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Review Article

Cryotherapy in the Treatment of Adenocarcinoma of The Prostate Gland: A Review and Update

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Abstract

Cryotherapy is a terminology that has been coined for the ablation of tissue through local induction of extremely cold temperatures. Cryotherapy can be utilized both for the primary treatment of localized cancer of the prostate gland and for the salvage treatment of disease refractory to radiotherapy or localized recurrent or residual tumour ensuing other minimally invasive treatments for prostate cancer. Following the finding of a localized recurrent tumour or residual tumour following cryotherapy for a localized prostate cancer, the tumour can still be treated utilizing various treatment options including (a) repeat cryotherapy, (b) salvage radiotherapy, (c) salvage irreversible electroporation of the prostate cancer, (d) salvage High Frequency Focused Ultrasound (HIFU) treatment of the prostate cancer, (e) salvage radical prostatectomy. Because generally cryotherapy is minimally invasive in comparison with radical prostatectomy, patients who have been offered radical prostatectomy as initial treatment of localized prostate cancer can also be offered an alternative treatment option of cryotherapy of the prostate cancer followed by salvage radical prostatectomy or salvage radiotherapy in the event of persistent prostate cancer or residual prostate cancer following cryotherapy of localized prostate cancer of curative intent. Relative contraindications to the undertaking of cryotherapy include previous trans-urethral resection of prostate (TURP) with a large tissue defect, as well as significant symptoms of urinary tract obstruction. A history of abdominoperineal resection for rectal cancer, rectal stenosis, or other major rectal pathology is also a relative contraindication. A pre-procedure serum prostate-specific antigen (PSA) test is pertinent or pivotal for assessing risk and establishing a baseline from which the PSA level can be tracked after treatment. Other pre-procedure laboratory studies include the undertaking of following: (a) Urine culture; (b) Complete blood cell (CBC) count with platelet count; (c) Coagulation tests for example, prothrombin time [PT] and activated partial thromboplastin time [APTT]). Utilization of a cryotherapy system does entail placement of cryoprobes under ultrasound scan-guidance bilaterally in the anteromedial, posterolateral, and posteromedial regions of the gland, to the proximal extent of the prostatic capsule. Some of the complications that tend to ensue cryotherapy of prostate cancer include: the following: (a) Impotence, (b) urinary incontinence, (c) Tissue sloughing, (d) Pelvic and rectal pain, (e) Penile numbness, (f) Rectourethral fistula, (g) Urethral stricture, (h) Hydronephrosis, (i) Small-bowel obstruction, and (j) sloughing from the urethra. It would be recommended that globally Urology and Oncology departments should develop cryotherapy units so that cryotherapy for localized prostate cancer as well as other malignancies could be available as an alternative treatment option for the management of localized adenocarcinoma of prostate gland of curative intent.

Keywords: prostate cancer; cryotherapy; radical prostatectomy; radiotherapy; hormonal therapy; survival; complications; local recurrence; serum prostate specific antigen; PSA; complications; survival

Introduction

Cryotherapy is an option for the primary treatment of localized prostate cancer, along with radical prostatectomy, external beam radiation therapy (EBRT), and brachytherapy. Previous studies and meta-analyses have not found significant differences in the rates of failure between these primary treatments, although cryotherapy was associated with poorer sexual function posttreatment. [1] [2] [3]

Early cryotherapy systems had significant genitourinary (GU) and gastrointestinal (GI) toxicities, but advances in trans-trans-rectal guidance, urethral warming, and third-generation cryotherapy and the use of focal cryotherapy have decreased treatment-associated side effects and increased rates of use. [1] [4] [5] [6] A review of the national Cryo On-Line Database Registry found a > 1000-fold increase in the use of focal cryotherapy between 1997 and 2007. [7] As the number of patients undergoing primary cryotherapy increases, so too will the number of local recurrences that require salvage treatment. A review of the national Cryo On-Line Database Registry found a > 1000-fold increase in the use of focal cryotherapy between 1997 and 2007. [7] As the number of patients undergoing primary cryotherapy increases, so too will the number of local recurrences that require salvage treatment.

Although it is known that local recurrence can occur in >20% of patients treated with primary cryotherapy, there is a paucity of data on salvage treatments after failure.

[6] [8] [9] [10] Salvage prostatectomy after cryotherapy has been noted to be extremely difficult because of tissue reaction and fibrosis. [11]

[12] External beam radiotherapy (EBRT) as an option for salvage treatment has been little evaluated in the literature. [6] [8] [10]

Of those reports that have been published, the majority have focused on the use of 3-dimensional conformal radiation therapy (CRT) with 2 studies combining 3-dimensional CRT with intensity modulated radiation therapy (IMRT). Recent advances in image-guided radiation therapy utilizing IMRT (IG-IMRT) have been shown to decrease the rates of toxicities in comparison with non–IG-IMRT at the same dose level in the primary treatment of prostate cancer. [13]

The ensuing summations had been made regarding the approach considerations related to cryotherapy and other miscellaneous facts that need to take into consideration when undertaking cryotherapy to the prostate gland lesions: [14]

Approach Considerations

Utilization of a cryotherapy system does entail placement of cryoprobes under ultrasonographic guidance bilaterally in the anteromedial, posterolateral, and posteromedial regions of the prostate gland, to the proximal extent of the prostatic capsule.

Cryotherapy does exert its antineoplastic effects through many postulated pathways, including the ensuing: [14]

Direct cytolysis through extracellular and intracellular ice crystal formation

Intracellular dehydration and pH changes

Ischemic necrosis through vascular injury

Cryoactivation of antitumor immune responses

Induction of apoptosis

Together with cold-induced damage, additional injury does occur during warming, with osmotic cellular swelling and vascular hyperpermeability. [14] Endothelial damage does lead to platelet aggregation and micro-thrombosis. Histological changes, including necrosis, hyalinization, and inflammation, could persist for at least a year pursuant to treatment, as could residual indolent cancer. [14] Hyalinization might be more prominent in more effectively treated prostates (for example, those with no residual cancer). [15]

Factors that affect the efficiency of tissue destruction include the following:

Velocity of cooling

Nadir temperature

Duration of freezing

Velocity of thawing

Number of freeze-thaw cycles

Proximity of large blood vessels, which act as heat sinks

In general, a minimum freezing temperature of –40°C (–40°F) maintained for 3 minutes is believed to be necessary for efficient tumour eradication. [16] [17] [18]

Considering that cryotherapy as treatment of adenocarcinoma of the prostate gland is not available in some Urology and Oncology centres in some parts of the world, there is the likelihood that some clinicians would not be familiar with the treatment of prostate cancer with utilization of cryotherapy. The ensuing article on cryotherapy in the treatment of adenocarcinoma of the prostate gland is divided into two parts: (A) Overview which has discussed miscellaneous general aspects of adenocarcinoma of the prostate gland and cryotherapy and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Cryotherapy as a treatment option for Adenocarcinoma of the Prostate Gland.

Aim

To review and update the literature on cryotherapy in the treatment of primary adenocarcinoma of the prostate gland.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Cryotherapy of adenocarcinoma of prostate; Cryotherapy of prostate cancer; cryoablation of adenocarcinoma of prostate. One hundred and seven references were identified which were used to write the article that has been divided into two parts: (A) Overview which has discussed miscellaneous general aspects of adenocarcinoma of the prostate gland and cryotherapy and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Cryotherapy as a treatment option for Adenocarcinoma of the Prostate Gland.

Results

[A] Overview

Definition / general statements [19]

- Adenocarcinoma is the commonest malignant tumour of the prostate gland
- Adenocarcinoma of the prostate gland affects individuals in every country in the world.
- Adenocarcinoma of the prostate gland originates from prostatic secretory epithelium

Essential features [19]

- The symptoms and clinical examination findings upon assessment of individuals who have adenocarcinoma of the prostate gland as well as other types of prostate cancer tend to be non-specific and would not specifically diagnose adenocarcinoma of prostate specifically with regard to the cell type of tumour. [19]
- It has been pointed out that the clinical and radiological image features of adenocarcinoma of prostate gland is neither sensitive nor specific for diagnosis of adenocarcinoma of the prostate gland. [19]
- Adenocarcinoma of the prostate gland is quite often diagnosed by the undertaking of non-targeted needle biopsies of the prostate gland when investigating raised serum prostate specific antigen (PSA) and pathology examination of the prostate biopsy specimen does demonstrate features of the adenocarcinoma of prostate gland.
- Adenocarcinoma of the prostate gland also tends to be diagnosed based upon pathology examination of targeted biopsies of the prostate gland with evidence of the tumour in targeted areas of the prostate gland. [19]
- With regard the adenocarcinoma of the prostate gland, histopathology examination of a specimen of the tumour does tend to demonstrate absence of absence of basal cell layer which is a pathognomonic histological feature of the tumour. [19]
- It has been pointed out that pathognomonic diagnostic features of adenocarcinoma of the prostate gland do include: circumferential perineural invasion, glomerulations as well as collagenous micronodules (mucinous fibroplasia) [19]

- Other histopathology examination features of primary adenocarcinoma of prostate gland include the following: infiltrative architecture of the tumour, nucleolar prominence within the tumour, amphophilic cytoplasm and some intraluminal contents (crystalloids, blue mucin, pink amorphous material) within the tumour. [19]

Terminology

- Some of the utilized terminologies for primary adenocarcinoma of the prostate gland include: [19]

Prostate cancer

- Prostate adenocarcinoma
- Sub-types of prostatic adenocarcinoma that had been described include the ensuing: acinar adenocarcinoma, ductal adenocarcinoma, atrophic adenocarcinoma, pseudo-hyperplastic adenocarcinoma, microcystic adenocarcinoma, foamy gland adenocarcinoma, mucinous adenocarcinoma, signet ring variant of adenocarcinoma, pleomorphic giant cell adenocarcinoma, sarcomatoid adenocarcinoma
- Adenocarcinoma of the prostate gland has also been referred to as prostatic cancer, cancer of the prostate gland.

Epidemiology

- Second most common cancer and second leading cause of cancer related death in American men (SEER [20]
- Ninety two percent (92%) of United States of America (U.S.A) cases of adenocarcinoma are diagnosed in men aged who are over 55 years of age; and in 19.5% of men who are aged more than 75 years (SEER data available at [20]
- Primary adenocarcinoma of prostate gland is found at autopsy in 40% of men who are aged more than 60 years [21]
- It has been iterated that incidental primary prostate cancer has been reported in about 25% of cystoprostatectomies undertaken for the treatment of urinary bladder cancer [19] [22]
- It has been pointed out that globally, highest age standardized rates of prostate cancer had been recorded in Oceania, North America, Europe [19] [23]
- It has also been documented that lower rates of primary adenocarcinoma of the prostate gland had been recorded in developing countries and this may be due to different screening programs and diagnostic pathways
- It has additionally been pointed out that there is a higher incidence of primary adenocarcinoma of the prostate gland in men of African heritage [19] [23]

Sites

- It has been stated that majority of tumours are multifocal.[24]
- It has been stated that 75% to 80% of adenocarcinoma of prostate gland are within the posterior / posterolateral peripheral zone of the prostate gland. [19]
- It has furthermore been stated that about 13% to 20% of primary adenocarcinoma of the prostate gland are within the transition (periurethral) zone [25] [26]
- It has also been pointed out that majority of clinically significant cancers of the prostate gland do arise within the peripheral zone of the prostate gland which has been sampled by needle biopsies of the prostate gland. [19]
- It has been iterated that transition zone prostate cancer is associated with favourable pathology examination features and better recurrence free survival [19] [27]
- It has been iterated that adenocarcinoma of the prostate gland less frequently does involve the anterior lobe of the prostate gland most likely due to inadequate sampling using the standard biopsy approach [19] pathology outlines. [28]

Pathophysiology

It has been pointed out that Germline variants could be associated with an increased risk for the development of prostate adenocarcinoma: [19]

- Somatic mutations in genes such as ERG, ETV1/4, FLI1, SPOP, FOXA1, IDH1, PTEN, TP53, MYC, CDH1. [29] [30]
- It has been documented that the most common somatic genomic rearrangement in patients who have adenocarcinoma of the prostate gland is fusion of the androgen regulated gene TMPRSS2 with a member of the ETS transcription family. [30]

Aetiology

- It has been pointed out that obesity increases the risk for the development of adenocarcinoma of prostate gland [19] [31]
- It has been summated that non-modifiable risk factors for the development of primary adenocarcinoma of prostate gland include the ensuing: age, race and family history [19] [32]
    - Genetic susceptibility has been linked to African heritage [32]
    - There is an increased risk for the development of primary adenocarcinoma of the prostate gland with a first degree relative having prostate cancer. [32]
    - BRCA2 mutations do increase the risk for the development of prostate cancer by 5-fold; and BRCA2 associated cancers do occur at a lower age and they have worse survival outcomes. [19] [30] [33]
    - It has been documented that additional germline variants associated with increased cancer risk do occur in HOXB13. [30]
    - Increased risk of adenocarcinoma of prostate gland does occur in Lynch syndrome. [34]
- It has been pointed out that numerous single nucleotide polymorphisms (SNPs) that have a low to moderate effect on risk / progression had been identified [19] [35]
- It has been documented that high levels of IGF1 may confer increased risk for the development of adenocarcinoma of the prostate gland [19] [36]
- Clinical features
- It has been stated that primary adenocarcinomas of the prostate gland generally do tend to be asymptomatic unless they are locally advanced or metastatic [19] outlines
- It has also been iterated that quite often primary adenocarcinoma of the prostate gland is diagnosed following investigation of non-specific lower urinary tract symptoms. [19]
- It has been pointed out that in cases of primary adenocarcinoma of prostate gland, digital rectal examinations (DREs) do demonstrate the ensuing findings: the prostate gland may feel normal or may be enlarged / asymmetrical / hard / have a palpable nodule present. [19]

Diagnosis

The ensuing summations have been made regarding some aspects of the diagnosis of primary adenocarcinoma of the prostate gland: [19]

- Primary adenocarcinoma of the prostate gland generally has tended to be diagnosed by the undertaking of systematic trans-rectal ultrasound scan-guided prostate biopsies
- Trans-perineal needle biopsies of the prostate gland are increasingly utilized due to the fact that it tends to be associated with lower risk of infection

- It has been clearly pointed out that pre-biopsy MRI scan of the prostate that ensued by systematic biopsies of the prostate gland supplemented with targeted biopsies from any radiological abnormality within the prostate gland leads to better identification of clinically significant prostate cancer in comparison with systematic prostate biopsy alone. [37]
- It has been highlighted that incidental prostate cancer sometimes has been diagnosed in transurethral resection of prostate glands undertaken for lower urinary tract symptoms that had been undertaken to improve voiding that had been presumed to be related to benign prostate hypertrophy but the pathology examination features of the resected specimen demonstrate features of primary adenocarcinoma of the prostate gland. [19]
- Immunohistochemistry staining studies of specimens of the prostate with utilization of basal cell markers (HMWCK, p63) and AMACR do establish the diagnosis of pure adenocarcinoma of the prostate gland in equivocal cases [19]

It is worth pointing out that other types of immunohistochemistry staining study tumour markers are used to ascertain features of other cell type variants of prostate cancer.

Genomic / molecular genetics studies are now being undertaken in well-equipped and well-resourced centres in the world to provide further information related to adenocarcinoma of prostate gland that would help the multi-disciplinary team to recommend other types of treatment for primary adenocarcinoma of prostate gland especially in cases of a strong family history of prostate cancer as well as a family history of other cancers.

Some prostate cancers are not adenocarcinomas and they would tend not to be associated with raised serum PSA levels due to the fact that they are of stromal origin and in these cases despite the finding of abnormal digital examination findings of the prostate gland, the serum PSA level would be low or normal and an example of such a tumour is prostate stromal sarcoma and this tumour could be associated with raised serum PSA levels when these tumours are associated with a contemporaneously synchronous pure primary adenocarcinoma of the prostate gland within another area of the prostate gland.

Laboratory

The ensuing summations had been made related to various laboratory test findings and recommendations that had been made regarding adenocarcinoma of the prostate gland:

- Raised serum PSA levels generally tend to be associated most cases of adenocarcinoma of the prostate gland.
- Different serum PSA level cutoffs are being utilized to prompt prostate needle biopsy
- It has been pointed out that age specific serum PSA level cutoffs, serum PSA velocity (rate of change in PSA over time) and serum PSA density (PSA per unit prostate volume - ng/mL/cc) may increase the sensitivity and specificity of serum PSA testing. [38]
    - The United States of America (U.S). Preventative Services Task Force (USPSTF) had recommended against serum PSA based screening for prostate cancer in men who are 70 years and older than 70 years.
    - With regard to men who are aged between 55 years and 69 years, periodic PSA based screening should be an individual choice
    - It has been pointed out that screening in this age group does offer a small potential benefit of reducing the chance of death from prostate cancer in some men; nevertheless, many men will experience potential harm [39]
- The American Urological Association (AUA) does not recommend serum PSA screening in men who are under age 40 years or in men who are aged between 40years and 54 years who are at average risk for the development of adenocarcinoma of prostate gland.
    - For men who are aged between 55 years and 59 years, shared decision making is desirable
    - For men who are aged 70 years and over or men with < 10-years to 15 years life expectancy, Serum PSA screening is not recommended. [40]
- It has been iterated that potential urine biomarker for prostate cancer is PCA3. [30]

Radiology description

The ensuing summations had been made related to some aspects of radiology imaging in adenocarcinoma of prostate cases: [19]

- Ultrasound scan (USS) is generally used to guide prostate biopsies and upon ultrasound scan prostate cancer may appear hypoechoic but USS is neither sensitive nor specific for establishing a diagnosis of adenocarcinoma of the prostate gland.
- Multiparametric Magnetic Resonance Imaging (MRI) scan is commonly used for local tumour staging and MRI scan may also be utilized to identify abnormalities within the prostate gland for targeting at biopsy
- MRI scan abnormalities generally tend to be reported using either PI-RADS (Prostate Imaging - Reporting and Data System) or Likert score. PI-RADS 4 and PI-RADS 5 prostate lesions are biopsied due to the fact that the lesions are regarded to have high risk of adenocarcinoma of the prostate gland and PI-RADS 1 and 2 lesions are regarded to be benign and PI-RADS 3 lesions are observed.
- CT scan is undertaken to identify metastatic disease in lymph nodes
- Isotope Bone scan is used to detect bony metastases
- PET scan is used to identify micro-metastatic disease in selected patients, such as men with raised serum PSA levels after treatment.

Computed Tomography scan of the thorax, abdomen and pelvis (CT TAP) is used for the full staging and follow-up assessment of patients who have undergone treatment of curative intent for adenocarcinoma of the prostate gland.

Positron Emission Tomography / Computed Tomography (PET/CT) scan is more can detect areas of small metastatic lesions that are not big enough to be identified by CT scan and MRI follow-up scans

In areas where facilities are not easily available for the undertaking of CT-Scan and MRI Scan, or the patient cannot afford to pay for the cost of CT scan and MRI scan, chest radiograph and ultrasound scan of abdomen and pelvis including the prostate tend to be undertaken in the initial staging and follow-up of patients who have primary adenocarcinoma of the prostate gland.

Laboratory tests

Urine

Urinalysis, urine microscopy and culture are general tests that tend to be undertaken in patients who manifest with lower urinary tract symptoms which the common symptoms of patients who have primary adenocarcinoma of the prostate gland and generally the results would tend to be normal and if there is any evidence of urinary tract infection, it would be treated appropriately based upon the antibiotic sensitivity pattern of the organism to ensure the patient is well to undergo the appropriate management of the prostate cancer based upon the tumour stage.

Haematology Blood Tests

Full blood count and INR, are routine tests that tend to be undertaken in cases of primary adenocarcinoma of the prostate and in majority of cases, the results would be within normal range but if there is any evidence of anaemia, it would be investigated and treated accordingly to improve upon the general condition of the patient to enable the patient to go through the appropriate effective treatment.

Biochemistry Blood Tests

CRP, Urea and electrolytes, Liver function tests, Bone Profile, and Random blood glucose are routine tests that tend to be undertaken in cases of primary

adenocarcinoma of the prostate and in majority of cases, the results would be within normal range but if there is any evidence of an abnormality, it would be investigated and treated accordingly to improve upon the general condition of the patient to enable the patient to go through the appropriate effective treatment.

Prognostic factors

The prognostic factors associated with primary adenocarcinoma of the prostate gland have been summated to include the following:

- Biopsy Specimen: The prognostic features based upon the pathology examination of the prostate biopsy of the tumour include: The extent of the tumour extent (mm or percentage core involvement), the grade of the tumour (Gleason score and grade group), presence or absence of peri-neural invasion, presence or absence of extra-prostatic extension of the tumour.
- Radical prostatectomy specimen: the tumour size, Gleason score and grade group of the tumour, stage of the tumour, the margin status of the tumour
- Cribriform morphology and intraductal carcinoma associated with invasive prostate cancer are stated to be adverse prognostic indicators for adenocarcinoma of prostate gland. [41]
- Small cell carcinoma component is stated to be associated with aggressive behaviour and this is treated differently. [19]
- Some expert groups had recommended incorporating intraductal component of the adenocarcinoma of the prostate gland into the Gleason score while others had recommended reporting it separately in a comment. [42] [43] [44]

Treatment

The ensuing summations had been made regarding the treatment options of primary adenocarcinoma of the prostate gland: [19]

- Preoperative risk stratification of primary adenocarcinoma of the prostate gland is based upon serum PSA level of the patient, the clinical stage of the tumour, biopsy pathology examination parameters of the tumour (the extent of the tumour, the grade of the tumour, cribriform morphology features within the tumour, intraductal carcinoma, presence or absence of perineural invasion)
- Primary treatment options of primary adenocarcinoma of prostate gland are based upon preoperative risk stratification and this has been divided into the ensuing options:
  - Active surveillance
  - Focal therapy (cryotherapy, high intensity ultrasound)
  - Radical prostatectomy
  - Brachytherapy
  - External beam radiotherapy
  - Hormone therapy (e.g., luteinizing hormone releasing hormone [LHRH] analogues, antiandrogens)
  - Orchidectomy (rare in contemporary practice)
  - Chemotherapy (for metastatic disease)
- Postprostatectomy options: Pursuant to the undertaking of radical prostatectomy whether by open prostatectomy, laparoscopic prostatectomy, or robotic radical prostatectomy, the following tend to be undertaken:
  - Generally, serum PSA monitoring and early salvage therapy if there is rising serum PSA
  - Less commonly adjuvant therapy for high stage disease or margin positivity
- Other treatment options that are undertaken by other clinicians and oncologists include:
- Neoadjuvant or adjuvant Hormonal treatment in association with the undertaking of radical prostatectomy of curative intent for localized adenocarcinoma of the prostate gland.
- Adjuvant or Neoadjuvant radiotherapy or chemotherapy or chemoradiation
- Immunotherapy

Other treatment options that tend to be utilized pursuant to the development of localized recurrence of a localized tumour following treatment of curative intent by radiotherapy could entail: salvage prostatectomy, plus or minus chemotherapy and immunotherapy, plus or minus hormonal treatment.

Treatment of metastatic prostate cancer may entail the undertaking of hormonal treatment, radiotherapy, chemotherapy, plus or minus immunotherapy.

Treatment of localized back bone pain due to a localized bone metastasis may entail local radiotherapy to the bone metastasis and in cases of back bone metastasis associated with compression of associated nerves and weakness and paralysis of lower limbs, the neuro-surgeons could undertake surgical operation for decompression of the nerves plus use of steroids. Pathological fractures related to bone metastasis may require internal fixation by metallic equipment.

Other treatment options that have been occasionally used to treat few primary adenocarcinomas of the prostate gland as treatment of curative intent or to reduce the size of the tumour to enable further treatment options include the ensuing:

a) Cryotherapy of the adenocarcinoma of prostate
b) Radiofrequency ablation of the prostate cancer
c) Irreversible electroporation of the prostate cancer.
d) Selective angiography and super-selective embolization of the branch of the artery supplying the prostate tumour to reduce the size of the tumour or to stop bleeding from the tumour in an emergency scenario when there is a well-trained vascular interventional radiologist.
e) High frequency focused ultrasound (HIFU) therapy of the prostate cancer.
f) In the unlikely event of excessive bleeding from adenocarcinoma of the prostate gland, the bleeding could potentially be treated by means of selective angiography and super-selective embolization of the branch of prostatic artery to the bleeding tumour in an effort to stop the bleeding.

Gross description

Macroscopy examination of adenocarcinoma of prostate specimen has been summated as follows:

- Upon gross examination often the tumour has tended to be grossly inapparent or not visually identifiable
- The tumour may form a visible cream mass within the prostate gland

Microscopic (histopathology examination) description

The microscopy histopathology examination features of primary adenocarcinoma of the prostate gland had been summated as follows: [19]

- The Gleason grading is based upon the architecture of the tumour found during microscopy examination of the tumour.
- Gleason grades represent a morphological spectrum from well-formed glands (pattern 3) to increasingly complicated glandular proliferations (pattern 4) to almost no glandular differentiation (pattern 5). [45]
- Glandular crowding and infiltrative growth pattern of the tumour.
- Nuclear enlargement, nucleolar prominence within the tumour
- Round generally monomorphic nuclei within the tumour
- Amphophilic cytoplasm within the tumour
- Mitoses evidence in the tumour
- Apoptotic bodies present within the tumour
- Stromal desmoplasia within the tumour
- Intraluminal contents: the intraluminal contents of the tumour include: crystalloids, pink amorphous secretions, blue mucin.

- Glomerulations, collagenous micronodules (mucinous fibroplasia) tend to be seen in the tumour.
- Absence of basal cell layer tends to be seen in the tumour and generally this requires immunohistochemical confirmation. [19] [46]

Cytology description

The role of cytology examination in adenocarcinoma of the prostate gland has been summarized as follows:

- It has been pointed out that the undertaking of urine cytology for the detection of prostate cancer has a very low sensitivity. [47]
- Urine cytology is not used clinically with regard to the diagnosis of prostate cancer
- Fine Needle Aspiration (FNA) cytology examination of metastatic prostate cancer to a lymph node may show micro-acinar complexes / cell clusters / single cells with fragile cytoplasm and prominent nucleoli. [48]
- Immunohistochemistry Staining of Adenocarcinoma of Prostate Gland

Positive staining

Adenocarcinoma of the prostate gland is stated to exhibit positive immunohistochemistry staining features to the ensuing tumour markers: [19]

- PSA
- NKX3.1.
- AMACR (P504S, racemase)
- Prostein (P501S)
- PSMA
- Rare adenocarcinoma of prostate tumours may have exhibit aberrant expression of p63. [49] [50]

Negative staining

Adenocarcinoma of the prostate gland has been stated to exhibit negative immunohistochemistry staining for the following tumour markers: [19]

- CK 7
- CK 20
- High molecular weight cytokeratins including 34 beta E12, CK 5, CK5/6
- p63
- CDX2
- GATA3
- TTF1 [51]

Molecular / cytogenetics description

Summations related to the molecular / cytogenetics features of adenocarcinoma of the prostate gland include the following: [19]

Prostate cancer is a heritable disease

Family history of a first degree relative with prostate cancer does increase the risk for the development of prostate cancer by 2-fold. [52]

It has been pointed out that 30% to 40% of familial risk is due to genetic factors. [30]

Genetic factors associated with the development of adenocarcinoma of the prostate gland include highly penetrable rare variants and more common low to moderate risk variants. [30]

It has been iterated that highly penetrant variants occur in BRCA2 and HOXB13

It has been documented that more than 280 SNPs had been identified as prostate cancer risk factors. [30]

It has been stated that for majority of SNPs, the molecular mechanism of cancer association is generally unknown, as they occur in noncoding regions of the genome [30]

It has been documented that somatic mutations occur in genes such as ERG, ETV1/4, FLI1, SPOP, FOXA1, IDH1, PTEN, TP53, MYC, CDH1. [30] [53]

It has been pointed out that most common somatic genomic rearrangement is fusion of the androgen regulated gene TMPRSS2 with a member of the ETS transcription family. [30]

It has been iterated that somatic mutation profiles of prostate cancer are associated with clinical and pathological outcomes

There are 7 major subtypes, which are defined by either specific gene fusions of ETS transcription family members (ERG, ETV1, ETV4 and FLI1) or mutations (SPOP, FOXA1, IDH1). [54]

It has been pointed out that different subtypes have different molecular profiles, for example.: [54]

ETS subset (59% of cases) are enriched in PTEN mutations

SPOP mutant subset (11%) of cases have distinct somatic copy number alteration profiles, including deletions of CHD1, 6q and 2q

Differential diagnoses of adenocarcinoma of prostate gland

Some of the differential diagnoses of primary adenocarcinoma of the prostate gland have been summarized to include the following: [19]

- Benign prostate tissue which upon microscopy examination demonstrates the following features:
  - Pale cytoplasm
  - Corpora amylacea
  - No other intraluminal contents
  - Basal cell marker immunoreactivity
- Prostate atrophy which upon microscopy examination demonstrates the following features:
  - Lobular architecture
  - Scant cytoplasm
  - Basal cell marker immunoreactivity
- Adenosis of Prostate which upon microscopy examination demonstrates the following features:
  - Lobular architecture
  - Basal cell marker immunoreactivity (often scattered)
- Atypical small acinar proliferation (ASAP) which upon microscopy examination demonstrates the following features:
  - Small size
  - Lack of significant cytological atypia, including a lack of macronucleoli
- High-grade prostatic intraepithelial neoplasia (HGPIN) which upon microscopy examination demonstrates the following features:
  - Less architectural atypia
  - Maintained basal cells
- Post-atrophic hyperplasia which upon microscopy examination demonstrates the following features:
  - Some glands atrophic
  - Basal cell marker immunoreactivity (often scattered)
- Partial atrophy which upon microscopy examination demonstrates the following features:
  - Atrophic glands with abundant lateral pale cytoplasm
  - Irregularly distributed nuclei
  - Basal cell marker immunoreactivity (often scattered)
- Radiation Atypia which upon microscopy examination demonstrates the following features:
  - Glandular atrophy
  - Nuclear irregularity and pleomorphism
  - Atypical stromal cells
  - Basal cell marker immunoreactivity
- Urothelial carcinoma which upon microscopy examination demonstrates the following features:
  - Nuclear irregularity and pleomorphism
  - Hyaline dense eosinophilic cytoplasm
  - Desmoplastic stromal reaction
  - Immunoreactivity for urothelial markers (GATA3, CK7, p63)
  - No expression of prostatic immunomarkers (PSA, PSAP, NKX3.1)

Cryotherapy [55]

The ensuing iterations had been made regarding an overview of cryotherapy: [55]

- Cryotherapy, which is sometimes referred to as cold therapy, is the local or general utilization of low temperatures in medical therapy.
- Cryotherapy may be utilized to treat a variety of tissue lesions. [56]
- The most prominent utilization of the term refers to the surgical treatment, which is specifically known as cryotherapy or cryoablation. Cryosurgery is a terminology which is used for the application of extremely low temperatures to destroy abnormal or diseased tissue and is used most commonly to treat skin conditions.
- Cryotherapy is utilized in an effort to relieve muscle pain, sprains and swelling after soft tissue damage or surgery. For many decades, cryotherapy has been commonly used to accelerate recovery in athletes following their exercise. Cryotherapy decreases the temperature of tissue surface to minimize hypoxic cell death, oedema accumulation, and muscle spasms, all of which ultimately alleviate discomfort and inflammation of individuals. [57]
- Cryotherapy could be a range of treatments from the application of ice packs or immersion in ice baths which is generally known as cold therapy, to the use of cold chambers.
- While cryotherapy is widely utilized, there is little evidence as to its efficacy that has been replicated by or demonstrated in large controlled studies.
- The long-term side effects of cryotherapy had also not been studied. [58] [59]
- Nevertheless, cryotherapy is stated to be important in that individuals should note that a number of studies had shown a possible association between cryotherapy and adverse effects. The adverse events associated with cryotherapy had been documented to include the risk of frostbite, superficial nerve palsies, Raynaud's phenomenon, cold urticaria and delayed regeneration. [55]
- The potential harm of cryotherapy had raised doubts regarding its utilization and effectiveness which had led to guidance against the use of cryotherapy. [60] Nevertheless, a study which had been undertaken had concluded that cryotherapy had had reported a positive impact upon the short-term recovery of athletes. Cryotherapy helped to manage muscle soreness and facilitate recovery within the first 24 hours following a sport-related activity. It was stated that athletes who utilize cryotherapy within the first 24 hours to alleviate pain had recovered at a faster rate than athletes who did not use cryotherapy after their sport-related activity. [57]
- Even though there are many positive effects of cryotherapy in athletes' short-term recovery, in recent years, there had been much controversy regarding whether cryotherapy is actually beneficial or might be causing the opposite effect.
- While inflammation which occurs post-injury or from a damaging exercise might be detrimental to secondary tissue, it is beneficial for the structural and functional repair of the damaged tissue. In view of this, some researchers are now recommending that ice should not be used so as not to delay the natural healing process following an injury.
- The original RICE (rest, ice, compression, elevation) method was rescinded due to fact that the inflammatory response is necessary for the healing process, and this practice might delay healing instead of facilitating it.
- Animal studies had also shown that a disrupted inflammatory stage of healing may lead to impaired tissue repair and redundant collagen synthesis. [61]
- Furthermore, if undertaken regularly post-exercise, cryotherapy could have a negative effect upon muscle mass, strength gains, and rate of muscle protein synthesis. This is due to the fact that cryotherapy does blunt the chronic skeletal muscle adaptations from resistance training exercises. It has been stated that these harmful effects could be easily avoided by not using cryotherapy during an athlete's training season or pre-season phase. [61]

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, And Studies Related to Cryotherapy for The Management of Primary Adenocarcinoma of The Prostate Gland.

Izawa et al. [62] undertook a study to determine the long-term disease-specific survival (DSS) and disease-free survival (DFS) rates after salvage cryotherapy for locally recurrent adenocarcinoma of the prostate and to identify pre-treatment factors that have an impact upon DSS and DFS. Izawa et al. [62] stated that between July 1992 and January 1995, 131 patients who had received definitive radiotherapy treatment (XRT) had undergone salvage cryotherapy for locally recurrent adenocarcinoma of the prostate gland. Izawa et al. [62] stated that they had defined cryotherapy failure as an increasing post-cryotherapy serum prostate-specific antigen (PSA) level of > 2 ng/mL above the post-cryotherapy nadir, a positive prostate biopsy, or radiography image evidence of metastatic disease. Izawa et al. [62] studied clinical variables to determine whether there was an association with the DSS and DFS. Izawa et al. [62] summarized the results as follows:

- The median follow-up was 4.8 years.
- The 5-year DSS rates were 87% for patients who had a pre-cryotherapy Gleason score < 8 and 63% for those with Gleason scores of 9 and 10 (P.012).
- The 5-year DFS rates were 57% for patients with a pre-cryotherapy serum PSA level of < 10 ng/mL and 23% for those with a serum PSA level greater than 10 ng/mL (P.0004).
- The 5-year DSS rates for patients with a pre-XRT clinical stage of T1 to T2 and those with a clinical stage of T3 to T4 were 94% and 72%, respectively (P.0041). The 5-year DFS rates for these groups were 90% and 69%, respectively (P.0057).

Izawa et al. [62] made the following conclusions:

- Androgen-independent local recurrences, Gleason score, and pre-XRT clinical stage were important factors that had an impact upon DSS and DFS.
- The subset of patients cured by salvage cryotherapy seems to be small, and patient selection is important.

Pisters et al. [63] undertook a phase I/II study to evaluate the efficacy and complications of salvage cryotherapy as a treatment option for locally recurrent prostate cancer following full dose radiotherapy and/or systemic therapy. Pisters et al. [63] compared the efficacy of single and double freeze-thaw cycles using posttreatment prostate specific antigen (PSA) levels and prostate biopsies as end points. Pisters et al. [63] reported that a total of 150 patients with locally recurrent prostate cancer following radiotherapy, hormonal therapy and/or systemic chemotherapy underwent salvage cryotherapy using a single free thaw cycle which included 71 men, with a mean follow-up of 17.3 months or double-free thaw cycle which comprised of 79 men, who had a mean follow-up of 10.0 months. Pisters et al. [63] measured serum PSA approximately every 3 months postoperatively and they repeated sextant biopsies 6 months postoperatively. Pisters et al. [63] assessed the complications by retrospective chart review and a mailed quality of life survey. Pisters et al. [63] summarized the results as follows:

- Overall, 45 patients that amounted to 31% of the patients had persistently undetectable serum PSA.
- Patients who had a history of radiation therapy only who underwent a double freeze-thaw cycle had a higher negative biopsy rate which was 93% versus 71%, $p < 0.02$ and lower biochemical failure rate which they had defined as an increase in serum PSA of 0.2 ng./ml. above the nadir value,

44% versus 65%, p <0.03 in comparison with those who underwent a single freeze-thaw cycle.

- The main complications of salvage cryotherapy were urinary incontinence which occurred in 3% of the patients, obstructive symptoms which occurred in 67%, impotence which occurred in 72% of the patients and severe perineal pain which occurred in 8% of the patients.

Pisters et al. [63] made the ensuing conclusions:

- Salvage cryotherapy does impact local tumour control as evident by the high frequency of negative posttreatment biopsies.
- A double freeze-thaw cycle does appear more effective than a single cycle.
- Like salvage prostatectomy, salvage cryotherapy does cause significant morbidity.

Rodriguez et al. [64] stated that published data about 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. Rodriguez et al. [64] undertook a prospective study with standardized follow-up protocol in their institution. Rodriguez et al. [64] undertook a prospective study of a series of cases including 108 patients who were diagnosed with localized PC at clinical stage T1c-T2c which had been treated by primary cryoablation and who had a median follow-up of 61 months. Rodriguez et al. [64] unified the criteria of biochemical recurrence according to the American Society for Therapeutic Radiology and Oncology (ASTRO). End points were biochemical progression-free survival (BPFS), cancer-specific survival, and overall survival. The rate of complications was reported. Rodriguez et al. [64] summarized the results as follows:

- The BPFS for low-, medium-, and high-risk patients was 96.4%, 91.2%, and 62.2%, respectively. Cancer-specific survival was 98.1%.
- The overall survival had reached 94.4%.
- The complications included incontinence in 5.6%, urinary tract obstruction in 1.9%, urethral sloughing in 5.6%, haematuria in 1.9%, perineal pain in 11.1%, and prostate-rectal fistula in 0.9%.
- Erectile disfunction was found in 98.1% of the patients.
- Rodriguez et al. [64] concluded that cryotherapy is an effective and minimally invasive treatment for primary PC in well-selected cases, with low surgical risk and good results in terms of BPFS, cancer-specific survival, and overall survival.

Chad and Katz edited by Gill [5] stated the following:

- Minimally invasive options to treat low-risk prostate cancer are more desirable than radical therapy.
- Technological improvements in cryotherapy had increased its use, and long-term data on its efficacy are emerging.

Chad and Katz, Gill editor. [5] discussed contemporary data on cryotherapy with specific focus on studies using the newest technology. Chad and Katz, Gill editor, [5] made the ensuing iterations.

- With respect to biochemical recurrence rates, cryotherapy had appeared to be as effective treatment for low-risk prostate cancer as other treatment modalities.
- The definition of recurrence had remained problematic, even though contemporary studies had been more consistently using both the American Society for Therapeutic Radiation Oncology and Phoenix criteria.
- Erectile dysfunction rates are universally high after whole-gland cryoablation, but incontinence and urethrorectal fistula rates had appeared to be low with third-generation cryo systems.
- Focal cryotherapy had encouraging short-term efficacy in terms of biochemical disease-free survival rate for unifocal disease, and rates of erectile dysfunction were dramatically lower than those seen with whole-gland cryoablation.

Chad and Katz, edited by Gill et al. [5] made the ensuing summations:

- Cryosurgery has a promising role to play in primary and salvage treatment of select prostate cancer patients.
- Focal cryotherapy for unilateral disease does offer the added benefit of minimal adverse effects.
- Long-term data were emerging to support cryosurgery, and large multi-centre databases had been developed to answer questions regarding optimal treatment outcomes and patterns.

[65] Alexandre de la Taille, Omar Hayek, Mitchell C Benson, Emilia Bagiella, Carl A Olsson, Marie Fatal, Aaron E Katz,

De la Taille et al. [65] stated that cryotherapy of the prostate represents a potential treatment option for localized recurrent prostate cancer after radiotherapy. De la Taille et al. [65] reported their experience and evaluated the predictive factors for prostate-specific antigen (PSA) recurrence. De la Taille et al. [65] reported that between October 1994 and April 1999, 43 patients had undergone salvage cryoablation. They also stated that all of the patients had biopsy-proven recurrent prostate cancer without seminal vesicle invasion, negative bone scans, and negative lymph node dissection. The patients had received 3 months of combined hormonal therapy preceding their cryosurgery. Biochemical recurrence-free survival (bRFS) was defined by de la Taille et al. [65] as a serum PSA value less than 0.1 ng/mL. The results of the study were summarized by de la Taille et al. [65] as follows:

- The complications had included incontinence which occurred in 9% of the patients, obstruction which had occurred in 5% of the patients, urethral stricture which had occurred in 5% of the patients, rectal pain which had occurred in 26% of the patients, urinary infection which had occurred in 9% of the patients, scrotal oedema which had occurred in 12% of the patients, and haematuria which had occurred in 5% of the patients.
- The mean follow-up was 21.9 months and this had ranged between 1.2 months to 54 months.
- Twenty-six patients that amounted to 60% of the patients had reached a serum PSA nadir of less than 0.1 ng/mL, 16 patients which amounted to (37% of the patients had a serum PSA of less than 4 ng/mL, and 1 patient that amounted to 3% of the patients had a serum PSA of less than 10 ng/mL.
- The bRFS rate was 79% at 6 months and 66% at 12 months. The bRFS rate was higher for patients who had an undetectable post-cryotherapy serum PSA than for patients who did not reach a serum PSA of less than 0.1 ng/mL which amounted to 73% versus 30%, P = 0.0076.
- Utilizing multivariate analysis, a serum PSA nadir greater than 0.1 ng/mL was an independent predictor of PSA recurrence.

De la Taille et al. [65] made the following conclusions:

- Current salvage cryotherapy of the prostate could result in undetectable serum PSA levels with low morbidity.
- Their data had supported the current safety and efficacy profile.
- They believed that cryotherapy is a viable option in the treatment of patients who have biopsy-proven local failure after radiation therapy for prostate cancer.
- Further refinements in technique and equipment might enhance cryosurgical results.

Ghafar et al. [65] stated that cryosurgical ablation of the prostate had been reported to be a potential treatment for radioresistant clinically localized prostate cancer. Ghafar et al. [65] reported their experience with the safety and efficacy of salvage cryosurgery using the argon based CRYOCare system (Endocare, Inc, Irvine, California. Ghafar et al [65] stated that between October 1997 and September 2000, 38 men who had a mean age of 71.9 years had undergone salvage cryosurgery for recurrent prostate cancer after the radiotherapy they had undergone failed. All of the patients had biochemical disease recurrence, which they had defined as an increase in prostate specific antigen (PSA) level of greater than 0.3 ng. /ml. above the post-radiation serum PSA nadir. Subsequently prostate biopsy was noted to be positive for cancer. Pre-cryosurgery bone scan had demonstrated no evidence of metastatic disease. In addition, these patients received 3 months of neoadjuvant androgen deprivation therapy before cryotherapy. Ghafar et al. [65] summarized the results as follows:

- The serum PSA nadir was 0.1 or less, 1 or less and greater than 1 ng./ml. in 31 patients that amounted to 81.5%, 5 patients which amounted to 13.2% and 2 patients which amounted to 5.3% of the patients, respectively.
- Biochemical recurrence-free survival calculated from Kaplan-Meier curves was 86% at 1 year and 74% at 2 years.
- The reported complications included rectal pain in 39.5% of cases, urinary tract infection in 2.6%, incontinence in 7.9%, haematuria in 7.9% and scrotal oedema in 10.5%.
- The rate of rectourethral fistula, urethral sloughing and urinary retention was 0%.

Ghafar et al. [65] made the following conclusions:

- Their study outcome had supported cryosurgery of the prostate as safe and effective treatment in patients in whom radiation therapy fails.
- Utilizing the CRYOCare machine had resulted in a marked decrease in complications.

Pisters et al. [66] undertook a study to identify clinical pretreatment factors associated with early treatment failure after salvage cryotherapy. Pisters et al. [66] reported that between 1992 and 1995, 145 patients had undergone salvage cryotherapy for locally recurrent adenocarcinoma of the prostate. Pisters et al. [66] defined treatment failure as an increasing post-cryotherapy serial prostate-specific antigen (PSA) level of more than or equal to 2 ng/mL above the post-cryotherapy nadir or as a positive posttreatment biopsy. Pisters et al. [66] evaluated the following factors as predictors of treatment failure: tumour stage and grade at initial diagnosis, type of prior therapy, stage and grade of locally recurrent tumour, number of positive biopsy cores at recurrence, and pre-cryotherapy PSA level. Pisters et al. [66] summarized the results as follows:

- Among patients who had a prior history of radiotherapy therapy only, the 2-year actuarial disease-free survival (DFS) rates were 74% for patients who had a pre-cryotherapy serum PSA of less than 10 ng/mL and 28% for patients who had a pre-cryotherapy serum PSA of more than 10 ng/mL, $P < .00001$.
- The DFS rates were 58% for patients who had a Gleason score of less than or equal to 8 recurrence and 29% for patients who had a Gleason score greater than or equal to 9 recurrence, $P < .004$.
- Among patients who had a pre-cryotherapy serum PSA of less than 10 ng/mL, the DFS rates were 74% for patients who had a prior history of radiotherapy only and 19% for patients with a history of prior hormonal therapy plus radiation therapy, $P < .002$.

Pisters et al. [66] made the following conclusions:

- Patients failing initial radiotherapy with a serum PSA level of more than 10 ng/mL and Gleason score of the recurrent cancer more than or equal to 9 were unlikely to be successfully salvaged.
- Patients who had failing initial hormonal therapy and radiotherapy were less likely to be successfully salvaged than patients failing radiation therapy only.

Loening et al. [67] reported cryosurgical destruction of primary adenocarcinoma of the prostate gland which was undertaken through the perineal route in 215 patients during a 12-year period. The average age of the patients was 66 years. The stage of the disease had varied from B to D. With regard to 74% of the patients, Loening et al. [67] did not find any clinical evidence of tumour within the prostatic fossa pursuant to the cryotherapy. Few of the patients needed to undergo trans-urethral surgery and none of the patients needed repeated trans-urethral resections of prostate for obstructive symptoms. Loening et al. [67] stated that this experience had suggested that local destruction of carcinoma of the prostate gland can be achived with little morbidity as well as mortality.

Grampass et al. [68] undertook a study to evaluate the potential for salvage radical prostatectomy after failure of transrectal ultrasound (TRUS)-guided percutaneous cryosurgical ablation of the prostate. An additional purpose of the study was to determine the accuracy of intraoperative TRUS to delineate the extent of freeze destruction that results from cryosurgery. Grampass et al. [68] reported that six patients with biopsy-confirmed, Stage T3 prostate cancer had undergone salvage radical prostatectomy 3 months to 10 months after failing prostate cryosurgery. Zones of freeze destruction (resolving coagulative necrosis) and residual adenocarcinoma were mapped on the coverslips of whole-mount sections. Grampass et al. [68] compared histologically proven zones of freeze destruction correlating to successfully treated prostatic tissue to the hypoechoic ice ball treatment zones seen on intraoperative TRUS images. Grampass et al. [68] summarized the results as follows:

- The whole mounts were found to contain necrotic areas of cryo-destruction which appeared much smaller than predicted by intraoperative ultrasound.
- Each of the cases were also found to have contained residual viable adenocarcinoma.
- All of the patients were alive and clinically free of localized disease 0.5 months to 12 months after salvage radical prostatectomy.

Grampass et al. [68] made the following conclusions:

- Salvage radical prostatectomy does offer an effective treatment option in patients who have failed trans-perineal cryosurgery of the prostate.
- Intraoperative TRUS had predicted that the entire prostate would show freeze destruction.
- Whole-mount analysis; nevertheless, had revealed areas of remaining unaffected adenocarcinoma and normal prostatic parenchyma.
- TRUS, therefore, had overestimated the area of prostatic tissue destroyed by extreme cold. This finding had challenged the assumption that the entire prostate is lethally frozen when its boundaries are included within the hypoechoic ice ball witnessed on TRUS.

Mouraviev and Polascik [69] stated that with the recent introduction of novel, minimally invasive procedures for the treatment of prostate cancer, cryotherapy had become a feasible option as a viable alternative treatment option to traditional radical surgery and radiotherapy. In this review we update recent data concerning the basic science of cryobiology, technical trends, oncologic results and complications of this procedure. Mouraviev and Polascik [69] stated that as a result of better understanding of tumour cryo-destruction at a molecular level, refinements in cryo-techniques and improved patient selection, the results of cryotherapy were becoming more promising. In addition, the dramatic decrease in the number of complications following modern cryotherapy had led to a better quality of life, which might be a preferable option, especially for elderly patients with comorbidities. Current trends towards nerve-sparing and focal cryoablation are also discussed. Recent advances in cryobiology had opened up new opportunities to apply cryotherapy in combination with chemotherapy or radiotherapy for patients with intermediate or high-risk cancers. Mouraviev and Polascik [69] stated that potential directions for future developments in cryosurgery do include concepts to reduce side effects such as minimizing cryodamage of the neurovascular bundles (nerve-sparing procedure), and focal ablation of a specific tumour site in patients in whom saturation biopsy supports unifocal prostate cancer.

Wake et al. [70] stated that cryosurgical ablation of the prostate had recently become recognized as a therapeutic option in the treatment of localized adenocarcinoma of the prostate. To assess the efficacy of cryoablation in this disease process several centres had instituted treatment protocols. Wake et al. [70] reported that their overall series had included 117 ultrasound-scan guided percutaneous trans-perineal cryoablations performed on 104 patients who had localized adenocarcinoma of the prostate. The follow-up of the patients had consisted of digital rectal examinations and measurement of serum prostate specific antigen levels at 3-month intervals following the cryosurgery. In addition, prostate biopsies were obtained 3 months to 6 months postoperatively.

Wake et al. [70] summarized the results as follows:

- Out of 63 patients who had undergone initial cryosurgery and follow-up biopsy 47 patients that amounted to 75 percent of the patients had negative findings.
- Out of the 16 patients with positive biopsies 10 consented to undergo a second cryosurgical ablation, and 7 of these patients subsequently had negative follow-up biopsies. Therefore, their disease-free rate at 3 months after 1 or 2 cryosurgical procedures was 95 percent.
- A total of 46 protocol patients in their series completed 12 months of evaluation and 40 of the patients that amounted to 87 percent of the patients had no evidence of disease.
- This same cohort had shown only minimal disease progression, with disease-free rates of 96, 93, 87 and 87 percent at 3, 6, 9 and 12 months, respectively.
- Major complications were infrequent.

Wake et al. [70] made the following conclusions:

- At 1-year follow-up their clinical experience had shown cryoablation of the prostate to be an effective therapy in select cases of prostatic adenocarcinoma.
- Long-term efficacy is still in question but, based upon current disease-free rates, this therapeutic modality merits continued clinical investigation.

Ellis [71] described the technique and recent experience incorporating cryosurgery into our community practice for primary treatment of localized prostate cancer. Ellis [71] reported that between December 2000 and December 2001, a total of 93 patients had undergone targeted cryoablation for localized prostate cancer. Ellis [71] reported that out of the 93 patients, 18 had failed radiotherapy, and cryotherapy was undertaken as salvage therapy. The remaining 75 patients underwent targeted cryoablation of the prostate as primary therapy. A single urologist using an argon-based cryoablation system undertook the procedure. Cryoprobes and thermos-sensors were placed under transrectal ultrasound guidance through a trans-perineal route. A double freeze-thaw cycle was utilized with anterior-to-posterior probe operation. Strategically placed thermos-sensors were utilized to monitor and control the freezing, and a warming catheter was used to protect the urethra. Ellis [71] stated that they achieved a nadir serum prostate-specific antigen (PSA) level of ≤0.4 ng/mL in 84% of the entire population they had studied which included 63 patients out of the 75 patients. Post-surgery complications were noted to be minimal. Incontinence had developed in 4 patients, as did post-suprapubic catheter removal urinary retention. Erectile dysfunction was noted to have developed in 28 of 34 patients who were potent pre-operatively, with 6 out of the 34 patients regaining potency pursuant to surgery. No rectourethral fistula formation had occurred. Urethral sloughing was found in 5 patients, 1 of whom had developed a scrotal abscess during the treatment of the sloughing. Ellis [71] concluded that the use of cryoablation of the prostate for the treatment of localized adenocarcinoma of the prostate is feasible and it can easily be transferred from the pioneering centres to the community hospitals without sacrificing safety or efficacy.

Shelley et al. [72] stated the following:

- Prostate cancer is a common cancer in elderly men and in some prostate cancer will prove fatal.
- Standard treatments for localized prostate cancer disease include surgery entailing radical prostatectomy, radiotherapy and active monitoring.
- New emerging therapy options are being evaluated with the aim of reducing the complication rate associated with standard therapies, as well as developing an effective treatment. One such modality of treatment is cryotherapy, a procedure which does introduce probes directly into the prostate tumour and kills the malignant cells by a freezing process.

Shelley et al. [72] undertook a review of the literature which was aimed to evaluate the relative clinical and economic benefits of cryotherapy compared to standard therapies for the primary treatment of localized prostate cancer. The search of Shelley et al. [72] included an electronic search of MEDLINE from 1996 to December 2006, plus EMBASE (Exerpta Medica Database), the Cochrane library, ISI Science Citation Index, Database of Abstracts and Reviews of Effectiveness (DARE), and LILACS to identify all relevant published randomized trials of cryotherapy for localized prostate cancer. Cancerlit→ and HealthSTAR databases were searched to their final date. Handsearching of relevant journals was undertaken. Shelley et al. [72] reported 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 with localized prostate cancer were eligible for inclusion in this review. Shelley et al. [72] extracted data from eligible studies, and included study design, participants, interventions and outcomes. Primary outcome measures were biochemical disease-free survival, disease-free survival and treatment-induced complications. Secondary outcomes included disease-specific survival, overall survival, quality-of-life outcome measures and economic impact measures. Shelley et al. [72] summarized the results as follows:

- There were no randomized trials found that compared cryotherapy with other therapies for the primary treatment of localized prostate cancer.
- All studies they had identified were case series.
- In order to indicate the level of the available evidence, studies which had evaluated cryotherapy as a primary therapy, with the use of transrectal ultrasound guidance and urethral warming in at least 50 patients who had localized prostate cancer, and a minimum of one year follow up, were reviewed.
- Eight case series were identified that had complied with these criteria; two were retrospective studies.
- The patients who were recruited had totalled1483) and they had an age range from 41 years to 84 years, stages T1 = 0 to 43%, T2 = 24 to 88%, T3 = 1 to 41%, and T4 = 0 to 14% of tumours. The mean pre-operative serum PSA level had ranged from 9.7 to 39 ng/mL, with Gleason scores < 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 identified and reviewed. In this study the success rates, which was defined as a post-treatment serum PSA of 0.2 ng/mL or less, were reported as 96% for total cryotherapy, 49% for standard cryotherapy and 73% for radical prostatectomy. Four studies did not monitor the temperature of the cryo-procedure and these studies reported that 17% to 28% of 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 used thermocouples to monitor the temperature of the cryo-procedure and these studies reported progression-free survival rates of 71% to 89% with 1.4% to 13% of patients having a positive biopsy post-cryotherapy. At 5 years, the overall survival was reported as 89% to 92% in two studies, and disease-specific survival as 94% in one study. The major complications which were observed in all studies included impotence 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 patients, stricture in 2.2% to 17% of patients and pain in 0.4% to 3.1% of patients. Most patients were sent home the following day and this had ranged between 1 day to 4 days.

Shelley et al. [72] made the following conclusions:

- Cryotherapy does offer a potential alternative to standard therapies for the primary treatment of localized prostate cancer.
- However, the poor quality of the available studies has made it difficult to determine the relative benefits of this modality.
- Randomized trials are required to fully evaluate the full potential of cryotherapy in men with this disease.
- Patients who select cryotherapy as their therapeutic option should be made fully aware of the reported efficacy,

complications and the low-grade evidence from which these data had been derived.

Cresswell et al. [73] presented the early results of the use of third-generation cryotherapy in primary and recurrent prostate cancer at one United Kingdom (UK) centre. Cresswell et al. [73] reported that over a 14-month period, 51 patients had undergone cryotherapy for prostate cancer. In 31 patients, cryotherapy was used as the primary treatment and in 20 patients, cryotherapy was used as a salvage treatment after radiotherapy or hormone ablation. Cresswell et al. [73] collected data prospectively and the median follow-up was 9 months. Cresswell et al. [73] summarized the results as follows:

- The serum prostate-specific antigen (PSA) level had decreased to <0.5 ng/mL in 79% of patients undergoing primary treatment and in 67% of patients undergoing salvage treatment.
- A higher Gleason grade and serum PSA levels were associated with a poorer outcome.
- No patient developed a fistula, 4% developed urinary retention requiring transurethral prostatectomy and 4% had persistent incontinence. The rates of erectile dysfunction were high (86%). The median inpatient stay was 2 days.

Cresswell et al. [73] made the following conclusions:

- Early results had suggested that cryotherapy does offer a safe alternative treatment for primary and recurrent prostate cancer, particularly for older and less fit patients.
- Long-term data are required to assess the durability of response and the effect on survival.

Greene et al. [74] determined serum nadir prostate specific antigen (PSA) after salvage cryotherapy to distinguish patients who are potentially cured from those at risk for subsequent biochemical and biopsy proved failure Greene et al. [74] reported that a total of 146 patients who had undergone salvage cryotherapy were followed-up for a median of 21 months and the follow-up had ranged from 3 months to 47 months with regular serum PSA analysis and digital rectal examination. Sextant biopsies were undertaken at 6 months or earlier when serum PSA had increased greater than 2 ng./ml. from the nadir value (biochemical failure) or there was a palpable local recurrence. Greene et al. [74] compared the incidence of biochemical failure and biopsy specimens positive for cancer to pretreatment serum PSA and posttreatment nadir serum PSA.

Greene et al. [74] summarized the results as follows:

- In 59 of the 146 patients which amounted to 40% of the patients, serum PSA had decreased to an undetectable level within a median of 3 months.
- In 85 of the 109 patients which amounted to78% of the patients who underwent biopsy the specimens were negative for cancer.
- Low serum PSA nadir values were found to be associated with low pre-treatment serum PSA and a low incidence of biochemical failure.
- In 6 of 60 patients that amounted to 10% of patients in whom serum PSA nadir was 0.5 ng./ml. or less and in 18 of 49 patients which amounted to 37% with a higher serum PSA nadir biopsy was positive for cancer.
- Greene et al. [74] made the following conclusions:
- A PSA nadir of 0.5 ng. /ml. or less should be achieved following salvage cryotherapy.
- Higher serum PSA nadirs are more likely to be associated with increasing post-treatment serum PSA and positive biopsies.
- Serum PSA nadir is a better prognostic indicator of biochemical and biopsy proven failure after salvage cryotherapy than pretreatment serum PSA.

Hepel et al. [6] analysed the results of intensity-modulated radiotherapy after cryotherapy ablation for adenocarcinoma of the prostate gland. Hepel et al. [6] summarized the methods of a study they had undertaken as follows:

- Patients were either treated by adjuvant therapy following their undergoing targeted cryotherapy or they were treated for salvage therapy after local failure of standard whole-prostate cryotherapy.
- The patients were treated with intensity-modulated radiotherapy to a minimum dose of 73 Gy (mean dose, >75Gy).
- Prostate-specific antigen (PSA) failure was defined according to the Radiation Therapy Oncology Group–American Society for Therapeutic Radiology and Oncology 2006 consensus definition.
- Late gastrointestinal and genitourinary toxicity were graded based upon the Radiation Therapy Oncology Group late toxicity scale and the Late Effects of Normal Tissue–Subjective, Objective, Management, and Analytic scale.

Hepel et al. [6] summarized the results as follows:

- A total of 16 patients had undergone treatment from 1997 to 2007.
- Three patients were treated as adjuvant therapy, and 13 patients were treated for local failure.
- The mean pre-cryotherapy serum PSA value was 8.7 ng/mL. The mean serum PSA value before irradiation was 6.0 ng/mL.
- Majority of the patients were intermediate to high risk.
- The median follow-up was 33 months.
- No grade 3 or greater toxicity was seen.
- Biochemical (serum PSA) control was achieved in 12 of the 16 patients at their last follow-up.

Hepel et al. [6] concluded that:

- Full-dose intensity-modulated radiotherapy after cryotherapy is well tolerated, without excess late morbidity.
- The results of the study had supported the use of radiation for cryotherapy failure salvage. Furthermore, the combination of cryotherapy and irradiation may be considered in a phase II trial.

Jung et al. [75] stated the following:

- Traditionally, radical prostatectomy and radiotherapy with or without androgen deprivation therapy had been the main treatment options to attempt to cure men who have localized or locally advanced prostate cancer.
- Cryotherapy is an alternative option for the treatment of prostate cancer that involves freezing of the whole prostate (whole gland therapy) or only the cancer (focal therapy), but it is unclear how effective cryotherapy is in comparison to other treatments.

Jung et al. [75] stated that they had undertaken a study to assess the effects of cryotherapy (whole gland or focal) compared with other interventions for primary treatment of clinically localized (cT1-T2) or locally-advanced (cT3) non-metastatic prostate cancer. Jung et al. [75] iterated that they had updated a previously published Cochrane Review by performing 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. [75] also searched the reference lists of other relevant publications and conference proceedings. Jung et al. [75] did noy apply any language restrictions to their search. Jung et al. [75] included randomized or quasi-randomized trials comparing cryotherapy to other interventions for the primary treatment of prostate cancer. Jung et al. [75] reported that two independent reviewers had screened the literature, extracted data, as well as assessed risk of bias. Jung et al. [75] performed statistical analyses using a random-effects model and interpreted them according to the Cochrane Handbook for Systematic Reviews of Interventions. Jung et al. [75] rated the quality of evidence (QoE) according to the GRADE approach. Jung et al. [75] summarized the results as follows: They had included only one comparison of whole gland cryotherapy versus external beam radiotherapy, which was informed by two trials with a total of 307 randomized participants. The median age of the included studies was around 70 years. The median follow-up of included studies ranged from 100 to 105 months. Jung et al. [75] summarized the outcomes which were divided into primary outcomes and secondary outcomes as follows:

Primary outcomes:

- They were uncertain about the effect of whole gland cryotherapy compared to radiation therapy 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); this would correspond to zero fewer death from prostate cancer per 1000 men (95% CI 85 fewer to 520 more).

- They were equally uncertain about the effect of quality of life-related urinary function and bowel function (QoL) at 36 months using the UCLA-Prostate Cancer Index score for which higher values (range: 0 to 100) 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 uncertain 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 uncertain of 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); this corresponded to 10 fewer major adverse events per 1000 men (95% CI 58 fewer to 86 more).

Secondary outcomes:

- They were very uncertain about the effects of cryotherapy on 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).
- 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 used for analyses.
- They found no trials that compared whole gland cryotherapy or focal cryotherapy to other treatment forms such as radical surgery, active surveillance, watchful waiting or other forms of radiotherapy.

Jung et al. [75] made the ensuing conclusions:

- Based upon very low-quality evidence, primary whole gland cryotherapy has uncertain effects on oncologic outcomes, QoL, and major adverse events compared to external beam radiotherapy.
- Reasons for downgrading the QoE included serious study limitations, indirectness due to the use of lower doses of radiation in the comparison group than currently recommended, and serious or very serious imprecision.

Choi et al. [10] summarized their results of intensity-modulated radiation therapy (IMRT) for prostate adenocarcinoma after cryotherapy failure. Choi et al. [10] reported that the patients had undergone Intermittent modulated radiation therapy (IMRT) with curative intent for biochemically recurrent prostate cancer after cryotherapy. Radiotherapy was delivered to a minimum dose of 72 Gy (range, 72-81 Gy). Acute and late treatment-related gastrointestinal and genitourinary effects were scored according to Common Toxicity Criteria version 3.0. Prostate-specific antigen failure was defined by Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology 2006 consensus definition. Choi et al. [10] summarized the results as follows:

- Nine patients had undergone treatment from 2008 to 2010.
- The median follow-up was 31 months and the follow-up had ranged between 15 months and 40 months.
- The mean pre-radiotherapy serum prostate-specific antigen was 4.3 ng/mL and this had ranged between 1.07 and15.6 ng/mL.
- The median elapsed time between cryotherapy and IMRT was 20.5 months and this had ranged from 8.5 months to 56.5 months.
- Biochemical control was achieved in 7 patients.
- Two patients developed distant metastases shortly after completion of radiotherapy.
- None of the patients experienced grade 3 or higher toxicities.

Choi et al. [10] made the following conclusions:

- Their results had suggested that high-dose IMRT after cryotherapy failure is well tolerated, without severe morbidity.
- The results had also shown that IMRT can render a significant number of patients biochemically free of disease after initial cryotherapy.
- High-dose IMRT should be considered as a treatment option for these potentially salvageable cases.
- Ross et al. [76] stated the following:
- Monotherapy with immune checkpoint inhibitors had generally been unsuccessful in men with advanced prostate cancer.
- Preclinical data had supported the notion that cryotherapy may improve immune-mediated and anti-tumour responses.

Ross et al. [76] undertook a study with the objective of assessing the safety and feasibility of whole-prostate gland cryotherapy combined with pembrolizumab and androgen deprivation in men with oligometastatic hormone-sensitive prostate cancer. Ross et al. [76] undertook a single-institution, pilot trial which recruited 12 patients with newly diagnosed oligometastatic prostate cancer between 2015 and 2016. Patients underwent whole-prostate cryoablation combined with short-term androgen deprivation for eight months and 6 doses of pembrolizumab. The primary clinical endpoints of the study were the number of patients with a PSA level of <0.6 ng/mL at one year and the frequency of adverse events. Other outcome measures included progression-free survival and systemic therapy-free survival. Exploratory analyses included PD-L1 protein expression. Ross et al. [76] summarized the results as follows:

- Forty two percent (5/12) of patients had a serum PSAs of <0.6 ng/mL at one year though only 2 of these patients had recovered their testosterone at this time point.
- The median progression-free survival was 14 months, and median systemic therapy-free survival was 17.5 months. PD-L1 expression was not detectable by IHC in patients with evaluable tissue.
- All adverse events were grade ≤2, and there were no apparent complications from the cryotherapy.

Ross et al. [76] made the following conclusions:

- Whole-prostate cryoablation combined with short-term androgen deprivation and pembrolizumab treatment was well tolerated and no safety concerns were identified in men with oligometastatic prostate cancer.
- Even though local disease appeared effectively treated in the majority of men, the regimen only infrequency led to sustained disease control following testosterone recovery.

Tsaur et al. [77] stated the ensuing:

- Prostate cancer (PCa) is the commonest malignant tumour in men and the cause for the second commonest cancer-related death within the western world.
- Despite ongoing development of new approaches such as second-generation androgen receptor targeted treatments, metastatic disease has still remained fatal.
- In prostate cancer (PCa), immunotherapy had not attained a treatment breakthrough in comparison with other solid tumours yet.
- They had aimed to highlight the underlying cellular mechanisms that are crucial for immunotherapy (IT) in PCa and to provide an update of the most essential past as well as on going clinical trials within the field.

Tsaur et al. [77] searched for relevant publications on molecular as well as cellular mechanisms which are entailed in the PCa tumour micro-environment and response to IT as well as completed and ongoing IT studies and screened appropriate abstracts of international congresses. Tsaur et al. [77] summarized the results as follows:

- Tumour progression and patient outcomes depend upon complex cellular as well as molecular interactions of the tumour with the host immune system, driven rather dormant in case of PCa.
- Sipuleucel-T and pembrolizumab were the only registered immune-oncology medicaments to treat this malignant tumour.

- A plethora of studies had assessed combination immunotherapy with other agents or treatment modalities like radiotherapy which might increase its anti-neoplastic activity.
- No robust and clinically relevant prognostic or predictive biomarkers had been established yet.

Tsaur et al. [77] concluded that despite immunosuppressive functional status of PCa microenvironment, current evidence, based on cellular and molecular conditions, encourages further research in this field.

Jin et al. [78] stated that for localized prostate cancer (PCa) with a low disease burden, whole-gland resection seems like over-treatment, while focal therapy, including cryosurgery, could achieve similar outcomes. Jin et al. [78] undertook a study which was aimed at comparing the long-term survival outcomes of cryotherapy and radical prostatectomy (RP) and further exploring whether RP can be replaced by cryosurgery for those with low-risk PCa. Jin et al. [78] conducted analyses from the Surveillance, Epidemiology, and End Results (SEER) database (2004-2015) and performed propensity score matching and used an instrumental variate to reduce the influence of bias and unmeasured confounders to the greatest extent. Jin et al. [78] summarized their results as follows:

- In the multivariate regression, patients who had received cryotherapy had higher risk of overall mortality (OM) (hazard ratio [HR] = 2.52, 95% confidence interval [CI] 1.99-3.20, $p < 0.001$), but no significant difference was observed in decreasing cancer-specific mortality (CSM) (HR = 1.38, 95% CI 0.63-3.03, $p = 0.41$) after adjusting the confounders.
- After propensity score matching, patients who had undergone cryotherapy had higher OM and CSM rates (HR = 2.70 [95% CI 1.99-3.66, $p < 0.001$] and HR = 2.99 [95% CI 1.19-7.48, $p = 0.02$], respectively). In the IV-adjusted analyses, RP was superior to cryotherapy in decreasing OM (HR = 2.52, 95% CI 1.99-3.20), while no obvious decrease of CSM was observed in the comparison of RP and cryotherapy (HR = 1.38, 95% CI 0.63-3.03).
- The subgroup analyses had shown that RP displayed an obvious benefit in decreasing CSM (HR = 5.02, 95% CI 1.30-19.39, $p = 0.02$) for those with a prostate-specific antigen (PSA) level higher than 10 ng/ml.
- Jin et al. [78] concluded that RP ranked as the best treatment with regard to tumor control, but the advantages of cryotherapy became evident when taking functional and oncological outcomes into account, especially for low- and intermediate-risk PCa with low PSA levels.

Mercander et al. [79] stated the following:

- Prostate cryotherapy is an available treatment option for localized prostate cancer (PC) included on minimal invasive therapies but still under evaluation.
- They had commenced their cryotherapy program in 2008 for selected patients who had localized PC.
- Their objective was to evaluate the oncological and functional outcomes of primary cryotherapy in men with clinically localized PC.

Mercander et al. [79] retrospectively evaluated all patients who had undergone primary cryotherapy for localized PC treatment within their centre between January 2008 and December 2017. In order to downsize prostates between 40 cc and 60cc neoadjuvant 3-month hormonal therapy was administered. Primary endpoint of the study was biochemical progression-free survival (BPFS) rate as defined by the Phoenix criteria. Secondary endpoints were cancer-specific survival (CSS), overall survival (OS), patient reported functional outcomes and complication rates. Factors influencing de BPFS were evaluated individually using Kaplan–Meyer and Cox regression models and in a multivariate model using Cox regression. Mercander et al. [79] summarized the results as follows:

- During the mentioned period, a total of 177 men had undergone treatment with cryotherapy.
- With a mean follow-up of 60 months (SD 32.9), the Kaplan–Meier analysis had shown an overall BPFS rate was 67%.
- 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 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, intermediate and high -risk groups, respectively.
- In 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 fully maintained in 95% of patients after the procedure.
- Postoperative complications identified 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 patients had acute urinary retention which solved conservatively.

Mercander et al. [79] concluded that cryotherapy is a safe option for selected patients with localized prostate cancer that provides competitive oncologic outcomes and a low morbidity profile.

Sack et al. [80] investigated the outcomes and quality of life measures in men who had undergone cystectomy and urinary diversion for devastating lower urinary tract toxicity after undergoing prostatic radiotherapy and/or cryotherapy for the treatment of prostate cancer. Sack et al. [80] retrospectively reviewed the records of patients who underwent cystectomy and urinary diversion for the management of a devastated lower urinary tract following prostatic radiotherapy or cryotherapy. A postoperative, retrospective quality of life (QOL) survey was designed specific to the patient subset and obtained by telephone interview. Sack et al. [80] summarized the results as follows:

- Extirpative surgery with urinary diversion for management of a devastated lower urinary tract was undertaken on 15 patients with a mean age of 72 years (range 63-82).
- Toxicities leading to urinary bladder removal included bladder neck contractures, prostatic necrosis, incontinence, osteomyelitis, bladder calculi, fistulae, urethral strictures, abscesses, necrotizing fasciitis, and radiation/ haemorrhagic cystitis.
- The mean number of failed conservative-, minimally invasive interventions per patients prior to cystectomy was 3.7 and this had ranged from 1 to 12.
- The average time period from major complication following radiotherapy/cryotherapy to cystectomy was 29.1 months (range 5-65).
- The QOL survey showed that all of the patients who completed the survey (n = 13) would undergo the procedure again and 11 (85%) would have undergone the procedure an average of 13.2 months sooner (range 5-36).
- Sack et al. [80] made the following conclusion:
- Toxicities secondary to prostatic radiotherapy or cryotherapy might be debilitating.
- Their results had demonstrated that cystectomy with urinary diversion can improve QOL in patients with a devastated lower urinary tract.

Saliken et al. [81] stated the following:

- Prostate cancer is now the most prevalent malignancy among men in North America, and with an aging population, the incidence of new cases is expected to rise further.
- With improved prostate cancer detection, particularly with prostate specific antigen (PSA) testing, 74% of men are now diagnosed with cancer which is localized to the gland or the immediate peri-glandular region (i.e., T1-T3 N0 M0), and many prostate cancers are diagnosed at a relatively young age.
- The standard treatments for local cancer include radical prostatectomy, radiotherapy and several evolving permutations of these techniques, including brachytherapy and conformal 3-

dimensional radiotherapy. As well, some physicians continue to advocate "watchful waiting" for selected men.

- Nevertheless, all treatments are compromised by shortcomings, including residual local cancer, early recurrence and various complications (e.g., incontinence, impotence, rectal dysfunction, treatment failure and, rarely, death).
- Watchful waiting is compromised by disease progression.
- Cryotherapy, the use of extremely low temperatures, in situ, to eradicate tissue, had recently been reintroduced to the list of treatments that are offered for local prostate cancer.
- Cryotherapy had been practised in various forms since 1850, but liquid cryogens were first utilized to freeze prostate cancer in the 1960s. The original procedures yielded very promising short- and long-term cancer control, but were crude and complicated by serious injury to the rectum and the urethra.
- Over the last 3 decades, cryogenic and imaging technologies had vastly improved, leading to the modern transrectal ultrasound-guided percutaneous procedure that was introduced in 1989 by the radiologist-urologist team.

Bahn and Lee [82] stated the following:

- Adenocarcinoma of the prostate gland is the most common malignancy in men and still the leading cause of death from cancer in American men.
- Current data and published reports had indicated that cryotherapy for clinically localized prostate cancer could be an effective treatment method in selective patients. Since 1993, 643 cryosurgical procedures had been performed, including 68 patients who had failed radiotherapy, and 20 patients who failed initial cryotherapy.
- Recently developed targeted cryotherapy techniques, using 6-8 probes, had shown promising initial results.
- The complication rates have also compared favourably to the established therapies for prostate cancer.
- Cryotherapy is a minimally invasive procedure with a high patient's acceptance rate.
- Cryotherapy is a highly operator-dependant procedure with a steep learning curve coupled with constantly evolving technology.

Hooper et al. [83] stated the following:

- Cryotherapy is an option for the primary treatment of localized prostate cancer, along with radical prostatectomy, external beam radiation therapy, and brachytherapy.
- Even though it is known that local recurrence can occur after primary cryotherapy in >20% of patients treated unfortunately there is a paucity of data on later salvage treatments.
- Utilization of external beam radiotherapy is an attractive option after cryotherapy failure, but there is little data on its efficacy and toxicity.

Hooper et al. [83] evaluated the biochemical control and complication rates of salvage dose-escalated image guided intensity modulated radiation therapy (IG-IMRT) after cryotherapy failure. Hooper et al. [83] reported that patients who were treated within their institution from 2005 to 2016 were reviewed for those who had undergone cryotherapy as initial treatment followed by salvage IGRT. The patients were treated with dose-escalated IG-IMRT using standard treatment margins of 3 mm posterior and 7 mm in all other directions and daily cone beam computed tomography or kv imaging to implanted fiducial markers. Hooper et al. [83] defined biochemical progression was defined in accordance with the Phoenix consensus conference definition. Hooper et al. [83] summarized the results as follows:

- Eight patients were identified as having undergone post-cryotherapy salvage radiation within the study period.
- The median total dose was 77.7 Gy (range, 75.6-81.0 Gy). Median follow-up was 55 months (range, 6-88 months).
- Six patients had remained biochemically controlled at the latest follow-up.
- One patient had developed distant metastases after 22 months and one patient had experienced biochemical failure at 30 months with no evidence of distant metastases. No patients experienced acute gastrointestinal toxicities of grade 2 or higher. There were no cases of late gastrointestinal or genitourinary toxicity.

Hooper et al. [83] made the following conclusions:

- High-dose IG-IMRT results in high rates of salvage and extremely low rates of serious late toxicity for patients with locally recurrent prostate cancer after cryotherapy.
- Even though the results were encouraging, given the small number of patients in their series and other series, they had remained cautious with regard to this treatment and they believe the use of salvage radiotherapy after cryotherapy warrants further study.

Shah et al. [84] stated the following:

- Focal therapy has increasingly become an accepted option of patients who have localized cancer of the prostate gland.
- Majority of follow-up protocols utilize a mixture of protocol biopsies or “for cause” biopsies triggered by a rising serum PSA.

Shah et al. [84] undertook a literature search and reviewed the post-treatment biopsy results from studies related to focal HIFU as well as focal cryotherapy. Shah et al. [84] subsequently reviewed the results of three recently published consensus statements that had been released discussing many of the issues concerning focal therapy. Shah et al. [84] summarized their results as follows:

- Research had suggested that 1 in 5 of all post-treatment biopsies after focal therapy tend to be positive.
- Nevertheless, the majority of these seemed to be from the untreated portion of the gland or met criteria for clinically insignificant disease.
- In addition, re-treatment is possible whilst maintaining a low-side effect profile.
- Shah et al. [84] concluded that debate was ongoing about the clinical significance of various levels of residual disease pursuant to focal therapy and the exact threshold at which to call failure within a patient who has had focal therapy.

Gestaut et al. [85] stated the following:

- Cryotherapy and brachytherapy are definitive local treatment options for the management of low- to intermediate-risk prostate cancer.
- There are both prospective and retrospective data for brachytherapy, but the use of cryotherapy had been limited primarily to single-institution retrospective studies.
- Currently, no published evidence had compared low-dose-rate brachytherapy versus cryotherapy.

Gestaut et al. [85] obtained institutional review board approval in order to undertake a retrospective chart review of consecutive patients who had undergone treatment within their institution from 1990 to 2012. For inclusion, patients must have received a prostate cancer diagnosis and must have been considered to have low- to intermediate-risk disease according to the National Comprehensive Cancer Network criteria. All of the patients had undergone brachytherapy or cryotherapy treatment. Disease specifics and failure details were collected for all of the patients. Gestaut et al. [85] defined failure as serum prostate-specific antigen nadir +2 ng/mL Gestaut et al. [85] summarized the results as follows:

- A total of 359 patients were analysed.
- 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 serum prostate-specific antigen (PSA) follow-up periods were 85.6 months (LRC), 59.2 months (IRC), 74.9 months (LRB), and 59.8 months (IRB).

- The 5-year biochemical progression–free survival (bPFS) rate was 57.9% in the cryotherapy group versus 89.6% in the brachytherapy group (P<.0001).
- The 5-year bPFS rate was 70.0% (LRC), 51.4% (IRC), 89.4% (LRB), and 89.7% (IRB). The bPFS rate was significantly different between brachytherapy and cryotherapy for low- and intermediate-risk groups (P<.05).
- The mean nadir temperature that was reached for cryotherapy patients was −35°C and this had ranged between −96°C and −6°C).
- Cryotherapy utilized a median of 2 freeze-thaw cycles (range, and this had ranged between 2 and 4 freeze-thaw cycles.

Gestaut et al. [85] made the following conclusions:

- The results from their study had suggested that cryotherapy is inferior to brachytherapy for patients with low- to intermediate-risk prostate cancer.
- Patient selection criteria for consideration of cryotherapy and brachytherapy are similar in terms of anaesthesia candidacy. Therefore, cryotherapy would not be recommended as a first-line local therapy for this particular patient subset.

White et al. [86] reported the longitudinal quality of life outcomes in a national observational cohort of men with locally advanced prostate adenocarcinoma. White et al. [86] used thee CaPSURE® registry to evaluate the quality of life in men who had clinical T3 or T4 prostate adenocarcinoma who had undergone primary treatment and had a minimum follow-up assessment of 2 years. White et al. [86] reviewed the records for treatment, patient age, T stage, prostate specific antigen at diagnosis, body mass index, and initial and posttreatment quality of life using the SF-36® and UCLA-PCI questionnaires, which can each be scored from 0 to 100 with higher scores indicating better outcomes. White et al. [86] evaluated the association of treatment type and quality of life changes after treatment with multivariate mixed model analysis, adjusting for age, time of quality-of-life assessment, and interaction between treatment and time. White et al. [86] summarized the results as follows:

- Out of the 13,740 men who were enrolled in CaPSURE 608 that amounted to 4.42% of the patients had manifested with T3 or T4 tumours. In this subgroup 151 men had completed baseline and a minimum of 2 years of follow-up assessment with quality-of-life data available. These men had undergone primary treatment with radical prostatectomy in 21% of the cases, cryotherapy in 8% of the cases, brachytherapy in 17% of the cases or hormonal ablation in 54% of the cases.
- The treatment cohort of patients had demonstrated significant decreases in quality of life, most profoundly in urinary and sexual function. Mean urinary function was 91 at baseline, which had decreased to 82, 83 and 82 at 1 year, 2 years and 3 years after treatment, respectively ($p = 0.04$). the mean sexual function was 38 at baseline, which had decreased to 15, 16 and 14 at 1 year, 2 years and 3 years after treatment, respectively ($p < 0.01$). On multivariate analysis the quality of life had varied significantly by treatment type ($p < 0.01$).

White et al. [86] made the following conclusions:

- Treatment for locally advanced prostate adenocarcinoma is associated with a significant burden in patients, notably decrements in urinary and sexual function.
- Clinicians should consider the impact that treatment imparts upon the quality of life when counselling patients who have locally advanced disease.

Bargawi et al. [87] undertook a randomized pilot study of patients who were assigned to either cryotherapy alone (Control group) or in combination with GMCSF (Treatment group). The impact of treatment upon the development of T- and B-cell responses against tumour-related antigens was studied by bargawi et al. [87] using enzyme-linked immune absorbent spot (ELISpot) and protein microarray panels (Sematrix) assays, respectively. Bargawi et al. [87] calculated fold changes in response to treatment by normalization of post-treatment ELISpot values against the mean pre-cryoablation response. Bargawi et al. [87] performed student t tests between treatment and control groups at 4 weeks and 12 weeks across all the antigens. Bargawi et al. [87] summarized the results as follows:

- They had randomized a total of 20 patients to either control or treatment arm.
- At 4 weeks following cryotherapy, the treatment group had demonstrated an average fold change in cancer antigen-related antibodies of 2.8% above their mean baseline values, whereas the controls had averaged an 18% change below the mean baseline ($p < 0.05$).
- At 12 weeks, antibody response within the treatment group had increased to 25% above baseline, while the average of the control group patients had remained at 9% below the baseline ($p < 0.05$).
- Patients in the treatment group had displayed, on average, higher ELISPOT readings for the 4- week and 12-week times points (527 vs 481 for serum PSA and 748 vs 562 for PAP).

Bargawi et al. [87] made the ensuing conclusions:

- GMCSF had appeared to broadly elevate antibodies against prostate-specific and nonspecific antigens.
- Prostate antigen-specific T-cell responses were found to be more enhanced over non-prostate-specific responses, preferentially in the treatment group.
- Their findings had suggested a possible therapeutic effect of adjuvant immunotherapy in association with cryotherapy for the treatment of prostate cancer.

Philippou et al. [88] reported the experience of a tertiary centre in the management of recurrent prostate cancer after radiotherapy by salvage cryotherapy. Philippou et al. [88] stated that between February 2006 and August 2008, 19 patients had undergone ssalvage cryotherapy for radio-recurrent prostate cancer. Post-radiotherapy recurrence was confirmed by pathology examination of prostatic biopsy specimens. Philippou et al. [88] used the 'Phoenix definition' to define biochemical failure after salvage cryotherapy. Philippou et al. [88] summarized the results as follows:

- The mean age at cryotherapy was 69.2 years and the mean time from radiotherapy to cryotherapy was 72.3 months.
- Patient characteristics preceding the cryotherapy included a mean serum PSA level of 6.84 ng/ml and a median Gleason score of 7.
- The mean post-cryotherapy follow-up was 33.3 months.
- The 2-year biochemical disease-free survival rate was 58%.
- The median post-cryotherapy serum PSA nadir was 0.20 ng/ml and this had ranged between 0.005 ng/ml and 8.260 ng / ml.
- There were no procedure-related or cancer-related deaths.
- The complications included incontinence in 10.5% of the cases, erectile dysfunction in 89% of the cases and fistula formation in 5.3% of the cases.

Philippou et al. [88] concluded that the relatively high rates of biochemical response support the use of cryotherapy as a salvage procedure for radio-recurrent prostate cancer.

Murray et al. [89] reported that in 1996, a 42-year-old African American man with a prostate-specific antigen (PSA) level of 14 ng/mL (level on repeat testing, 16 ng/mL) was diagnosed as having prostate cancer. Pathology reports of his prostate biopsy specimens indicated he had Gleason score 6 (3+3) adenocarcinoma on the right side of his prostate gland, in clinical stage T1c. His American Urological Association (AUA) symptom score was reported as 1, and his erectile function score was reported as 3 out of 5 (reported on a 5-point scale, with 1 being no erections and 5 being normal erections without difficulty). He elected treatment with iodine-125 brachytherapy and neoadjuvant hormone suppression. His serial serum PSA levels had shown appropriate response with a serum PSA nadir <1.0 ng/dL until 10 years after his treatment, when he met criteria for biochemical failure. His PSA level was 1.1 ng/mL and results of a bone scan he had undergone were negative. He underwent trans-perineal prostate biopsy and pathology examination of the specimen revealed Gleason score 6 (3+3) cancer in 1 of 16 cores, in the right anterior zone. His AUA score was 7, and

his erectile function score was reported as 3 of 5. He was offered salvage, partial-gland prostate cryoablation and this was applied uneventfully to his right hemi-gland of the prostate gland, utilizing a urethral warmer and two freeze-thaw cycles. After cryoablation, no radiology imaging was obtained to formally assess prostate gland treatment.

Two years pursuant to his cryoablation, his PSA level had continued to rise up to 3.76 ng/mL which prompted the undertaking of repeat trans-rectal ultrasound (TRUS) biopsy of the prostate and seminal vesicles, and the pathology of the specimen results were negative (46 cores). His AUA symptom score was 14, and his erectile function score was reported as 1 of 5. He received dilations for a membranous urethral stricture. Five years after his cryoablation treatment, his serum PSA level was 4.5 ng/mL, and the serum PSA continued to elevate to 10.2 ng/mL, and then to 14 ng/mL. He underwent a digital rectal examination which revealed an abnormality upon the right side of his prostate gland. A repeat prostate biopsy was undertaken, and pathology examination of the biopsy specimen revealed Gleason 7 (3+4) prostate cancer in 1 of 12 cores in the right lateral apex of the prostate. He then self-referred to the institution of the authors for salvage management options. He reported severe erectile dysfunction (score, 2 of 5) and weak urinary flow. He had cystoscopy which confirmed he had a membranous urethral stricture.

He had multi-parametric magnetic resonance imaging (MRI) of the prostate which showed a 17.6-mL prostate gland with heterogeneous signal changes which were consistent with prior treatment effect and artifacts from brachytherapy implants. A suspicious region was reported as an asymmetric lesion on the right peripheral zone from the middle to the base of the gland. Heterogeneous signal was found in his seminal vesicles, and the lymph nodes were reported as nonsuspicious of cancer. The rectal wall was reported to be in close contact with the gland with evidence that was consistent with fibrosis. He had a bone scan which revealed nothing remarkable.

Three months after IRE PGA, the patient's serum PSA level was undetectable (<0.05 ng/mL).

He was provided a full discussion of his management options including a referral to a colorectal surgeon for a discussion of potential surgical risks for rectal wall injury. The patient requested evaluation for candidacy for partial-gland ablation (PGA) therapy with irreversible electroporation (IRE). A confirmatory biopsy of the prostate and seminal vesicles was undertaken by the trans-perineal approach (38 cores), which identified Gleason score 7 (3+4) prostate cancer in two of four cores from the right anterior base, with a maximum of 7.7 mm in length and 20% of core involvement. The seminal vesicles were normal.

After the patient was counselled regarding the potential risks and after he had provided informed consent, he was treated with IRE PGA which was applied to the right lobe of his prostate gland utilizing five probes which were placed under TRUS guidance; a 5-mm clearance from the urethra, rectum, and bladder was utilized to avoid collateral tissue damage. He underwent cystoscopy evaluation of the urethra and urinary bladder, and treatment was applied using 90 pulses per electrode pair. The total voltage delivered between the probe sets ranged from 1200 to 2160 V/cm. The procedure lasted 108 minutes. A urethral urinary drainage catheter was left in situ for 24 hours after the procedure. The patient was able to void pursuant to removal of the catheter.

Three months after IRE PGA, the patient's serum PSA level was undetectable (<0.05 ng/mL). Results of a traditional TRUS-guided prostate biopsy performed 4 months after treatment was negative for cancer, identifying only fibrosis and focal acute inflammation. Since treatment with IRE PGA, the patient has remained without biochemical recurrence (PSA <0.05 ng/mL) for 3.25 years. PSA levels after therapies are shown in Figure 2

Some of the summating discussions made by Murray et al. [89] include the following:

- Rates of urethral stricture following primary and salvage radiotherapy and ablative techniques, including cryotherapy, had been reported to have ranged from 3% to 15%, dependent on time of follow-up. [90] [91] [92]
- As had been demonstrated by posttreatment contrast MRI studies, the IRE PGA treatment was applied close to the urethra but not circumferentially in order to avoid the risk of profound ischemic involvement.
- Nevertheless, this finding had also served to highlight that the "tissue-sparing" properties which had been suggested by studies in normal tissues are neither absolute nor necessarily universal to all tissue types. [94] [95].
- Like any surgical intervention, care needs to be exercised when considering use of IRE near sensitive organ sites or in compromised tissues in which damage to these tissues may risk collateral dysfunction. [96]
- Measuring treatment outcomes following PGA therapies presents a major challenge, to such an extent that regulatory agencies do not allow the use of IRE or other ablation device technologies to be referred to as a "treatment" for oncologic conditions unless there is demonstrable proof of efficacy. The use of PSA dynamics as an outcome measure is problematic and has not been validated; nevertheless, it is a commonly used observatory metric.
- The study undertaken by Valerio and colleagues [97] utilizing primary focal IRE for anterior gland ablation reported a roughly 50% decrease in median PSA by 6 months following PGA (6.1 ng/mL preoperatively and 3.2 ng/mL postoperatively).
- Similar changes had been found with other modalities that employ hemi-ablation in the primary setting. [98] [99] [100]
- In the case presented, the profound change in PSA, we believe, is clinically meaningful due to the long duration of the undetectable PSA level; however, this finding needs to be placed in the context of multiple prior whole-gland therapies. Still, this finding is somewhat unusual, as it is rare to develop undetectable levels of PSA following whole-gland radiation or cryotherapy procedures. [99] [101] [102]
- In their reported patient's procedure, treatment was applied to only half of the prostate gland, and it was expected that PSA would remain detectable due to the untreated remnant of the gland.
- One possibility includes the formation of an immune response against prostate tissue or PSA generated from multiple therapies applied to this tissue.
- Such responses following surgical and ablative treatments have been described, although these responses are rare.
- In their reported case, they had no evidence to support this speculation with subsequent histology findings demonstrating only nonspecific inflammatory changes and severe fibrosis without viable prostatic glands in the biopsies from the left side of the prostate.
- Exploration of this hypothesis does require the undertaking of prospective and specific studies.
- Continued follow-up for their reported patient would include serial serum PSA testing and further studies, such as prostate biopsy or imaging, considered in the case of biochemical or clinical evidence of recurrence.

The salient points related to their case report and discussions were summarized as follows:

Salient Points

- Therapeutic options for locally recurrent cancer of the prostate following radiation treatment include hormone therapy, salvage prostatectomy, cryoablation, and high intensity focussed ultrasound. In appropriately selected patients, oncological control may be reasonably achieved with the undertaking of salvage radical prostatectomy; nevertheless, the rate of complications, including urinary incontinence, bladder neck strictures, and rectal injury could be high.
- Salvage cryoablation of the prostate gland had emerged as a less invasive technique with similar effectiveness in local cancer control as salvage radical prostatectomy. Nevertheless, failure

after the undertaking of salvage treatments, represents a unique challenge and majority of men in this situation, do find themselves on hormone treatment.

- Irreversible electroporation (IRE) is an energy-based system that produces tissue ablation by means of short high-voltage electrical pulses which are delivered through metal needle electrodes preplaced within the tissue to be ablated. It can be utilized as a second-line salvage treatment modality in a patient with locally recurrent prostate cancer.
- Care does need to be exercised when considering utilization of IRE near sensitive organ sites or in compromised tissues in which damage to these tissues might risk collateral dysfunction.
- It is important to note that this type of response may not be applicable to other patients, but it may hold promise for future trials of IRE in a salvage setting.
- It is worth noting that they and others had carefully performed IRE for local failure following radiation in selected cases and have not witnessed this form of response in those cases.
- Further accumulated experience will help to add to the understanding of IRE effects in previously radiated or otherwise ablated tissues, including the effects of serially repeated IRE procedures.
- Risks for identifiable adverse events such as urethral stricture disease, collateral injury, functional loss, and inflammatory and infectious complications require further evaluation.

Lian et al. [103] presented the intermediate results of the use of third-generation cryotherapy as salvage treatment for locally recurrent adenocarcinoma of prostate gland following radiotherapy. Lian et al. [103] reported that from January 2006 to July 2010, 32 patients with locally recurrent prostate cancer after radiotherapy had undergone salvage cryoablation utilizing third-generation technology. Lian et al. [103] defined biochemical recurrence-free survival (BRFS) as the time period from salvage therapy to date of biochemical recurrence (Phoenix definition of nadir + 2 ng/ml). Lian et al. [103] classified complications as grades 1 – 5 according to the modified Clavien system. Lian et al. [103] performed multivariate logistic regression analysis to identify potential risk-factors associated with recurrence after salvage cryotherapy. Lian et al. [103] summarized the results as follows:

- The median follow-up was 63 months and the follow-up had ranged between 38 months and 92 months.
- The mild complications of grades 1 and 2, included mild incontinence in 9.4% of the patients, acute rectal pain in 31.3% of the patients, haematuria in 6.3% of the patients, scrotal oedema in 9.4% of the patients, urinary tract infection in 3.1% of the patients, lower urinary tract symptoms in 15.6% of the patients, and erectile dysfunction in 57.1% of the patients.
- Severe events of grade 3 included severe incontinence in 3.1% of the patients and urethral sloughing in 3.1% of the patients.
- The rate of rectourethral fistula and urinary retention was absent.
- The 5-year overall survival was 92.3%.
- The 5-year cancer-specific survival was 100%
- The 5-year BRFS rate utilizing the Phoenix definition was 43.5%
- A multi-variate analysis had disclosed that serum PSA level at cryotherapy was the only predictive factor for biochemical recurrence.
- A multi-variate analysis had disclosed that serum PSA level at cryoablation was the only predictive factor for biochemical recurrence.

Lian et al. [103] made the ensuing conclusions:

- Salvage cryotherapy utilizing third0generation technology does offer a safe and effective alternative option of treatment for locally recurrent cancer of the prostate gland after radiotherapy.
- Additional studies with longer follow-up assessments are necessary in order to ascertain the sustained efficacy of this procedure.

Lu et al. [104] stated the following:

- Salvage cryotherapy is a potentially curative option of treatment but perhaps salvage cryotherapy had been an underutilized treatment modality for patients who have prostate adenocarcinoma who recur locally after undergoing definitive radiation therapy (RT).
- Data upon appropriate patient selection and outcomes utilizing modern cryoablation technology were limited.

Lu et al. [104] undertook a retrospective review of their institutional data to evaluate factors associated with improved freedom from biochemical failure (FFBF) in patients who had been treated with modern salvage cryotherapy technology for locally recurrent prostate cancer following definitive RT. Lu et al. [104] reported that between January 2005 and August 2015, 75 patients had undergone treatment within their institution with salvage cryotherapy for biopsy-proven locally-recurrent prostate adenocarcinoma pursuant to undergoing previous definitive RT. A negative bone scan and soft tissue metastatic workup were required. Lu et al. [104] defined biochemical failure (BF) following cryotherapy as a serum prostate-specific antigen (PSA) level of ≥2 ng/mL above the post-cryotherapy nadir. Lu et al. [104] summarized the results as follows:

- The median age at the time of cryotherapy was 75 (range 54-84).
- Previous definitive RT had entailed external-beam RT for 78% and brachytherapy for 22% of patients.
- Androgen deprivation therapy (ADT) was provided with RT in 25% of patients.
- The risk groups by D'Amico risk classification at time of cryotherapy were recorded as: 23% low-risk, 54% intermediate-risk, and 23% high-risk.
- The median serum PSA nadir ensuing the cryotherapy was 0.2 ng/mL (range 0-18.9).
- With a median follow-up time of 47.3 months, 49% of the patients had experienced BF pursuant to their cryotherapy with a median time to BF of 17.6 months.
- In comparison with patients who had experienced BF, patients who did not experience BF had a longer median time to serum PSA nadir after definitive RT (21.7 vs 11.8 months, P = 0.004), a lower pre-cryotherapy PSA density (0.2 vs 0.3 ng/mL/cm3, P = 0.012), and a lower post-cryotherapy PSA nadir (0.1 vs 0.8 ng/mL, P<0.001).
- Patients who had not experienced post-cryotherapy BF were less likely to develop metastatic disease (0% vs 27%, P<0.001) as well as receive subsequent ADT (0% vs 62%, P<0.001).
- The five-year FFBF was 62%, 48%, and 17% in patients who had a pre-cryotherapy PSA of 0-3.9 ng/mL, 4-6.9 ng/mL, and 7-19 ng/mL, respectively (P = 0.033).
- The five-year FFBF was 84%, 20%, and 0% in patients with a post-cryotherapy serum PSA nadir of ≤0.1 ng/mL, 0.11-0.5 ng/mL, ≥0.51 ng/mL, respectively (P<0.001).
- The five-year FFBF was 43%, 61%, 57%, and 0% in patients who had pre-cryotherapy Gleason score of 6, 7, 8, and 9-10, respectively (P = 0.031).
- Lu et al. [104] made the ensuing conclusions:
- Salvage cryotherapy is an effective treatment modality for select patients who do fail locally following their undergoing of definitive RT.
- Pre-cryotherapy serum PSA, post-cryotherapy serum PSA nadir, and pre-cryotherapy Gleason score are predictive of FFBF following salvage cryotherapy.

Ahmad et al. [105] stated the following:

- Tissue cryoablation is a potential curative option of treatment for solid malignancies, including radiation recurrent prostate cancer (RRPC).
- Case series of salvage cryotherapy (SCT) in RRPC had reported promising disease -free survival (DFS) outcomes and acceptable toxicity profile.
- While many men receive SCT, no predictive factors for treatment induced side effects were known.

Ahmad et al. [105] undertook a study which was aimed to validate the oncological outcome of SCT in a large multi-centre patient cohort and to identify potential parameters were associated with an increased risk of micturition symptoms. Ahmad et al. [105] undertook a retrospective analysis, in which they studied 283 consecutive patients with RRPC who had undergone treatment by SCT in three independent United Kingdom centres between 2001 and 2011. Two freeze-thaw cycles of trans-perineal cryotherapy were undertaken under trans-rectal ultrasound scan-guidance by a single surgeon in each of the 3 sites. Ahmad et al. [105] analysed clinical-pathological factors against tumour response. Ahmad et al. [105] assessed the functional outcomes by continence status and IPSS questionnaire. Ahmad et al. [105] also analysed the predictive factors for SCT-induced micturition symptoms in a sub-group (n=42) of consecutive cases. Ahmad et al. [105] summarized the results as follows:

- They had found that nadir post-SCT PSA levels were strongly associated with DFS.
- The DFS rates at 12 months and 36 months were 84% and 67% for the ≤1 ng/ml group and 56% and 14% for the >1 ng/ml group, respectively (p<0.001).
- Correlative analysis had revealed highly significant association between the patients' post-SCT micturition status with prostate gland and ice-ball lengths pursuant to the SCT.
- They had found that finally, in a reduction model, both gland length and maximal length of ice-ball were highly associated with the patients' IPSS outcome (p<0.001).

Ahmad et al. [105] made the ensuing conclusions:

- They had reported the largest European patient cohort who had undergone treatment with SCT for RRPC.
- Oncological outcome guided by nadir PSA of <1 ng/ml was consistent with earlier single-centre series.
- For the first time, they had identified physical parameters to predict micturition symptoms following SCT.
- Their data would directly assist on-going and future trial design in cryotherapy in prostate cancer.

Tan et al. [106] reported the impact of focal therapy (FT) on multi-domain functional outcomes in a Phase II prospective clinical trial (NCT04138914) in focal cryotherapy for clinically significant prostate cancer (csPCa). The primary outcome of the study was the detection of a ≥5 point deterioration in any of the four main expanded prostate index composite (EPIC) functional domains. Pretreatment multiparametric magnetic resonance imaging (mpMRI) and trans-perineal targeted and systematic saturation biopsy were used to select patients who had serum prostate-specific antigen (PSA)≤20 ng/mL, Gleason grade group (GG) ≤4, mpMRI lesion volume ≤ 3 mL (for a single lesion) or ≤1.5 mL (where two lesions were present). Focal cryotherapy was undertaken with a minimum 5 mm margin encompassing each target lesion. EPIC scores were obtained at baseline and after treatment at 1 month, 3 months, 6 months, and 12 months. Mandatory repeat mpMRI and prostate biopsy were undertaken at 12 months to ascertain the infield and outfield recurrence. Tan et al. [106] summarized the results as follows:

- Twenty-eight patients were recruited into the study.
- The mean age of the patients was 68 years, with serum PSA of 7.3 ng/mL and PSA density of 0.19 ng/mL2.
- No Clavien–Dindo ≥3 complications developed.
- Transient worsening of EPIC urinary (mean diff 16.0, p < 0.001, 95% confidence interval [CI]: 8.8–23.6) and sexual function scores (mean diff 11.0, p:0.005, 95% CI: 4.0–17.7) were identified at 1-month post-treatment, with recovery by Month 3 months.
- A sub-group who had ablation which had extended to the neurovascular bundle had a trend to having delayed recovery of sexual function to Month 6 months.
- At 12-month follow-up assessment by repeat mpMRI and biopsy, 22 patients (78.6%) did not have any detectable csPCa.
- Out of the six patients (21.4%) who had csPCa recurrences, four were GG2, one GG3, and one GG4.
- Four patients underwent repeat FT, one underwent radical prostatectomy, while the remaining one patient who had low-volume GG2 cancer opted for active surveillance.

Tan et al. [106] concluded that FT utilizing cryotherapy was associated with a transient deterioration of urinary and sexual function with resolution at 3 months pursuant to treatment and with reasonable early efficacy in well-selected csPCa patients.

Shah et al. [107] stated that focal therapy (FT) ablates areas of prostate cancer rather than treating the whole gland. Shah et al. [] compared oncological outcomes of FT to radical prostatectomy (RP). Shah et al. [107] stated that using prospective multicentre databases of 761 FT and 572 RP cases (November/2005-September/2018), patients with PSA < 20 ng/ml, Gleason </= 4 + 3 and stage </= T2c were 1-1 propensity score-matched for treatment year, age, PSA, Gleason, T-stage, cancer core length and use of neoadjuvant hormones. FT included 1-2 sessions. Primary outcome was failure-free survival (FFS) defined by need for salvage local or systemic therapy or metastases. Differences in FFS were determined using Kaplan-Meier analysis with log-rank test. Shah et al. [107] summarized the results as follows:

- 335 radical prostatectomy and 501 focal therapy patients were eligible for matching.
- For focal therapy, 420 had HIFU and 81 had cryotherapy.
- Cryotherapy was utilized predominantly for anterior cancer.
- After matching, 246 RP and 246 FT cases had been identified.
- For radical prostatectomy, the mean (SD) age was 63.4 (5.6) years, median (IQR) PSA 7.9 g/ml (6-10) and median (IQR) follow-up 64 (30-89) months. For focal therapy, these were 63.3 (6.9) years, 7.9 ng/ml (5.5-10.6) and 49 [34-67] months, respectively.
- At 3, 5 and 8 years, FFS (95%CI) was 86% (81-91%), 82% (77-88%) and 79% (73-86%) for radical prostatectomy compared to 91% (87-95%), 86% (81-92%) and 83% (76-90%) following focal therapy (p = 0.12).
- Shah et al. [107] concluded that in patients with non-metastatic low- intermediate prostate cancer, oncological outcomes over 8 years were similar between focal therapy and radical prostatectomy.

Conclusions

- Available information on published that has revealed that cryotherapy is an effective treatment and minimally invasive, with low surgical risk, low morbidity, with good results in the long follow-up in terms of survival, biochemical recurrence, cancer-specific survival and overall survival.
- Cryotherapy is a valid technique that has at times been used for the treatment of organ-confined tumours and preferably in low- and intermediate-risk groups. It is a safe alternative for patients with high surgical risk or contraindication for radiotherapy, with a low rate of complications.
- Cryotherapy can be repeated in case of biochemical relapse after histological confirmation of local recurrence or evidence of persistence of prostate cancer after initial treatment of cancer by cryotherapy.
- Cryotherapy of prostate cancer can also be undertaken as salvage therapy following evidence of persistence of the tumour or localized recurrence following previous radiotherapy, or irreversible electroporation of localized prostate cancer.
- Salvage radiotherapy of curative intent or salvage radical prostatectomy can be undertaken for recurrence or persistence of localized prostate cancer following initial treatment of curative intent of the prostate cancer by cryotherapy.

Conflict Of Interest

None.

References

1. Hopper AB, Sandhu APS, Parsons JK, Rose B, Einck JP. (2017). Salvage image guided radiation therapy to the prostate after cryotherapy failure. Adv Radiat Oncol. 27;3(1):52-56.
2. Xiong T, Turner RM, Wei Y, Neal DE, Lyratzopoulos G, et al. (2014). Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. BMJ Open. 15;4(5): e004285.
3. Donnelly BJ, Saliken JC, Brasher PM, Ernst SD, Rewcastle JC, et al. (2010). A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. 15;116(2):323-330.
4. Shore N. (2014). Management of early-stage prostate cancer. Am J Manag Care. 20: S260-272.
5. Ritch CR, Katz AE. (2009). Prostate cryotherapy: current status. Curr Opin Urol. 19(2):177-181.
6. Hepel JT, MacAusland SG, Long JP, Wazer DE, DiPetrillo T. (2008). Intensity-modulated radiotherapy of the prostate after cryotherapy: initial experience. Urology.72(6):1310-1314.
7. Ward JF, Jones JS. (2012). Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int.109(11):1648-1654.
8. Burton S, Brown DM, Colonias A, Cohen J, Miller R, et al. (2000). Salvage radiotherapy for prostate cancer recurrence after cryosurgical ablation. Urology. 1;56(5):833-838.
9. McDonough MJ, Feldmeier JJ, Parsai I, Dobelbower RR Jr, Selman SH. (2001). Salvage external beam radiotherapy for clinical failure after cryosurgery for prostate cancer. Int J Radiat Oncol Biol Phys. 1;51(3):624-627.
10. Choi M, Kim CR, Hung AY. (2013). Salvage intensity-modulated radiation therapy for locally recurrent prostate cancer after cryotherapy. Clin Genitourin Cancer.11(2):85-88.
11. Shinohara K. (2003). Prostate cancer: cryotherapy. Urol. Clin North Am.30(4):725-736.
12. Cox RL, Crawford ED. (1995). Complications of cryosurgical ablation of the prostate to treat localized adenocarcinoma of the prostate. Urology. 45(6):932-935.
13. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, et al. (2012). Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys.1;84(1):125-129.
14. F (Specialty Editor Board), Kim E D, (Chief Editor), (2020). Cryotherapy in Prostate Cancer Technique. Medscape (E Medicine). 24.
15. Izawa JI, Busby JE, Morganstern N, Vakar-Lopez F, Scott SM, (2006). Histological changes in prostate biopsies after salvage cryotherapy: effect of chronology and the method of biopsy. BJU Int. 98(3):554-558.
16. Shinohara K, Connolly JA, Presti JC Jr, Carroll PR. (1996). Cryosurgical treatment of localized prostate cancer (stages T1 to T4): preliminary results. J Urol. 156(1):115-120.
17. Hoffmann NE, Bischof JC. (2002). The cryobiology of cryosurgical injury. Urology. 60:40-49.
18. Han KR, Belldegrun AS. (2004). Third-generation cryosurgery for primary and recurrent prostate cancer. BJU Int. 93(1):14-18.
19. Short E, Varma M. (2023). Adenocarcinoma. PathologyOutlines.com website.
20. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, et al. (2013). Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst. 17;105(14):1050-1058.
21. Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Stenzl A, et al. (2017). Clinicopathological Features and Prognostic Value of Incidental Prostatic Adenocarcinoma in Radical Cystoprostatectomy Specimens: A Systematic Review and Meta-Analysis of 13,140 Patients. J Urol. 197(2):385-390.
22. Rawla P. (2019). Epidemiology of Prostate Cancer. World J Oncol.10(2):63-89.
23. Løvf M, Zhao S, Axcrona U, Johannessen B, Bakken AC, et al. (2019). Multifocal Primary Prostate Cancer Exhibits High Degree of Genomic Heterogeneity. Eur Urol.75(3):498-505.
24. Reissigl A, Pointner J, Strasser H, Ennemoser O, Klocker H, et al. (1997). Frequency and clinical significance of transition zone cancer in prostate cancer screening. Prostate. 1;30(2):130-135.
25. Matzkin H, Patel JP, Altwein JE, Soloway MS. (1994). Stage T1A carcinoma of prostate. Urology. 43(1):11-21.
26. Lee JJ, Thomas IC, Nolley R, Ferrari M, Brooks JD, et al. (2015). Biologic differences between peripheral and transition zone prostate cancer. Prostate. 75(2):183-190.
27. Fine SW, Reuter VE. (2012). Anatomy of the prostate revisited: implications for prostate biopsy and zonal origins of prostate cancer. Histopathology. 60(1):142-152.
28. (2015). Cancer Genome Atlas Research Network. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 5;163(4):1011-1025.
29. Faisal FA, Lotan TL. (2020). The Genomic and Molecular Pathology of Prostate Cancer: Clinical Implications for Diagnosis, Prognosis, and Therapy. Adv Anat Pathol. 27(1):11-19.
30. Lavalette C, Trétarre B, Rebillard X, Lamy PJ, Cénée S, et al. (2018). Abdominal obesity and prostate cancer risk: epidemiological evidence from the EPICAP study. Oncotarget. 2;9(77):34485-34494.
31. Gann PH. (2002). Risk factors for prostate cancer. Rev Urol. 4 Suppl 5(Suppl 5): S3-S10.
32. Junejo NN, AlKhateeb SS. (2020). BRCA2 gene mutation and prostate cancer risk. Comprehensive review and update. Saudi Med J. 41(1):9-17.
33. Haraldsdottir S, Hampel H, Wei L, Wu C, Frankel W, et al. (2014). Prostate cancer incidence in males with Lynch syndrome. Genet Med. 16(7):553-557.
34. Allemailem KS, Almatroudi A, Alrumaihi F, Makki Almansour N, Aldakheel FM, (2021). Single nucleotide polymorphisms (SNPs) in prostate cancer: its implications in diagnostics and therapeutics. Am J Transl Res. 15;13(4):3868-3889.
35. Roberts CT Jr. (2004). IGF-1 and prostate cancer. Novartis Found Symp. 262:193-199.
36. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, et al. (2017). Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 25;389(10071):815-822.
37. NCCN Guidelines: Prostate Cancer: Early Detection (2018). US Preventive Services Task Force. Final Recommendation Statement. Prostate Cancer Screening.
38. Carter HB, Albertsen PC, Barry M J et al. (2013). Early detection of prostate cancer: AUA Guideline. The clinical guideline on Early Detection of Prostate Cancer discusses the detection of disease at an early, pre-symptomatic stage through the use of screening tools, such as PSA. Early detection allows for more conservative management, if

needed, via means such as active surveillance and watchful waiting. J Urol. 190: 419.
39. Kweldam CF, van der Kwast T, van Leenders GJ. (2018). On cribriform prostate cancer. Transl Androl Urol.7(1):145-154.
40. van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, et al. (2020). ISUP Grading Workshop Panel Members. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. 44(8): e87-e99.
41. F, Aron M, Baydar DE, Beltran AL, Brimo F, et al. (2021). The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. Arch Pathol Lab Med. 1;145(4):461-493.
42. Varma M, Epstein JI. et al. (2021). Head-to-head: should the intraductal component of invasive prostate cancer be graded? Histopathology. 78(2):231-239.
43. Short E, Warren A Y, Varma M. (2019). Gleason Grading of Prostate Cancer: A Pragmatic Approach. Diagnostic Histopathology. 31; 25(10): 371 – 378.
44. Humphrey P A. (2017). Histopathology of Prostate Cancer. 7: a0304111 - 22
45. Eskra JN, Rabizadeh D, Pavlovich CP, Catalona WJ, Luo J. (2019). Approaches to urinary detection of prostate cancer. Prostate Cancer Prostatic Dis. 22(3):362-381.
46. Rosa M, Chopra HK, Sahoo S. (2007). Fine needle aspiration biopsy diagnosis of metastatic prostate carcinoma to inguinal lymph node. Diagn Cytopathol. 35(9):565-567.
47. Tan HL, Haffner MC, Esopi DM, Vaghasia AM, Giannico GA, et al. (2015). Prostate adenocarcinomas aberrantly expressing p63 are molecularly distinct from usual-type prostatic adenocarcinomas. Mod Pathol. 28(3):446-456.
48. Epstein JI, Egevad L, Humphrey PA, Montironi R. (2014). Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group. Best practices recommendations in the application of immunohistochemistry in the prostate: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol. 38(8): e6-e19.
49. Immunohistochemistry in Diagnostic Urologic Pathology Group. (2014). Best practices recommendations in the application of immunohistochemistry in the prostate: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol. 38(8): e6-e19.
50. Eeles R, Goh C, Castro E, Bancroft E, Guy M, et al. (2014). The genetic epidemiology of prostate cancer and its clinical implications. Nat Rev Urol. 11(1):18-31.
51. The Cancer Genome Atlas Research Network, (2015). The Molecular Taxonomy of Primary Prostate Cancer, Cell 163: 1011–1025
52. Inamura K. (2018). Prostatic cancers: understanding their molecular pathology and the 2016 WHO classification. Oncotarget. 16;9(18):14723-14737.
53. Wikipedia the free encyclopedia. Cryotherapy.
54. Unger J G, Amiriak B, Kenkel J F, Vinson R P, Heyman W R, Morgan A J.et al. (2022). Cryotherapy Medscape.
55. Jinnah, Alexander H; Luo, Tianyi David; Mendias, Christopher; Freehill, Michael (2019). "Cryotherapy duration is critical in sh 2022 ort-term recovery of athletes: a systematic review". Journal of ISAKOS. 4 (3): 131–136.
56. Novella, Steven. (2017). Whole Body Cryotherapy. Science-Based Medicine.
57. Cryotherapy in Cancer Treatment. National Cancer Institute. (2005).
58. Klintberg, Ingrid Hultenheim; Larsson, Maria EH. (2021). Shall we use cryotherapy in the treatment in surgical procedures, in acute pain or injury, or in long term pain or dysfunction? – A Systematic Review. Journal of Bodywork and Movement Therapies. 1; 27: 368–387.
59. Kwiecien S Y, McHugh M P. (2021). The cold troth truth: the role of cryotherapy in the treatment of injury and recovery from exercise. Eur. J. Appl. Physiol.121: 2125 – 2142.
60. Jonathan I. Izawa, Lydia T. Madsen, Shellie M. Scott, Jean-Paul Tran, Edward J. McGuire, (2002). Andrew C. von Eschenbach, and Louis L. Pisters Salvage Cryotherapy for Recurrent Prostate Cancer After Radiotherapy: Variables Affecting Patient Outcome Journal of Clinical Oncology, pp 2664-2671
61. Pisters LL, von Eschenbach AC, Scott SM, Swanson DA, Dinney CP, et al. (1997). The efficacy and complications of salvage cryotherapy of the prostate. J Urol. 157(3):921-925.
62. Rodríguez SA, Arias Fúnez F, Bueno Bravo C, Rodríguez-Patrón Rodríguez R, Sanz Mayayo E, et al. (2014). Cryotherapy for primary treatment of prostate cancer: intermediate term results of a prospective study from a single institution. Prostate Cancer. 571-576.
63. Ghafar MA, Johnson CW, De La Taille A, Benson MC, Bagiella E, et al. (2001). Salvage cryotherapy using an argon-based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. J Urol. 166(4):1333-1337
64. Pisters L L, Perrotte P, Scott S M, Greene G, von Eschenbach a C. (2016). Patient Selection for Salvage Cryotherapy for Locally Recurrent Prostate Cancer After Radiation Therapy. Journal of Clinical Oncology.
65. Loening S, Hawtrey C, Bonney W, Narayana A, Culp D A. (1980). Cryotherapy of prostate cancer. The Prostate.1(3): 279 – 286
66. Grampsas S A, Miller G J, E. David Crawford E D. (1995). Salvage radical prostatectomy after failed transperineal cryotherapy: histologic findings from prostate whole-mount specimens correlated with intraoperative transrectal ultrasound images. Urology. 45(6): 936-941.
67. Mouraviev, V; Polascik, TJ. (2006). Prostate Cancer Update on cryotherapy for prostate cancer in; Current Opinion in Urology. 16(3): 152 – 156.
68. Wake R W, Hollabaugh R S, Bond K. (1996). Cryosurgical Ablation of the Prostate for Localized Adenocarcinoma: A Preliminary Experience. Journal of Urology. 155(5): 1663 – 1666.
69. Ellis D S. (2002). Cryosurgery as primary treatment for localized prostate cancer: a community hospital experience. Urology. 60:34-39.
70. Shelley M, Wilt TJ, Coles B, Mason M. (2007). Cryotherapy for localised prostate cancer. Cochrane Database of Systematic Reviews.
71. Cresswell J, Asterling S, Chaudhary M, Sheikh N, Greene D. (2006). Third-generation cryotherapy for prostate cancer in the UK: a prospective study of the early outcomes in primary and recurrent disease British Journal of Urology International. 97(5): 969 -974.
72. Greene G F, Pisters L L, Scott S M, ANDREW C. von Eschenbach a C.
73. (1998). Predictive value of prostate specific antigen nadir after salvage cryotherapy. The Journal of Urology. 160(1): 86-90.
74. Jung JH, Risk MC, Goldfarb R, Reddy B, Coles B, (2018). Primary cryotherapy for localised or locally advanced prostate cancer. Cochrane Database of Systematic Reviews.

75. Ross, A.E., Hurley, P.J., Tran, P.T. et al. (2020). A pilot trial of pembrolizumab plus prostatic cryotherapy for men with newly diagnosed oligometastatic hormone-sensitive prostate cancer. Prostate Cancer Prostatic Dis 23; 184–193.
76. Tsaur, I., Brandt, M.P., Juengel, E. Manceau C, Ploussard G. (2021). Immunotherapy in prostate cancer: new horizon of hurdles and hopes. World J Urol. 39, 1387–1403.
77. Jin K, Qiu S, Zheng X, Li Y, Zhang S, et al. (2020). Cryotherapy shows no inferiority compared with radical Prostatectomy for low-risk and intermediate-risk localized Prostate Cancer: a real-world study from the SEER database. Journal of Cancer.11(19):5738.
78. Mercander C, Musuquera M, Franco A, Alcarez A, Ribal M J. (2020). Primary cryotherapy for localized prostate cancer treatment. Aging Male. 23(5): 1460 – 1466.
79. Sack BS, Langenstroer P, Guralnick ML, Jacobsohn KM, O'Connor RC. (2016). Cystectomy and urinary diversion for the management of a devastated lower urinary tract following prostatic cryotherapy and/or radiotherapy. Wmj.115(2):70-73.
80. Saliken JC, Wiseman D, Rewcastle J, Donnelly BJ, Ernst S. (2001). Prostate cryotherapy: practicalities and applications from the Calgary experience. Canadian Association of Radiologists Journal. 1;52(3):165.
81. Bahn DK, Lee F. (2000). Cryosurgical ablation therapy for prostate cancer. Archivio Italiano di Urologia, Andrologia: Organo Ufficiale [di] Societa Italiana di Ecografia Urologica e Nefrologica. 1;72(4):302-304.
82. Hopper A B, Sandhu A P S, Parsons K J, Rose B, Einck J P., (2018). Salvage image guided radiation therapy to the prostate after cryotherapy failure, Advances in Radiation Oncology. 3(1): 52-56.
83. Shah TT, Kasivisvanathan V, Jameson C, Freeman A, Ahmed HU. Et al. (2015).j Histological outcomes after focal high-intensity focused ultrasound and cryotherapy. World J Urol. 33(7):955-64.
84. Gestaut M M, Cai W, Vyas S, Patel B J, Hasan S A, et al. (2017). Low-Dose-Rate Brachytherapy Versus Cryotherapy in Low- and Intermediate-Risk Prostate Cancer. International Journal of Radiation Oncology*Biology*Physics. 98(1): 101-107.
85. White W M, Sadetsky N, Waters W B, Carroll P R, Litwin M S. (2008). Quality of life in men with locally advanced adenocarcinoma of the prostate: an exploratory analysis using data from the CaPSURE database. The Journal of urology. 180(6):2409-3414.
86. Barqawi, A.B., Rodrigues Pessoa, R., Crawford, E.D. et al. (2021). Boosting immune response with GM-CSF optimizes primary cryotherapy outcomes in the treatment of prostate cancer: a prospective randomized clinical trial. Prostate Cancer Prostatic Dis. 24;750–757.
87. Philippou P, Yap T, Chinegwundoh F. (2012). Third-generation salvage cryotherapy for radiorecurrent prostate cancer: a centre's experience. Urologia Internationalis. 88(2):137-144.
88. Murray KS, Akin O, Coleman JA. (2017). Irreversible Electroporation for Prostate Cancer as Salvage Treatment Following Prior Radiation and Cryotherapy. Rev Urol. 19(4):268-272.
89. Rodríguez SA, Arias Fúnez F, Bueno Bravo C, et al. (2014). Cryotherapy for primary treatment of prostate cancer: intermediate term results of a prospective study from a single institution. Prostate Cancer. 571-576.
90. Zelefsky MJ, Wallner KE, Ling CC, et al. (1999). Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. J Clin Oncol. 17:517–522.
91. Elliott SP, Meng MV, Elkin EP, et al. (2007). Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. J Urol. 178: 529–534.
92. Herschorn S, Elliott S, Coburn M, et al. (2014). SIU/ICUD consultation on urethral strictures: posterior urethral stenosis after treatment of prostate cancer. Urology. 83: S59–S70.
93. Deodhar A, Monette S, Single GW, et al. (2011). Renal tissue ablation with irreversible electroporation: preliminary results in a porcine model. Urology. 77:754–760.
94. van den Bos W, Jurhill RR, de Bruin DM, et al. (2016). Histopathological outcomes after irreversible electroporation in prostate cancer; results of an ablate-and-resect study. J Urol.196:552–559
95. Srimathveeravalli G, Silk M, Wimmer T, et al. (2015). Feasibility of catheter-directed intraluminal irreversible electroporation of porcine ureter and acute outcomes in response to increasing energy delivery. J Vasc Interv Radiol. 26:1059–1066.
96. Valerio M, Stricker PD, Ahmed HU, et al. (2014). Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. Prostate Cancer Prostatic Dis. 17 :343–347.
97. Murray KS, Ehdaie B, Musser J, et al. (2016). Pilot study to assess safety and clinical outcomes of irreversible electroporation for partial gland ablation in men with prostate cancer. J Urol. 196:883.
98. Williams AK, Martínez CH, Lu C, et al. (2011). Disease-free survival following salvage cryotherapy for biopsy proven radio-recurrent prostate cancer. Eur Urol. 60:405–410.
99. Azzouzi AR, Barret E, Bennet J, et al. (2013). TOOKAD® soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer. BJU Int. 112:766–774.
100. Pisters LL, Rewcastle JC, Donnelly BJ, et al. (2008). Salvage prostate cryoablation: initial results from the cryo online data registry. J Urol. 180:559–563.
101. Wenske S, Quarrier S, Katz AE. (2013). Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol. 64:1–7.
102. Lian H, Yang R, Lin T, Wang W, Zhang G, et al. (2016). Salvage cryotherapy with third-generation technology for locally recurrent prostate cancer after radiation therapy. International urology and nephrology.48:1461-1466.
103. Lu SM, Cosmatos H, Finley DS, Kim DW, Slezak JM, Safavy S, Jabaji RB, Williams SG. Predictors of Biochemical Control Following Salvage Cryotherapy for Radio recurrent Prostate Cancer. International Journal of Radiation Oncology, Biology, Physics.1;96(2): E259.
104. Ahmad I, Kalna G, Ismail M, Birrell F, Asterling S, McCartney E, et al. (2013). Prostate gland lengths and iceball dimensions predict micturition functional outcome following salvage prostate cryotherapy in men with radiation recurrent prostate cancer. Plos one. 9;8(8): e69243.
105. Tan YG, Law YM, Ngo NT, Khor LY, Tan PH, et al. (2023). Patient-reported functional outcomes and oncological control after primary focal cryotherapy for clinically significant prostate cancer: A Phase II mandatory biopsy-monitored study. The Prostate. 83(8):781-791.

106. Shah TT, Reddy D, Peters M, Ball D, Kim NH, et al. (2021). Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study. Prostate Cancer Prostatic Dis.24(2):567-574.