases.
- Positron Emission -Computed tomography scans also tend to be undertaken in the follow-up assessments of patients who have undergone treatment of curative intent for localized prostate cancer to ascertain if they have developed small active metastases in order to provide another treatment to eradicate the small recurrent tumour or tumours.
- Prognostic factors
- Some of the documented prognostic factors associated with the management of adenocarcinoma of the prostate gland include: [46]
- Stage of the tumour, the Gleason score but the Gleason score of the tumour is stated not to be useful with regard to minimal tumour. [68] surgical margins (involvement and non-involvement of the surgical margins by the tumour), preoperative serum prostate specific antigen (PSA) level, perineural invasion
- Angiolymphatic invasion [69]
- The size of lymph node metastases [70]
- The prognosis tends to be poor if the Gleason score is > 6, serum PSA > 40 ng/mL, and the tumour stage is 3 or higher, Caucasian [1] [46]
- Patients who are aged less than < 20 years and even though such a type of: carcinoma is rare in less than 20-year-old individuals, such types of tumours usually tend to be associated with obstructive symptoms, advanced stage of tumour, high grade of tumour, poor response to treatment, as well as survival < 1 year.[46]
- Recurrence pursuant to radical prostatectomy: [46]
- The median interval has tended to be 40 months
- The mean sized of the tumour 3.2 mm
- Often tends to lack overt histological features of malignancy, but they need lower threshold for the diagnosis because atypical prostate glands should not be present at all. [72]

Treatment

The common forms of treatment of significant prostate cancers that are localized include:

- Radical prostatectomy.
- Radical radiotherapy by means of external beam radiotherapy or brachytherapy.
- Some of the other less invasive treatment options for localized prostate cancer that are low-risk and medium (intermediate) - risk tumours include:
- Radiofrequency ablation of the prostate cancer.
- Irreversible electroporation of the prostate cancer
- Cryotherapy of the prostate cancer.
- Microwave therapy of prostate cancer.

It has been stated that radical prostatectomy is not warranted if there is evidence of tumour positive pelvic nodes, and that brachytherapy which entails insertion of radioactive seeds tends to be undertaken in some centres. Targeted focal cryotherapy, external beam radiotherapy, tend to be undertaken in some oncology centres.

Active surveillance tends to be adopted in cases of low-grade tumours in the younger age group and if there is any subsequent increase in the size of the tumour or repeated increase in the serum PSA levels then treatment of curative intent tends to be undertaken but tumours that do not demonstrate further growth in size or rise in serum PSA continue to be managed by active surveillance.

Watchful waiting tends to be adopted for low grade tumours, localized tumours or in individuals who have limited life expectancy.

Chemotherapy or hormonal therapy (LHRH analogs, antiandrogens, orchidectomy tend to be provided in cases of advanced prostate cancers.

With regard to adenocarcinomas of the prostate gland it has been iterated that majority of the prostate cancers tend to be androgen sensitive and that serum serial PSA level testing is used to monitor the response of prostate cancer to treatment.

Immunotherapy is an additional treatment which tends to be provided in a number of oncology departments in well-resourced and developed countries.

Macroscopic features [46]

- Gritty and firm, grey-yellow, poorly delimited, more easily felt than seen
- Accurate identification of prostate cancer by gross inspection is possible in only 63% of cases, with a 19% false positive rate [73]
- Microscopy histopathology features [46]
- Pattern depends upon the Gleason grade of the tumour.
- Small glands, sometimes medium to large glands, papillary or cribriform glands or solid growth, single cells or necrosis
- Cytoplasm usually finely granular, may be clear/foamy due to intracellular lipid
- Nuclear enlargement, hyperchromasia, prominent nucleoli (>3 microns is specific for malignancy, >1 micron is suggestive)
- 75% of high-grade PIN may abuts carcinoma [74]
- Mitotic figures extremely rare except in high grade tumours
- Malignant transformation is accompanied by loss of basal cells, first reported by Totten in 1953 [75]
- Glands are “too many, too small, too crowded” (need not be clustered)
- Most common pattern is infiltrative, small to medium sized glands (Gleason 3) - detect on low power as closely packed glands with irregular outline, smooth luminal surface, splitting stromal fibres
- Large gland pattern also occurs and resembles atrophy
- Less common, usually in transition zone or central zone, is a Gleason 2 pattern of small sized glands forming expansive nodules on low power, regular round glands, small size, usually not multifocal.

- Assignment of Gleason 1 is discouraged in all instances and assignment of Gleason 2 is discouraged in biopsies (see Grading).
- Cribriform pattern may appear intraductal with preserved basal cell layer, but is usually invasive and if so should be graded as Gleason 4. [76]
- Single cell infiltration (Gleason 5 pattern) may resemble lobular carcinoma of breast
- Ancillary findings in adenocarcinoma: perineural invasion, glomerulation, mucinous fibroplasia (collagenous micronodules, rarely, perineural invasion is the only diagnostic feature of malignancy [77]
- Features favoring but not diagnostic of adenocarcinoma: small glands between larger glands, crowded glands that stand out from adjacent benign glands, prominent nucleoli in at least 10% of cells, nuclear enlargement, hyperchromatic nuclei, luminal blue mucin, amphophilic cytoplasm, mitotic figures, crystalloids, adjacent high-grade PIN. [77]
- Features associated with false positive diagnoses: atrophic cytoplasm, atypical glands associated with inflammation, small crowded glands merging with larger benign glands (adenosis), distinctive features in Central Zone [78]
- high grade PIN, small atypical crowded glands adjacent to high grade PIN (may be tangential sectioning of PIN)
- Note: As discussed in later sections, the diagnosis of ASAP (atypical small acinar proliferation suspicious for cancer) may apply if strict cancer criteria are not met
- Angiolymphatic invasion
- Not commonly seen [46]
- Calcifications
- More common in benign than malignant prostate, but present in Gleason pattern 5 with comedo-type necrosis (dystrophic calcification), within lumina of Gleason pattern 3 cribriform and small acinar types, and within collagenous micronodules. [46] [79]
- Cellularity of vessels
- In radical prostatectomy specimens, increased vessel cellularity may be associated with higher grade tumours. [46] [80]
- Corpora amylacea [new 46]
- Don't confuse with crystalloids
- Benign but may be found in tumour
- May arise from release of prostate secretory granules
- Remnants condense to form eosinophilic bodies, which adsorb and layer onto surface of prostatic corpora amylacea, causing them to enlarge [81]
- Crystalloids [46]
- Resemble Bence-Jones crystals (Ig kappa/lambda)
- Seen in lumina of 10-23% of carcinomas, usually Gleason 3
- Rarely seen in benign glands or metastatic foci [82]
- Composed of inorganic sulphur
- Deeply eosinophilic, rhomboid
- In benign specimens, not a significant risk factor for subsequent diagnosis of cancer [82] [83]
- Same sulphur content as prostate secretory granules and corpora amylacea [81]
- Mucin [46]
- Acidic mucin found in lumina in 2/3
- Looks basophilic or deeply eosinophilic, confirm with Alcian blue or colloidal iron stains
- Normal prostate secretes neutral mucins, although acid mucins also seen in adenosis and postradiotherapy
- Perineural invasion (PNI) [46]
- Common (85% of all tumours)
- When present in needle core biopsy, suggests extra-prostatic extension, [84] but other authors [85] stated that neither presence or absence of peri-neural carcinoma or number or percentage of tumour positive nerves related to the pathological stage of the prostate cancer in univariate or multivariate analyses. The amount of carcinoma within the prostate needle biopsy tissue, using multiple measurements but not perineural invasion, is a significant histologic attribute predictive of pathologic stage and margin status for men who have prostate specific antigen screening detected prostatic carcinoma predict the pathology stage of the tumour. Reporting of several measures of carcinoma extent in needle biopsy tissue is recommended. [85]
- Diameter of perineural invasion may be prognostic factor [86]
- May mediate local tumour spread via tumour expression of nerve cell adhesion molecule [87]
- Outdated theories are: (a) tumour spreads via perineurial lymphatics (they don't exist); (b) perineurial space represents tissue plane of least resistance, [88] but this doesn't explain why morphologically similar tumours have varying neurotropism); (c) there is different nerve distribution in malignant vs. benign specimens (actually is similar, S100 not useful for identifying PNI, [89]
- Prostatic secretory granules [46]
- Identifiable with strong glutaraldehyde fixation
- 1 micron, brightly eosinophilic granules (PSA+, PAP+) that fill cytoplasm of secretory cells
- Reduced in carcinoma and high-grade PIN [90]
- Formaldehyde causes granules to appear empty [91]
- Differential diagnosis of adenocarcinoma of the prostate gland. [46]
- Clinical differential diagnosis of firm prostate is granulomatous prostatitis, nodular hyperplasia, tuberculosis of the prostate, infarct of the prostate, lithiasis of the prostate.
- Differential diagnosis of elevated PSA is nodular hyperplasia (mild increase in PSA), acute or chronic prostatitis, [92] infarct, trauma (biopsy, TURP), and rarely other tumours (salivary duct carcinoma may secrete PSA. [[93]
- For benign disease, increase in PSA is usually transient

[B] Miscellaneous Narrations And Discussions From Some Case Reports, Case Series, And Some Studies Related to Cryotherapy Of Prostate Cancer As Treatment Of Curative For Localized Prostate Cancer As Well As Palliative Treatment For Radical Prostatectomy, Radical Radiotherapy / Hormone Treatment Persistence Or Recurrence Of Tumour (Biochemical Failure Or Overt Recurrence / Persistence Of Tumour.

Aus [94] in 2006 evaluated the current status of high-intensity focused ultrasound (HIFU) and cryosurgery as the primary treatment option in patients who had prostate cancer. Aus [94] undertook a Med Line search utilizing specified search terms on February 28, 2005. This search had rendered 150 papers related to HIFU and 566 papers related to cryosurgery. Aus found that very few of the papers had presented original outcome data which Aus included in the review documentation. Aus [94] summarised the results as follows:

- No controlled trial was available for analysis, and no survival data had been reported
- No validated biochemical, surrogate end point was available for any of the two treatment options
- The undertaking of HIFU was associated with progression-free survival, based upon serum prostate-specific antigen results ± histopathology findings of biopsy data of 63–87% which was projected between 3 years to 5 years data, but the median follow-up in the studies had ranged from 12 months to 24 months.
- Negative postoperative biopsies were obtained in 82% to 94% of the patients.
- The complications had been reduced by the combination of transurethra resection of the prostate gland and HIFU.
- Cryosurgery of prostate cancer was associated with a progression-fre survival of 36% to 92% which was projected from 1 year to 7 years data depending upon the risk groups and definition of failure.
- Negative prostate biopsies were obtained in 72% to 87% of the cases, bu no biopsy data were available for the currently utilized third-generatio cryotherapy machines.
- The complications did appear to be lower with the third-generatio machines.

Aus [94] made the following conclusions:

- None of the evaluated treatment options had enough dat available to support their use as an alternative treatment t established treatment options of surgery, and radiotherapy fc localised adenocarcinoma of the prostate gland. cancer.
- Until further data become available, the utilization of bot treatment options should be restricted to patients who are not fit to undergo the established treatment options who still have the need for local treatment.

Tsivian et al. [95] stated that focal treatment for carcinoma of the prostat gland had emerged as an interesting concept as a less morbid option for th therapy of localized low-risk primary adenocarcinoma of the prostate gland Tsivian et al. [95] iterated that despite the growing interest in focal treatmen this approach had not yet at the time of publication of their article gained sufficient popularity not had provided enough supporting data to be discussed outside the confines of experimental application. Tsivian et al. [95] summarized the available data related to focal cryotherapy of prostate cancer and they focussed upon the targets that need to be achieved in order to increase the utilization of focal cryotherapy of carcinoma of the prostate gland to clinical practice. Tsivian et al. [95] advised that a cautious approach to the selection of candidates as well as the generation of solid scientific data would result in wide consensus opinion on the selection strategies for patient as well as follow-up schemes would provide the necessary tools to take the path of focal cryotherapy. At the time of publication of their article focal cryotherapy data had reported excellent short-term results and a favourable quality of life profile. Tsivian et al. [95] iterated that even though the future of focal cryotherapy has been debatable, a growing amount of science had been generated in support of cryotherapy which is a minimally invasive treatment option for carcinoma of the prostate gland.

Anastasiadis et al. [96] iterated that recent advances in cryosurgery of the prostate had led to the ability to treat tumours successfully with associated decreased morbidity. The patients' perspectives of this relatively new treatment technique; nevertheless, had not yet been addressed. Anastasiadis et al. [96] undertook a study in order to compare health related quality of life (QoL) as well as prostate-associated symptoms in patients pursuant to primary and salvage cryoablation for clinically localized prostate cancer with utilization of a self-administered questionnaire. With regard to the methods, Anastasiadis et al. [96] reported that a total of 131 consecutive patients who had undergone cryoablation of the prostate gland between 1997 and 2001 were included in their confidential mailing study. The patients were reported to be either (a) patients who had localized prostate cancer with contraindications for them to undergo radical surgery, including patients who had refused other forms of treatment, or (b) patients who had locally recurrent prostate cancer after failure of radiotherapy. All of the patients had received 3 months of neoadjuvant androgen deprivation therapy preceding their cryosurgery and they were surgically treated by the same surgeon with the utilization of an argon-based system. Anastasiadis et al. [96] utilized the EORTC QLQ-C30, a commonly used, multi-dimensional instrument together with a supplementing, prostate-cancer-specific module. Anastasiadis et al. [96] summarized the results as follows:

- Eighty-one out of the 131 patients that amounted to a response rate 62%, had returned the questionnaires.
- The two groups were comparable with regard to age with the mean age of 72.8 years versus 70.1 years for the primary and the salvage group of patients, respectively; p=0.22).
- The overall QoL scores were high in both groups.
- The primary cryotherapy patients had fared significantly better with regard to their physical (p=0.005) and social (p=0.024) functioning in comparison with the salvage cryotherapy patients.
- The most prominent prostate-related symptom associated with both patient groups was sexual dysfunction which was followed by urinary symptoms, which were significantly more severe in the salvage cryotherapy treatment group of patients (p=0.001).
- Incontinence rates were 5.9% and 10% in the primary and the salvage cryotherapy group of patients, respectively.
- Severe erectile dysfunction was reported in 86% and 90% of the primary cryotherapy and the salvage cryotherapy group of patients, respectively.

Anastasiadis et al. [96] made the ensuing conclusions:

- Their study had demonstrated that, in selected patients, cryotherapy is a treatment option which does have a functional outcome that is comparable to traditionally utilized prostate cancer treatments.
- More information regarding QoL is necessary for the appropriate counselling of patients and individual decision-making in the presence of various treatment alternative options.

Loening et al. [97] reported that cryosurgical destruction of primary adenocarcinoma of the prostate gland was undertaken via the perineal route in 215 patients during a 12-year period. Loening et al. [97] stated the following:

- The average age of the patients was 66 years.
- The stage of the disease had varied from stage B to D.
- In 74% of the patients, no clinical evidence of tumour was found within the prostatic fossa pursuant to the cryosurgery.
- Few of the patients did need to undergo transurethral surgery and none of the patients had needed repeated transurethral resections for obstructive symptoms.

Loening et al. [97] concluded that their experience had suggested that local destruction of prostatic carcinoma could be achieved with little morbidity and mortality.

Bonney et al. [98]] reported that from 1969 through 1976 they had undertaken cryosurgery in 229 cases of carcinoma of the prostate gland. They stated that their article had presented the survival in cryosurgery and other treatment groups. Bonney et al. [98] additionally stated that in every stage, despite a preponderance of large primary tumours and poor-risk patients, cryosurgery did match total prostatectomy and did compare favourably to other modalities of treatment, including radiotherapy, within their centre and elsewhere. Bonney et al. [98] iterated that according to previous authors, and in view of the findings from their studied data, eradication of the local lesion is associated with better survival even in advanced cases. Bonney et al. [98] concluded that

cryosurgery does provide a safe, and effective method of treatment for prostate cancer.

Bonney et al. [99] reported that from 1969 through 1976, they had performed cryosurgery in 229 cases of carcinoma of the prostate gland. They stated that majority of the patients had bulky, locally extensive primary tumours, and one-half of them had disseminated disease. They also stated that via the open perineal approach, which gave exposure for an adequate freeze, cryosurgery had been well tolerated by the patients. The primary surgical goal was to reduce or eliminate the local lesion in order to minimize subsequent cancer-related lower urinary tract problems as well as to cure those patients who had truly localized disease. They found that with regard to every case, cryosurgery had produced dramatic shrinkage of the local lesion. Four to eight weeks pursuant to the cryotherapy treatments a local recurrence was suspected in 13 per cent of the cases, and 41 per cent of the patients eventually had some evidence of a recurrent cancer nodule or persistent cancer in the urinary bladder neck. In a series of statistical analyses, they had related these recurrences to other clinical factors. Bonney et al. [99] concluded that cryosurgery of prostate cancer had been a safe, and effective way to reduce or eliminate the primary carcinoma of the prostate gland, even in patients who had large local lesions.

Pisters [100] iterated that even though serum prostate-specific antigen testing and treatment of prostate cancer does undoubtedly save lives, growing concerns do exist regarding the overtreatment of prostate cancer. They additionally stated that there had also been a shift toward less invasive approaches to the treatment of prostate cancer including cryotherapy. They also said that cryotherapy had undergone considerable change and that it is important for clinicians to be aware of the existence of cryotherapy to support its use. Pisters [100] made the following iterations about cryotherapy: Pisters made the following general statements about cryotherapy:

- Technical improvements in the delivery of cryotherapy systems had reduced the complications associated with primary cryotherapy to a low as well as an acceptable level.
- With the latest generation argon-based cryoprobes, the risk of developing long-term incontinence which has been defined as pad usage tends to be typically less than 5% and the risk of developing rectal fistula tends to be 0.5% or less than 0.5%.
- The Cryotherapy-On-Line Data Registry (COLD) utilized the Phoenix (nadir + 2 ng/ml definition to report 5-year biochemical disease-free survival in 1198 patients as 91% in low-risk prostate cancer, 78% in intermediate-risk prostate cancer, as well as 62% in high-risk prostate cancer patients.
- These biochemical results did compare quite favourably to the results of radiotherapy as a monotherapy option of treatment.
- A recent trial of cryotherapy in comparison with radiotherapy did show similar biochemical outcomes and significantly lower rates of positive post-treatment prostate biopsies for carcinoma in the cryotherapy treated group of patients.
- Routine prostate biopsies were negative for carcinoma of the prostate in 87% to 98% of patients pursuant to one or more cryotherapy treatments.
- The undertaking of focal cryotherapy did demonstrate promising early results with regard to potency rates that were between 71% and 90% in the treated patients.
- Pisters [100] made the ensuing summations:

- Cryotherapy of whole-gland of the prostate is ready for prime based upon favourable biochemical outcomes, a high rate of tumour negative post-treatment biopsies as well as a low as well acceptable rate of complications.
- The long-term biochemical outcomes pursuant to cryotherapy of prostate cancer do compare favourably to those that had been achieved pursuant to radiotherapy as monotherapy.
- The rate of tumour negative post-treatment biopsies of the prostate did appear to be higher for cryotherapy in comparison with following initial radiotherapy of prostate cancer.
- Taken together, the results had indicated that clinicians need to regard cryotherapy as an alternative treatment option to initial radiotherapy.
- Focal cryotherapy of prostate cancer was associated with high potency rates and cryotherapy of prostate cancer does warrant further investigation.

Berglund et al. [101] made the ensuing iterations related to adenocarcinoma of the prostate gland:

- Carcinoma of the prostate gland is the most common cause of cancer in men within the United States of America and the third leading cause of cancer death within the United States of America.
- The majority of men who do develop carcinoma of the prostate gland will either have their cancer successfully treated or they will die with and not of carcinoma of the prostate gland.
- Since the introduction of serum prostate-specific antigen (PSA) screening, the risk of an American man dying of carcinoma of the prostate gland had been reduced by over 40 %, but at a cost of treating many clinically insignificant adenocarcinomas of the prostate gland.
- Cryotherapy of the prostate gland for the treatment of primary or recurrent carcinoma of the prostate gland is efficacious and safe relative to the other radical treatments which are available.
- Focal cryotherapy for prostate cancer has remained investigational, even though appealing for the preservation of sexual function.
- Bahn et al. [102] made the ensuing general statements related to cryotherapy of prostate cancer:
- The evolution of cryotherapy for carcinoma of the prostate gland is likely to emanate in parenchyma-sparing modifications adjacent to the urethra as well as neuro-vascular bundle.
- The results of the initial series of focal therapy in order to minimize cryotherapy-related morbidity without compromising the oncology control had been encouraging; nevertheless, it had been limited in short-term outcomes.

Bahn et al. [102] reported their retrospective study to document (1) the median 3.7 year- follow-up experience of primary focal cryotherapy in the treatment of clinically unilateral adenocarcinoma of the prostate gland with the oncology and functional outcomes, as well as (b) matched-pair analysis with contemporaneous patients who had undergone radical prostatectomy (RP). With regard to the design, setting, and participants of the study, Bahn et al. [102] stated that over 8.5 years between September 20002 and March 2011, focal cryoablation which had been defined as ablation of one lobe of the prostate gland was undertaken in 73 carefully selected patients who had biopsy-proven, clinically unilateral, low-intermediate risk carcinoma of the prostate gland. All of the patients had undergone trans-rectal ultrasound scan (TRUS) and Doppler-guided sextant and targeted biopsies at entry. With regard to the Outcome, measurements and statistical analysis, [102] Bahn et al. [102] reported that the post-therapy follow-up had included measuring serum prostate-specific antigen (PSA) level every 3 months to 6 months; the undertaking of TRUS biopsies at 6 months to 12 months and yearly; as was indicated; as well as utilization of validated symptom questionnaires. Matched-pair analysis was utilized to compare the oncology outcomes of focal cryotherapy and radical prostatectomy (RP) and these were matched for

age, serum PSA, clinical stage of the tumour, and the biopsy Gleason score. Bahn et al. [102] summarized the results as well as limitations of the study as follows:

- Complete follow-up was available in 70 patients and the follow-up had ranged between 1 year and 8.5 years and the median follow-up was 3.7 years.
- No patient had died or developed metastases.
- The pre-cryotherapy mean serum PSA level was 5.9 ng/ml and the Gleason score was 6 (n=30) or 7 (n=43).
- The post-cryotherapy mean serum PSA level was 1.6 ng/ml (which amounted to 70% reduction in serum PSA in comparison with the pre-cryotherapy; p<0.001).
- Of 48 patients who had undergone post-cryotherapy biopsy of the prostate, 36 patients that amounted to 75% of the patients, had tumour negative biopsies; positive biopsy for cancer in 12 cases (n=12) and out of these 11 occurred in the untreated contralateral (n=11) prostate lobe and 1 occurred in the treated ipsilateral lobe (n=1) prostate lobe.
- Complete continence (no pads) and potency sufficient for intercourse were documented in 100% and 86% of patients, respectively.
- Matched-pair comparison of focal cryotherapy and radical prostatectomy (RP) revealed similar oncology outcome, which was defined as needing salvage treatment.
- Bahn et al. [102] concluded that:
- Primary focal cryoablation for low-intermediate risk unilateral cancer did demonstrate encouraging oncology and functional outcomes over a median follow-up of 3.7 years.
- Close surveillance with the undertaking of follow-up whole-gland biopsies is mandatory pursuant to focal cryotherapy for prostate cancer.

Izawa et al. [103] stated that severe complications of salvage cryotherapy could be debilitating as well as chronic, but these complications could be managed by the undertaking of definitive extirpative surgical procedures. Izawa et al. [103] evaluated the effectiveness of the major surgical procedures undertaken to manage these complications and they assessed patient survival as well as the complications that ensued the extirpative surgery. With regard to the materials and methods of the study, Izawa et al. [103] reported that between 1992 and 1995, salvage cryotherapy was undertaken in 150 men who had prostate biopsy proven, locally recurrent carcinoma of the prostate gland pursuant to radiotherapy and / or systemic therapy. Izawa et al. [103] retrospectively reviewed the charts of the patients in order to assess the complications that were managed by extirpative surgery. Izawa et al. [103] summarized the results as follows:

- Extirpative surgery was undertaken in 6 out of the 150 patients for serious complications which included the following: uncontrollable haematuria, osteitis pubis, recto-urethral fistula, refractory perineal pain, urinary bladder outlet obstruction, as well as complete urinary incontinence.
- Cystoprostatectomy was undertaken on 4 patients out of which 3 patients had undergone en-bloc pubic symphysectomy. With regard to the remaining 2 men, salvage prostatectomy was undertaken with closure of the bladder neck and creation of a continent catheterizable stoma.
- The undertaking of the surgery, successfully managed the severe cryotherapy complications in all 6 cases.
- The complications of extirpative surgery did include: superficial wound infection in 1 patient, and incisional hernia in another patient.
- Serum prostate specific antigen (PSA) was undetectable in 4 of the 6 men at 36 months, 38 months, 39 months, and 42 months, and serum PSA was detectable in 2 men at 31 months, and 41 months respectively.
- Izawa et al. [103] made the following conclusions:
- Extirpative surgery could successfully alleviate severe salvage cryotherapy complications without major additional morbidity.

Long survival duration does justify the undertaking of extirpative surgery in select patients who develop severe complications pursuant to undergoing salvage cryotherapy.

Ismail et al. [104] reported the short- to intermediate- term experience of utilizing salvage targeted cryoablation of prostate (TCAP) for the treatment of recurrence of localized carcinoma of the prostate after radiotherapy. With regard to the patients and methods, Ismail et al. [104] reported that between May 2000 and November 2005, 100 patients had undergone salvage TCAP for recurrent carcinoma of the prostate gland pursuant to undergoing radiotherapy. The mean follow-up of the patients was 33.5 months. All of the patients had biopsy confirmed recurrent carcinoma of the prostate gland. They defined biochemical recurrence-free survival (BRFS) utilizing a serum prostate-specific antigen (PSA) level of < 0.5 ng / ml, as well as by applying the American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical failure. The patients were stratified into three risk groups including high risk group that comprised of 68 men, intermediate-risk group which comprised of 20 men and low-risk group that comprised of 12 men.

Ismail et al. [104] summarised the results as follows:

- There were no operative or cancer-related deaths.
- The 5-year actuarial BRFS was documented to be 73%, 45% and 11% for the low-, intermediate- and high-risk groups, respectively.
- The complications did include: incontinence in 13% of the patients, erectile dysfunction in 86% of the patients, lower urinary tract symptoms in 16% of the patients, prolonged perineal pain in 4% of the patients, urinary retention in 2% of the patients, and recto-urethral fistula in 1% of the patients.

Ismail et al. [104] concluded that salvage TCAP is a safe as well as an effective treatment for localized prostate cancer recurrence after radiotherapy.

Shelley et al. [105] stated that carcinoma of the prostate gland is a common cancer which tends to affect elderly men and in some of these men the carcinoma will prove fatal. They also stated that standard treatments for localized carcinoma of the prostate gland do include surgery (radical prostatectomy), radiotherapy and active monitoring. They furthermore iterated that new emerging treatment options are being evaluated with the aim of reducing the complication rates that tend to be associated with standard treatments of prostate cancer as well as developing an effective treatment and also that one such modality is cryotherapy, which is a procedure that introduces probes directly into the tumours within the prostate gland and kills the malignant cells by a freezing process. Shelley et al. [105] undertook a review which was aimed at evaluating the relative clinical as well as economic benefits of cryotherapy in comparison with standard treatments for the primary therapy of localized carcinoma of the prostate gland. With regard to the methods of their search, Shelley et al. [105] included an electronic search of MEDLINE from 1996 to December 2006, and also EMBASE (Exerpta Medica Database), the Cochrane library, ISI Science Citation Index, Database of Abstracts and Reviews of Effectiveness (DARE), and LILACS tin order to ascertain all relevant published randomized trials of cryotherapy for localized carcinoma of the prostate gland. They also searched Cancerlit→ and HealthSTAR databases to their final date. They additionally undertook handsearching of relevant journals. With regard to their selection criteria, Shelley et al. [105] iterated that only published randomized trials which had compared the effectiveness of cryotherapy with radical prostatectomy, radiotherapy or active monitoring for the primary treatment of men who had localized carcinoma of the prostate gland were eligible for inclusion in their review. With regard to the collection and analysis of data, Shelley et al. [105] extracted data from eligible studies, and they had included study design, participants, interventions and outcomes. They also stated that their primary outcome measures included biochemical disease-free survival, disease-free

survival as well as treatment-induced complications. Their secondary outcomes did include disease-specific survival, overall survival, quality-of-life outcome measures and economic impact measures. Shelley et al. [105] summarized the results as follows:

- There were no randomized trials found which had compared cryotherapy with other treatment options for the primary treatment of localized carcinoma of prostate gland.
- All studies that they had identified were case series.
- In order to indicate the level of the available evidence, studies which evaluated cryotherapy as a primary treatment, utilizing trans-rectal ultrasound scan-guidance and urethral warming in at least 50 patients who had localized carcinoma of the prostate gland and a minimum of one year follow up, were reviewed by Shelley et al. [105].
- Shelley et al. [105] identified eight case series which complied with these criteria; two of the case series were retrospective. The patients that were recruited were 1483 in total and their ages had ranged between 41 years and 84 years. The stages of the carcinomas were stages T1 = 0 to 43%, T2 = 24 to 88%, T3 = 1 to 41%, and T4 = 0 to 14%.
- The mean pre-operative serum prostate specific antigen (PSA) level of the patients had ranged from 9.7 ng/mL to 39 ng/mL, with their Gleason scores were < 7 and ranging from 6 to 37%.
- One additional study which had compared cryotherapy (total cryotherapy and standard cryotherapy with urethral preservation) with radical prostatectomy was also found and reviewed. With regard to this study the success rates, which was defined as a post-treatment serum PSA of 0.2 ng/mL or less than 0.2 ng/mL, were reported as 96% for total cryotherapy, 49% for standard cryotherapy and 73% for radical prostatectomy.
- Four studies had not monitored the temperature of the cryotherapy procedure and they reported that 17% to 28% of the patients had a positive biopsy following cryotherapy with a mean serum PSA nadir of 0.55 to 1.75 ng/mL (median 0.4 to 1.85 ng/mL).
- The other four studies utilized thermocouples to monitor the temperature of the cryo-procedure and they reported progression-free survival rates of 71% to 89% with 1.4% to 13% of the patients having a carcinoma positive biopsy post-cryotherapy.
- At 5 years, the overall survival rate was reported to be 89% to 92% in two studies, and disease-specific survival as 94% in one study.
- The major complications that were found in all of the studies included impotence in 47% to 100% of the patients, incontinence in 1.3% to 19% of the patients, and urethral sloughing in 3.9% to 85% of the patients, with less common complications of fistula in 0% to 2% of the patients, bladder-neck obstruction in 2% to 55% of the patients, stricture in 2.2% to 17% of the patients and pain in 0.4% to 3.1% of the patients.
- Majority of the patients were sent home the following day which was reported to have ranged from 1 day to 4 days.
- Shelley et al. [105] made the ensuing conclusions:
- Cryotherapy does offer a potential alternative option of treatment to standard therapies for the primary treatment of localized carcinoma of the prostate gland.
- Nevertheless, the poor quality of the available studies had made it difficult to ascertain the relative benefits of cryotherapy of prostate cancer.
- Randomized trials are required to fully evaluate the full potential of cryotherapy in men who have this disease.
- Patients who select cryotherapy as their treatment option for prostate cancer should be made fully aware of the reported efficacy, complications and the low-grade evidence from which these data were derived.

Jung et al. [106] made the ensuing iterations:

- Traditionally, radical prostatectomy and radiotherapy with or without androgen deprivation treatment had been the main treatment options that tend to be attempted to cure men who have localized or locally advanced carcinoma of the prostate gland.

Cryotherapy is an alternative treatment option for carcinoma of the prostate gland which involves freezing of the whole prostate gland which is referred to as whole gland therapy or only the cancer which is referred to as focal therapy, however, it is not clear how effective cryotherapy is in comparison to other treatment options.

Jung et al. [106] assessed the effects of cryotherapy (whole gland or focal) compared with other interventions for the primary treatment of clinically localized (cT1-T2) or locally-advanced (cT3) non-metastatic carcinoma of the prostate gland. With regard to the search methods, Jung et al. [106] updated a previously published Cochrane Review by undertaking a comprehensive search of multiple databases (CENTRAL, MEDLINE, EMBASE), clinical trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform) and a grey literature repository (Grey Literature Report) up to 6 March 2018. Jung et al. [106] also searched the reference lists of other relevant publications and conference proceedings. Jung et al. [106] did not apply any language restrictions. With regard to the selection criteria, Jung et al. [106] included randomized or quasi-randomized trials which had compared cryotherapy with other interventions for the primary treatment of carcinoma of the prostate gland. With regard to data collection and analysis, Jung et al. [106] stated that two independent reviewers had screened the literature, extracted data, as well as they assessed the risk of bias. Jung et al. [106] undertook statistical analyses utilizing a random-effects model and they interpreted them according to the Cochrane Handbook for Systematic Reviews of Interventions. Jung et al. [106] rated the quality of evidence (QoE) according to the GRADE approach. Jung et al. [106] summarized the main results as follows:

They had included only one comparison of whole gland cryotherapy versus external beam radiotherapy, which was informed by two trials that included a total of 307 randomized participants.

The median age of the patients in the included studies was around 70 years.

The median follow-up of the patients in the included studies had ranged from 100 months to 105 months.

Jung et al. [106] summarized the primary outcomes as follows:

They were uncertain about the effect of whole gland cryotherapy in comparison with radiotherapy on time to death from prostate cancer; hazard ratio (HR) of 1.00 (95% confidence interval (CI) 0.11 to 9.45; 2 trials, 293 participants; very low QoE); which would correspond to zero fewer death from prostate cancer per 1000 men (95% CI 85 fewer to 520 more).

They were equally not certain about the effect of quality of life-related urinary function and bowel function (QoL) at 36 months utilizing UCLA-Prostate Cancer Index score for which higher values (range: 0 to 100) do reflect better quality of life using minimal clinically important differences (MCID) of 8 and 7 points, respectively; mean difference (MD) of 4.4 (95% CI −6.5 to 15.3) and 4.0 (95% CI −73.96 to 81.96), respectively (1 trial, 195 participants; very low QoE).

They were also not certain about sexual function-related QoL using a MCID of 8 points; MD of −20.7 (95% CI −36.29 to −5.11; 1 trial, 195 participants; very low QoE).

Finally, they were also not certain about the risk for major adverse events; risk ratio (RR): 0.91 (95% CI 0.47 to 1.78; 2 trials, 293 participants; very low QoE); which does correspond to 10 fewer major adverse events per 1000 men (95% CI 58 fewer to 86 more).

With regard to the secondary outcomes, Jung et al. [] stated that they were very uncertain about the effects of cryotherapy upon the time to death from any cause (HR 0.99, 95% CI 0.05 to 18.79; 2 trials, 293 participants; very low

QoE), and time to biochemical failure (HR 2.15, 95% CI 0.07 to 62.12; 2 trials, 293 participants; very low QoE).

- The rates of secondary interventions for treatment failure and minor adverse events had either not been reported in the trials, or the data could not be utilized for analyses.
- They found no trials which had compared whole gland cryotherapy or focal cryotherapy to other treatment options such as radical surgery, active surveillance, watchful waiting or other forms of radiotherapy.
- Jung et al. [106] made the following conclusions:
- Based upon very low-quality evidence, primary whole gland cryotherapy had uncertain effects upon oncology outcomes, QoL, and major adverse events compared to external beam radiotherapy.
- The reasons for downgrading the QoE had included serious study limitations, indirectness because of the use of lower doses of radiation in the comparison group in comparison with the radiation doses that are currently recommended, and serious or very serious imprecision.

Williams et al. [107]] stated that the optimum treatment of carcinoma of prostate recurrence following radiation therapy (RT) does remain controversial in view of the lack of long-term data. Williams et al. [107] reviewed the survival of patients who had undergone salvage cryotherapy to the prostate gland for histopathology biopsy-proven recurrent prostate cancer and who had established prognostic indicators. With regard to the design and settings of their review as well as participants, Williams et al. [107] stated the following:

- They had undertaken a retrospective analysis on all patients who had undergone salvage cryotherapy at an academic urology unit for biopsy-proven locally recurrent prostate cancer after radiotherapy (RT) from 1995 to 2004.
- They reviewed and recorded the patients' preoperative, perioperative, and postoperative data.
- With regard to intervention, Williams et al. [107] stated that two freeze-thaw cycles of trans-perineal cryotherapy were undertaken under trans-rectal ultrasound scan-guidance by a single surgeon. With regards to the measurements, Williams et al. [107] stated that the primary outcome was survival and the secondary outcomes included: disease-free survival (DFS), metastasis-free survival, and progression to androgen-deprivation therapy. Williams et al. [107] summarized the results and limitations of their study as follows:
- Out of 187 patients, 176 patients had records that were available for follow-up which gave follow-up rate of 94%.
- The mean follow-up was 7.46 years and the follow-up had ranged from 1 year to 14 years.
- Fifty-two patients were followed for longer than 10 years
- The disease-free survival (DFS) at 10 years was 39%.
- Risk factors for recurrence of prostate cancer were pre-salvag serum prostate-specific antigen (PSA), pre-radiation, and pre salvage Gleason score. A serum PSA nadir >1.0 ng/dl was highl predictive of early recurrence.
- Williams et al. [107] made the following conclusions:
- Salvage cryotherapy had led to an acceptable 10-yearr disease free survival (DFS).
- Pre-salvage serum PSA and Gleason score were the bes predictors of disease recurrence.
- A serum PSA nadir >1 ng/dl following cryotherapy had indicate a poor prognosis, and recurrence of disease was universal in thes patients.

Alvarez Rodríguez et al. [108] stated that published data related to cryotherapy for prostate cancer (PC) treatment had been based upon case series with a lack of clinical trials and the inexistence of a validated definition of biochemical failure. Alvarez Rodríguez et al. [108] conducted a prospective study with standardized follow-up protocol within their institution. With regard to material and methods, Alvarez Rodríguez et al. [108] stated that they undertook a prospective study of a series of cases that included 108 patients who were diagnosed as having localized prostate cancer (PC) at clinical stage T1c-T2c who were treated by primary cryoablation and who also had a median follow-up of 61 months. They stated that the criteria of biochemical recurrence were unified based upon the American Society for Therapeutic Radiology and Oncology (ASTRO). The end points were biochemical progression-free survival (BPFS), cancer-specific survival, as well as overall survival. They reported the rate of complications. Alvarez Rodríguez et al. [108] summarised the results as follows:

The BPFS for low-, medium-, and high-risk groups of patients was 96.4%, 91.2%, and 62.2%, respectively.

The cancer-specific survival was 98.1%.

The overall survival reached 94.4%.

The complications had included incontinence in 5.6% of the patients, urinary tract obstruction in 1.9% of the patients, urethral sloughing in 5.6% of the patients, haematuria in 1.9% of the patients, perineal pain in 11.1% of the patients, and prostate-rectal fistula in 0.9% of the patients. Erectile disfunction was found in 98.1% of the patients.

Alvarez Rodríguez et al. [108] concluded that cryotherapy is an effective and minimally invasive treatment for primary prostate cancer (PC) in well-selected cases, with low surgical risk and good results with regard to BPFS, cancer-specific survival, and overall survival.

Pisters et al. [109] compared the treatment outcomes of salvage radical prostatectomy and savage cryotherapy for patients who had locally recurrent carcinoma of the prostate gland pursuant to initial radiotherapy for prostate cancer. With regard to materials and methods, Pisters et al. [109] retrospectively the medical records of patients who had undergone salvage radical prostatectomy at the Mayo Clinic between 1990 and 1999, and those who had undergone salvage cryotherapy at M. D. Anderson Cancer Center between 1992 and 1995. Pisters et al. [109] reported that the eligibility criteria were serum prostate specific antigen (PSA) less than 10 ng/ml, post-radiotherapy biopsy showing Gleason score 8 or less adenocarcinoma of the prostate gland and prior radiotherapy alone without pre-salvage or post-salvage hormonal therapy. Pisters et al. [109] assessed the rates of biochemical disease-free survival, disease specific survival and overall survival in each group. Pisters et al. [109] assessed biochemical failure using the 2 definitions of (1) prostate specific antigen greater than 0.4 ng/ml and (2) 2 increases above the nadir prostate specific antigen. Pisters et al. [109] summarized the results as follows:

The mean follow-up was 7.8 years for the salvage radical prostatectomy group of patients and 5.5 years for the salvage cryotherapy group of patients.

In comparison with salvage cryotherapy, salvage radical prostatectomy had resulted in superior biochemical disease-free survival by both definitions of biochemical failure (serum prostate specific antigen greater than 0.4 ng/ml, salvage cryotherapy 21% versus salvage radical prostatectomy 61% at 5 years, $p < 0.001$; 2 increases above nadir with salvage cryotherapy 42% vs salvage radical prostatectomy 66% at 5 years, $p = 0.002$) and in superior overall survival (at 5 years salvage cryotherapy 85% versus salvage radical prostatectomy 95%, $p = 0.001$).

There was no significant difference with regard to the disease specific survival (at 5 years salvage cryotherapy 96% versus salvage radical prostatectomy 98%, $p = 0.283$).

After adjusting for post-radiotherapy biopsy Gleason sum and pre-salvage treatment serum prostate specific antigen on multivariate analysis salvage radical prostatectomy had remained superior to salvage cryotherapy for the end points of any increase in serum prostate specific antigen (PSA) greater

than 0.4 ng/ml (HR 0.24, p <0.0001), 2 increases in serum prostate specific antigen (PSA) (HR 0.47, p = 0.02) and overall survival (HR 0.21, p = 0.01).

Pisters et al. [109] concluded that young, healthy patients who had recurrent adenocarcinoma of the prostate pursuant to radiotherapy should consider salvage radical prostatectomy as it does superior biochemical disease-free survival and it may potentially offer the best chance of cure. Despite this conclusion, some clinicians could argue that patients who have been declared not to be medically fit to undergo salvage radical prostatectomy should be offered salvage cryotherapy with an explanation that the biochemical disease-free survival may be shorter than that associated with salvage radical prostatectomy which they cannot undergo because of their comorbidities but does offer better outcome in comparison with being left alone without any alternative treatment of curative intent.

Cresswell et al. [110] presented the early results of utilization of third generation cryotherapy in primary and recurrent prostate cancer within one UK centre. With regard to the patients and methods, Cresswell et al. [110] reported that over a period of 14 months, 51 patients had undergone cryotherapy for carcinoma of the prostate gland. They also stated that with regard to 31 patients, cryotherapy was utilized as the primary treatment and with regard to 20 patients, cryotherapy was undertaken as a salvage treatment after radiotherapy or hormone ablation. The data were of the patients were collected prospectively and the median follow-up of the patients was 9 months. Cresswell et al. [110] summarized the results as follows:

- The serum prostate-specific antigen (PSA) level had decreased to less than 0.5 ng/mL in 79% of the patients who had undergone cryotherapy of prostate cancer as primary treatment and in 67% of patients who had undergone salvage cryotherapy treatment.
- A higher Gleason grade and serum prostate-specific antigen (PSA) levels were found to be associated with a poorer outcome.
- No patient developed a fistula, 4% of the patients developed urinary retention that required transurethral prostatectomy and 4% of the patients had persistent incontinence.
- The rates of erectile dysfunction were high and had which had developed in 86% of the patients.
- The median inpatient stay following cryotherapy of prostate cancer was 2 days.
- Creswell et al. [110] made the following conclusions:
- Their early results had indicated that cryotherapy does offer a safe alternative treatment option for primary and recurrent prostate cancer, particularly for older men and less fit patients.
- Long-term data are needed in order to assess the durability of response to cryotherapy of prostate cancer and the effect of cryotherapy of prostate cancer upon survival of patients

Boissier et al. [111] described the technique and the oncological as well as the salvage outcomes related to partial salvage prostatic cryoablation (SCAP) with regard to the treatment of local recurrent prostate cancer following primary radiotherapy. With regard to the materials and methods, Boissier et al. [111] stated that the indications for partial SCAP were: PSA < 10 ng /mL local recurrence with single focus on multi-parametric MRI (mpMRI) and on prostate biopsy, negative metastatic work-up, life expectancy of > 10 years and serum PSA doubling time of longer than 12 months. Cryoablation was undertaken with the Precise © device (Galil Medical ®, arden Hills, Minnesota, USA). With regard to the results, Boissier et al. [] reported that survival was 4.4 years, and 71% of the patients were free of third-line treatment at the time of the last evaluation. None of the patients had developed metastasis, and of the patients were alive at the time of their evaluation. De novo urinary incontinence was reported in one patient as well as de novo erectile dysfunction was reported in one patient. Boissier et al. [111] concluded that: (a) partial SCAP was an alternative treatment to salvage prostatectomy as well as whole gland ablation for highly selected patients who have locally recurrent prostate cancer after radiotherapy; (b) Partial SCAP significantly avoided or at least delayed the need for androgen derived therapy (ADT).

Gestaut et al. [112] obtained their institutional review board approval to undertake a retrospective chart review of consecutive patients who had undergone treatment within their institution from 1990 to 2012. For inclusion in the study, the patients must have received a diagnosis of carcinoma of the prostate gland and they must have been considered to have low- to intermediate-risk disease based upon the National Comprehensive Cancer Institute Criteria. All of the patients, had received brachytherapy or cryotherapy treatment. They collected the disease specifics as well as failure details for all the patients. They defined failure as serum prostate-specific antigen nadir of + 2 ng / mL Gestaut et al. [112] summarized the results as follows:

A total of 359 consecutive patients were studied. The groups had comprised of 50 low-risk cryotherapy (LRC), 92 intermediate-risk cryotherapy (IRC) 133 low-risk brachytherapy (LRB), and 84 intermediate-risk brachytherapy (IRB) patients.

The median prostate-specific antigen follow-up periods were reported to be: 85.6 months for the LRC group, 59.2 months for the IRC group, 74.9 months for the LRB group, and 59.8 months for the IRB group.

The 5-year biochemical progression-free survival (bPFS) rate was 57..9% in the cryotherapy group versus 89.6% in the brachytherapy group (P<0.0001).

The 5-year bPFS rate was 70.0% in the LRC group, 51.4% in the IRC group, 889.4% in the LRB group, and 89.7% in the IRB group.

The bPFS rate was found to be significantly different between brachytherapy and cryotherapy that was undertaken for low-risk and intermediate-risk groups (P<0.05).

The mean nadir temperature that was reached for cryotherapy patients was -35 degrees centigrade with a range from between – 96 degrees centigrade to – 6 degrees centigrade.

Cryotherapy utilized a median of 2 freeze-thaw cycles with a range of between 2 to 4 freeze-thaw cycles.

Gestaut et al. [112] made the ensuing conclusions:

The results of their study had suggested that cryotherapy is inferior to brachytherapy for patients who have low- to intermediate-risk carcinoma of the prostate.

Patient selection to be considered for cryotherapy or brachytherapy are similar with regard to terms of anaesthesia candidacy.

In view of this, cryotherapy would not be recommended as a first-line local treatment for this particular patient subset.

Gursel et al. [113] reported 39 patients who had metastatic carcinoma of the prostate gland that was refractory to orchidectomy and oestrogens at the sites of metastases who had undergone sequential cryotherapy to the prostate gland in an attempt to palliate the pain. With regard to the result, Gursel et al. [113] reported that an excellent result was achieved in 20 patients and the response had lasted between six weeks to three years pursuant to the cryotherapy. They suggested the undertaking of early cryotherapy to obtain maximum immunological response in patients who have carcinoma of the prostate gland.

Lucan et al. [114] analysed the oncological outcomes in patients who were affected by low-risk carcinoma of the prostate gland who had undergone cryotherapy of the prostate gland. They undertook a prospective tricentric study of 434 patients who had undergone treatment with cryoablation of prostate for low-risk carcinoma of the prostate gland. By low-risk, Lucan et al. [114] referred to the D'Amico's risk classification. Two cycles of freezing / thawing were run for each patient following the technique that was described by Onik. Lucan et al. [114] summarised the results as follows:

For the 434 patients, their median age was 66 years with a standard deviation of +/- 2.13, the mean volume of the prostate gland was 35.59 cc, the median prostate volume was 34.00 cc, with a standard deviation of +/- 7.89.

Biochemical failure did occur in 67 patients that amounted to 15.4% of the patients.

- The pre-operative erectile function in the men was distributed as follows: severe in 95 patients that amounted to 19.2% of the patients, moderate in 95 patients that amounted to 19.2% of the patients, medium-to moderate in 180 patients that amounted to 36.4% of the patients, mild in 92 patients that amounted to 18.6% of the patients, and no erectile dysfunction in in 32 patients that amounted to 6.5% of the patients.
- The post-operative erectile function that was measured 1 month pursuant to cryotherapy was distributed as follows: severe in in 321 patients that amounted to 65% of the patients, moderate in 69 patients which amounted to 14% of the patients, medium-moderate in 79 patients that amounted to 16% of the patients, mild in 23 patients that amounted to 4.4% of the patients, and no dysfunction in only 2 of the patients that amounted to 0.4% of the patients.
- Post-operative erectile dysfunction of the patients after 3 months was distributed as follows: severe in 233 patients that amounted to 47.2% of the patients, moderate in 66 patients that amounted to 13.4% of the patients, medium-moderate in 122 patients that amounted to 24.7% of the patients, mild in 65 patients that amounted to 13.2% of the patients and no sexual dysfunction in in 8 patients that amounted to 1.6% of the patients.
- Urinary incontinence was reported by 21 patients that amounted to 4.8% of the patients after 3 months but the incontinence dropped to 13 patients that amounted to 2.9% of the patients after 6 months.
- Lucan et al. [114] made the ensuing conclusions:
- Cryotherapy in the treatment of carcinoma of the prostate gland does remain a viable alternative viable therapy.
- The availability of new cryoprobes and the utilization of new diagnostic means such as fusion magnetic resonance would make the cryotherapy a more precise as well as more effective method of treatment.
- Taha et al. [115] undertook a study to compare the oncological as well as functional outcomes of primary whole gland cryoablation of the prostate with utilization of the variable ice cryoprobe (V-probe®) and the conventional fixed-size ice probe. With regard to the materials and methods, Taha et al. [116] reviewed the Cryo On-Line Data Registry for men who had undergone treatment who had primary whole gland prostate cryoablation from 2000 through 2017. They utilised a multivariate Cox proportional hazards model in order to compare the timing to biochemical recurrence between the V-Probe® and fixed-size ice probe after adjusting for preoperative serum prostate-specific antigen (PSA), neoadjuvant androgen deprivation therapy, preoperative Gleason score, and preoperative T stage. Taha et al. [] summarized the results as follows:
- A total of 1124 men were included in the study.
- The median age, Gleason score, and pre-treatment serum PSA were 70 years (interquartile range [IQR]: 65–74 years), 7 (IQR: 6–7) and 5.9 ng/mL (IQR: 4.6–8.1 ng/mL), respectively.
- The median follow-up time was 25.0 months (IQR: 11.2–48.6 months).
- V-Probes® were utilized in 269 patients that amounted to 23.9% of the patients and fixed-size ice probes in 858 patients that amounted to 76.1% of the patients.
- After adjusting for clinical T stage, serum PSA, neoadjuvant androgen deprivation therapy and preoperative Gleason score, on the multivariate Cox regression model, they had found that there was no significant difference between the type of probe and timing to biochemical recurrence ($p = 0.35$).
- Upon multivariate logistic regression, utilizing the V-Probe® was associated with a 91% increase in postoperative urinary retention in comparison with the fixed-size ice probe ($p = 0.003$).

Taha et al. [115] concluded that:

Utilization of V-Probe® versus conventional fixed-size ice probe was not associated with a difference in biochemical recurrence in patients who undergo primary cryoablation of the prostate gland tumour.

Guo et al. [116] stated that cryoablation (CA), high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), and vascular-targeted photodynamic therapy (VTP) had been evaluated as new strategies for selected patients who have prostate cancer (PCa). Guo et al. [16] undertook a study to ascertain the current status of literature regarding the clinical outcomes among these minimally invasive therapies. Guo et al. [116] undertook a systematic search of PubMed, EMBASE, and the Cochrane Library for all English literature published from January 2001 to December 2019 to identify studies that had evaluated the outcomes of CA, HIFU, IRE or VTP on prostate cancer (PCa). Proportionality with 95% confidence intervals (CIs) was undertaken with utilization of STATA version 14.0. Guo et al. [116 found 56 studies consisting of 7383 participants to report data of interest and which had fulfilled the inclusion criteria in the final meta-analysis. Guo et al. [116] reported the following:

The pooled proportions of positive biopsy after procedure were 20.0%, 24.3%, 24.2%, and 36.2% in CA, HIFU, IRE and VTP, respectively.

The pooled proportions of biochemical recurrence-free survivals (BRFSs) were 75.7% for CA and 74.4% for HIFU.

The pooled proportions of CSS were noted to be 96.1%, 98.2%, and 97.9% for CA, HIFU, and IRE, respectively.

The pooled proportions of overall survival (OS) were 92.8% for CA and 85.2% for HIFU.

The pooled proportions of FFS were 64.7%, 90.4%, and 76.7% for CA, IRE and VTP, respectively.

The pooled proportions of MFS were 92.8% for HIFU and 99.1% for IRE.

Guo et al. [116] concluded that the meta-analysis had shown that CA, HIFU, IRE, and VTP are promising treatment options for prostate cancer (PCa) patients with similar clinical outcomes. Nevertheless, further larger, well-designed randomized controlled trials would be required to confirm this assertion.

Phillips et al. [117] stated that cryotherapy has increased in view of technological advances. Phillips et al. [117] undertook a review of the literature to evaluate the efficiency as well as outcomes of whole gland, salvage, as well as targeted focal cryotherapy with regard to the management of carcinoma of the prostate gland. Phillips et al. [117] summarized their review findings as follows:

Utilization of cryotherapy had increased over the preceding 10 years with a trend towards focal ablation.

Whole gland cryotherapy, salvage cryotherapy, as well as focal cryotherapy biochemical recurrence rates did appear to be comparable to other treatment modalities that have been utilized to treat low-risk disease; nevertheless, biochemical failure has remained difficult to compare across studies in view of lack of consensus opinion regarding appropriate end points for the evaluation of cryotherapy.

Short-term focal therapy outcomes have appeared to be encouraging.

The side effect profiles of cryotherapy had improved significantly with utilization of fourth generation systems while salvage cryotherapy has continued to carry a slightly higher risk of incontinence in comparison with primary whole gland cryotherapy.

The incidence of erectile dysfunction pursuant to focal cryotherapy is dramatically lower in comparison with whole gland ablation.

Phillips et al. [117] made the ensuing conclusions:

Cryotherapy does continue to have an active role with regard to the primary as well as salvage therapy of carcinoma of the prostate gland.

- Further long-term data is required in order to support targeted therapy in addition to direct comparison with other treatment modalities.

Gao et al. [118] stated the following:

- Cryotherapy (CS) had been undertaken on patients who have clinically localized prostate cancer (PCa) for more than 10 years. Nevertheless, clinical studies which had evaluated the effectiveness and safety of cryotherapy of prostate cancer had reported conflicting results.
- They had undertaken a systematic assessment in order to obtain comprehensive evidence regarding the potential benefits as well as safety of cryotherapy (CS) in comparison with those of radiotherapy (RP) and radical prostatectomy (RP), respectively.
- All controlled trials that compared CS with RT or RP and single-arm studies that reported the results of CS were identified via comprehensive searches of PubMed, the Cochrane Library and Embase.

With regard to the results, Gao et al. [118] summated the ensuing:

- Ten publications from seven trials, with a total of 1252 patients were included in their meta-analysis, which had demonstrated no significant differences in comparisons of CS versus RT and CR versus RP for overall survival as well as disease specific survival.
- Nevertheless, a significantly lower disease-free survival could be observed for CS in comparison with RP.
- Additionally, a systematic review of the literature with a focus upon comparative data of data bases as well as materials of single-arm trials had revealed satisfactory survival results in both primary as well as salvage CS.
- Gao et al. [118] concluded that:
- Their results had shown that cryosurgery would be a relatively effective option of treatment for clinically localized carcinoma of the prostate gland with survival results that are comparable to the survival results of radiotherapy and prostatectomy.
- Nevertheless, the large percentage of complications that are caused by cryotherapy should be carefully monitored by clinicians.

Chin et al. [119] stated the following: (a) Radiation refractory prostate cancer (RRPCa) is a common cancer and salvage cryotherapy for RRPCa has been emerging as a viable local treatment option. (b) Nevertheless, there is a paucity of long-term data. (c) They had undertaken a study in order to determine long-term outcomes following salvage cryotherapy for RRPca. With regard to the materials and methods, Chin et al. [119] stated that they had prospectively accrued patients who were undergoing salvage cryotherapy for biopsy-proven, localized RRPCa from 1992 through 2004 at two centres. Chin et al. [119] reviewed the pre-operative characteristics, perioperative morbidity and postoperative data from their database. The primary outcomes included the overall survival (OS) and disease-specific survival (DSS). The secondary outcomes were freedom from castration-resistant prostate cancer (CRPC) and freedom from androgen deprivation therapy (ADT). Chin et al. [119] summarized the results as follows:

- They had identified a total of 268 patients who had a median follow-up of 10.3 years.
- They had recorded a total of 223 complication events; of them, 168 were Clavien I-II events and 55 Clavien III events.
- At 10 years, 69% of the patients had freedom from ADT and 76% had freedom from CRPC.
- The 10-year DSS rate was 81%, and the 10-year OS rate was 77%.
- A pre-salvage prostate serum specific antigen level of >10 ng/ml was associated with an increased risk of developing CRPC and initiation of ADT but was not associated with DSS or OS.
- Utilization of neoadjuvant ADT was associated with improved OS and DSS but did not affect freedom from CRPC or adjuvant ADT.
- Chin et al. [119] concluded that (a) Salvage cryotherapy for RRPCa does provide excellent long-term freedom from ADT, CRPC and DSS with acceptable morbidity. OS at 10 years was 77%. (b) Prospective trials would be needed for validation of their results.

Guo et al. [120] compared the oncological outcomes of cryoablation (CA) and radical prostatectomy (RP) in patients who had low- and intermediate-risk localized prostate cancer (PCa). With regard to the materials and methods, Guo et al. [120] sated that they had identified PCa patients who had received CA or RP between 2004 and 2015 from the Surveillance, Epidemiology, and End Results database. They utilized Multivariable Cox proportional hazard analysis to compare the prostate cancer-specific survival (CSS) and overall survival (OS). Guo et al. [120] conducted 1:3 propensity score matching and adjusted standardized mortality ratio weighting (SMRW) to balance the clinicopathological characteristics. Guo et al. [120] summarized the results as follows: Ninety-seven thousand seven hundred eighty-three patients were identified following preliminary screening. After matching, the cryotherapy (CA) and radical prostatectomy (RP) groups had included 1,942 and 5,826 patients and they had median follow-up periods of 85 and 72 months, respectively. Cryotherapy (CA) had lower CSS and OS rates (hazard ratio [HR], 2.07; $P = 0.007$; HR, 2.09; $P < 0.001$, respectively) in comparison with radical prostatectomy (RP), which was consistent in the SMRW model (CSM: HR, 2.66; $P < 0.001$; OS: HR, 2.29; $P < 0.001$). The 10-years CSS and OS for cryotherapy (CA) versus radical prostatectomy (RP) were 98.1 versus. 99.2% and 61.3 versus 79.9%, respectively. Guo et al. [120] concluded that: (a) In patients who had low- to intermediate-risk localized prostate cancer (PCa), cryotherapy (CA) had lower CSS rates in comparison with radical prostatectomy (RP). (b) Nevertheless, the high 10-years CSS rates had indicated that cryotherapy (CA) could be a treatment option for those individuals who are not radical prostatectomy (RP) candidates. (c) Additional high-quality trials are required to confirm and expand their findings.

Mercander et al. [121] iterated that cryotherapy of prostate is an available treatment option for localized prostate cancer (PC) which has been included on minimal invasive treatment options but cryotherapy of prostate is still under evaluation. Mercander et al. [121] started their cryotherapy program in 2008 for selected patients who had localized prostate cancer (PC). Mercander et al. [121] evaluated the oncology and functional outcomes of primary cryotherapy in men who had clinically localized prostate cancer (PC). Mercander et al. [121] retrospectively evaluated all patients who had undergone primary cryotherapy for localized prostate cancer (PC) treatment within their centre between January 2008 and December 2017. In order to downsize prostates that measured between 40cc and 60cc, they administered neoadjuvant 3-month hormonal therapy to the patients. The primary endpoint was biochemical progression-free survival (BPFS) rate as was defined by the Phoenix criteria. The secondary endpoints were cancer-specific survival (CSS), overall survival (OS), patient reported functional outcomes and complication rates. Factors that influenced the BPFS were evaluated individually using Kaplan-Meyer and Cox regression models and in a multivariate model using Cox regression. With regard to the results of the study, Mercander et al. [121] reported the following: During the mentioned period, a total of 177 men were treated with cryotherapy. The mean follow-up of the patients was 60 months (SD 32.9), the Kaplan-Meier analysis showed an overall BPFS rate of 67%. The BPFS by risk group was 70.2%, 70.3% and 50.0% for the low, intermediate and high-risk groups, respectively ($p = 0.925$). The overall time to biochemical recurrence (BR) was 93.67 months (SD 2.84, IC95%: 88.10-99.24): 95.91 (SD 3,44), 93.23 (SD 4.81) and 89.77 (SD 6.67) months for the low-risk, intermediate-risk and high-risk groups, respectively. With regard to both univariate and multivariate analysis, the only predictor of biochemical progression was the serum PSA nadir (HR 1.56 IC95%: 1.50-1.63). Continence was noted to be fully maintained in 95% of the patients after the procedure. The post-operative complications had included urinary tract infection (UTI) in 17.5% of the patients, haematuria in 9.6% of the patients, perineal hematoma in 11% of the patients and postoperative pain in 4.5% of the patients. No fistulas were reported. 8.5% of

the patients had acute urinary retention which was managed conservatively. Mercander et al. [121] concluded that cryotherapy is a safe option of treatment for selected patients who have localized prostate cancer that provides competitive oncology outcomes and a low morbidity profile.

Sze et al. [122] iterated that in view of their location away from the nerve bundles, anterior prostate cancers (APC) do tend to represent a rational target for image-guided cryoablation. Sze et al. [122] reported the feasibility and short-term outcomes of anterior focal cryosurgery. Sze et al. [122] undertook a retrospective review between 2012 and 2016 of patients who had clinically localized APC who had undergone treatment with anterior gland cryoablation. They utilized descriptive statistics to report: the age, serum PSA, prostate volume, prostate cancer grade group (PGG), median time to follow-up, and changes in functional status that were measured with the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF-5) score. With regard to the results, Sze et al. [122] reported the following: A total of 17 patients had undergone anterior focal cryoablation with a median follow-up of 15 months. The median age and serum PSA at the time of diagnosis of the prostate cancer were 67 years and 8.7 ng/mL. Pre-operative PGG1 was identified in 12 patients that amounted to 71% of the men and PGG2 in 5 men that amounted to 29% of the men. The median (IQR) lesion volume was 2 mL (0.86, 3.1). The pre-operative median IIEF-5 and IPSS scores were 19.5 and 5, and these had decreased to 19 and 4, post-operatively. All of the patients remained continent with no change in sexual function. All post-procedure targeted biopsies of the treated cancers were negative for prostate cancer. Sze et al. [122] utilized radiology imaging to identify the tumours which were targeted and examples of the position of the tumours was demonstrated as shown in figures 1 and 2. Sze et al. [122] concluded that their pilot study had demonstrated the feasibility of treating APCs with radiology image-guided targeted focal cryoablation as a good balance between short-term oncologic control and near complete preservation of genitourinary function. Further follow-up is required in order to examine the potential benefits long-term.

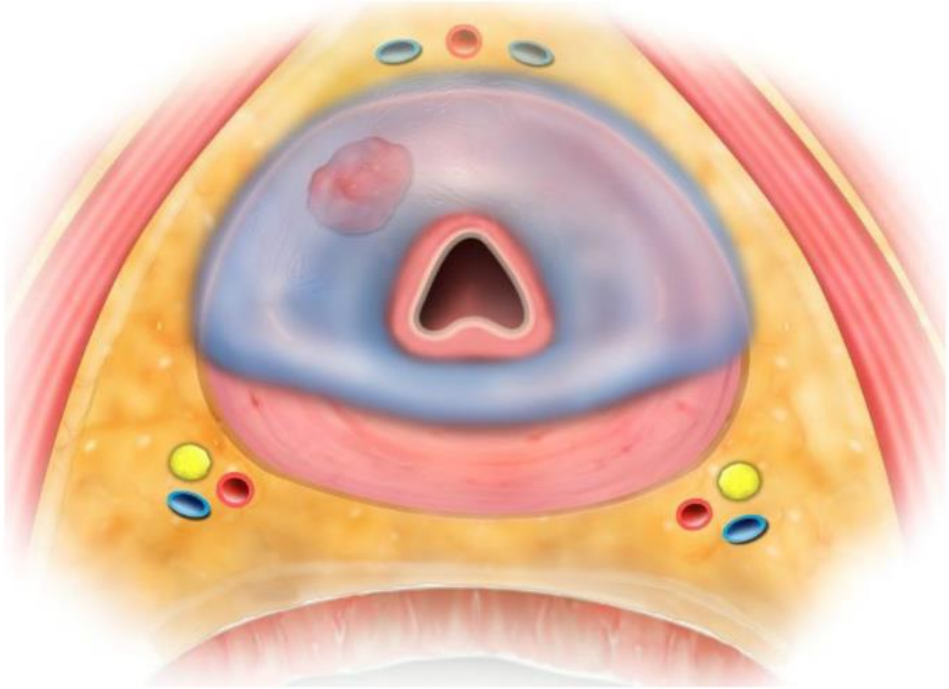

Figure 1:

Trans-axial view of the prostate illustrating anterior cryoablation template. Ice, depicted in transparent blue, can be run posteriorly all the way to the peripheral zone leaving the neurovascular bundles [yellow/red/blue circles] untouched. Tumour depicted anteriorly in red, urethra in centre of schematic. Reproduced from: [122] Sze, C., Tsivian, E., Tay, K.J, Schulman A A, Davis L G, Gupta R T, Polascik T J. Anterior gland focal cryoablation: proof-of-concept primary prostate cancer treatment in select men with localized anterior cancers detected by multi-parametric magnetic resonance imaging. *BMC Urol* **19,** 127 (2019). https://doi.org/10.1186/s12894-019-0562-5 under copyright **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

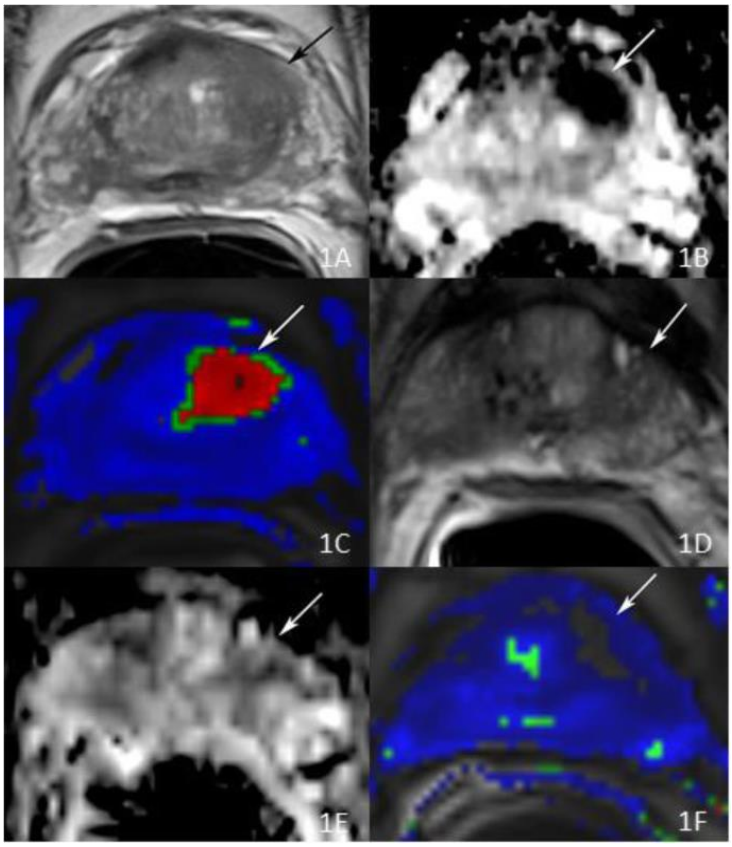

Figure 2:

a Axial T2-weighted (T2W) image reveals ill-defined decreased T2 signal at the level of the left anterior transition zone at the level of the base (arrow). **b** Axial apparent diffusion coefficient (ADC) map demonstrates markedly restricted diffusion in this region (arrow). **c** Coloured perfusion map created using post-processing software from dynamic contrast-enhanced MRI (DCE-MRI) acquisition demonstrates suspicious perfusion kinetics for prostate cancer (arrow), corresponding to the findings seen on T2W and DWI. This lesion was scored as a PI-RADS 4 and patient underwent MRI-US fusion biopsy which revealed Gleason $3 + 3 = 6$ prostate0 cancer at the targeted area. Based on these findings, patient elected to undergo anterior focal cryoablation of this lesion. **d**,**e**,**f** Axial T2W image, ADC map and coloured perfusion map created using post-processing software from DCE-MRI acquisition in the post-ablation setting reveals ablation defect with no suspicious findings in the area of treatment and specifically, no abnormal perfusion kinetics. Patient's PSA continued to decrease with a nadir at 0.6 ng/mL confirming successful targeted anterior cryoablation. Reproduced from: [122] Sze, C., Tsivian, E., Tay, K.J. Schulman A A, Davis L G, Gupta R T, Polascik T J. Anterior gland focal cryoablation: proof-of-concept primary prostate cancer treatment in select men with localized anterior cancers detected by multi-parametric magnetic resonance imaging. *BMC Urol* **19,** 127 (2019). https://doi.org/10.1186/s12894-019-0562-5 under copyright **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

It has been iterated that a number of reported case series had reported utilization of cryotherapy as salvage treatment pursuant to radical prostatectomy or pursuant to radical radiotherapy. [1] [123] [124] [125] [126] It had been ascertained that utilization of cryotherapy pursuant to failure of radiotherapy had resulted in lower biochemical relapse rates in comparison with the biochemical relapse rates that had been achieved pursuant to salvage radical prostatectomy following failure of radical radiotherapy. [1] It has been iterated that the five-year biochemical relapse-free rates of 55% to 69% [1] [127] [128] [129] [130] had been reported following the undertaking of salvage radical prostatectomy but on the other hand, the five-year biochemical relapse-free after salvage cryotherapy had varied based upon the definition that was utilized; nevertheless, these were generally lower. [126] [131] It had been documented that the complication rates that had been associated with salvage cryotherapy had been demonstrated to be higher in comparison with following primary cryotherapy of curative intent, especially with regard to the rates of incontinence as pelvic pain. [126] It has been iterated that cryotherapy is regarded to be associated with having a potential as a palliative treatment with regard to patients who have locally advanced carcinoma by providing relief of associated pain for up to 6 months. [1] [132] It has been stated that with regard to the experience with cryotherapy for prostate cancer, patients who do fail cryotherapy, can undergo a repeat cryotherapy procedure with rarely an increased risk of side effects. They also iterated that even though experience in the area of cryotherapy of prostate cancer is limited, early results had indicated that a good outcome could be obtained pursuant to the undertaking of a second cryotherapy of prostate cancer procedure. It has been documented that the target serum prostate specific acid (PSA) nadir pursuant to cryotherapy is a level that is equal to or less than 0.5 ng ml $^{-1}$ (optimal below detection level), however, a level that is equal to or less than 1.0 ng ml $^{-1}$ with stable readings also tends to be regarded as acceptable by the group. It has also been iterated that published case series had defined

biochemical recurrence pursuant to cryotherapy as an increase in serum prostate specific antigen (PSA) of equal to or higher than 0.2 ng ml^{-1} over the nadir [133] or a serum prostate specific antigen (PSA) level of 0.5 ng ml^{-1} or 1.0 ng $ml^{-1.}$ [134] It has furthermore been iterated that the American Society of Therapeutic Radiology and Oncology ASTRO guidelines had also been utilized to define failure pursuant to cryotherapy, which is three consecutive rises in serum prostate specific antigen (PSA) after the serum prostate specific acid (PSA) had been reached. Furthermore, a prostate cancer positive biopsy confirmed by pathology examination of a repeat prostate biopsy is required to establish this diagnosis.

It has been documented that serum prostate specific antigen (PSA) nadir pursuant to cryotherapy usually tends to be observed 3 months pursuant to cryotherapy of the prostate cancer. It had been iterated that a Cochrane data base review of the literature pertaining to cryotherapy of prostate cancer had been published in 2007 when cryotherapy was undertaken as a primary treatment for localized prostate cancer. [1] [135] With regard to this review of the literature, in order to be included in the review, the studies needed to have included 50 patients who had undergone a minimum follow-up assessment of 1 year. The authors had identified eight case series which had included a total of 1483 patient who had a mean pre-operative serum prostate specific antigen (PSA) level of 9.7 ng ml^{-1} to 39 ng ml^{-1}. Four out of the eight case studies had not monitored the temperature of the cryo-procedure and the studies had reported a prostate cancer tumour positive repeat biopsy in 17% to28% of patients pursuant to cryotherapy with a mean serum prostate specific antigen (PSA) nadir of 0.55 ng ml -1 to 1.75 ng ml^{-1} (median 0.4 ng ml -1 to 1.85 ng $ml^{-1)}$. The remaining four case studies utilized thermocouples to monitor the temperature of the cryotherapy procedure which reported progression-free survival rates of 71% to 89% with 1.4% to 1.3% of the patients having a prostate cancer tumour positive biopsy pursuant to cryotherapy. The studies reported that at 5 years, the overall survival was 89% to 92% with regard to two studies, as well as the disease-free survival rate was 94% in one study.

Another study reported an online database of patients who had undergone treatment by means of whole gland cryotherapy as primary treatment and this study published the outcome of cryotherapy of prostate cancer in 1198 patients. [136] The results of the study were summarized as follows:

- The mean (s.d) pre-treatment serum prostate specific antigen (PSA) was 9.6 (8.6) ng ml^{-1}.
- The mean (s.d) 5-year biochemical disease-free status for the entire population was found to be 77.1% (2.1%) based upon the ASTRO criteria as well as 72.9% based upon the newer Phoenix definition of serum prostate specific antigen (PSA) nadir +2 ng $ml^{-1.}$

Conclusions

- Cryotherapy as treatment option is a safe and effective treatment option for localized low-risk and medium-risk prostate cancer.
- The complications of erectile / sexual dysfunction, and urinary incontinence / voiding dysfunction following cryotherapy for prostate cancer tends to be more transient in comparison with following radical prostatectomy or radical radiotherapy.
- It may be that cryotherapy of localized prostate cancer of low-risk, and medium-risk patients may have a slightly inferior long-term oncology outcome in comparison with radical prostatectomy, radical radiotherapy and other minimally invasive treatment options of curative intent but this needs to be further investigated through a large global multicentre treatment comparative study of various treatment options with a long-term follow-up.
- Nevertheless, cryotherapy of prostate cancer does represent a minimally invasive alternative treatment for localized prostate cancer as treatment of curative intent and it can also be used to treat persistent/locally recurrent prostate cancer following radical radiotherapy and radical prostatectomy.

Conflict of interest – None

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