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International Journal of Clinical Reports and Studies

Anthony Kodzo-Grey Venyo*

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Review Article

Cryotherapy of Urinary Bladder Cancer An Update

Anthony Kodzo-Grey Venyo

Anthony Kodzo-Grey Venyo, Retired Urologist and Clinician, Reviewer of Articles for Journals, Medical Examiner Member of Royal College of Pathologists, London. United Kingdom.

***Corresponding Author**: Anthony Kodzo-Grey Venyo, Retired Urologist and Clinician, Reviewer of Articles for Journals, Medical Examiner Member of Royal College of Pathologists, London. United Kingdom.

Received Date: November 19, 2024 | Accepted Date: January 30, 2025 | Published Date: February 12, 2025

Citation: Grey Venyo AK, (2025), Cryotherapy of Urinary Bladder Cancer An Update, *International Journal of Clinical Reports and Studies*, 4(1); **DOI:**10.31579/2835-8295/089

Abstract

Urinary bladder cancer is iterated to be among the top 10 most frequent malignancies within the world, which accounts for more than half a million new cases yearly. About 25% of urinary bladder cancers invade the muscular layer at the time of the initial diagnosis and are known as muscle-invasive urinary bladder cancer (MIBC). Prevention of tumour recurrence and progression of the tumour is crucial for patients who are afflicted by early-stage disease. Instillations of intravesical Bacillus Calmette-Guerin (BCG) and treatment with immune checkpoint inhibitors (ICIs) do play important roles in the treatment of urinary bladder cancer. Nevertheless, 30% to 50% of patients who are afflicted by non-muscle-invasive bladder cancer (NMIBC) do demonstrate no clinical response to BCG, and 10% to 15% do progressed to MIBC. Likewise, ICIs demonstrate treatment responses in only 20% of patients, which does hinder their practical application. Cryotherapy is an ablative treatment which is based on extreme hypothermia that induces necrosis and apoptosis of living cells, and is associated with less surgical trauma when compared with conventional surgical resection. Hypothermia-induced necrosis has the potential to elicit systemic antitumour immunity due to the release of tumour antigens, indicating that cryotherapy might function as an autologous tumour vaccine. Nevertheless, there has been limited evidence regarding utilisation of cryotherapy in the treatment of intraluminal tumours including urinary bladder cancer), as the existing clinical applications mainly target solid organ malignancies such as the prostate gland, the liver, as well as the breast. Endoscopic cryoablation does eliminate tumour cells and releases tumour antigens, promoting long-lasting tumour-specific immunity to inhibit bladder tumour recurrence. Combining endoscopic cryoablation with ICIs does offer new treatment options for patients with advanced bladder cancer.

Keywords: bladder cancer; urothelial cancer; biopsy; radiotherapy; trans-urethral resection, cystectomy; chemotherapy; cryotherapy; local recurrence; distant metastasis

Introduction

It has been pointed out that urinary bladder cancer is one of the most common malignant tumours that are encountered globally. [1] [2]. It has been iterated that within China, the incidence and mortality rate of carcinoma of the urinary bladder cancer does rank first among all genitourinary neoplasms. [1] [3] It has been documented that the undertaking of trans-urethral resection (TUR) of urinary bladder tumours is the optimal choice for diagnosing the diagnosis of urinary bladder cancer and for the treatment of non–muscle-invasive urinary bladder cancer (NMIBC). [1] [4] [5] It has been pointed that the high 3-month recurrence rate pursuant to the undertaking of trans-urethral resection (TUR) of urinary bladder cancer, illustrated that TUR only might constitute incomplete treatment, which has tended to contribute to subsequent development of early recurrence of bladder tumour in the majority of patients. [1] [6] It has been documented that the immediate single instillation (SI) of intravesical chemotherapy had been recommended as a class I level A adjuvant therapy pursuant to TUR by 2016 European Association of Urology/American Urological Association/National Comprehensive Cancer Network guidelines. [1] [4] It has been pointed out that within China, urinary bladder cancer had been one of the most common adjuvant treatments that tend to be provided for the prevention of non-muscle invasive urinary bladder cancer (NMIBC) recurrence inside the urinary bladder. [1] [7] It has been pointed out that even though intravesical Bacillus Calmette-Guerin (BCG) instillation had gradually become popular over the recent years, SI has generally tended to be adopted in a majority of bladder cancer patients, subsequent diagnostic TUR in China due to the lower cost and medical insurance issues. [1]

It has been iterated that percutaneous cryoablation had been widely undertaken to treat malignancies within solid organs, including the ensuing: the liver, the kidney, and the prostate gland. [1] It has been pointed out that in terms of intraluminal tumours, the undertaking of endoscopic cryoablation had been introduced over the recent years. [1] [8] Despite the aforementioned, it has been iterated that only a few clinical trials had reported the application of endoscopic cryoablation for precancerous gastrointestinal lesions and neoplasms, most of which had been single-arm or retrospective studies. [1] [9] [10] [11] [12] It has been documented that the inspiration to undertake endoscopic balloon cryoablation (EBCA) had been derived from the FIRE AND ICE study, which had compared cryo-balloon with radiofrequency ablation in paroxysmal atrial fibrillation. [1] [13] It has been documented that one recent study, had demonstrated the efficacy and safety of a nitrous oxide cryo-balloon in the eradication of Barrett oesophagus. [1] [14]

Xu et al. [1] in 2023, reported the first prospective randomized clinical trial (RCT) of cryotherapy plus standard TUR for patients with bladder cancer. The liquid nitrogen–based cryo-balloon was designed to be applied under a cystoscope and resectoscope. The feasibility and safety of cryoablation for bladder tumours were validated in both animal models and a small-sample, single-arm preclinical trial. [1] [15] [16] Xu et al. [1] in their study, had hypothesized that EBCA could eradicate residual tumour inside the urinary bladder pursuant to the undertaking of TUR, and thus could reduce the risk of the development of recurrence of urinary bladder cancer. It had furthermore, been iterated that EBCA would be an adjuvant therapy which at least is demonstrated not to be inferior to SI in terms of efficacy and safety.

The ensuing summations had been made about cryotherapy: [17]

- Cryoablation is a hypothermic modality which is exercised as a focal therapy for annihilating cancer lesions.
- Its application does leave the ablated tumour in situ, enabling multifarious tumour antigens to be available to the host's immune system.
- This ensues the activation of innate and adaptive immunity against the tumour antigens. Therefore, cryoablation could be employed as an in vivo vaccination tool to fortify the impact of immunotherapies.
- Application of checkpoint inhibitors, toll-like receptor agonists, adoptive cell therapies and epigenetic modulators has been shown to galvanize the immune system against tumours.
- Preliminary data had shown an excellent synergy between cryoablation and immunotherapies.
- Future endeavours should focus upon tailoring cryo-immunotherapies based upon the tumour's immune signature and testing alternative approaches to circumvent treatment-associated toxicities and maximize efficacy.

It has been pointed out that there is an undisputable need for the development of new treatment strategies and medical devices that could be utilised for the treatment of both local and metastatic urinary bladder cancer lesions. [18] It has been iterated that the World Cancer Research Fund and other groups had reported that there were about 550,000 new cases of urinary bladder cancer within the entire world in 2018 and it had been projected that more than 200,000 individuals would die from urinary bladder cancer globally in 2019. [18] [19] [20] [21] [22] [23] It had furthermore, been iterated that, urinary bladder cancer has the highest lifetime treatment costs per patient of all cancers afflicting the human body. [18] [24]. It had also been pointed out that even though urinary bladder cancer, urinary bladder cancer is slightly less common in women, and that it is the fourth most common cancer which afflicts men. It had been iterated that about half of newly diagnosed cases of urinary bladder cancers are non-invasive cancers, that tend to be contained within the inner layer of the wall of the urinary bladder. [18] It had also been documented that about 33% of cases urinary bladder cancers are more locally advanced with muscle invasion having spread into deeper layers of the urinary bladder at the times of their initial diagnoses, as well as that the remaining cases of urinary bladder cancer do constitute metastatic urinary bladder cancers. [18] [25] It has been pointed out that based upon documentations of the American Cancer Society, the survival rate of urinary bladder cancer does vary based upon the SEER stage as follows: Localized urinary bladder cancer (69%); urinary bladder carcinoma in situ alone (95%); urinary bladder cancer which is associated with regional of local metastasis (35%); urinary bladder cancer which is associated with distant metastasis (5%); and 77% for all SEER stages combined. [18 [23]

It had been explained that the treatment of urinary bladder cancer is dependent upon the grade of the tumour and the stage of the tumour. [18] It had furthermore been iterated that: Low grade, early-stage non-invasive cancers could be treated successfully with a combination of transurethral resection of bladder tumour (TURBT) and intravesical therapy, where by a chemotherapeutic or immunotherapy agent is instilled into the urinary bladder for up to two hours. [18] [26] It has been iterated that urinary bladder cancer which has grown deeply into the wall of the urinary bladder or had metastasized outside the confines of the urinary bladder is treated with radiotherapy, and that systemic chemotherapy, and/or radical cystectomy. Cisplatin, 5-Fluorouracil, Mitomycin, and Gemcitabine are the most common chemotherapeutic agents that are used, as well as often in some combination with or without radiotherapy. [18] It has been pointed out that various options of treating urinary bladder cancer exist but a number of issues had been reported, including high cost of the treatment, patient discomfort, complications emanating from the treatment, incomplete treatment, procedural invasiveness, and poor efficacy, among others. [18]

It has been iterated that whilst there had been advances and shifts in the neoadjuvant chemotherapy that is utilised pursuant to the undertaking of radical cystectomy in patients who are afflicted by invasive urinary bladder cancer (e.g. methotrexate, vinblastine, doxorubicin and cisplatin to now gemcitabine and cisplatin), [27] [28] there had been few advances in ablative approaches for the treatment of urinary bladder cancer. [18] It has been pointed out that cryotherapy is an established method of ablation of solid tumour, which had been documented to offer comparable disease-free survival rates to other modalities in the treatment of prostate cancer. [18] [29] and that cryotherapy is also utilised in kidney, liver, and breast cancers. [18] [30] [31] [32] It has been explained that cryotherapy does extract heat from tissues and does create a dynamic thermal environment in which ultralow temperatures nearest to the cryoprobe induce cell rupture. [18] It has furthermore, been iterated that warmer sub-freezing isotherms that extend radially from the cryotherapy probe's surface result in a zone of complete necrosis, which is followed by a transitional zone characterized by necrotic, apoptotic and living cells due to a combination of factors including ice crystal formation, hypoxia, pH, ionic changes, energy deprivation, free radical formation, and others. [18] [33] [34] It has been iterated that temperature exposure within the range of −25°C to 0°C (cancer type dependent) are characteristic of this transitional zone of heterogeneous cell death and survival. As such, this transitional zone region does present an increased probability for cancer reoccurrence in vivo and thereby represents a prime target for combination strategies utilising sensitizing agents with the goal of synergistically increasing cell death while reducing the need for prolonged freezing. [18] [34]

As a minimally invasive modality, it has been iterated that cryotherapy is an attractive option for the treatment of superficial or muscle invasive urinary bladder cancers. [18] It has been documented that some studies had been published, which had demonstrated the ability of cryotherapy to freeze through the wall of the urinary bladder without damage to the urinary bladder structure. [18] [35] [36] [37] [38] It has also been iterated that whilst demonstrating promise, utilization of cryotherapy to treat urinary bladder cancer had remained limited clinically and that this had been considered to be due in part to a lack of data related to urinary bladder cancer cell response to freezing, including minimal temperature and exposure time necessary (dosing) to assure lethality, concerns with perforation of the urinary bladder wall, few cystoscopy compatible cryo-devices, extended procedure time, cost as well as the ability to target metastatic disease which limit widespread application of cryotherapy. [18]. It has been documented that analysis of two urinary bladder cancer variants had been undertaken because some studies had demonstrated that different stages and molecular dispositions of similar cancers (tissue type) could respond differently to similar treatments. [18] [39]

It had been pointed out that in order to ascertain the potential of cryotherapy, a number of studies had revealed the benefit of adjunctive strategies that entail freezing in combination utilization of various chemotherapy and nutraceutical agents to augment cancer cell death in various cancer types. [18] [40] [41] [42] [43]

It has also been iterated that within the area of urinary bladder cancer treatment, some studies which had been undertaken had demonstrated that thermal therapy (heat and freezing) alone or in combination with chemo/radiotherapy does offer an effective approach to treat unresectable pT4b urinary bladder cancer as well as other types of urinary bladder cancer and ureteral cancer. [18] [44]

It has been pointed out that whilst adjunctive studies had been limited, they nevertheless had demonstrated the potential of this approach. It had been

postulated or suggested that pre-treatment with low dose cisplatin would sensitize the urinary bladder cancer cells so that when combined with mild freezing (−15°C) complete cell destruction would be achieved under conditions in which either the drug or freezing alone yield minimal to no impact.

Considering the fact that generally, cryotherapy has not been used for the treatment of urinary bladder cancer in most urology and oncology centres in the world, it would be envisaged that the majority of urologists and oncologists in all health care establishments in the world would not be familiar with utilization of cryotherapy for the treatment of urinary bladder cancer. The ensuing extended article has been divided into two parts: (A) Overview which has discussed general overview aspects of urinary bladder cancer, and (B) miscellaneous narrations and discussions from some case reports, case series, and studies related to cryotherapy in the treatment of urinary bladder cancer.

Overview [45]

Definition / general

- It has been iterated that invasive urothelial carcinoma that has not infiltrated the urinary bladder muscle is a terminology that is used for urothelial carcinoma that has penetrated the basement membrane and invaded into the lamina propria or deeper. [45]

Essential features

The essential features of urothelial carcinoma had been summated as follows: [45]

- Histopathology examination characterization and depth of invasion are iterated to represent the most important factors for determining the prognosis of the tumour. [46]
- It has been pointed out urothelial carcinoma is morphologically heterogenous with many variants and sub-types [47]
- It has been iterated that invasive urothelial carcinoma involving the lamina propria (T1) is often treated with conservative intravesical therapy and mucosal resection [48]
- It has also been iterated that invasive urothelial carcinoma involving the muscularis propria (T2) is often treated with radical cystectomy [48]

Terminology

It has been pointed out that the ensuing terminologies had tended to be used for invasive urothelial cancer. [45]

- Invasive transitional cell carcinoma (historical term)
- **WHO classification 2016:** [49]
    - Infiltrating urothelial carcinoma
    - Urothelial carcinoma with divergent differentiation
        - With squamous differentiation
        - With glandular differentiation
        - With trophoblastic differentiation
    - Nested urothelial carcinoma
        - Including large nested variant
    - Microcystic urothelial carcinoma
    - Micropapillary urothelial carcinoma
    - Lymphoepithelioma-like urothelial carcinoma
    - Plasmacytoid / signet ring / diffuse urothelial carcinoma
    - Sarcomatoid urothelial carcinoma
    - Giant cell urothelial carcinoma
    - Poorly differentiated urothelial carcinoma
    - Lipid rich urothelial carcinoma
    - Clear cell (glycogen rich) urothelial carcinoma

Epidemiology

The epidemiology of urothelial cancer had been summated as follows: [45]

- Urothelial cancer is stated to be the fourth most common malignancy in the United States of America (U.S.A.) men
- Urothelial cancer is stated to be the eight most common malignancy associated with death in U.S. men
- It has been stated that the median age of individuals afflicted by urothelial cancer is 69 years in men and 71 years in women [46]

Incidence:

- It has been iterated that the incidence of urothelial cancer is 4x higher in men than women
- It has been iterated that the incidence of urothelial cancer is 2x higher in white men than in black men

Sites

The sites for the development of urothelial cancer had been summated as follows: [45]

- Lower tract urothelial carcinoma: It has been iterated that urothelial cancer of the urinary bladder and urethra represent 90% to 95% of all urothelial cancers [50]
- Upper tract urothelial carcinoma: It has been iterated that urothelial cancer afflicting the ureter and renal pelvis represent 5% to 10% of all cases of urothelial cancer. [50]

Pathophysiology

- It has been iterated that smoking or other chemical exposures do commence the process of carcinogenesis by altering the DNA of the bladder mucosa; these genetic alterations lead to unregulated cell growth [51]

Aetiology

The aetiology of urothelial carcinoma had been summated as follows: [45]

- **Tobacco smoking**: It has been iterated the population attributable risk for ever smoking is 50% for both men and women in U.S. [52]
- **Occupational exposures**: It has been iterated that occupational exposure to the ensuing had been associated with the development of urothelial cancer: aromatic amines, chlorinated hydrocarbons and polycyclic aromatic hydrocarbons including benzidine [52]
- **Genetic predisposition:** It has been iterated that there is a genetic predisposition to the development of urothelial cancer [52]
- Unlike **squamous cell carcinoma**, urothelial cancer is stated not to be due to indwelling catheters

Clinical features

- It has been iterated that some of the manifesting symptoms of urothelial cancer include the ensuing: Haematuria, irritation /

pain during urination, increased urinary frequency or urgency [53]

Diagnosis

It has been iterated that assessments that are taken to establish a diagnosis of urothelial cancer include the ensuing: [45]

- Urine cytology on voided samples [54]
- Cystoscopy with biopsy or transurethral resection [54]

Radiology description

The radiology imaging features of urothelial cancer has been summated as follows: [45]

- CT scan image findings of urothelial carcinoma include: urothelial thickening / hyperenhancement, asymmetric collecting duct system, urothelial calcifications or the presence of a nodule / mass [55]
- MRI T2 weighted images of urothelial cancer are iterated to demonstrate hypointense thickening of bladder wall **[**56**]**

Prognostic factors

Summations that had been made regarding factors of prognostication of urothelial carcinoma include the ensuing: [45]

- **5-year relative survival:** The 5-year relative survival of urothelial cancer has been iterated to be: 69% with local disease, 37% with regional disease and 6% with distant disease [57]
- **Stage:** It has been iterated that stage, with histologic characterization and involvement of the muscularis propria (detrusor muscle) is an important factor for determining prognosis [46]
- **Morphological variants associated with poor prognosis, possibly due to late-stage diagnosis and aggressive behaviour include:** [45]
    - Urothelial carcinoma with divergent differentiation **(squamous or glandular)**
    - **Micropapillary urothelial carcinoma**
    - **Plasmacytoid urothelial carcinoma**
    - **Nested urothelial carcinoma** [46]

Treatment

The treatment of urothelial cancer has been summated as follows: [45]

- Conservative therapy is often offered for invasion into the lamina propria (T1) [48]
- Conservative therapy includes Bacillus Calmette-Guérin (BCG) intravesical immunotherapy [58]
- Radical cystectom**y** is usually required for invasion into the muscularis propria (T2) [48]
- Locally advanced cancers are typically treated with chemotherapy, immunotherapy and occasionally radiation **[**59**]**

Gross description

- It has been stated that macroscopic findings of specimens of urothelial cancer range from subtle bladder wall thickening to obvious exophytic mass [60]

Frozen section description

- Positive margin is defined by the presence of **in situ** or invasive urothelial carcinoma on frozen section [61]
- Ureteric intraoperative frozen sections have significant clinical limitations due to skip lesions, which often occur in multifocal urothelial carcinoma in situ [62]

Microscopic (histologic) description

Microscopy histopathology examination features of urothelial carcinoma had been summated as follows: [45]

- The neoplastic cells upon microscopy examination are seen to be arranged in irregular nests or single cells invading the lamina propria and muscularis propria
- During microscopy pathology examination of specimens of urothelial cancer retraction artifact is often seen and this could simulate vascular invasion [63]
- High grade nuclear features: Microscopy pathology examination of specimens of high-grade urothelial carcinoma tend to demonstrate nuclear pleomorphism, hyperchromasia, high N/C ratio with frequent mitotic figures [63]
- Nested urothelial carcinoma specimen would demonstrate upon pathology examination bland, low-grade cytology [64]

Cytology description

The cytology examination features of urothelial carcinoma had been summated as follows: [45]

- Urine cytology detection of urothelial carcinoma has sensitivity and specificity of 13 - 75% and 85 - 100%, respectively [65]
- Diagnostic categories are based on The Paris System for Reporting Urinary cytology [66]
- Cytologic diagnosis of high-grade urothelial carcinoma requires > 10 cells with high N/C ratio, irregular chromatin pattern and hyperchromatic nuclei [67]

Positive stains

It has been iterated that immunohistochemistry staining studies on specimens of urothelial cancer do demonstrate positive staining for the ensuing tumour markers: [45]

- **GATA3, CK7, CK20, p63, p40, uroplakins II and III, HMWCK thrombomodulin** [68] [69]
- **PDL1** in tumour cells characterized by ≥ 1% is expressed in 13.3 - 46.7% cases [70] [71]
- Immunostaining could differentiate between luminal and basal phenotypes [72]
    - **Luminal: CK20, GATA3, FOXA1, XBP1, CD24**
    - **Basal: HMWCK (CK5, CK6 and CK14), CDH3, CD44**

Negative stains

It has been iterated that immunohistochemistry staining studies on specimens of urothelial cancer do demonstrate negative staining for the ensuing tumour markers: [45]

- **PSA, NKX3.1, AMACR, PAX8,** [69] [73]

Molecular / cytogenetics description

The molecular / cytogenetics features of urothelial cancer had been summated as follows: [45]

- Most commonly mutated genes are associated with cell cycle progression, including TP53, PIK3CA, RB1 and FGFR3 [74]
- UroVysion is an FDA approved fluorescent in situ hybridization (FISH) that detects aneuploidy in chromosomes 3, 7 and 17 and loss of 9p21 locus (72% sensitivity and 83% specificity) [75] [76]

- Nuclear matrix proteins (NMP22): group of proteins produced by cancerous cells
    - NMP22 BladderChek test is an FDA approved qualitative assay for surveillance and detection of bladder cancer (50% sensitivity and 87% specificity) [76]
- Bladder tumor antigen (BTA): antigen produced by cancerous cells
    - BTA Trak (quantitative) and BTA Stat (qualitative) are FDA approved assays for surveillance (68 - 77.5% sensitivity and 50 - 75% specificity)

Differential diagnoses

The differential diagnoses of urothelial cancer had been iterated to include the following: [45]

- **Inverted urothelial papilloma:**
    - Smooth or dome shaped surface with monotonous cells growing in an endophytic pattern without the presence of lamina propria invasion [77]
- **Adenocarcinoma of the prostate gland:**
    - Prostatic adenocarcinoma demonstrates monomorphic cytology with prominent nucleoli
    - Adenocarcinoma of prostate gland specimens upon immunohistochemistry staining studies stain negatively for **GATA3 / CK7** and positively for **PSA / NKX3.1**
- **Paraganglioma:**
    - Similar nested architecture, prominent vascular network and distinguishable by immunohistochemistry
    - Positive for **S100 (sustentacular pattern), synaptophysin and chromogranin** [78]
    - Negative for **AE1 / AE3 and CK7**
    - **Potential pitfall:** also positive for **GATA3** [79]
- Nephrogenic adenoma:
    - Rare nuclear atypia and distinguishable by immunohistochemistry: positive for **PAX8, PAX2, and AMACR** [78]
- **Cystitis cystica / glandularis:**
    - Lacks cytologic atypia, necrosis, stromal reaction and invasion into lamina propria and muscularis propria [78] [80]
- **Renal cell carcinoma (for renal pelvis tumour):**
    - Lack of urothelial carcinoma in situ is the most helpful distinguishing factor
    - Positive **PAX8,** negative **p63 and** negative **GATA3** immuno-profile favours renal cell carcinoma; however, stain interpretation and immunohistochemical profile overlap can create diagnostic challenges [81] [82]

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, And Studies Related to Invasive Urothelial Cancer

Liang et al. [38] made the ensuing iterations:

- Urinary bladder cancer is the most common malignancy of the urinary tract and in many patients is metastatic at diagnosis.
- Chemotherapy is the standard treatment for these patients; however, chemotherapy is associated with serious side effects and in many patients is not tolerated.
- In order to avoid the side effects of systemic chemotherapy, patients with late-stage bladder cancer had sought cryotherapy within their hospital.

Liang et al. [38] reviewed data over the preceding 4years to evaluate the safety and efficiency of percutaneous cryotherapy in 23 patients. They reported the results as follows:

- Within 3days after cryosurgery, all of the complications of bladder cancer including: visible haematuria, urinary irritation, hypogastralgia, and lumbago, had decreased to some degree.
- No new complications, for example, urinary bladder perforation, had developed and all of the complications had disappeared completely after 2weeks.
- The progression-free survival (PFS) of these patients was 14±8months.
- There was no effect on PFS of tumour location or histopathology examination findings; nevertheless, differentiation status and tumour size had influenced the therapeutic effect of percutaneous cryoablation.

Liang et al. [38] concluded that:

- Percutaneous cryotherapy might be a safe and efficacious treatment option in the treatment of metastatic bladder cancer.

Ma et al. [83] made the ensuing iterations:

- Urinary bladder cancer (BC) ranks as the tenth most common cancer globally based upon the histopathology examination features of tumours.
- BC is broadly categorized into urothelial and non-urothelial BC.
- Urothelial carcinoma constitutes more than 90% of BC in most regions globally.
- The standard treatment procedure for diagnosing and treating non-muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumours (TURBT).
- Currently, the standard of care for muscle-invasive bladder cancer (MIBC) is treatment with neoadjuvant chemotherapy followed by radical cystectomy.
- Cryoablation therapy is a medical technique which utilises extremely low temperatures to destroy diseased tissue.
- Cryotherapy serves as a therapeutic tool for both benign and malignant diseases within organs such as the kidney, prostate gland, the lung, the liver, and the breast, and cryotherapy is particularly effective for unresectable tumours, which does provide less trauma, quick recovery, good tolerability, and symptom control.
- Nevertheless, cryotherapy has its limitations.
- Over the preceding few years, cryotherapy had emerged as a new method for treating early BC.
- Cryotherapy treatment is minimally invasive, precise, and offers quick recovery, providing patients with a new treatment option.
- Even though randomized studies had been still limited, increasing evidence had indicated its potential application in urinary bladder cancer combined with transurethral resection (TURBT) or medication.
- Cryotherapy is not a standard therapy for bladder cancer.

- Cryotherapy treatment decisions should be discussed by a multidisciplinary team of urologists, oncologists, and interventional physicians and require more randomized controlled trials to define patient selection criteria and treatment approaches.

Zhang et al. [36] made the ensuing iterations:

- Radical cystectomy (RC) with pelvic lymph node dissection (PLND) and urinary diversion (UD) has been considered to be the standard treatment for muscle invasive bladder cancer (MIBC).
- In a part of patients, RC procedure is aborted due to unresectable disease, other followed treatment options like systemic chemotherapy, radiotherapy or cryotherapy might be a better option.
- They had reported the preliminary results of trans-perineal cryotherapy for unresectable muscle invasive urinary bladder cancer.

Zhang et al. [36] reported that: from January 2011 to August 2013, 7 male patients had pT4b unresectable urinary bladder cancer had undergone bilateral ureterocutaneostomy. Two had undergone a pelvic lymph node dissection (PLND). Then primary trans-perineal cryosurgery for preserved urinary bladder at the guidance of transrectal ultrasound (TRUS) was undertaken. All of the patients had undergone a dual freeze-thaw cycle using third-generation cryotechnology with ultrathin 17-gauge cryoneedles. Computer tomography (CT) and/or magnetic resonance image (MRI)were undertaken at 3-months intervals pursuant to the cryosurgery to ascertain whether progression or recurrence had developed. Zhang et al. [] summated the results as follows:

- All of the cryosurgery treatments were undertaken successfully, the mean operation time was 76.43 ± 25.12 min (range 50-120 min), the mean blood loss was 19.29 ± 15.92 ml (range 5-50 ml).
- The mean hospital stay was 3.86 ± 1.68 day (range 2-7 days).
- No operative related deaths had occurred.
- Four patients had died due to their developments of metastatic disease at the follow up time of 8 months, 15 months, 18 months and 37 months, respectively.
- Six patients had undergone post-operative therapy, of whom 5 patients were treated with combined chemoradiation, and the other one received chemotherapy alone.
- The progression free survival (PFS) of the 7 patients was 22.00 ± 14.61 months (range 3-40 months).
- The one year, two years and three years overall survival (OS) was 85.7%, 57.1% and 42.9%, respectively.

Zhang et al. [36] concluded that:

- Their results had indicated that cryosurgery combination with chemoradiotherapy does provide a safe and effective alternative method for unresectable pT4b bladder cancer. Longer follow-up is necessary to determine the sustained efficacy.

Liu et al. [16] made the ensuing iterations:

- The potential for transurethral resection (TUR) to result in residual tumours in patients with muscle invasive or high-risk non-muscle invasive bladder cancer (NMIBC) might affect local recurrence or progression of the tumour.
- This had attempted to evaluate the feasibility and safety of cryoablation as an adjuvant treatment with TUR to treat urinary bladder tumour.

Liu et al. [16] reported that patients who had met their inclusion criteria between December 2014 and August 2015 within their establishment were included in their study. The inclusion criteria were as follows: 1) urothelial carcinoma; 2) non-muscle-invasive bladder cancer or 3) stage T2 muscle invasive bladder cancer meeting with the following two conditions, solitary and less than 3 cm in size. Ten patients had undergone TUR, which was ensued by immediate transurethral cryoablation of the tumour resection bed. All of the patients had undergone pathology re-evaluation during the follow-up cystoscopy. Liu et al. [16] summated the results as follows:

- The cryoablation was successfully undertaken without urinary bladder perforation during the procedures.
- No grade II–V complications were identified.
- Among these patients, two had T2a stage tumours, three had T1 stage tumours and five had Ta stage tumours.
- The median follow-up of the cases was 9 months and the follow-up had ranged between 9 months and 14 months.
- During follow-up, tumour recurrence was identified in three patients.
- Only one recurrence had developed within the primary tumour site.

Liu et al. [16] made the ensuing conclusions:

- Cryoablation as an adjuvant therapy with TUR for bladder tumours was feasible and safe.
- The potential benefit of cryotherapy was to eliminate the residual tumour to the greatest extent.

Baust et al. [84] made the ensuing iterations:

- As the acceptance of cryotherapy treatments of non-metastatic cancers continues to grow, avenues for novel cryosurgical technologies and approaches had opened.
- Within the field of genitourinary tumours, cryosurgical treatments of urinary bladder cancers had remained largely investigational.
- Current modalities of cryotherapy employ percutaneous needles or transurethral cryoballoons or sprays, and while results had been promising, each technology is limited to specific types and stages of cancers.

Baust et al. [84] evaluated a new, self-contained transurethral cryocatheter, FrostBite-BC, for its potential to treat urinary bladder cancer. Baust et al. [86] assessed the thermal characteristics and ablative capacity using calorimetry, isothermal analyses, in vitro 3-dimensional tissue engineered models (TEMs), and a pilot *in vivo* porcine study. Baust et al. [86] summated the results as follows:

- Isotherm assessment had revealed surface temperatures below –20°C within 9 sec.
- In vitro TEMs studies had demonstrated attainment of ≤– 20°C at 6.1 mm and 8.2 mm in diameter following single and double 2 min freezes, respectively.
- Fluorescent imaging 24 hr post-thaw had revealed uniform, ablative volumes of 326.2 mm^3 and 397.9 mm^3 following a single or double 2 min freeze.
- In vivo results had demonstrated the consistent generation of ablative areas.
- The lesion depth was found to have correlated with freeze time wherein 15 sec freezes resulted in ablation confined to the sub-mucosa and ≥30 sec full thickness ablation of the bladder wall.

Baust et al. [84] made the ensuing conclusions:

- These studies had demonstrated the potential of the FrostBite-BC cryocatheter as a treatment option for urinary bladder cancer.
- Even though preliminary, the outcomes of these studies were encouraging, and had supported the continued investigation into the potential of the FrostBite-BC cryocatheter as a next generation, minimally invasive cryoablative technology.

Santucci et al. [18] made the ensuing iterations:

- Due to a rising annual incidence of urinary bladder cancer, there is a growing need for the development of new strategies for treatment.
- In 2018, the World Cancer Research Fund and other groups had reported that there were about 550,000 new cases worldwide of urinary bladder cancer.
- It had been further estimated that more than 200,000 individuals die each year from urinary bladder cancer worldwide.
- Various treatment options exist. Nevertheless, many if not all had remained suboptimal treatments.
- While the preferred chemotherapeutic options had changed over the preceding few years there had been few advances in the urinary bladder cancer medical device field.
- Cryoablation is now being evaluated as a new option for the treatment of urinary bladder cancer.
- While many studies had demonstrated cryoablation to be promising for the treatment of urinary bladder cancer, a lack of basic information pertaining to dosing (minimal lethal temperature) necessary to destroy bladder cancer had limited its use as a primary therapeutic option.
- Concerns regarding urinary bladder wall perforation and other side effects had also slowed down the adoption of cryotherapy for the treatment of urinary bladder cancer.

In an effort to detail the effects of freezing on bladder cancer, Santucci et al. [18] evaluated two human bladder cancer cell lines, SCaBER and UMUC3, were in vitro. Santucci et al. [18] stated that SCaBER, which is a basal sub-type of muscle invasive bladder cancer, and UMUC3, an intermediate transitional cell carcinoma, are both difficult to treat but are reportedly responsive to most conventional treatments. They reported that SCaBER and UMUC3 cells were exposed to a range of freezing temperatures from −10 to −25°C and compared to non-frozen controls. The data had shown that a single 5-minute freeze to −10°C did not affect cell viability, whereas −15°C and −20°C results in a significant reduction in viability 1 day post freeze to <20%. These populations, however, were able to recover in culture. A complete loss of cell viability was found following a single freeze at −25°C. Application of a repeat (double) freeze resulted in complete cell death at −20°C. In addition to freezing alone, studies investigating the impact of adjunctive low dose (1 μM) cisplatin pre-treatment (30 minutes and 24 hours) in combination with freezing were undertaken. The combination of 30-minute cisplatin pre-treatment and mild (−15°C) freezing had resulted in complete cell death. This had indicated that sub-clinical doses of cisplatin might be synergistically effective when combined with freezing. Santucci et al. [18] made the ensuing summating conclusions from their study:

- These in vitro results had indicated that freezing to temperatures in the range of −20 to 25°C results in a high degree of bladder cancer cell destruction.
- Further, the data describe a potential combinatorial chemo/cryo therapeutic strategy for the treatment of bladder cancer is necessary.

Xu et al. [85] made the ensuing iterations:

- Cryotherapy is a prevalent percutaneous ablative therapy for solid tumours.
- They had reported a novel device that uses liquid nitrogen for endoscopic cryotherapy of bladder cancer.

Xu et al. [85] iterated that in their multi-centre, randomized, parallel controlled, Phase 2 trial, they had compared endoscopic balloon cryoablation (EBCA) with a single instillation (SI) of pirarubicin after transurethral resection (TUR). Eligible participants were randomly assigned (1:1) to the TUR-EBCA or TUR-SI group. Repeat TUR or tissue biopsies were undertaken to evaluate for presence of residual tumour at 4 weeks to 6 weeks pursuant to the primary treatment. The primary end point was the local control rate. The secondary end points included the tumour upgrading/upstaging, catheter indwelling duration, and adverse events. Xu et al. [85] summated the results as follows:

- In total, 205 patients had received EBCA or SI after TUR between November 2017 and September 2020, of whom 163 completed all the required interventions.
- Within the per-protocol set, the local control rate was 91.5% (75/82) in TUR-EBCA group compared with 76.5% (61/81) in TUR-SI group (risk difference, 15%; 95% CI, 0.03–0.27, $p < .001$), meeting the criteria for noninferiority.
- Similar results were found in the modified intention-to-treat analysis.
- Tumour upgrading/upstaging was found in five patients from the TUR-SI group.
- There was no significant difference found in the catheter indwelling duration (5.1 vs. 5.2 days, $p = .76$) or serious adverse event rate (3.0% vs. 3.9%, $p = .52$).
- The median follow-up time of post hoc analysis was 31 and the follow-up time had ranged between 15 months and 50 months.
- Patients who were in the TUR-EBCA group had a better recurrence-free survival and progression-free survival.

Xu et al. [85] made the ensuing conclusion and summation:

- EBCA is a safe and effective adjuvant therapy with TUR for non–muscle-invasive bladder cancer.
- Their study was the first randomized trial which had evaluated endoscopic cryotherapy after transurethral resection (TUR) of bladder tumours. The efficacy and safety analysis had demonstrated that endoscopic balloon cryoablation (EBCA) is a promising alternative.
- The results had reported that EBCA is not inferior to a single instillation of intravesical chemotherapy in eliminating residual bladder tumour.
- Further analysis with about 3 years median follow-up had indicated a better prognosis in patients who received EBCA after TUR.

Tan et al. [86] compared the short-term oncology and functional outcomes of salvage focal cryotherapy (SFC) with those of salvage total cryotherapy (STC) for radiotherapy (RT)-persistent/recurrent prostate cancer. Tan et al. [86] queried the Cryo On-Line Database registry for men who had undergone SFC and STC of the prostate for RT-persistent or recurrent disease. Tan et al. [86] used propensity score weighting to match age at treatment, pre-salvage therapy prostate-specific antigen level, Gleason sum, and pre-salvage cryotherapy androgen deprivation therapy status. The primary outcome of the study was progression-free survival. Tan et al. [86] summated the results as follows:

- A total of 385 men with biopsy-proven persistent or recurrent prostate cancer after primary RT were included in the study.

- The median follow-up, age, prostate-specific antigen, and Gleason sum before salvage cryotherapy were found to be 24.4 months (first and third quartile, 9.8 and 60.3), 70 years (first and third quartile, 66 and 74 years), 4 ng/dL (first and third quartile, 2.7 and 5.6 ng/dL), and 7 (first and third quartile, 6 and 8), respectively.
- After propensity score weighting, the difference in progression-free survival was found not to be statistically significant between the patients who had undergone STC and those who had undergone SFC (79.8% vs. 76.98%; P = .11 on weighted log-rank test). SFC was associated with a lower probability of post-treatment transient urinary retention (5.6% vs. 22.4%; P < .001).
- No significant differences were found in the incidence of rectal fistula (1.4% vs. 3.8; P = .30), new-onset urinary incontinence within 12 months (9.3% vs. 15.1%; P = .19), or new-onset erectile dysfunction within 12 months (52.6% vs. 59.6%; P = .47) between the SFC and STC groups, respectively.

Tan et al. [86] made the ensuing conclusions:

- STC had resulted in similar 2-year oncologic outcomes compared with SFC in the RT-persistent/recurrent disease population.
- Nevertheless, patients who had undergone SFC had a lower urinary retention rate compared with those who had undergone STC.

Liu et al. [87] made the ensuing iterations:

- Transurethral resection of bladder tumour (TURBT) is the first-line treatment option for non-muscle invasive bladder cancer (NMIBC), but residual tumour often remains after TURBT, thereby leading to cancer recurrence.
- They had introduced combined use of in vivo Raman spectroscopy and in vivo cryoablation as a new approach to detect and remove residual bladder tumour during TURBT.

Liu et al. [87] had collected urinary bladder cancer (BCa) patients who were treated with TURBT within their urological department between Dec 2019 and Jan 2021. They had collected first, Raman signals collected from 74 BCa patients to build reference spectra of normal bladder tissue and of urinary bladder cancers of different pathological types. Then, they randomly categorized another 53 BCa patients into two groups, 26 patients had accepted traditional TURBT, 27 patients had accepted TURBT followed by Raman scanning and cryoablation if Raman detected existence of residual tumour. They compared the recurrence rates of the two groups until October 2022. Liu et al. [87] made the ensuing iterations regarding the results of their study:

- Raman was capable of discriminating normal bladder tissue and BCa with a sensitivity and specificity of 90.5% and 80.8 %; and discriminating invasive (T1, T2) and non-invasive (Ta) BCa with a sensitivity and specificity of 83.3 % and 87.3 %.
- During follow-up, 2 in 27 patients had developed cancer recurrence in Raman-
- Cryoablation group, while 8 in 26 patients had developed cancer recurrence in the traditional TURBT group.
- Combined use of Raman and cryoablation had significantly reduced cancer recurrence (p = 0.0394).

Liu et al. [87] concluded that:

- Raman and cryoablation could serve as an adjuvant therapy to TURBT to improve therapeutic effects and reduce recurrence rate.

Xu et al. [88] made the ensuing iterations:

- Cryotherapy is a prevalent percutaneous ablative therapy for solid tumours.
- Nevertheless, studies on the clinical practice of endoscopic cryotherapy for intraluminal malignancies had been lacking.
- They had explored the feasibility of endoscopic cryotherapy for urinary bladder cancer.

Xu et al. [88] compared in their multi-centre, randomized, parallel controlled, non-inferiority trial, endoscopic balloon cryoablation (EBCA) with a single instillation (SI) of pirarubicin after transurethral resection (TUR). Xu et al. [88] included men or women, who were aged between 18 years and 85 years who had a clinical diagnosis of urinary bladder cancer (tumour number no more than 3 and maximal tumour size no more than 3 cm). The exclusion criteria were as follows: locally advanced urinary bladder cancer (clinical stage T3 or T4), lymph node involvement (N1) or distant metastasis (M1), severe organ dysfunction, severe coagulation disorder, sepsis, concomitant neoplastic malignancy and other conditions that were not suitable for surgery or intravesical chemotherapy. Women in pregnancy or lactation were also excluded. The eligible participants were randomly assigned (1:1) to the TUR-EBCA or TUR-SI group. The primary endpoint was the residual-free rate at repeated TUR. A non-inferiority test was utilised to compare the primary endpoint with a chosen margin of 10%. The secondary endpoints had included the recurrence-free survival (RFS), progression-free survival (PFS) and adverse events. Xu et al. [88] summated the results as follows:

- They had recruited 227 participants between November, 2017, and September, 2020.
- In total, 205 patients had received EBCA or SI after TUR, of whom 163 completed all the required interventions and follow-up.
- In the per-protocol analyses, 75 (91.5%) of 82 patients were noted to have no residual tumour within the TUR-EBCA group compared with 61 (76.5%) of 81 in the TUR-SI group (risk difference 14.9%; 95% confidence interval [CI] 0.03 to 0.27, P < 0.001), meeting the criteria for non-inferiority.
- Similar results were found in the after intention-to-treat analysis.
- After a median follow-up of 21 months, the TUR-EBCA group had better RFS (HR = 0.49; 95% confidence interval [CI] 0.24 to 0.99; Log-rank *P* = 0.046) and PFS (HR = 0.25; 95% confidence interval [CI] 0.08 to 0.77; Log-rank *P* = 0.0092).
- There were no significant differences in the SAEs rate (3.0% vs. 3.9%, p = 0.52).

Xu et al. [88] concluded that:

- EBCA is a safe and effective adjuvant alternative to TUR for urinary bladder cancer with the potential advantage of "energetically resecting" the tumour base.

Conclusions

- Cryoablation of non-muscle invasive urinary bladder tumour is a safe and effective adjuvant therapy with TURBT.
- The efficacy and safety analysis of the results of few studies of cryotherapy in the management of non-muscle invasive urinary bladder tumours had demonstrated that cryotherapy of urinary bladder tumours is a promising alternative treatment option.
- Considering the paucity of reported information regarding utilization of cryotherapy of superficial urinary bladder tumours, there is a global need for the undertaking of a large multi-centre studies with medium-term, and long-term follow-up results on utilization of cryotherapy in the treatment of non-muscle invasive urinary bladder malignant neoplasms in order to

ascertain if cryotherapy as treatment should be adopted globally as an adjunctive treatment alternation in addition to TURBT in the management of cases of non-muscle invasive urinary bladder cancers.

Conflict Of Interest – Nil

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