Role of first check cystoscopy in non-muscle invasive bladder carcinoma- A prospective and historical cohort study
DECLARATION

This is to declare that the dissertation titled “Role of first check cystoscopy in non-muscle invasive bladder carcinoma- A prospective and historical cohort study” in the department of General Surgery is my own work done under the guidance of Dr. Vijay Abraham, Professor of General Surgery Unit III and Dr. Chandra Singh, Professor of Urology Unit I and submitted in partial fulfilment of the rules and regulations for the M. S. branch – I (General Surgery) examination, April 2017.

Pon Rachel V

M. S. Post Graduate trainee

Department of General Surgery

Christian Medical College, Vellore
BONAFIDE CERTIFICATE

This is to certify that the dissertation titled “Role of first check cystoscopy in non-muscle invasive bladder carcinoma- A prospective and historical cohort study” is a bonafide work of Dr. Pon Rachel V, in partial fulfilment of the rules and regulations for the M. S. branch – I (General Surgery) examination, April 2017.

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INTRODUCTION

Carcinoma of the bladder is the fifth most common cancer (1) in the UK and the eleventh most common cancer in the world. (2) Carcinogens and infections that inhibit the ability to detoxify the carcinogens effectively play a role in bladder cancer. Urinary stones and parasitic infection also predispose by causing chronic irritation.

Bladder tumours can either be papillary tumours which are the most common or bladder tumour. They resemble a tiny mushroom with the stalk attached to the lining of the bladder. The other type are the sessile tumours that grow as a "flat growth".
ACKNOWLEDGEMENTS

I thank Lord Almighty for all His mercies throughout the study.

I thank Dr. Vijay Abraham, Dr. Chandra Singh and Dr. Antony Devasia for their guidance and support which enabled me to complete this study successfully.

I would like to thank Dr. Rajat Arora (Urology) and Dr. Sudakar Chandran. B (General Surgery) for their constant encouragement and support.

I would like to thank Dr. Antony Samy and Mrs Grace Rebekah (Department of Biostatistics) for his guidance, encouragement and timely help.
September 02, 2015

Dr. Pon Rachel
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Sub: Fluid Research Grant NEW PROPOSAL:
- Role of first check cystoscopy in non-muscle invasive bladder carcinoma - A Prospective and historical cohort study.
- Dr. Pon Rachel, Emp. No: 29269, Dr. Sudakar chandran B. Emp. No: 30447,
- General Surgery 3, Dr. Antony Devasia, Dr. Chandrasingh, Dr. Rajat Arora, Dept.
- of Urology, Dr. Antonimany, Dept. of Biostatistics.

Ref: IRB Min No: 9462 [OBSEERVE] dated 05.06.2015

Dear Dr. Pon Rachel,

I enclose the following documents:

1. Institutional Review Board approval letter

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee),
Institutional Review Board

Cc: Dr. Sudakar Chandran, Dept. of Surgery, CMC, Vellore.
September 02, 2015

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Sub: Fluid Research Grant NEW PROPOSAL:
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Ref: IRB Min No: 9462 [OBESRVE] dated 05.06.2015

Dear Dr. Pon Rachel,

The Institutional Review Board (Blue, Research & Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled “Role of first check cystoscopy in non-muscle invasive bladder carcinoma – A Prospective and historical cohort study,” on June 05th 2015.

The Committee reviewed the following documents:
1. IRB Application Format
2. Patient Information Sheet and Informed Consent Form (English, Hindi, Telugu, Tamil)
3. Data Collection Form
4. CVs of Pon Rachel, Sudakar chandran B, Antony Devasia, Chandrasingh
5. No. of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on June 05th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632 002.

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# OFFICE OF RESEARCH

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*Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.*
*Tel: 0416 - 2284294, 2284202 Fax: 0416 - 2292788, 2264481 E-mail: research@cmovellore.ac.in*
We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: “Role of first check cystoscopy in non-muscle invasive bladder carcinoma – A Prospective and historical cohort study,” on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

4 of 5
Fluid Grant Allocation:
A sum of 5,000 - INR (Rupees Five thousand) will be granted for 3 years for stationery, printing, Xeroxing and computer charges (if computers used are within the Institution).

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board
Christian Medical College, Vellore

Ce: Dr. Sudakar Chandran, Dept. of Surgery, CMC, Vellore

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INTRODUCTION

Carcinoma of the bladder is the fifth most common cancer (1) in the United States and the eleventh most common cancer in the world (2). Carcinogens and inherited factors that inhibit the ability to detoxify the carcinogens effectively play a role in causing bladder cancer. Urinary stones and parasitic infection also predispose to malignancy by causing chronic irritation.

Bladder tumours can either be papillary tumours which are the most common type of bladder tumour. They resemble a tiny mushroom with the stalk attached to the inner lining of the bladder. The other type are the sessile tumours that grow directly in the lining of the bladder and can invade its muscular wall. But these tumours are less common.

The age standardised mortality rate for the European population was 8.5 per 1 lakh and in the US population was 7.3 per 1 lakh (2). In countries of the European sub-continent there has been a considerable decline in the incidence and mortality of bladder malignancies (3). This is likely due to better understanding of the disease pathology, good surgical practice and strict follow up. Amongst the population with bladder tumours non-muscle invasive tumours comprise of about 75% (4) and as expected they have a better mortality and morbidity rate as compared to the muscle invasive tumours.

The management of non-muscle invasive bladder tumours has been Trans urethral resection of the tumour followed by three monthly follow up with cystoscopy. But in the
recent past, even in the absence of macroscopic disease, Re-TURBT has been carried out to prevent under-staging of the tumour. In the background of this the necessity of three monthly check cystoscopy has been scarcely studied. Hence this study aims at looking at the necessity of the first check cystoscopy at three months in patients with non-muscle invasive bladder tumour and to try and stratify the high risk patients who need to be actually followed up on a regular basis.
AIMS & OBJECTIVES

1) To study the incidence of bladder tumour recurrence at three months following Re-Trans Urethral Resection of Bladder Tumours (TURBT) in non-muscle invasive bladder carcinoma (NMIBC).

2) To measure the compliance of patients to suggested follow up regime.

3) To identify factors that are associated with high risk of recurrence in those with NMIBC
**REVIEW OF LITERATURE**

**Anatomy of the Urinary Bladder:**

The urinary bladder is located in the anterior pelvis and is covered by the extra peritoneal fat. The space of Retzius aka the retro pubic space separated it from the pubic symphysis. The bladder neck is a fixed structure, its attachments being the pelvic fascia and the ligaments of the pelvis.

The body is supported inferiorly by the pelvic diaphragm in females and prostate in males. Laterally the obturator internus and levator ani muscles support the urinary bladder. The medial umbilical ligament provides attachment of the urinary bladder to the anterior abdominal wall and the umbilicus.

The bladder neck acts as the internal sphincter in women. At the bladder neck, the muscular bladder wall becomes more organized and we are able to identify 3 distinct layers become apparent namely

1. The inner longitudinal muscle layer: This layer merges with the inner longitudinal layer of the urethra
2. The middle circumferential muscle layer: This is most prominent layer. This layer fuses with the trigonal muscle layer

3. The outer longitudinal muscle layer: This layer also joins the deep trigonal fibres and the detrusor muscle

Multiple groups of muscles have to function synergistically to aid in the opening and closing of the bladder neck during micturition. In addition to this the pubourethral ligament also serves as a support the bladder neck and urethra.

In males, the bladder neck is continuous with the prostate and both serve together as the internal urethral sphincter. The puboprostatic ligaments attach the prostate to the pubis.

The trigone is a triangular portion of the bladder floor between the two ureteral openings and the bladder neck. The superior border of the trigone is known as the inter-ureteric ridge.

The arterial blood supply of the bladder originate from the internal iliac arteries. Umbilical artery is a branch of the internal iliac artery, which supplies the superior vesicle arteries. The inferior vesicle arteries can arise as a direct branch from the internal iliac artery in males or from the vaginal arteries in females. The obturator artery and inferior gluteal artery also take part in the blood supply to the urinary bladder. The venous return from the bladder drains into the internal iliac vein.
The lymphatic from the urinary bladder drains into the obturator, external iliac, internal iliac and common iliac lymph nodes. The internal iliac lymph nodes are usually the primary site of lymphadenopathy related to bladder pathology.
**Urothelium or bladder mucosa:**

The bladder mucosa is made up of transitional epithelium and is loosely connected to the muscular bladder wall by the lamina propria that serves as a connective-tissue layer. The bladder sub mucosa or lamina propria has a rich vascularity and overlies the detrusor muscle. At the trigone, the epithelium is more densely adherent to the underlying muscle. A layer of fatty connective tissue covers most of the anterior and lateral bladder in the retro pubic space and can be visualised cystoscopically in the case of a bladder perforation. The peritoneum covers the bladder posteriorly and separates it from the anterior vesicouterine pouch. A glycosaminoglycan layer coats the luminal surface of the bladder mucosa.
**PHYSIOLOGY:**

*Laplace's Law:*

The wall tension of a spherical body (bladder) is dependent on its internal pressure (Pves), the wall thickness (d) and radius (r) of the body.

\[
\text{Tension} = \frac{(\text{Pves} \times r)}{(2d)}
\]

Urinary retention increases the wall tension but the bladder pressure remains relatively constant resulting in overflow incontinence. The wall tension increases because of decrease in wall thickness and increase in the bladder diameter. This leads to an extremely dilated bladder.

*Bladder compliance:*

The compliance (elasticity) of the bladder depends on two factors

1) The amount of connective tissue in the bladder wall

2) Neuromuscular factors

The bladder compliance can be calculated by the increase in bladder volume as a function of intravesical pressure. The normal intravesical pressure is 20–60 ml/cm of water.

\[
\text{Compliance} = \frac{\text{change in volume}}{\text{change in bladder pressure}}
\]
Detrusor Pressure:

The detrusor pressure is the difference between the intravesical pressure and intra-abdominal pressure. These pressures can be measured by placing a catheter in the bladder and one in the rectum.

Detrusor pressure = intravesical pressure – abdominal pressure

Urethral Resistance:

The urethral resistance is calculated using the maximum urinary flow (Qmax) and the detrusor pressure at maximum urine flow (PdetQmax)

Urethral resistance = PdetQmax/ Q2max

Normal values for the urethral resistance men is <0.6 and for women is <0.2. The formula is applicable only when the voiding volumes are between 200–400 ml. The low urethral resistance is the reason why women have very low and sometimes immeasurable detrusor pressures in women during normal micturition.
Neural Control of the Bladder:

There are two functional states in which the bladder exists

1) The storage phase

2) The voiding phase

Storage Phase of the Bladder:

The filling of the bladder is brought about by the following factors

1) Contraction of the striated sphincter. This is innervated by the somatic nerves

2) Contraction of the smooth muscle sphincter. This is innervated by the sympathetic system

3) Inhibition of detrusor activity. This is again mediated by the sympathetic nervous system

Voiding Phase of the Bladder:

The voiding phase of the bladder includes the following components

1) Relaxation of the striated sphincter supplied by the somatic nerves

2) Relaxation of the smooth muscle sphincter
3) Opening of the bladder neck both of which are mediated by the sympathetic innervation

4) Detrusor contraction mediated by parasympathetic innervation

Neural Reflex Arcs to Control the Bladder Function:

The afferent signals from the volume receptors and the stretch receptors transmit signals about bladder filling to centres of the spinal cord and CNS. The pathways are as follows

1. Spinal pathways:

Spinal reflexes inhibit micturition during the filling phase and activate the striated sphincter via the pudendal nerve. They also inhibit the detrusor muscle and activate the smooth muscle sphincter via activation of the sympathetic nervous system. This pathway is activated by filling of the bladder. They also involve the pelvic floor, penis and the rectum thereby explaining the risk of retention of urine in the post-operative period following perineal operations. These same spinal reflexes form the basis for the therapy in an overactive bladder with sacral neuro stimulation.

2. Pontine Micturition Centre:

As the bladder gets filled up the micturition centre in the pons is activated. This centre is also known as the Barrington's nucleus. This causes inhibition of the spinal reflexes. This in turn results in the activation of the detrusors thereby inhibiting the urinary sphincter.
3. **Central pathways:**

These pathways are inhibitory to the micturition reflex. After a certain extent, the bladder distension reaches the consciousness of the person. This results in initiation of the micturition. This is a voluntary pathway. Lesions in this centre will remove all the inhibitory pathways and results in an overactive bladder.

The striated muscles of the external sphincter is voluntarily and is supplied by the pyramidal tract and the extrapyramidal system.

**Urethra to bladder reflexes:**

Urine flow or mechanical stretching of the urethra cause contraction of the bladder. This reflex is very important and aids in complete bladder emptying. The reflex is the cause for the combined urge and stress incontinence in women.
MALIGNANCY OF THE URINARY BLADDER:

Epidemiology:

Carcinoma of the bladder is the fifth most common cancer(1) in the united states and the eleventh most common cancer in the world.(2) The age standardised mortality rate for the European population was 8.5 per lakh and in the US was 7.3 per lakh.(2) In Europe there has been a considerable reduction in the incidence and mortality associated with bladder cancers.(3) This is due to better understanding of the disease pathology, good surgical practice and strict follow up regime. Amongst the population with bladder tumours, then on muscle invasive tumours comprise of about 75% (4) and they have a better mortality and morbidity rate as compared to the muscle invasive stages of the disease as expected.

As per the data from the Indian cancer registry bladder cancer is the ninth most common cancer among the men in India.(4) Men are affected 3 times more often than women and the age of incidence in men is 69 years whereas in women it is 71 years of age.(5)
CLINICAL FEATURES:

Symptoms:

Haematuria is the most common presenting symptom, which is intermittent, gross, painless, and present throughout micturition. Gross haematuria points more towards malignancy than microscopic haematuria. 10- 20% of patients with gross haematuria had carcinoma of the bladder. Only 2-5% with microscopic haematuria had carcinoma of the bladder.(6)

Pain as a symptom in bladder cancer occurs only with locally advanced disease. Flank pain may result when a tumour causes obstruction of the ureters. Though this is common with muscle invasive tumours, occasionally non- muscle invasive tumours can also cause obstruction when they are large in size and close to the ureteric orifice resulting in pain. The pain is similar to the pain associated with the passage of urinary stones. On the other hand, with locally advanced disease that is directly involving the peri vesicle soft tissues and nerves the patient might present with supra pubic pain. Obstruction to the urinary bladder, resulting in urinary retention will also have suprapubic pain. Hypogastric, rectal and perineal pain can be signs of disease involving the perirectal fat, obturator fossa, Presacral nerves or the urogenital diaphragm. Abdominal pain should alert the surgeon of possible intra-abdominal metastasis either to the lymph nodes or to the liver.
Voiding symptoms are seen in patients with carcinoma in situ (CIS) of the bladder and may result from dysfunctional bladder. Irritative voiding symptoms are highly suggestive of carcinoma in situ.

Constitutional symptoms including fatigue, anorexia, and weight loss are indicative of metastatic disease.

**Physical examination:**

A complete physical examination should be performed in patients with bladder cancer. This should include a bimanual examination of the vagina and rectum in women and digital rectal examination in men. Abnormal findings that can be seen include the following:

A solid pelvic mass in locally advanced disease

Induration of the prostate gland if there is involvement of the bladder neck and invades the prostate

The base and lateral walls of the bladder should be palpated for induration or fixation.

Inguinal adenopathy, though not a common site for metastasis, may be present.
**Aetiology:**

The most common and most important risk factor for this is tobacco smoking(7) and account for approximately 50% of the cases. Polycyclic aromatic hydrocarbons and aromatic amines are mostly excreted by the renal system. Any form of exposure to them increases the risk. The second most common cause (10%) for exposure is related to occupation in paint, dye and petroleum industry.(7)(8) The risk associated with personal permanent hair dye used is doubtful and is yet to be validated.(9)

Chlorination of drinking water is said to be potentially a risk factor due to the trihalomethanes formed due to chlorination.(10)

Increased fluid intake may dilute excreted urinary carcinogens and may reduce the contact time with the urothelium.(11)

Weak association between ionising radiation, cyclophosphamide and pioglitazone has been described in literature.(7)

Schistosomiasis resulting in chronic endemic cystitis is also a risk factor for bladder cancer.(7)

Augmentation cystoplasty is done when the bladder is small or if the compliance is poor. In patients who undergo this procedure there seems to be an increased risk of development of urothelial cancer.(12)

An increased risk following pelvic radiation has been noticed(13) but the magnitude of the risk appears to be small and also the results have not been consistent in all the
studies. But the patients who do develop malignancy following radiation seem to have advanced disease with poor prognosis.

Cyclophosphamide is used in the management of haematological malignancies. There is a nine fold increase in risk of developing bladder cancer, with a latency period of less than 10 years.(14)

A subset of population with NAT 2 genetic abnormality thereby resulting in slow acetylation are also predisposed to bladder cancer due to increased susceptibility to the other risk factors.(15)

Environmental exposures is the most common cause of bladder cancer. This "field concretisation" effect is one way to explain the multifocal occurrence of urothelial carcinomas of both the urinary bladder and the upper urinary tract.(16) The other theory is the monoclonal hypotheses. They originate from a single genetically altered cell, which then spreads through the urothelium by intraepithelial migration or intraluminal seeding.(17) Although the two hypotheses appear to conflict each other they are both probably operative in urothelial carcinogenesis.
Classification:

The Tumour, Node and Metastasis (TNM) classification system as approved by the Union International Contre le Cancer (UICC), is the most commonly used classification system (Annexure 6). Papillary tumours confined to the mucosa are classified as Ta and those which have invaded the lamina propria are classified T1. They are together grouped as non-muscle invasive bladder cancers (NMIBC) for treatment purposes. Also included are flat, high-grade tumours that are confined to the mucosa, and classified as carcinoma in situ (CIS).

pTa carcinoma is defined as non-invasive papillary carcinoma with no invasion of the lamina propria. In p Ta tumours the most important prognostic factor is the histological grading.(18)

pT1 carcinoma is defined by invasion into lamina propria, but not involving the muscularis propria. Identification of invasion of the lamina propria invasion might be difficult due to tangential section, poor specimen orientation, obscuring inflammation and thermal injury. pT1 carcinomas often invade the underlying stroma as single cells, irregularly shaped nests of tumour cells or finger-like extensions arising from the base of the papillary tumour.(19) The invading nests are cytologically different from the non-invasive cells. Invasive tumour cells have abundant cytoplasm and less nuclear pleomorphism than in situ carcinoma. Paradoxical differentiation is seen in microinvasive carcinoma where at low power magnification they appear to be more differentiated than the cells with carcinoma in situ.
George Farrow, beginning in 1976, defined micro invasive carcinoma as a tumour invading up to 5mm into the lamina propria. After multiple studies the criteria for micro invasion has been refined. The current criteria defines micro invasion as less than or 20 invading cells, as measured from the stromal–epithelial interface. Further investigation is necessary to assess the clinical significance of this diagnostic category.

pT2 includes carcinoma which invades the muscularis propria. pT3 is tumour invasion into the peri vesicle fat and pT4 is invasion into adjacent organs.

The nodal status is categorized based on the number and size of positive lymph nodes. Lymph node density is the ratio of positive lymph nodes to the total number of lymph nodes sampled. It was found to be an independent predictor of cancer survival. The largest dimension of metastasis, extra nodal extension, and anatomic location of positive nodes might be useful too. Extra nodal extension has been found to be the strongest predictor of clinical outcome. The summary of this is given in Annexure 4.

The World Health Organisation (WHO) and the International Society of Urological Pathology have published a new grading of the tumours. The currently followed classification has low-grade (LG) and high grade (HG) urothelial carcinomas (Annexure5).
Diagnosis

Urinary cytology:

Being a non-invasive test, this is the first diagnostic test to be done in view of diagnosing bladder malignancy. It detects exfoliated tumour cells in voided urine or bladder washings. The sensitivity of this test is variable and depends on the grade of the tumour ranging between 28-100%(23). Since the sensitivity of urine cytology is highly variable, it is not useful as a single test and is useful only when done with cystoscopy. The other disadvantages of urine cytology is the high inter observer variability and a positive cytology does not mean malignancy specific to the urinary bladder.(24) Confounding factors to this test are ongoing infections, calculi and prior interventional procedures.(25)

CT scan:

CT of both the abdomen and pelvis should be done with and without contrast, and must also include delayed images to identify filling defects in the collecting system. CT is also useful to find out extra vesicle extension if any, nodal metastasis and tumour involvement of the upper urinary tract or hydroureteronephrosis due to distal obstruction. CT provides better visualization of tumours when compared to ultrasound but they may not pick up tumours less than 1 cm in size, especially those in the trigone of the urinary bladder. The other disadvantage of the CT is that it cannot differentiate the depth of bladder-wall invasion. Also when CT is done after resection it may be difficult to differentiate extra vesicle tumour extension from inflammatory or iatrogenic oedematous changes.
Although a thickened bladder wall may indirectly suggest muscle-invasion, biopsy is required to confirm the diagnosis. On the other hand CT is 80% accurate in differentiating locally advanced tumours from the less invasive tumours.

**Intravenous urography:**

Intravenous Urography (IVU) can be done as an alternative for CT when it is not available. But the yield from IVU is very low and hence its usefulness as routine diagnostic tests is questionable.\(^{(26)}\) In a patient who is being evaluated for haematuria this can be a good investigation to start with. Intravenous urography is more sensitive for detection of small lesions of the ureter or renal pelvis. Ideally the test should be done prior to TURBT to avoid misinterpretation of postoperative changes.

Intravenous urography should be used with caution in patients with renal failure, diabetes or other conditions where the patients are at risk of acute kidney injury. In patients in whom the ureters and renal pelvis are not visualised adequately with intravenous urography, retrograde pyelogram scan be performed during cystoscopy if necessary.

The cystogram phase detects from 60 to 85% of large bladder tumours, but the smaller tumours are missed more frequently. The tumours are seen as irregular, frond-like, or nodular filling defects which are persistent in all the phases of the study. The classic description of the urogramatic findings of an upper tract transitional cell carcinoma is a meniscus-shaped ureteral filling defect known as the goblet sign or the Bergmann sign and the stipple sign is due to the trapping of contrast in the fronds of a papillary tumour.
MRI

MRI is as reliable as CT maybe better for evaluating bladder dome tumours. MRI is useful in patients who are allergic to the contrast dye but it is difficult to be tolerate by claustrophobic patients and cannot be used in patients who have pacemakers or other metallic implants or foreign bodies.

Ultrasound:

It provides information about space occupying lesions in the bladder, obstructive findings like hydroureteronephrosis and renal masses if present. Ureteric urothelial tumours and CIS cannot be diagnosed.

Among the radiological investigations CT urography is the best test available. CIS can’t be diagnosed by any of the above mentioned imaging techniques.
**Cystoscopy:**

Philipp Bozzini, a surgeon of the German Army in 1809 invented the first cystoscope. Though it was very primitive as compared to the current scope that was the ancestor to the modern cystoscope. He designed the model out of frustration due to the inability of locating bullets in his patients. The device was a metal chimney, with a candle inside and covered by shark skin. There was also a mirror inside to reflect the candle light. There was a viewing window through which the urethra/ vagina or the pharynx cold be viewed. This device was also known as the Lichtleiter. The disadvantages of the instrument were that it was difficult to use, became heated quickly, was not of adequate length and could not be used on live patients.

The next improved version was designed by Antoine Desormeaux. The difference being the use of a lamp fuelled by petroleum instead of a candle. But this also had the same problems as the previous instrument.

In 1860 Phillip Skinner Wales from the University of Pennsylvania developed a new instrument. His instrument contains a metal shaft with a very acute beak and an ophthalmologic mirror to reflect light down the channel. Compared to its predecessors this was light, elegant, and easy to use.

But the true endoscope was designed by a German urologist Maximilian Carl-Friedrich Nitze, in 1878 in collaboration with an instrument maker- Leiter. This had a tungsten system for the light source but again this got heated up quite fast. There was a provision
for this in the form of a complex water cooling system. Even though this was a landmark invention, this was nowhere close to the modern model.

The next improvement was by Dr. Henry Koch and Charles Preston when they created the mignon bulb. This was a tiny light bulb with a low-amperage light bulb that was small enough to fit into the tip of a cystoscope. This eliminated most of the problems associated with the previous models. But the problem with this instrument was that the light burnt out half way through the procedure.

In 1890, Reinhold developed a new instrument known as the Tilden-Brown composite cystoscope. This instrument had a lens to look straight forward, one at a slight angle, and another at a right angle. This assisted in inserting the scope under vision.

Dr Leopold Casper, made the catheterizing cystoscope which had a very complex mirror system between the eyepiece and the shaft. But the advantage which overshadowed all its disadvantages was that it allowed ureteral catheterization. However, the instrument lacked a deflector to guide the catheter tip into the urethral. Alexander Brenner (1859-1936) in Vienna, Austria, was one of the first, along with Karl Pawlik in Prague, to catheterize the female ureter. Brenner taught his procedure to James Brown, who returned to Hopkins and managed to catheterize a male ureter. Such an instrument from 1890 is shown in Figure 9. The channel for catheter insertion can be seen clearly. The catheter would come straight out of the shaft, but a mechanism to change the course of the catheter was still lacking.
By 1900, there were instruments to catheterize the ureters and to irrigate the urethra and the bladder. French urologist Joaquín Albarrán added a turn screw by the side of the cystoscope. This came along with a deflector, also known as the Albarrán deflector which assisted in manipulating the urethral catheter. The problem with this instrument came in the form of difficulty in sterilising it.

Dr. Leo Buerger, based his design on the one by Tilden Brown and created an instrument which remained the workhorse for the urologists for almost 60 years. It was easy to use, provided a great image and also enabled catheterization of the ureters.

The power to illuminate the bulb was produced by a transformer which was either a larger wood-encased apparatus or a small metal-encased device which was worn around the waist of the urologist.

Then revolutionary change came when fibre optics were discovered. The ability of light to follow a curved glass rod was finally harnessed for clinical use. The first attempt at creating a fibre optic endoscopy system was made in 1930 in Germany. This attempt was unsatisfactory. Twenty years later, Victor F. Marshall described the first fibre ureteroscope produced by ACMI.

Next a urologic surgeon from Liverpool along with Professor Harold H. Hopkins in London, developed the Hopkins lens system. Karl Storz, saw the future of this new system and bought the patent creating the current model.

The next big problem was the need to line up the glass fibres in a coaxial fashion, so that every fibre had the same position at the eyepiece as it had at the other end in the patient.
**Indications for cystoscopy:**

A) **Diagnostic:**

- Storage or voiding lower urinary tract symptoms
- Haematuria - gross/ microscopic
- Urethral or bladder diverticulum
- Urologic fistulas
- Congenital anomalies
- Sample collection for cytological and histologic studies
- Evaluation of the urethra, bladder, and ureters intraoperative during repair for incontinence or prolapse
- Retrograde pyelography

B) **Therapeutic: Urethral strictures**

- Bladder neck repair/ incision
- Intravesical procedures for calculi, ulcers, and tumours; removal of foreign, ureteral catheterization
- Vesicouretral reflux
**Contra indications:**

Febrile patients with urinary tract infections (UTIs)

Severe coagulopathy

Antibiotic prophylaxis cystourethroscopy is indicated only in patients with risk factors like older age group, active UTI, anatomic anomalies of the urinary tract, nutritionally depleted, immunocompromised, long hospital stay and long term steroid use

All patients who undergo cystourethroscopy with instrumentation should receive antibiotic prophylaxis.

Lithotomy is the most commonly used position for cystoscopy but most males can undergo flexible cystoscopy in supine position.(27)

This is the gold standard test in the diagnosis of bladder cancer. Flexible cystoscopy is preferred in men. The procedure begins with a bimanual examination under anaesthesia (EUA) to look for a palpable mass. This is useful for identifying locally advanced disease, which may present as extra vesicle extension, involvement of adjacent organs, or pelvic wall involvement.

The cystoscope is then inserted into the bladder under sterile precautions. A bladder wash specimen may be obtained by irrigating the bladder with sterile saline and this provides the highest sensitivity for detection of malignant cells. The bladder is inspected, and a detailed description including the size, number, appearance, location, and growth pattern (papillary or solid) of all lesions must be specifically recorded. This information
serves as a reference for subsequent cystoscopic examinations. The status of the normal mucosa should be recorded as well.
Urinary molecular marker tests:

Since cytology has been poor in diagnosing bladder cancer many markers and techniques are being evaluated to come up with a marker similar to PSA for prostate cancer. Many of these are based upon immunologic detection of soluble molecules in the urine. But most of these are under evaluation and need further evidence to be accepted as diagnostic tests. (28)(29). The various urinary markers are attached in Annexure 6
**Imaging for metastatic disease:**

The decision to perform additional diagnostic studies depends on the histopathological stage of the disease.

**Lung lesions:**

Chest radiographs are adequate for the initial evaluation and monitoring in patients for lung metastasis. They can pick up lesions up to 1 cm. These metastatic lesions appear as well defined non-calcified soft tissue densities. In patients with suspicious chest X ray findings and in patients with advanced disease where the chance of distant metastasis is high, CT thorax may be a valuable investigation to perform.

**Bone scan:**

Radionuclide bone scans to detect bone metastases are recommended only in patients with skeletal symptoms or unexplained elevations in serum alkaline phosphatase. Increased uptake is not a specific finding, and can be due to degenerative change, trauma, previous fracture or a metastatic disease. In case of a suspicious lesion, CT or MRI may be necessary to confirm a metastasis.

**PET:**

Positron emission tomography (PET) has limited value in patients with localized disease as 18F-fluorodeoxyglucose (FDG) is excreted in the urine.(30) PET may have a role in detecting disseminated disease in patients with locally advanced disease. Sensitivity for distant metastasis is 80% or above.
**Treatment strategy:**

**Trans urethral resection:**

This procedure can be done under local or general anaesthesia. The risk of infection after urinary tract instrumentation is 1%. So a single dose of antibiotic is given prior to the procedure.

R0 resection/ complete surgical resection is the goal of this operation. Most of the urothelial malignancies are papillary and hence can be resected easily. The tumour is transected at its base. Following this a biopsy is taken from the base to

1. Confirm complete resection
2. Rule out invasion of the muscle as this will upstage the disease

The tumours can be resected en mass or piecemeal depending on the size of the tumour. But this piecemeal resection must be done before transecting the stalk to prevent leaving behind tumour.

Some techniques to be followed during resection is to pull the cutting loop away from the tumour than pushing it towards the tumour. While cutting the tumour should be lifted off and away from the bladder mucosa. Also small friable tumours can be partially resected without turning the electricity on. All these will prevent perforation of the bladder wall.
Post procedure the urinary catheter may be removed or left in place. The indications for leaving in the catheter are

1. Perforation
2. Large tumour requiring extensive resection
3. for future use for instillation of chemotherapy

If the catheter is to be removed it has to be done after fully draining the bladder. If there is no perforation and haemostasis was adequate, chemotherapy can be instilled left for an hour prior to drainage. Active bleeding may result in increased absorption and thereby results in increased chemotherapy related complications.

**Complications:**

TURBT is associated with a low overall complication rate 5%. The complications include

1. Bleeding
2. Bladder perforation
3. TUR syndrome
4. Urethral lesion or creation of false passage
5. Sepsis
6. Skin burn or plaque
Bleeding is the most common complication. This can be avoided with meticulous haemostasis. Major bleeding presenting as urinary retention due to clots or requiring transfusion will require surgical evacuation of the clot and fulguration.

Bladder perforation is the more serious complication. The perforation can be intraperitoneal or extra peritoneal. Most recognised perforations are extra peritoneal and small. These can be managed conservatively by catheter. Intraperitoneal perforations are very rare. It will require open surgical repair.

TUR syndrome is very rare with bladder resection unlike in prostate resection. It usually occurs due to fluid absorption secondary to perforation. Direct intravascular absorption like in prostate resection does not happen.

Late complications include

A. Complications secondary to manipulation and/or dilatation of the urethra
   a. Meatal stenosis
   b. Urethral stenosis

B. Complications secondary to fulguration of the ureteral orifice
   a. Ureteral stenosis
   b. De novo vesicoureteral reflux

Transurethral resection of bladder tumours is the procedure of choice for non-muscle invasive tumours of the bladder. The aim of this procedure is to get an accurate pathological staging and grading of the tumour at the same time removing all visible
tumour. Complete resection at the first surgery plays an important role in the prognosis of the disease and this depends on the operating surgeon and his experience.(31) Removal of the detrusor along with the sample is necessary for an accurate pathological grading and absence of the muscle in the sample has been associated with increased residual disease resulting in recurrence. Thus it has been used as a surrogate marker in prognostication.(32) To avoid leaving behind residual disease a new technique known as extended TURBT has been suggested. This procedure involves identification and resection of diseased region with the assistance of photodynamic method.(33) 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL) will be instilled into the bladder prior to the procedure and then visualizing with an UV light. This is very useful in detecting CIS.

Photodynamic diagnosis pDD has lower specificity than white-light endoscopy (63% vs. 81%).(34) False-positivity can be caused by inflammation or recent operation or instrumentation of the bladder and during the first 3 months after the treatment with intravesical BCG. In the hexaminolaevulinic acid (HAL) study there was an increase in detection of tumour. This indirectly had resulted in absolute reduction of less than 10% in recurrence rates within 12 months.(35)

Narrow-band imaging (NBI), differentiates normal urothelium from the hyper vascular cancer tissue. This reduction of recurrence rate with the use of narrow band imaging is yet to be confirmed.

There is significant risk of residual tumour after initial TURB done for a Ta, T1 lesions. As per statistics this is observed inupto33-55% of patients with T1 disease and 41.4% of
patients with TaG3 disease. (36) There is also a high chance that the tumour could be under staged, depending on the experience of the operating surgeon. And the treatment of a T1 disease is completely different from that of a T2 disease. And hence a second TURBT can provide better staging and thus improve the prognosis of the disease. (36)
Re-resection/ Scar Resection:

There is always a risk of residual tumour/ recurrence after the first resection- 12.7% of Ta tumours, and in 36.2% of T1 tumours(37). A second transurethral resection reduces tumour burden and will facilitate adjuvant therapy(38). The estimated recurrence free survival rate in patients undergoing Re- TURBT at 3 and 5 years is 68% and 63% as compared to 48% and 40%(39). Having said this, the question arises whether the check cystoscopy should be repeated at 3 months following a Re- TURBT or can it be prolonged. To our knowledge there are no studies looking at this specifically. Though there are recommendations saying the second cystoscopy in low risk tumours can be done 9 months following the first 3 monthly check cystoscopy(40), whether this can be extrapolated to the above group is yet to be answered.

A second transurethral resection of the tumour is recommended in a select set of individuals as mentioned below

- Incomplete initial resection
- Absence of muscle in the initial specimen with exception of low grade Ta tumours
- All T1 tumours and primary CIS
- High grade tumours

The second resection should be within 6 weeks of the primary resection.
Pathologic report

The pathologic report should contain the following information:

- Location of the sample
- Grade of the tumour
- Depth of the tumour invasion
- Presence/absence of CIS
- Presence or absence of detrusor muscle in the specimen
- Lymph vascular invasion (LVI)
- Aberrant histology if any
**Prognosis of carcinoma in situ:**

In patients with carcinoma in situ without any treatment, 54% will progress to muscle-invasive disease.\(^{(41)}\). The risk of recurrence also depends on the risk category the patient’s fall into. They are classified into low, intermediate and high risk based on the following factors.

**Risk stratification:**

Patients can be stratified into 3 groups based on the EORTC tables.

Low-risk:

- Primary
- Single
- Ta
- Low grade
- <3 cm
- CIS- absent

Intermediate-risk:

- All tumours that do not belong in the low or the high risk category

High-risk tumours:

- Recurrent disease
- Multifocal
- T1
• High grade
• CIS present
• >3cm
**Adjuvant intravesical chemotherapy:**

As the disease is known for its recurrence and progression even after resection intravesical chemotherapy should be considered for all patients. A single instillation or multiple instillation depends on the stage and grade of the tumour. Early single instillation has been proven to be beneficial probably by destroying the circulating tumour cells resulting from TUR and by ablative effect on residual tumour cells.(42)(43) Prevention of tumour cell implantation should be within the first hours after cell seeding and hence the instillation must be administered within 24 h. Immediate instillation of postoperative chemotherapy is contra indicated in case of perforation and bleeding that require bladder irrigation. For high risk patients a single immediate instillation might be inadequate. A meta-analysis showed a 44% reduction in the odds of recurrence at 1 year in favour of chemotherapy instillations along with resection as opposed to resection alone but there was no proven benefit with regards to tumour progression.(44)
**Adjuvant Bacillus Calmette-Guerin intravesical therapy:**

There are many studies that have compared resection versus BCG after resection and have found that BCG along with resection is superior to just resection in the prevention of recurrence of tumour. Also BCG has been found superior to mitomycin. There was a 32% reduction in recurrence with BCG as compared to the 28% with Mitomycin. The effect of BCG has been found to be long lasting, and has been proven to delay if not prevent recurrence. Also with BCG there were significant reduction in distant metastases and better overall survival and disease-specific survival.

BCG instillations are given as a 6-weekly schedule. It has been shown that only patients who received maintenance BCG benefited. But a definitive protocol is yet to be formulated. At least 1 year of maintenance is required to achieve the benefit of BCG. (49) (50) There is no consensus currently on the number of doses or the duration of adjuvant BCG instillation and the frequency at which these instillations are to be carried out.

Having said all this the disadvantage with BCG intravesical treatment is that it is associated with more side effects compared with intravesical chemotherapy. Most of these side effects occur during the induction rather than the maintenance phase. (51)

The contraindications for BCG instillation are as follows:

- Macroscopic haematuria 2 weeks following TURBT
- Traumatic catheterisation
- Symptomatic urinary tract infection
Relative contraindications

- Immunocompromised patients

Disregarding these can lead to life threatening systemic complications

In view of the toxicity associated with BCG, it should not be used in all patients. The risks and benefits of BCG were studied and BCG is currently recommended for patients with high risk disease.
Radical cystectomy in Non-Muscle Invasive Bladder Cancer:

Patients are said to have failed BCG therapy if they fall into one of the following categories

- Detection of muscle-invasive tumour during follow-up

The tumour is said to be refractory if

- High grade tumour persists even after 3 months of treatment.
- CIS is present after 3-6 months of treatment.
- A new high grade lesion appears during BCG therapy

In the above mentioned cases and in patients who develop serious side effects during induction of BCG therapy radical cystectomy is the preferred as this reduces the financial burden on the patient. The benefit of this procedure must be weighed against the impact on the patient’s quality of life. In some patient who have a high risk of progression, radical cystectomy and conservative therapy with BCG should be offered to the patient as the available options of management.

The risk factors are as mentioned below (52)

- Multiple
- Recurrent
- >3 cm
- T1
- High grade
- Concurrent CIS
- Micro papillary variant of urothelial carcinoma
**Follow-up:**

As per the current recommendation, the first cystoscopy is at 3 months following resection and is considered the most important prognosticating factor.

Low-risk tumours

If the check cystoscopy at 3 months negative, subsequent cystoscopy is advised 9 months later, and then yearly.

Intermediate-risk tumours

Cystoscopy and cytology are recommended with a scheme which is adapted according to personal and subjective factors.

High-risk tumours

- Cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.

- Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours

- Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.

- During follow-up in patients with positive cytology and no visible tumour in the bladder, random bladder biopsies or biopsies with photodynamic diagnosis, and investigation of extravesical locations (CT urography, prostatic urethra biopsy)
In low-risk the follow up has to be continued up to 5 years and in high risk tumours the patients have to be followed up for life long.(53)
MATERIALS & METHODS

This study is a historical and prospective observational study of recurrence at 3 months in patients with non-muscle invasive bladder cancer following a Trans urethral resection of the bladder cancer. Patients managed for the same between March 2013 and February 2016 were assessed for the outcome parameters.

Inclusion Criteria:

All patients with non-muscle invasive bladder tumour (Ta and T1 stage tumours) who have undergone TURBT

Exclusion criteria:

Muscle invasive bladder carcinoma

Brief Procedure:

The outcome information of the patient managed under the department of Urology from March 2013- February 2015 was obtained retrospectively using maintained records from the Medical Records Department. All patients who were treated for non-muscle invasive
bladder cancer were included in this study. Prospective compilation of the data was done for all patients from March 2015- February 2016.

The patient’s in the prospective arm were explained about the benefits of follow-up and advised to follow up after the resection at 3 months with a check cystoscopy.

At the time of resection the tumour details including the number, size, stage, grade and presence of CIS were recorded.

The patient was followed up. If he/she had undergone a scar resection or re- TURT the tumour details were again recorded. The patient was followed up for 3 months following this and the presence or absence of recurrence at the 3 month check cystoscopy was studied.
**Sample size:**

Based on a previous study (Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials) depending on the risk strata is between 15% and 60%. From this a mid-value of 35% was selected.

A sample of 243 subjects will be required to achieve 95% confidence interval with precision +/- 6% around an incidence of recurrence rate of 35 % and the adjusted for 15% lost to follow up would be 285.

\[ N = \frac{4pq}{d^2} \]

\[ N = \frac{4 \times 35 \times 65}{6 \times 6} \]

\[ N = 243 \]
**Statistical methods:**

Data was entered in EXCEL sheet and analysed using SPSS software. The quality of data was further scrutinized through frequencies, histograms and Box-Cox plots. As the risk of recurrence post resection is calculated based on multiple independent variables odds ratio and chi square test was used in data analysis.
Parameter’s studied:

Number of tumours

Size: 3cm or more

T category: Ta/ T1

CIS: present/absent

Grade: low/ high grade

The recurrence at 3 month check scopy and the relation between the above mentioned factors and recurrence.
OBSERVATION & RESULTS

Descriptive data:

Based on the inclusion and exclusion criteria 239 patients were recruited. These patients were within the age of 24 and 93 years with a mean age of 57.54 years. Out of these 239 patients 87.4 % were male and 12.6 % were female.
CHART 2: SEX DISTRIBUTION

- Males
- Females

64
The patients included were those with non-muscle invasive bladder tumour. Out of the 239 patients included 132 had T1 disease and 106 had Ta disease. One patient had both T1 and Ta component and was hence included as inconclusive.
Prostate was involved in only 1 patient and is about 0.4% of the data. But since it is only one patient it is not statistically significant.
Out of all the patients included 16.3% of the patients had carcinoma in situ and 83.7% patient did not have carcinoma in situ.

CHART 4: CARCINOMA IN SITU

![Chart showing the distribution of patients with and without carcinoma in situ.]

- Yes
- No
180 of the patients had high grade tumour and 59 patients had low grade tumour.
Out of the 239, 7 patients had required second resection. Out of these patients there was an almost equal distribution with regards to high/low grade, CIS presence/absence and Ta/T1.
There were 107 patients who had undergone scar resection. Out of these there were 12 patients who had residual malignancy. But none of them had progression of the disease.

CHART6: SCAR RESECTION
Amongst all these patients 178 underwent check cystoscopy – 151 by 3 months post resection and the remaining 27 after a delay ranging between 6 months to 1 year.

Patients were contacted when the follow up was delayed and the reasons were as follows

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladeshi</td>
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</tr>
<tr>
<td>Distance</td>
<td>1.7</td>
</tr>
<tr>
<td>Familial issues</td>
<td>.4</td>
</tr>
<tr>
<td>Follow up elsewhere</td>
<td>.4</td>
</tr>
<tr>
<td>monetary</td>
<td>.4</td>
</tr>
<tr>
<td>Other medical issues</td>
<td>.4</td>
</tr>
<tr>
<td>Personal</td>
<td>.4</td>
</tr>
</tbody>
</table>

Table 1: Reasons for defaulting check cystoscopy
Of the various categories of patients who were studied recurrence was seen in 19 patient which compromises 7.9% of the total population studied.
SUB GROUP ANALYSIS IN THE RECURRENCE GROUP:

Of the 239 patients recruited only 19 had recurred. The following analysis was carried out to identify risk factors which predisposed to recurrence. The following data pertains to the 19 patients who had recurred.

There were 17 males and 2 females in this group. There was no particular age group associated which had increased recurrence rates.
Out of the 176 patients with tumour size less than or equal to 3 cm 11 patients had recurrence. 55 patients had tumour larger than 3 cm out of which 8 had recurred.

The p value was 0.092.
In patients with single tumour out of the 128, 6 had recurred and in patients with multiple tumours out of the 111, 13 patients had recurred. The p value was 0.039

CHART 8: NUMBER & RECURRENCE
155 patients had high grade tumour of which 14 had recurred. Out of the 54 patients who had low grade tumour 5 patients had recurred. The p value was 0.525.
There were 29 patients who had carcinoma in situ out of which 10 patients had recurred. Out of the 191 patients who did not have carcinoma in situ only 9 patients had recurrence. The p value was 0.000.
There were 7 patients who underwent 2\textsuperscript{nd} resection or completion TURT. These were followed by scar resection. Of these 3 patients had recurred. Out of the 232 who were considered to have had adequate resection in the first time only 16 patients had recurred. The p value was 0.012.

**CHART 11: 2ND RESECTION & RECURRENCE**

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<th>Category</th>
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<td>Category 2</td>
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<td>93.1</td>
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</table>
Summarising the data

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<th>Risk Factors for Recurrence</th>
<th>Recurrence</th>
<th>No Recurrence</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>192</td>
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</tr>
<tr>
<td>Female (R)</td>
<td>2</td>
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<td></td>
</tr>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;=3</td>
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<tr>
<td>&gt;3</td>
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<td>2\textsuperscript{nd} Resection</td>
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<td>Yes</td>
<td>3</td>
<td>4</td>
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<tr>
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<td>216</td>
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TABLE 2: VARIOUS FACTORS AND RECURRENCE
The recurrence in the prospective and retrospective group were compared. The findings are as given below

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<th>Prospective</th>
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</thead>
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<td>Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECURRENT No E</td>
<td></td>
<td></td>
<td>135</td>
<td>85</td>
<td>220</td>
</tr>
<tr>
<td>% within</td>
<td></td>
<td></td>
<td>61.4%</td>
<td>38.6%</td>
<td>100.0%</td>
</tr>
<tr>
<td>RECURRENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% within group</td>
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<td></td>
<td>90.0%</td>
<td>95.5%</td>
<td>92.1%</td>
</tr>
<tr>
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<td>Count</td>
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<td>15</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>% within</td>
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<td></td>
<td>78.9%</td>
<td>21.1%</td>
<td>100.0%</td>
</tr>
<tr>
<td>RECURRENT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% within group</td>
<td></td>
<td></td>
<td>10.0%</td>
<td>4.5%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
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<td>150</td>
<td>89</td>
<td>239</td>
</tr>
<tr>
<td>% within</td>
<td></td>
<td></td>
<td>62.8%</td>
<td>37.2%</td>
<td>100.0%</td>
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<tr>
<td>RECURRENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% within group</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
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### Chi-Square Tests

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<th>Value</th>
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<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
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<tr>
<td>Pearson Chi-Square</td>
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<td>.128</td>
<td>.146</td>
<td>.099</td>
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<td>Likelihood Ratio</td>
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<td>.099</td>
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<tr>
<td>Fisher's Exact Test</td>
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<td></td>
<td></td>
<td>.146</td>
<td>.099</td>
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<tr>
<td>N of Valid Cases</td>
<td>239</td>
<td></td>
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</table>

Table 3: Comparison of recurrence in the prospective and retrospective groups.
In a subgroup analysis of recurrence, the patients were divided into 2 groups

Group A: Low risk (Single, Ta, Low grade, <3 cm, CIS- absent)

Group B: High risk (Multiple, T1, High grade, >3cm, CIS present)

These patients were further subdivided into with and without scar resection.

The results were as follows

<table>
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<tr>
<th>Scar resection</th>
<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Yes</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>10</td>
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</table>

Even though this was statistically insignificant, population wise this could be significant. And patients in low risk group need not undergo such frequent follow up and cystoscopies. They can be followed up at longer intervals.
DISCUSSION

In our study 239 patients were recruited. Out of this only 15% were females. The rest were males. As shown in the earlier studies, bladder malignancy has been a disease of the elderly men and our study has followed the same pattern. Most of the patients in our study group were within 45-75 years of age. The mean age was 57.5. The initial stage of the bladder tumours were almost equal with 55% in the T1 group and 45% in the Ta group. Most of the patients had high grade tumour (75%) and the rest were low grade. In our study, the number of tumours range from 1 to 20 with the mean number being 3. There were not many patients who had carcinoma in situ in the biopsy. Only 16.3% of the patients had carcinoma in situ.

In our study group only 2.9% of the patients had required second resection to achieve adequate resection.

In our study group 70% of the patients had come for the first check cystoscopy. 30 % had not come for various reasons. These patients were contacted and the most common reason for this default was the distance. The other reasons being financial constraint and lack of awareness of the disease. Among the patients who had come for follow up 85% of the patients had come on time. The remaining 15% were late for follow up and had come for follow up between 6 months to 1 year.
In our study group there were only 19 recurrences. The various factors with regards to the tumour and its histopathology were assessed to look for association with increased incidence of recurrence. There was no difference in the incidence of recurrence with regards to size or grade of the tumour. But there was a statistically significant increase in the recurrence of multifocality, presence of carcinoma in situ and patients who had required second resection.

As evidenced by the study, recurrence is not very common at 3 months following resection. There are few factors which strongly predispose to recurrence like multifocality, presence of carcinoma in situ and incomplete tumour resection in the first resection. The other group of patients need not be on 3 monthly follow up. This will provide a huge relief on the financial burden of the patient and might improve his/her follow up.

On the other hand patients with risk factors of recurrence should be educated on the high chance of recurrence of the disease and the importance of the check cystoscopy at 3 months must be emphasised. They should be kept on strict follow up with a low threshold for further management. Radical cystectomy upfront is an option that should be discussed with the patient and his relatives. They should be explained regarding the conventional method of treatment, the need for regular follow up, and in patients who are not willing for such a strict follow up, radical cystectomy should be strongly advocated.
LIMITATIONS

1) The use of intravesical chemotherapy and their role in post resection recurrence was not studied in this study.

2) A larger population should be studied prospectively to get a better understanding and to draw recommendations regarding the class of patients who do not need 3 monthly follow up.

3) As evidenced in table 3 there was not much difference in the recurrence rates between the prospective and retrospective groups. Better visual and other informative tools such as brochures should be developed, to educate patients on recurrence and emphasise on follow up.
CONCLUSION

In patients with non-muscle invasive carcinoma of the urinary bladder, post resection, recurrence is more common in multifocal tumours, presence of carcinoma in situ and in patients who had a second resection. These patients need a 3 month check cystoscopy. The follow up of patients who fall in the low risk group and have had a scar resection donot need such close follow up. The patients who follow up in the intermediate group need to be studied further prior to extending the follow-up period.
SUMMARY

In patients with non-muscle invasive carcinoma of the urinary bladder, post resection, recurrence is more common in multifocal tumours, presence of carcinoma in situ and in patients who had a second resection. These patients need a 3 month check cystoscopy. The follow up for the rest of the patients can be delayed.
BIBLIOGRAPHY:


ANNEXURES
Annexure 1:

Abstract

Title:
Role of first check cystoscopy in non-muscle invasive bladder carcinoma - A prospective and historical cohort study

Aims & Objectives:

1) To study the incidence of bladder tumour recurrence at three months following Re-TURBT in non-muscle invasive bladder carcinoma (NMIBC).

2) To measure the compliance of patients to suggested follow up regime.

3) To identify factors that are associated with high risk of recurrence in those with NMIBC

Methodology:

Patients managed for non muscle invasive bladder cancers were studied retrospectively from March 2013- February 2015 and prospectively from March 2015- February 2016. After getting permission from the medical records department and the Institutional ethics committee the patients were recruited in the above mentioned period. In this study a total of 239 patients were included (150 as retrospective and 89 as prospective). Patient details were entered in the specific proforma and analysed.
RESULTS:

Our study included 239 patients, out of which 19 patients had recurred at the 3 month check cystoscopy. 17 of these were males and 2 were females. Out of the 19 cases with recurrence, 11 had tumours ≤ 3 cm and 8 had > 3 cm. The p Value was 0.092. 6 patients had solitary tumour and 13 had multifocal tumour (p Value: 0.039). 14 patients had high grade tumour and 5 had low grade tumour (p Value: 0.525). Of the 19 patients, 10 had carcinoma in situ and 9 did not have carcinoma in situ (p Value: 0.000). 16 patients had recurred in patients who hadn’t required 2nd resection and 3 in patients who had required 2nd resection (p Value: 0.012)

CONCLUSION:

Patients with multifocal tumours, carcinoma in situ and inadequate first resection had a higher risk of recurrence. The patients need 3 monthly follow up. The other patients do not need such a strict follow up regime.
ANNEXURE 2:

Proforma

Data collection form

Name:

Age:

Sex:

Hospital number:

Tumor details (intraop):

Number: 1/ 2-7/ 8 or more

Size: <1cm/ 1-2cm/ 3cm or more

T category: Ta/ T1/ inconclusive

CIS: present/absent

Grade: G1/G2/G3

Second resection: yes/no

If yes Malignant: yes/no
If yes:

Number: 1/ 2-7/ 8 or more

Size:    <1cm/ 1-2cm/ 3cm or more

T category: Ta/ T1/ inconclusive

CIS: present/absent

Grade: high/ low

Underwent scar resection:

yes/no Interval: in weeks

3 month check cystoscopy:

Interval:

On time: Yes/ no

If no was the patient

contacted: Reason for delay

Recurrence: yes/no

Progression: yes/no
ANNEXURE 3:

Consent forms:

Informed Consent form to participate in a research study

Study Title:

Study Number: __________

Subject’s Initials: ________________ Subject’s Name: _________________________________

Date of Birth / Age: ___________________________

(i) I confirm that I have read and understood the information sheet dated ___________
for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the investigator of the study, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw. I agree to this access. However, I
understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Signatory

Date: ____/____/_____

Signatory’s Name: _________________________________Signature:

Or

Representative: _________________

Date: ____/____/_____

Signatory’s Name: _________________________________
Signature of the Investigator: ________________________

Date: ____/____/____

Study Investigator’s Name: _________________________

Signature or thumb impression of the Witness:  
___________________________

Date: ____/____/____

Name & Address of the Witness:
______________________________
Information sheet:

Cystoscopy three months after bladder tumour resection – should it be continued in all patients?

You are requested to kindly give permission to participate in an observational research. This is to study on the incidence of recurrence of tumour at the check cystoscopy that is routinely done at 3 months following TURBT. Please read this form carefully and ask any questions you may have before agreeing to take part in the study.

What the study is about:

The purpose of this study is to learn the recurrence of tumour in patients like you who have bladder tumour requiring follow up cystoscopy, to learn, in which group the cystoscopy is most important.

What we will ask you to do:

You need to do nothing different or extra. Your treatment involves cystoscopy after three months to detect any new tumour and our request is to come for this cystoscopy without fail.

Risks and benefits:
There is no added complication because of the study. Since nothing different is being done to you, you will not have any added benefit either. If we find that some patients require cystoscopy more often or less often based on this study, it will benefit patients with bladder cancer in future – either by cutting down the expense or more effective bladder tumour treatment.

Confidentiality:

The information of your disease will be kept confidential. The records of this study will be kept private. In any sort of report we make public we will not include any information that will make it possible to identify you. Research records will be kept in a locked file (soft copy); only the researchers will have access to the records.

Taking part is voluntary:

Taking part in this study is completely voluntary. If you decide not to take part it will not affect your current or future treatment. If you decide to take part, you are free to withdraw at any time.

If you have questions:

Dr. Pon Rachel. V,

Surgery III office,

Paul Brand building,

CMCH, Vellore-04

Ph: 0416 2282079, rachel15987@gmail.com
**ANNEXURE 4**

**TNM staging:**

**T** - Primary tumour

TX- Primary tumour cannot be assessed

T0- No evidence of primary tumour Ta-

Non-invasive papillary carcinoma Tis-

Carcinoma in situ: ‘flat tumour’

T1- Tumour invades sub epithelial connective tissue

T2- Tumour invades muscle

  T2a- Tumour invades superficial muscle (inner half)

  T2b- Tumour invades deep muscle (outer half)

T3- Tumour invades perivesical tissue

  T3a- Microscopically

  T3b- Macroscopically (extravesical mass)

T4- Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

  T4a- Tumour invades prostate, uterus or vagina
T4b- Tumour invades pelvic wall or abdominal wall

N - Lymph nodes:
NX- Regional lymph nodes cannot be assessed
N0- No regional lymph node metastasis
N1- Metastasis in a single lymph node in the true pelvis (hypo gastric, obturator, external iliac, or presacral)
N2- Metastasis in multiple lymph nodes in the true pelvis (hypo gastric, obturator, external iliac, or presacral)
N3- Metastasis in common iliac lymph node(s)

M - Distant metastasis:
MX- Distant metastasis cannot be assessed
M0 - No distant metastasis
M1- Distant metastasis
ANNEXURE 5

Grading

1973 WHO grading Urothelial papilloma:

Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

2004 WHO grading system [papillary lesions]:

Urothelial papilloma (completely benign lesion) papillary urothelial neoplasm of low malignant potential (pUNLMp)

Low-grade (LG) papillary urothelial carcinoma

High-grade (HG) papillary urothelial carcinoma
## ANNEXURE 6

**Urinary molecular markers**

**Urinary tests for the detection of bladder cancer that analyze exfoliated cells**

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<th>Target</th>
<th>Sensitivity</th>
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<th>False positive in</th>
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<tr>
<td>Nuclear morphology abnormalities</td>
<td>59 to 69 percent</td>
<td>73 to 93 percent</td>
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<td>Cytokeratin 20</td>
<td>78 to 87 percent</td>
<td>55 to 80 percent</td>
<td>Urinary tract infection, calculi, post-BCG</td>
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<tr>
<td>Telomerase</td>
<td>70 to 100 percent</td>
<td>60 to 70 percent</td>
<td>Infection</td>
</tr>
<tr>
<td>Microsatellite DNA</td>
<td>72 to 97 percent</td>
<td>80 to 100 percent</td>
<td>BPH, inflammation</td>
</tr>
<tr>
<td>Chromosomal abnormalities (chromosomes 3, 7, 17, and 9p21)</td>
<td>69 to 87 percent</td>
<td>89 to 96 percent</td>
<td>BPH, inflammation, hematuria</td>
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<tr>
<td>Carcinoembryonic antigen (CEA), mucoproteins</td>
<td>70 to 80 percent</td>
<td>60 to 70 percent</td>
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<td>DD23 antibody</td>
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<td>Lewis X antigen</td>
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### Urinary molecular markers for the detection of bladder cancer

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<td>Fibrin degradation products (FDP)</td>
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<td>Hyaluronic acid, hyaluronidase</td>
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Annexure 7

Master chart:
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<th>AGE</th>
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<th>TUMOR DETAILS</th>
<th>PROSTATE T CATEGORY</th>
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