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The Final Thesis

BCG Therapy for Upper Urothelial Carcinoma. Literature Review

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1. Abbreviations

BCG	Bacillus Calmuette-Guerin
UT	Upper urinary tract
UTUC	Upper urinary tract urothelial carcinoma
UBC	Urothelial carcinoma of the bladder
EAU	European Association of Urology
RNU	Radical nephroureterectomy
KSS	Kidney-sparing surgery
CIS	Carcinoma in situ
FAP	Fibronectin attachment protein
PAMP	Pathogen-associated molecule pattern
IL	Interleukin
TNF	Tumor necrosis factor
INF	Interferon
NK cells	Natural killer cells
TRAIL	Tumor necrosis factor related apoptotic ligand
HNPCC	Hereditary nonpolyposis colorectal cancer
AA	Aristolochic acid
TNM classification	Tumor, node, metastasis classification
MDCTU	Multidetector computed tomography urography
FISH	Fluorescence in situ hybridization
WHO	World Health Organization
LG	Low grade
HG	High grade
CKD	Chronic kidney disease
ESRF	End-stage renal failure
SU	Segmental ureterectomy
MMC	Mitomycin C
VUR	Vesicoureteral reflux
RU	Renal units

2. Keywords

BCG therapy, upper urothelial carcinoma, intravesical therapy, urothelial carcinoma

3. Abstract

This literature review will discuss and examine bacillus Calmuette-Guerin (BCG) therapy, it's history, mechanism and how it relates to the treatment of upper urothelial carcinoma. The information collected in this review should aid in the understanding of upper urothelial carcinoma as well as BCG therapy and how BCG therapy should be applied in the treatment of upper urothelial carcinoma.

4. Introduction

Urothelial carcinomas (UC) are the sixth most common tumors in developed countries.[1] They can be located in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract (UT).[2] Upper urinary tract urothelial carcinomas (UTUC) are uncommon and account for only 5-10% of UCs. Furthermore, the annual incidence in Western countries is approximately one or two new cases per 100,000 inhabitants.[1] Comparatively, urothelial carcinoma of the bladder (UBC) therefore accounts for 90-95% of UCs. Due to UTUCs significantly lower incidence, much of the treatment parameters have been adjusted to its Bladder counterpart, with only one major urological organization the European Association of Urology (EAU) having released treatment guidelines regarding UTUCs.[2] Whereas other acknowledged institutions have only mentioned UTUC management as a subset of bladder cancer guidelines. [3]

Radical nephroureterectomy (RNU), which was first described in 1934 has long been the gold standard when it comes to treatment of UTUCs.[4] In recent years, kidney-sparing approaches have found more popularity in order to retain renal function and to hinder long-term complications that are related to chronic kidney disease. Kidney-sparing surgery (KSS) is now indicated in patients with low grade cancer. The recurrence rate of patients treated with KSS ranges between 15-90%. [5] As a result, a similar approach in treatment as in UBCs has been proposed, in which adjuvant endocavitary instillations are to be installed in patients treated with KSS, with the aim at halting the progression of low risk papillary UTUCs and to treat patients with upper tract carcinoma in situ (CIS). The perfusion of the upper urinary tract can occur with the use of chemotherapeutic agents (mitomycin C, epirubin and thiopeta) and immunotherapeutic agents (bacillus Calmette-Guerin and interferon).[6] Currently, bacillus Calmette-Guerin is the most used perfusion agent regarding CIS.[7] Hence, the efficacy of endocavitary installations regarding CIS as well as in treatment of high-risk non-muscle invasive tumors of the bladder in the adjuvant setting has been settled. However, its efficacy regarding the adjuvant treatment of UTUCs is still considered debatable.

This comprehensive review will look to outline BCG therapy as well as discuss the disease of upper urinary carcinoma and how BCG therapy is related to its treatment.

5. BCG Therapy

5.1. History

Albert Calmette and Camille Guerin first discovered bacillus Calmette-Guerin at the Pasteur institute in 1921 through culturing Mycobacterium bovis in bile potato medium for over 10 years.[8] Primarily, it is known for its use in the protection from tuberculosis as a vaccine. [9] Following the creation of the BCG vaccine, studies pertaining information about an inverse relation between cancer and tuberculosis. [10] In 1969, was when Mathe et al. first reported positive effects of BCG in the treatment of acute lymphocytic leukemia.[11] Followed by the first report of Morales et al. in 1976 of success in BCG therapy for Bladder Cancer.[12] Currently it is the gold standard in adjuvant treatment of non-muscular invasive bladder cancer in the high-risk category.[13] Whereas the first reported usage of BCG perfusion in for upper tract carcinoma in situ by Herr et al. was in 1985.[14]

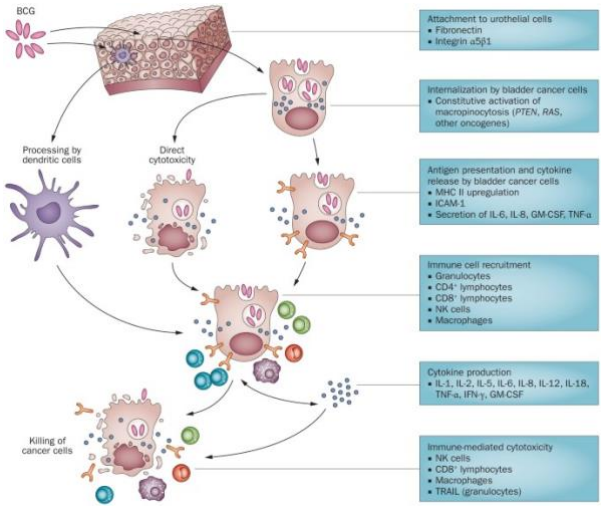

Figure 1. Proposed mechanism of BCG interaction with urothelial and/or bladder cancer cells 15

5.2. Mechanism of BCG

Several possible mechanisms have been linked regarding the interaction between BCG with urothelial and bladder cancer cells.[15] However, to date the complete mechanism hasn't yet been fully explained. Kawai et al., amongst others, suggests a scheme to gain understanding of the mechanism of these complex pathways, which are: infection of the urothelial and/or bladder cells, the induction of the innate immune response as well as the introduction of anti-tumor effects. It is expected that with increased research overtime, our knowledge of these principle will further illustrate the multifactorial ways in which BCG acts.

5.2.1. **Infection of the urothelial and/or bladder cells**

For any interaction between the BCG and the urothelium, instillation of the BCG is the obvious first step. Once instilled into the bladder, BCG can attach to the cell surface of both normal and cancerous urothelial cells. The mycobacterial fibronectin attachment proteins (FAPs) of the BCG cell wall surface host the urothelial fibronectin, which then attaches to the urothelial cells via the integrin α5β1.[16][17][18] The subsequent internalization of the BCG into the cancerous cells has been proven to be a paramount step in the immune response that follows. This was confirmed in experiments using an anti-fibronectin antibody. This antibody inhibited the antitumor effect of BCG. [19]

5.2.2. **Induction of immune response**

As with any kind of infection, our bodies stimulate a local immune response in conjunction with the infiltration of the urothelial cells by BCG. This is stimulated by the reticuloendothelial system. Cells that are included in this process are for instance macrophages, granulocytes, and T-helper cells. In urothelial tumor cells, BCG also escalates the surface expression of major histocompatibility complex class II. [20] As such, BCG acts as a pathogen-associated molecule pattern (PAMP) to induce pattern recognition receptors (PRR) on various cells. These include cells such as the antigen-presenting cells of macrophages or dendritic cells, as well as urothelial cancer cells.[21] It is believed that through this reaction, not only the cells of our own body immunity are responsible for the immune response, but also the cancer cells that have been infected with BCG play an important role.

Through urine analysis post instillation and administration, it has been shown that several cytokines are involved in this immune reaction such as interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF) and interferon (IFN). [22] Not all these cytokines are elicited immediately after the first dose but could also be present later over the course of the treatment. Recently, IL-17 has been shown to be critically involved in the recruitment of neutrophils as it relates to the bladder. Neutrophils are essential to the antitumor effect. [23]

5.2.3. **Antitumor effects**

It is well documented that T cells mediate the anti-tumor effects of BCG. In addition, CD4+ T cells and CD8+ cytotoxic lymphocytes mediated by Th1 or acquired immunity produce this effect. Contributing to the anti-tumor effects of the acquired immunity is the innate immunity

that is mediated by Th2 part of the immune system. Mice deficient in natural killer (NK) cells or given the antibody did not respond to BCG treatment.[24]

Neutrophils are the most common component found in urine post BCG treatment. Neutrophils can phagocytose and degranulate cancer cells, thus killing them. Furthermore, when stimulated by BCG the neutrophils can release tumor necrosis factor related apoptotic ligand (TRAIL), which plays a significant role in tumor cell apoptosis. Also, macrophages play a part in the BCG induced anti-tumor cascade. They seemingly have a role in both the presentation of cells to the adaptive immunity and the direct apoptosis of cancer cells. [25]

5.3. Summary of action

In short, BCG works by infecting urothelial/bladder tumor cells, causing more antigen-presenting molecules to surface. This triggers an immune response mediated by the release of cytokines. Both Th1 and Th2 cytokines are involved in this process, as well as IL-8 and IL-17. As a result of the immune response, anti-tumor effects are initiated and controlled by NK cells, neutrophils, macrophages and cytotoxic T lymphocytes.

6. Upper Urothelial Carcinoma

6.1. Epidemiology

When looking at gender prevalence, UTUC is three times likelier to appear in men than in women. It has a peak incidence in the age of 70-90 years of age. When looking at the anatomical positioning of the malignancies then the renal pelvis UTUCs occur almost double the time that they are found in the ureter. [26] In relation to its lower counterpart where only 15-25% of the bladder cancers that are found are classified as invasive, in UTUC 60% are invasive. [27]

When looking at risk factors for UTUCs, these are somewhat similar to UBCs such as smoking cigarettes and exposure to carcinogenic aromatic amines. [2] However, there are also some risk factors solely associated with UTUCs such as:

6.1.1. Arsenic

As stated previously the prevalence for UTUC is dominated by men. However, in the Blackfoot disease-endemic areas in southwest coastal region of Taiwan, ratio is 1:2 male to female. Due to the water being contaminated with arsenic and the higher exposure of women to arsenic fumes whilst cooking could be indication as to why this might be. This might be both through either ingestion of food or through inhalation of steam.[28]

6.1.2. Hereditary Nonpolyposis Colorectal Cancer (HNPCC, Lynch Syndrome)

Lynch syndrome a disease that debilitates DNA mismatch repair. It has a strong association to cancers of the colon as well as with ovarian, gastric, endometrial and urothelial cancers in the upper region. It is an autosomal dominant disease. Koornstra et al., has examined the prevalence of patients with Lynch syndrome and their subsequent development of UTUC. He has graded the chances as 22 times higher of developing UTUC with a known history of Lynch syndrome.[29] It has now become standard to screen patients with a high risk for Lynch syndrome and to send them to get DNA sequencing for themselves as well as family members. [2]

6.1.3. Balkan endemic and chinese herb nephropathy

Both these diseases have similar characteristics and have been linked to the same common thread, dietary exposure to aristolochic acid (AA), which can be found in Aristolochic plants (fangchi and clematis). Aristolactam-DNA is deposited in the kidney in balkan endemic nephropathy, which might explain the correlation to UTUC and not to Bladder cancer. The UTUCs that have a relation to AA exposure are usually low grade and bilateral in comparison to those not associated with it. [30] Whereas Chinese herb nephropathy leads to a renal fibrosis of a progressive magnitude that then creates a UTUC. Generally, AA exposure has resulted in poorer outcomes in UTUC patients.[31]

6.2. Staging and risk classification

Staging of UTUC occurs according to the tumor, node, metastasis (TNM) classification. [2] For T stage, the degree of invasion into the ureteral wall is critical. Its lower counterpart is graded similarly, and while this seems to work regarding UBCs, there are inherent issues associated with the staging of UTUCs. One of the biggest challenges in patient care for UTUCs is accurate grading due to the anatomic nature of the ureter and kidneys. In order to obtain the best possible assessment for UTUC one shall use a combination of imaging, biopsy tissue grade and urine cytology.

Table 1 T stage of renal pelvic and ureteral malignant tumors

Tx	Primary tumor cannot be assessed
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis
T3	(Renal pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs or through the kidney into perinephric fat

6.2.1. **Imaging**

Multidetector computed tomography urography (MDCTU) is regarded as the imaging of choice for UTUC, as it has been proven to have the highest specificity and sensitivity of over 90 percent.[32] If contraindicated, MRI urography can be used as a substitute. Both specificity and sensitivity do decrease the smaller the findings are, which is why often enough flat lesions are missed completely. [2] CT Urography works in three phases, these include a non-contrast phase, a contrast-enhanced nephrographic as well as an excretory (delayed) phase. In order to fully evaluate the state of the urinary tract malignancy all phases are essential in fully visualizing the anatomy of the patient. Lymph node detection is a struggle with both types of imaging, this is problematic as enlarged lymph nodes are a highly predictive indicator of metastasis.[33] In order to better evaluate the patient perioperatively, recent use of 18 F-Fluorodeoxglucose position emission tomography/computed tomography has garnered rates of 82 and 84 percent for sensitivity and specificity respectively regarding nodal metastasis.[34] Also, the finding of hydronephrosis has been associated with poorer outcomes in ureteral tumor, but not for pyelocaliceal tumors.[35]

6.2.2. **Diagnostic ureteroscopy and biopsy sampling**

Flexible ureteroscopy provides a means to visualize the ureter, renal pelvis as well as the collecting system and to biopsy any suspicious tissue.[2] The acquisition of biopsies is essential when it comes to pathological differentiation, grading and staging. Unfortunately, there are limitations in obtaining adequate biopsies via ureteroscopy, which it makes it substantially more difficult to obtain an adequate assessment of the depth of the tumor infiltration.[36] However, they are useful in applying a histological tumor grade but around 25% of samples turn out to have no diagnostic value.[37] Under or over grading can have an extremely detrimental effect on patient care and adequate choice of procedure as well as oncologic outcome with 50% of patients being reclassified at some point from non-invasive or low grade UTUC to a high grade stage of disease.[38] If for instance kidney sparing measurements are chosen initially, this might lead to extreme follow up measures for a under graded patient.[2]

6.2.3. **Cytology**

In UBCs, cytology is far more sensitive regarding clinical diagnosis then it is for UTUC. It can indicate high grade UTUC but only in the absence of any abnormalities in the bladder

and the prostatic urethra. It has been shown to be an insensitive prognostic tool. [39] If collected in a sufficient manner, barbotage cytology, has been shown to increase the accuracy to up to 91%.[40] Barbotage cytology is a procedure in which bladder washing is performed, this is procedure is done by irrigating the bladder with a fixative solution or saline. Molecular markers such fluorescence in situ hybridization (FISH) have shown a sensitivity of just 50%, which is why their clinical use remains questionable.[41]

6.2.4. Histological grading

Inherently the associations between UTUC and its counterpart in the bladder lead to similarities in classification and morphology. [2] In 1973, the World Health Organization (WHO) published a classification that separated papillary tumors into Grade 1, Grade 2 and Grade 3 tumors. However, this classification was replaced by the WHO in 2004 in which noninvasive urothelial tumors are categorized as flat and papillary. With papillary lesions being further divided into non-invasive papillary carcinoma low grade (LG) and high grade (HG). [13]

6.2.4.1. Flat lesions/Urothelial carcinoma in situ

Carcinoma that doesn't exhibit papillary features is called urothelial carcinoma in situ and is defined as high grade. It can be of differing thickness but will contain cytologically malignant cells. On histopathology, it presents with large pleomorphic cells that have hyperchromatic nuclei with one or more irregular nucleoli. It is sufficient to identify the presence of isolated malignant cells to confirm a diagnosis of CIS.

6.2.4.2. Non-invasive papillary urothelial carcinoma (Ta)

Papillary urothelial carcinomas are defined as papillary neoplastic proliferations that exhibit certain variance of cytological and architectural disorder, with no invasion beyond the basement membrane, as such being Ta. These are subdivided into non-invasive papillary urothelial carcinoma low grade and high grade. They are defined as exhibiting features such as thin fibrovascular cores that are covered in neoplastic urothelium of varying thickness. The current approach in grading the tumor is based on evaluation of the highest-grade component, with some authors advocating for 5% as a cut-off point.[42] In LG papillary urothelial carcinoma, the lesions have delicate papillae with extensive branching. Whereas, in HG the

papillae might in fact be fused. In LG there is some loss of polarity as well as mild nuclear irregularity and pleomorphism. However, in HG, cellular disorder, irregular and pleomorphic nuclei are visible at low magnifications.

6.2.5. **Risk Evaluation**

Given the current set of guidelines, risk management is still a controversial endeavor. In order to treat a patient accordingly, a proper outline of possible risks based on treatment options needs to be evaluated. According to the current EAU guidelines, the risk stratification is based on clinical and pathological features that separate tumors into low risk and high risk. In order to be classified as low or high-risk patients they would need to exhibit the following factors (shown in Table 2):

Table 2 Risk stratification of UTUC

Low risk	**High-risk**
Unifocal disease	Multifocal disease
Tumor size <2cm	Tumor size >2cm
Low-grade cytology	High-grade cytology
Low-grade ureteroscopic biopsy	High-grade ureteroscopic biopsy
No invasion on CTU	Previous radical cystectomy for bladder cancer
	Variant Histology
	Hydronephrosis

Despite the evaluative process of the diagnostic measures for UTUC being quite extensive, the system still lacks accuracy and provides clinicians with challenges when it comes to appropriately managing their patients' outcomes. With time and further developments, one can be hopeful that this might be improved in the future.

7. Disease management of low risk UTUC

7.1. Kidney sparing surgery (KSS)

Radical nephroureterectomy (RNU) with bladder cuff excision has long been the gold standard in patients with UTUC. [2] Even though the rates that have been reported about 5-year-recurence-free (69%) and cancer-specific survival (73%) are reasonable, there are extreme consequences to performing this type of procedure.[43] Post RNU, the nephron mass will be reduced by 50 percent or even more, this depends on whether there is a predisposition towards chronic kidney disease (CKD) or even end-stage renal failure (ESRF). Not even looking at the financial aspects of requiring lifelong hemodialysis, ESRF as well as CKD increase the risk of cardiovascular issues and mortality.[44] Research has now shown that kidney sparing management can have comparable outcomes to RNU if the patients are correctly selected. Initially utilized in patients with indications such as solitary kidney, bilateral disease or coexisting morbidity, which made RNU impossible. Nowadays, according to the EAU guidelines, KSS is recommended as the first-line treatment approach in patients presenting with low-risk disease as well as patients with serious CKD and solitary kidney.[2] Although a KSS approach can be beneficial to the patient, one must always be cautious due to the high risk of under staging the disease. Therefore, when choosing this treatment modality, patients must be warned about and be willing to adhere to a strict follow-up schedule that includes regular upper tract imaging, flexible cystoscopy, urine cytology, and ureteroscopy. Recommended approaches for KSS include endoscopic ablation via ureteroscopy or percutaneous access, segmental ureterectomy, and possible endocavitary instillations via BCG or chemotherapeutic agents.

7.1.1. Endoscopic management

Recently, as technology has improved, the retrograde approach via ureteroscopy has become more common because flexible scopes provide good distal tip deflection.[45] For tumors of the lower caliceal system where flexible ureteroscopy cannot reach the tumors, the antegrade approach is still used through a percutaneous approach. Furthermore, the antegrade approach provides the ability to clear larger tumor volumes but also increases the risk of tumor seeding.[46] Unfortunately, due to the nature of these approaches, there remains a big risk of under staging and under grading of this disease.

7.1.2. **Segmental ureterectomy**

The approach via segmental ureterectomy (SU) differs from RNU by preserving renal function in patients presenting with low-risk disease and provides similar oncological results. In comparison to its endoscopic counterpart, SU can provide complete tumor removal and lymphadenectomy can be performed. As suggested by the guidelines, complete distal ureterectomy with ureteroneocystostomy is recommended in patients with low-risk tumors in the distal ureter for whom endoscopic management is not an option and KSS in necessary.[12] The failure rates for the segmental resection of the upper and mid ureter are higher than that in the distal ureter.[2]

8. BCG Therapy for UTUC

The high recurrence rates in UTUC caused an extrapolation regarding the adjuvant therapy of UBC treatment. Intracavitary instillations have been described since the 1980s with the use of several different agents such as bacillus Calmette-Guerin (BCG) and mitomycin C (MMC) being the most common ones. However, in UBC these instillations have been made part of the guideline, whereas in UTUC not enough evidence has been found to support a definitive inclusion in the EAU guidelines.[2] The controversy regarding these treatments lies in the mode of administration as well the clinical efficacy.

8.1. Types of instillations

Current literature suggests three types of instillations for access to the upper urinary tract – antegrade perfusion via a percutaneous nephrostomy tube,[47] retrograde perfusion via an open-ended ureteric catheter, [48] or intravesical administration with vesicoureteral reflux via an indwelling ureteric stent. [49]

8.1.1. Antegrade perfusion via a percutaneous nephrostomy tube

Under ultrasound control, a 9F percutaneous nephrostomy tube would be inserted into the patient under local anesthesia. Between subsequent treatment sessions with BCG the catheter would remain closed. The perfusion would be performed for a period of two hours. Before each BCG perfusion unobstructed flow from the renal pelvis to the ileal conduit or bladder was confirmed and pyelovenous or pyelolymphatic backflow was excluded under fluoroscopy.[50] Furthermore, BCG therapy would only be started in absence of macrohematuria. This scheme can be observed below in Figure 2.

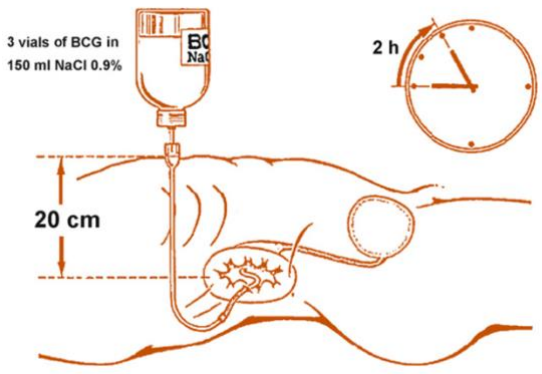

Figure 2 - Scheme of antegrade perfusion of the Upper urinary tract with bacillus Calmette-Guerin [60]

During the insertion of the nephrostomy tube there is a certain risk associated with missing the calyxes if the BCG solution, then flows into the ureter. Furthermore, it is believed that due to the nephrostomy tube having to stay in place for six weeks there is a higher risk in tumor seeding.

8.1.2. Retrograde perfusion via an open-ended ureteric catheter

In this approach, a 5F open-ended urethral catheter is inserted and is placed over a wire into the renal pelvis. If necessary, retrograde pyelography is performed to confirm the positioning of the catheter. After the infusion with BCG the catheter is removed, and the patient is advised to void within 1 hour.[48] Retrograde approach can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion.[2]

8.1.3. Intravesical administration with vesicoureteral reflux via an indwelling ureteric stent

In this scenario, a retrograde approach is also intended via vesicoureteral reflux (VUR), which is induced by a Double-J stent. Here a stent would be inserted retrogradely and left indwelling until the completion of the BCG treatment. The intravesical instillation of BCG was performed with the patient in the Trendelenburg position, held in position for 15 to 30 minutes, and voided 30 minutes to 2 hours after instillation. BCG instillation was scheduled at weekly intervals for a total of 6 weeks. After a course of BCG therapy, voided urine cytology was examined every month for the first 6 months and then every 3 months.[51] The problem with this approach is that the VUR wasn't achieved in a lot of the cases. Yossepowitch et al showed that only 59% of patients achieved reflux with the use of ureteric stents.[52]

8.2. BCG for Carcinoma in Situ

Instillation of topical therapy in carcinoma in situ (CIS) has shown considerably better results than in the adjuvant setting regarding Ta/T1 disease following KSS. In table 3 below the studies that summarize the efficacy regarding the use of BCG for CIS are shown. Most of the studies opted for a retrograde approach via an open-ended ureteric catheter or an indwelling ureteric stent. In them a total of 211 patients are treated using either an antegrade or

retrograde approach. Of these patients 71 (34%) experienced a UT recurrence whereas 37 (18%) had a UT progression.

Table 3 **Recurrence and progression rates of BCG therapy for CIS of upper urothelial tract**

Study	Participants	Scheme	UT recurrence (%)	UT progression (%)
Sharpe, 1993 [53]	11	Retrograde	2(18)	2(18)
Yokogi, 1996 [54]	5	Both	2(40)	1 (20)
Nonomura, 2000 [55]	11	Retrograde	3(27)	3(27)
Okubo, 2001 [56]	11	Retrograde	6(55)	4(36)
Miyake, 2002 [57]	16	Both	3(19)	2(13)
Hayashida, 2004 [58]	10	Both	5(50)	3(30)
Kojima, 2006 [59]	11	Retrograde	3(27)	2(18)
Giannarini, 2011 [60]	42	Antegrade	14(38)	2(5)
Shapiro, 2012 [61]	11	Retrograde	1(11)	0(0)
Anan, 2013 [62]	9	Retrograde	1(11)	0(0)
Horiguchi, 2018 [51]	38	Retrograde	17(45)	9(24)
Tomisaki, 2018 [63]	41	Retrograde	14(34)	9(22)

8.3. BCG for Ta/T1 Upper Tract Carcinoma

In the adjuvant setting, four studies were chosen and summarized below in Table 4. In total there were a total of 97 patients treated with BCG with only Patel et al. choosing to treat via a retrograde approach and all the others administering the BCG through a percutaneous nephrostomy tube. Here the recurrence rates range from 15-61 percent with a total of 36 patients having a recurrence. Regarding the UT cancer specific survival, only 8 patients succumbed to the disease despite the treatment.

Patel et al. investigated discovering new techniques for the instillation of adjuvant therapy in UTUC. They treated a total of 17 renal units (RU) in a total of 13 patients, with all the patients being staged as Ta whether G1 or G2. Clark et. al looked to determine the immediate and long-term results of percutaneous management of UTUC regarding rates of tumor

recurrence and preservation of renal function. [65] Of the patients treated in this study 12 had a solitary kidney with one further being treated bilaterally. The follow up ranged from 1.7 to 75.5 months, resulting in 11 being alive and 6 patients having died of which 3 progressed to metastatic transitional cell disease. Of the 13 patients suffering from solitary kidney only one had progressed to requiring dialysis.

Table 4 **Recurrence and progression rates of BCG therapy for Ta/T1 Upper urinary Tract Carcinoma of Low**

Study	Participants	Scheme	UT recurrence (%)	UT Cancer Specific Survival (%)	Median Follow-up (Months)	Stage
Patel, 1999 [64]	13	Retrograde	2(15)	13(100)	14.6	9/13 (G1pTa) 4/13 (G2pTa)
Clark, 1999 [65]	16	Antegrade	5(31)	14(88)	20.5	15/18 (Ta)
Rastinehad, 2009 [66]	50	Antegrade	18(36)	49(98)	61	27/50 (Low grade 23/39 (High grade)
Giannarini, 2011 [60]	22	Antegrade	11(61)	13(72)	42	Ta/T1

Rastinehad et. al is a study that attempted to determine whether there is an oncologic benefit of adjuvant BCG therapy. In total they had looked at 89 tumors of which each 15, 45, 22, 4 and 3 were categorized into Tx, Ta, T1, T2 and T3 respectively. The indications that allowed for the inclusion into the study for a nephron-sparing approach ranged from bilateral UTUC in 3 patients, advanced age and other comorbidities in 17 patients, a solitary kidney in 23 patients and a further 46 patients treated electively. [66] The main principle of such treatment is for cases of low to medium risk, however they conclude that it can also be beneficial regarding high-grade cases for patients with solitary kidney, as they state an 80% renal preservation rate for high-grade and 92% in patients with solitary kidney. Now what must be kept in mind is that high-grade has poor prognosis regardless of treatment, however they state

that endourologic management could delay the need for nephrectomy, dialysis and possible kidney transplant.

Giannarini et al. is a study that looked at patients with both CIS and papillary disease, looking at 37 patients with CIS as well as 18 patients with Ta/T1. Recurrence rates for were at 38% whereas UT progression was measured at only 5%. In comparison, they showed that UT recurrence in Ta/T1 was at 61%. Whilst this is only one study, these results are clearly more favorable regarding BCG treatment in CIS when comparing to Ta/T1.

9. Complications of BCG Therapy

When gathering data on complications that arise through adjuvant instillation a lot of the studies present similar data. They report bladder irritability or irritative urinary symptoms in all but one of the sampled studies. With numbers as high as 100 percent being reported in Hayashida et al. about bladder irritation. Other symptoms that seem to have a recurrent narrative are fever over 38 degrees celcius as well as transient hematuria being reported. Whereas, Giannarini et al. reported only one case of fatal E. coli septicemia, most other complications remained minor. Dependent on what type of instillation is used, the

Table 5 Summary of reports of complication in adjuvant therapies in UTUC

Study	Patients	Follow up (mean in months)	Complications (% of patients)
Sharpe, 1993 [53]	11	49	Irritative urinary symptoms (54.5%) Transient hematuria (27.3%) Flank pain (9.1%) Fever (9.1%)
Patel, 1999 [64]	13	14.6	Infection (15.4%) Infection with fever 7.7%
Miyake, 2002 [57]	16	30	Bladder irritability (75%) Fever >38℃ (56.3%)
Hayashida, 2004 [58]	10	50.9	Bladder irritation 100% Fever >38℃ 90% Hematuria 20% Hydronephrosis 20% Lumbago 10%

complications may vary regarding which placement is used to administer the treatment. The studies observed here are only the ones that deal with BCG instillation, however there are also studies concerned with MMC which report differing complications.

10. Discussion

Ever since 1934 when radical nephroureterectomy was first established, it has been the gold standard treatment regarding UTUCs. However, with the progression of time we have discovered that in certain low-risk case kidney sparing approaches can have similar results with better outcomes regarding the patient's quality of life and kidney function. Now we know that this has been established regarding the treatment of UTUCs. On the other hand, the role of intravesical therapy whether it be by BCG or chemotherapy is still debatable. In contrast to UBCs where adjuvant therapy has long been a part of the standard of care. The treatment of UTUCs with intravesical still remains problematic due to the anatomical difficulties that are provided by this region in our body. Whereas the bladder is a hollow organ which is easily perfused, the renal pelvis and ureter are not as easily accessible.

Since the first application of adjuvant BCG therapy for UTUC in 1985, studies have been proposed with either the curative intent for CIS or adjuvant intent for papillary Ta/T1 stage of the disease. The problem that we are facing here is that most available evidence is concerning the treatment of CIS, however, there have been no randomized controlled trials that have been conducted. Moreover, CIS is a topic that seems to have different criteria set by most studies and is shown to be hard to stage properly.

When looking at BCG therapy regarding Ta/T1 staged diseases, as seen in Table 4, there aren't many studies discussing it. Due to the fact, that it is a relatively rare disease as well as most research being shifted towards the application for CIS as it has seemingly better results regarding this type of therapy.

11. Conclusion

In this literature review, a comprehensive investigation into the current views and studies regarding the treatment of UTUC with BCG therapy was presented. When comparing most papers, one could claim that as of today the progression and recurrence rates don't provide sufficient evidence that the use of adjuvant therapy is as beneficial as it is in UBC for example. It is reasonable to believe that in the future with medical advancement being achieved regularly, that new ways to administer the drugs will improve its efficacy, which could lead to greater results in treating UTUC in an adjuvant manner.

12. Literature

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